EPIDEMIOLOGY OF DIABETES IN INDIA

BURDEN OF DIABETES

The impact of the worldwide explosion of type 2 diabetes mellitus (which accounts for approximately 85 to 95% of all cases of diabetes) will remain centered in the developing countries, since by the year 2025, 75% of all the people with diabetes will be in the developing countries as compared with 62% in 1995.9 By 2025, there will be a 42% increase from 51-72 million in the developed countries and 170% increase from 84-228 million, in the developing countries.9 India already faces a grave problem with the largest number of subjects with diabetes (approx 33 million in 2003) and it is escalate further with the number increasing to 57.2 million in the year 20259,10 and by the year 2030 it may be 80.9 million.11 The prevalence estimate by the International Diabetes Federation (IDF) reported the worldwide prevalence to be increasing from 5.1-6.3% (between 2003-2025).12 Diabetes mellitus is an iceberg disease in which 66% of patients are often undiagnosed and they present with the complications of diabetes.

As shown in (table 1) the greatest increase will be in India from 19.4 million to 57.2 million, while in China from 16 million to 37.6 million and USA from 13.9 million to 21.9 million during the same period, unless effective preventive measures are implemented to curb this enormous increase. Currently India has got the largest number of
diabetics and is being called as diabetic capital of the world. In (table 1) this number has been compared with the number of diabetics in other countries having large number of diabetics.

**Table 1** Top Ten Countries for their estimated number of adults with diabetes in millions

<table>
<thead>
<tr>
<th>No.</th>
<th>Country</th>
<th>Year 1995</th>
<th>Country</th>
<th>Year 2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>India</td>
<td>19.4</td>
<td>India</td>
<td>57.2</td>
</tr>
<tr>
<td>2</td>
<td>China</td>
<td>16</td>
<td>China</td>
<td>37.6</td>
</tr>
<tr>
<td>3</td>
<td>USA</td>
<td>13.9</td>
<td>USA</td>
<td>21.9</td>
</tr>
<tr>
<td>4</td>
<td>Russian Federation</td>
<td>8.9</td>
<td>Pakistan</td>
<td>14.5</td>
</tr>
<tr>
<td>5</td>
<td>Japan</td>
<td>6.3</td>
<td>Indonesia</td>
<td>12.4</td>
</tr>
<tr>
<td>6</td>
<td>Brazil</td>
<td>4.9</td>
<td>Russian Federation</td>
<td>12.2</td>
</tr>
<tr>
<td>7</td>
<td>Indonesia</td>
<td>4.5</td>
<td>Mexico</td>
<td>11.7</td>
</tr>
<tr>
<td>8</td>
<td>Pakistan</td>
<td>4.3</td>
<td>Brazil</td>
<td>11.6</td>
</tr>
<tr>
<td>9</td>
<td>Mexico</td>
<td>3.8</td>
<td>Egypt</td>
<td>8.8</td>
</tr>
<tr>
<td>10</td>
<td>Ukraine</td>
<td>3.6</td>
<td>Japan</td>
<td>8.5</td>
</tr>
<tr>
<td>All Other Countries</td>
<td>49.7</td>
<td>Total</td>
<td>135.3</td>
<td>300.0</td>
</tr>
</tbody>
</table>

In the developed countries further urbanisation is likely to be limited and the future incidence of type 2 diabetes, will be the aging population and also may be due to the increase in the population size. All these may not result in the alarming increase in the prevalence rate. However, in the developing countries, especially in India, industrialization and urbanisation is rapid and progressing. The process has brought about advancements at all fronts and has altered the lifestyle of the population from activity ridden to a more sedentary one. There is change in the dietary pattern too. Majority of the Indian population live in the rural areas and the rural population is also undergoing transition in their lifestyle. All these changes though have benefited the population for a better living; the darker side of the
advancements seems to be an increase in the incidence of lifestyle related diseases, especially Type 2 diabetes.

The life span of people has increased, but with a reduced quality of life.

After six decade of independence, we have more or less able to control infectious, parasitic or nutritional diseases. But life style related diseases have now replaced these diseases as the major cause of mortality and morbidity.

The impact of diabetes on personal and public health is considerable. The adverse effects of diabetes on morbidity, employment, productivity and premature mortality are sufficiently great to rank it as one of the most influences on world health.

**RISING PREVALENCE IN INDIA**

The epidemic pf diabetes in India needs to be viewed within the larger demographic and socioeconomic context. India is the second most populous country and has diverse groups of people with respect to caste and religion, habitat, socioeconomic status, education level, lifestyles and food habits, etc. The Population of India has almost tripled since the country's independence in 1947, although the population growth has declined from 2.3% in 1975-90 to 2.0% in 1990-2001. Life expectancy has doubled from 32 years in 1941-51 to 64 years in 2002. In addition, the average per capita income rose from 530 USD in 1975 to 2820 USD in 2001, and the proportion of people below poverty line fell from 55% in 1974 to 41% in 1992 and to 26% in 2001.\(^{13,14}\)
PREVALENCE OF DIABETES IN MIGRANT INDIANS

Epidemiological studies in India on diabetes were taken up following several reports showing that type 2 diabetes among migrant Asian Indian populations in several countries was high compared with the host population and other migrant ethnic groups. Irrespective of the differences in anthropometry, dietary and socioeconomic factors and migratory patterns—the migrant Indians showed a higher prevalence of type 2 diabetes than Europeans. (table 2)

Table 2 Studies of Prevalence in Migrant Indians in Different Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Age</th>
<th>Prevalence (%)</th>
<th>Population Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>1990</td>
<td>&gt;20</td>
<td>M/F 11.2/8.9</td>
<td>Asian European (mostly Punjabi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.8/4.3</td>
<td>Bhatia Community</td>
</tr>
<tr>
<td>UK</td>
<td>1995</td>
<td>&gt;15</td>
<td>7.4</td>
<td>Hindu Community</td>
</tr>
<tr>
<td>Tanzania</td>
<td>1991</td>
<td>&gt;15</td>
<td>9.1</td>
<td>Bhatia Community</td>
</tr>
<tr>
<td>Tanzania</td>
<td>1995</td>
<td>&gt;15</td>
<td>15.6</td>
<td>Hindu Indians</td>
</tr>
<tr>
<td>Mauritius</td>
<td>1990</td>
<td>&gt;25</td>
<td>12.4</td>
<td>Indians</td>
</tr>
<tr>
<td>Singapore</td>
<td>1992</td>
<td>18-</td>
<td>12.3</td>
<td>Indians</td>
</tr>
<tr>
<td></td>
<td></td>
<td>69</td>
<td>10.6</td>
<td>Chinese</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.7</td>
</tr>
<tr>
<td>South Africa</td>
<td>1994</td>
<td>&gt;25</td>
<td>9.8</td>
<td>Indians</td>
</tr>
<tr>
<td>USA</td>
<td>1996</td>
<td>&gt;20</td>
<td>7.6</td>
<td>Indians</td>
</tr>
</tbody>
</table>

Changes in environmental factors are believed to unmask the increased ethnic propensity for diabetes. Unmasking of ethnic propensity gets highlighted in another epidemiological study from Mauritius a multiethnic population, with 68% of Asian Indian origin and the remaining comprising of Chinese, African and Creole population. The prevalence of type 2 diabetes was found to be 18% in Indian migrants, 17% in Creoles and 11% in Chinese. The rate of prevalence of type 2 diabetes in the migrant Indian population of
Mauritius is similar to many of the urban rates of prevalence of diabetes in the mainland.

**PREVALENCE OF DIABETES IN INDIA**

The prevalence of diabetes has shown increasing trend in the last three decades in India.

**Table 3** Studies on Prevalence of DM in India from 1938 to 1978

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Place</th>
<th>Age(years)</th>
<th>Test Used</th>
<th>Prevalence Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1938</td>
<td>Chakravarty</td>
<td>Calcutta</td>
<td>&gt;5</td>
<td>U</td>
<td>0.73</td>
</tr>
<tr>
<td>1959</td>
<td>Patel et al</td>
<td>Mumbai</td>
<td>All ages</td>
<td>B</td>
<td>0.98</td>
</tr>
<tr>
<td>1963</td>
<td>Patel et al</td>
<td>Mumbai</td>
<td>All ages</td>
<td>B</td>
<td>2.36</td>
</tr>
<tr>
<td>1964</td>
<td>Ganguli et al</td>
<td>Lucknow</td>
<td>&gt;20</td>
<td>B</td>
<td>2.3</td>
</tr>
<tr>
<td>1964</td>
<td>Vaishnav et al</td>
<td>Vellore</td>
<td>All ages</td>
<td>B</td>
<td>2.56</td>
</tr>
<tr>
<td>1965</td>
<td>Ramadwar D K</td>
<td>Nagpur</td>
<td>&gt;20</td>
<td>B</td>
<td>2.4</td>
</tr>
<tr>
<td>1966</td>
<td>Berry et al</td>
<td>Chandigarh</td>
<td>&gt;15</td>
<td>U</td>
<td>1.53</td>
</tr>
<tr>
<td>1966</td>
<td>Sanani et al</td>
<td>Mumbai</td>
<td>All ages</td>
<td>B</td>
<td>2.24</td>
</tr>
<tr>
<td>1966</td>
<td>Saroj kumari</td>
<td>New Delhi</td>
<td></td>
<td>U</td>
<td>2.26</td>
</tr>
<tr>
<td>1966</td>
<td>Satyanarayan</td>
<td>Hyderabad</td>
<td>&gt;20</td>
<td>U</td>
<td>4.12</td>
</tr>
<tr>
<td>1966</td>
<td>Shanker et al</td>
<td>Hubli</td>
<td>All ages</td>
<td>U</td>
<td>2.24</td>
</tr>
<tr>
<td>1966</td>
<td>Ahuja et al</td>
<td>Delhi</td>
<td>All ages</td>
<td>U</td>
<td>9.4</td>
</tr>
<tr>
<td>1966</td>
<td>Vishwanathan</td>
<td>Madras</td>
<td>&gt;20</td>
<td>U</td>
<td>11.3</td>
</tr>
<tr>
<td>1966</td>
<td>Misra et al</td>
<td>Jabalpur</td>
<td>All ages</td>
<td>B</td>
<td>1.70</td>
</tr>
<tr>
<td>1966</td>
<td>Pai et al</td>
<td>Trivandram</td>
<td>&gt;20</td>
<td>U</td>
<td>8.7</td>
</tr>
<tr>
<td>1966</td>
<td>Gour K N</td>
<td>Varanasi</td>
<td>&gt;10</td>
<td>U</td>
<td>2.7</td>
</tr>
<tr>
<td>1966</td>
<td>Datta et al</td>
<td>Pondicheri</td>
<td>All ages</td>
<td>U</td>
<td>0.70</td>
</tr>
<tr>
<td>1968</td>
<td>Aggoankar S S</td>
<td>Mumbai</td>
<td>&gt;15</td>
<td>B</td>
<td>2.5</td>
</tr>
<tr>
<td>1970</td>
<td>Gupta et al</td>
<td>&gt;15</td>
<td>B &amp; U</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>1970</td>
<td>Moses</td>
<td>Ahmedabad</td>
<td>Adults</td>
<td>B &amp; U</td>
<td>3.8</td>
</tr>
<tr>
<td>1970</td>
<td>Tripathi et al</td>
<td>Madras</td>
<td>&gt;15</td>
<td>U</td>
<td>12.67</td>
</tr>
<tr>
<td>1971</td>
<td>Tripathi et al</td>
<td>Cuttack</td>
<td>&gt;10</td>
<td>B</td>
<td>1.2(Ur)</td>
</tr>
<tr>
<td>1972</td>
<td>Ahuja et al</td>
<td>Cuttack</td>
<td>&gt;15</td>
<td>B</td>
<td>2.3(Ur)</td>
</tr>
<tr>
<td>1972</td>
<td>Jaya Rao</td>
<td>New Delhi</td>
<td>&gt;20</td>
<td>B &amp; U</td>
<td>2.4</td>
</tr>
<tr>
<td>1973</td>
<td>Mukherjee A B</td>
<td>Hyderabad</td>
<td>All ages</td>
<td>GTT</td>
<td>0.7</td>
</tr>
<tr>
<td>1973</td>
<td>Parmoshware</td>
<td>Calcutta</td>
<td>&gt;5</td>
<td>B</td>
<td>0.81</td>
</tr>
<tr>
<td>1975</td>
<td>Gupta O P</td>
<td>Bangalore</td>
<td>&gt;15</td>
<td>U</td>
<td>2.16</td>
</tr>
<tr>
<td>1975</td>
<td>Mutallik</td>
<td>Ahmedabad</td>
<td>&gt;15</td>
<td>B &amp; U</td>
<td>2.48</td>
</tr>
<tr>
<td>1975</td>
<td>Pai et al</td>
<td>Poona</td>
<td>&gt;15</td>
<td>B &amp; U</td>
<td>1.81</td>
</tr>
<tr>
<td>1975</td>
<td>Tripathi B B</td>
<td>Trivandrum</td>
<td>&gt;15</td>
<td>B &amp; U</td>
<td>1.40</td>
</tr>
<tr>
<td>1975</td>
<td>Chetri et al</td>
<td>Cuttack</td>
<td>&gt;15</td>
<td>B &amp; U</td>
<td>1.63</td>
</tr>
<tr>
<td>1978</td>
<td>Gupta et al</td>
<td>Calcutta</td>
<td>&gt;15</td>
<td>B &amp; U</td>
<td>3.8(Ur)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ahmedabad</td>
<td>&gt;15</td>
<td>B &amp; U</td>
<td>1.93@</td>
</tr>
</tbody>
</table>

(B – Blood Glucose, U – Urine Glucose, GTT- Glucose tolerance test, Ur – Urban, R – Rural)
Since 1938, prevalence studies of DM have been conducted in our country. These studies have been carried out in different places, in various age groups and by using different methods of examination. [Urine, blood or both]. Only in 1970's, the methodology was somewhat standardized and the prevalence studies became more uniform. Most of these studies from 1938 to 1978 have been listed in (Table 3) and studies from 1979 to 2001 in (Table 4). The above studies were conducted in urban or in rural and urban populations of one particular region, which did not reflect true prevalence for the entire country.

Table 4 Studies of Prevalence of DM in India from 1979 till 2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Place</th>
<th>Prevalence Rate(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>Johnson et al</td>
<td>Madurai</td>
<td>0.5(U)</td>
</tr>
<tr>
<td>1984</td>
<td>Murthi et al</td>
<td>Tenali</td>
<td>4.7(U)</td>
</tr>
<tr>
<td>1986</td>
<td>Patel J C</td>
<td>Bhadran</td>
<td>3.8®</td>
</tr>
<tr>
<td>1988</td>
<td>Ramchandran et al</td>
<td>Kudremkh</td>
<td>5.0(U)</td>
</tr>
<tr>
<td>1989</td>
<td>Kodali et al</td>
<td>Gangarathi</td>
<td>2.2®</td>
</tr>
<tr>
<td>1989</td>
<td>Rao et al</td>
<td>Eluru</td>
<td>1.6®</td>
</tr>
<tr>
<td>1991</td>
<td>Ahuja et al</td>
<td>New Delhi</td>
<td>6.7®</td>
</tr>
<tr>
<td>1992</td>
<td>Ramchandran et al</td>
<td>Madras</td>
<td>8.2(U)</td>
</tr>
<tr>
<td>1997</td>
<td>Ramchandran et al</td>
<td>Madras</td>
<td>2.4®</td>
</tr>
<tr>
<td>1999</td>
<td>Ashabai et al</td>
<td>Chennai</td>
<td>11.6(U)</td>
</tr>
<tr>
<td>2000</td>
<td>Ramchandran et al (DESI)</td>
<td>National</td>
<td>17.4(U)</td>
</tr>
<tr>
<td>2000</td>
<td>Ramchandran et al (DESI)</td>
<td>National</td>
<td>12.1(U)</td>
</tr>
<tr>
<td>2001</td>
<td>Misra et al</td>
<td>Northern India</td>
<td>10 3(U)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15.2(IFG)</td>
</tr>
</tbody>
</table>

(U - Urban, ® - Rural, IFG - Impaired Fasting Glucose, DESI - Diabetic Epidemic Study in India)

There have been several studies from various parts of India, revealing a rising trend in the prevalence of type 2 diabetes in the urban population. A multicentric epidemiological study carried out by the Indian Council of Medical Research (ICMR) in the early seventies, reported the prevalence of diabetes to be 2.3% in the urban and 1.5% in the rural areas. The World Health Organisation (WHO) criteria were not available then.
Table 5 Increasing trend of prevalence of DM in India: Comparison between ICMR study (1978- Urban only(5)) and National Urban Diabetes Survey 2001-NUDS (6)

<table>
<thead>
<tr>
<th>City</th>
<th>Region</th>
<th>Prevalence in %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1978</td>
<td>Year 2001</td>
</tr>
<tr>
<td>Ahmedabad</td>
<td>West</td>
<td>3.8</td>
</tr>
<tr>
<td>Pune</td>
<td>West</td>
<td>1.86</td>
</tr>
<tr>
<td>Mumbai</td>
<td>West</td>
<td>11.6</td>
</tr>
<tr>
<td>Kolkata</td>
<td>East</td>
<td>1.78</td>
</tr>
<tr>
<td>Cuttack</td>
<td>East</td>
<td>2.02</td>
</tr>
<tr>
<td>Trivandrum</td>
<td>South</td>
<td>1.83</td>
</tr>
<tr>
<td>Chennai</td>
<td>South</td>
<td>12.4</td>
</tr>
<tr>
<td>Bangalore</td>
<td>South</td>
<td>16.6</td>
</tr>
<tr>
<td>Hyderabad</td>
<td>South</td>
<td>11.7</td>
</tr>
<tr>
<td>Delhi</td>
<td>North</td>
<td>0.95</td>
</tr>
</tbody>
</table>

A series of studies from Chennai showed that the percentage of adult urban subjects affected had increased from 5.2% in 1984 to 8.2% in 1989, 11.6% in 1995 and 13.9% in 2000\(^22\) which further increased to 14.3% in 2004\(^23\). A National Urban Survey in 2000 showed that the prevalence of diabetes in urban India was 12.1% in subjects aged >20 years.\(^24\) The prevalence in all the cities was more than 9% (varied from 9.3-16.6%). This study revealed that the prevalence of diabetes in the southern parts was higher than the eastern and southern parts of India (Chennai-13.5%, Bangalore-12.4%, Hyderabad-16.6%, Kolkata-11.7%, New Delhi-11.6% and Mumbai-9.3%).\(^24\) These two studies have been compared in (Table 5).

The PODIS survey\(^20\) reports a low prevalence rate when compared to other previous studies (5.6%) but the sampling criteria and population size were different. However, the final estimated prevalence of diabetes with reference to actual numbers is similar (35 million) to the
one derived from earlier studies. The urban population is exposed to a more detrimental lifestyle which is characterized by high fat, refined diet, sedentary habits, lack of physical exercise, obesity, smoking and stressful behavior, etc. This explains the high prevalence of diabetes in the urban areas.

A wide urban-rural difference in the rates of prevalence of diabetes was evident in the last decade (a four-fold difference). A study on the prevalence of diabetes in the rural population of south India was conducted in the year 1990, and the prevalence rate was reported to be 2.4%.25 The population was representative of people with low income, poor socioeconomic background, illiterate and most of them were hard working laborers. The study also reported a 3:1 ratio of newly detected to known diabetes, implication of poor socioeconomic condition and health care. Another study in the semi urban parts, reported a prevalence rate of 5.9% midway between the urban(11.6%) and the rural (2.4%).26 The sample population resembled the rural features in some but had access to certain urban facilities.

A recent survey in the rural Southern India (2003) is an indicator of the transition in the lifestyle of the rural population and it shows a striking increase in the rate of prevalence of diabetes (6.4%).27 The contributing factors were chiefly the improved socioeconomic condition which encompasses an increase in family income, educational status, availability of motorized transport, a shift in occupational structure. As a consequence of the lifestyle transition there is an increase in the prevalence of diabetes in the rural population too (from 2.2-6.4%).27
IMPARED GLUCOSE TOLERANCE (IGT) AND IMPAIRED FASTING GLUCOSE (IFG)

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are considered the forerunners of diabetes and both conditions have a high risk of conversion to diabetes. These stages are not only an indicator of future diabetes but also an index of impending rise in cardiovascular diseases.\textsuperscript{28} Hence, IGT & IFG have acquired great importance in recent times.

HIGH PREVALENCE OF IGT – SIGNIFICANCE

The ratio of IGT to Diabetes is considered to be an index of an epidemic state of Diabetes in the population
A high IGT / diabetes ratio is a predictor of future increase in diabetes
There is a higher prevalence of IGT (14.0\%) to diabetes (12.1\%) in India
A further conversion of IGT to diabetes is possible

The prevalence of IGT in urban and rural population has increased steadily suggesting scope for further rise in diabetes due to decompensation of IGT. IGT occurs at a young age in the Indians in the age group<40 years.\textsuperscript{22} The risk associations with anthropometric variables such as body mass index and with family history of diabetes were also different. The prevalence of IGT increased with age whereas IFG did not. Prevalence of IFG and IGT was similar in urban Indians (8.7 and 8.1 % respectively.)\textsuperscript{29} The horn study in the netherlands\textsuperscript{30}
and Botnia study in Finland\textsuperscript{31} showed similar prevalence in IFG and IGT.

Ramachandran et al from Chennai, in their study have reported the prevalence of IGT as 13\% which is significantly higher than DM (5\%) in the same population below 40 years of age\textsuperscript{32}. Ashabai et al also reported higher prevalence of IGT (25.2\%) as against the prevalence of DM (17.4\%) in a selected urban population in Chennai.\textsuperscript{33} Similarly in another study of age and gender standardized prevalence of DM and IGT in National Urban Diabetes Study, the prevalence of IGT was found to be higher than prevalence of DM in majority of the cities.\textsuperscript{34}

Laying emphasis on impaired fasting glucose (IFG), in another study, Misra et al have reported higher prevalence of IFG as 15.2\% than that of DM (10.3\%) in the same population.\textsuperscript{35}

It is also interesting to note that the prevalence of IGT was similar in both urban (8.1\%) and rural (7.8\%) areas, despite the wide urban-rural difference in the prevalence of diabetes (2.4\% in rural and 13.9\% in urban areas).\textsuperscript{24} The present estimate of approximately 33 million adults in India having diabetes may be an underestimation in view of the fact that increasing urbanisation in causing a further rise. Other recent reports from Kerala in southern India and other regions in India also have highlighted the increasing trend in the prevalence of diabetes and IGT.\textsuperscript{36,37} Not only is the number of diabetic subjects increasing, but also it seems to be affecting the younger population in the most productive years of their life. Social, economic and psychological impacts of these escalating health hazards could be a major national health problem.
Epidemiological studies conducted over the years have identified several risk factors associated with diabetes. These risk variables are similar across all countries but their expression and intensity vary widely between races and between geographical regions. It is well-known that there is a strong interaction between genetic and environmental risk factors, which are independently associated with diabetes.
CLASSIFICATION AND DIAGNOSIS OF DIABETES MELLITUS

Diabetes Mellitus is a group of metabolic diseases characterized by chronic hyperglycemia associated with disturbances of carbohydrate, fat, and protein metabolism due to absolute or relative deficiency in insulin secretion and/or action. Diabetes causes long term damage, dysfunction and failure of various organs; especially the eyes, kidneys, nerves, heart and blood vessels. In a nutshell diabetes is appropriately described as a "Metabolic cum Vascular disorder".

Recently the World Health Organization (WHO) in consultation with an expert committee of the American Diabetes Association (ADA) has reported a new classification (Table-6) and diagnostic criteria. The term insulin dependent diabetes mellitus and non-insulin dependent diabetes mellitus and their acronyms, IDDM and NIDDM are eliminated. These terms have been confusing and have frequently resulted in classifying the patient based on treatment rather than etiology.
Table 6 Types of Diabetes Mellitus
(Etiologic Classification of Diabetes Mellitus)

1. Type 1 (Beta cell destruction usually leading to absolute insulin deficiency)
   a) Autoimmune
   b) Idiopathic

2. Type 2
   a) Predominantly insulin resistance
   b) Predominantly insulin secretory defects

3. Other Specific Types of Diabetes
   A. Genetic defects of beta cell dysfunction, e.g. MODY 1 to 6
   B. Genetic defects in insulin action, e.g. Type A insulin resistance
   C. Diseases of Exocrine pancreas, e.g. Fibro calculus pancreatopathy.
   D. Endocrinopathies, e.g. Acromegaly, Cushings etc.,
   E. Drugs or chemical-induced, e.g. glucocorticoids
   F. Infections, e.g., congenital rubella.
   G. Uncommon forms of immune-mediated diabetes, e.g. Stiff Man Syndrome.
   H. Other Genetic syndromes.

4. Gestational Diabetes
   (ADA Criteria 2003)

STAGES OF DIABETES

Stages of diabetes range from normal glucose tolerance, through IGT, and IFG (impaired fasting glucose), into frank diabetes mellitus, which may be non-insulin requiring, insulin requiring for control and insulin requiring for survival. Type 1 DM can be found across the whole spectrum. In the early stages of treatment there can be a period of non-insulin requirement, but later followed by insulin requirement for
survival. In type 2 DM, insulin may be required during a period of ketoacidosis precipitated by severe stress or infection (Fig - 1).

**Figure 1** Disorders of Glycemia: Etiologic Types and Stages

<table>
<thead>
<tr>
<th>Types</th>
<th>Normoglycemia</th>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Glucose regulation</td>
<td>Impaired glucose tolerance Or Impaired fasting Glucose</td>
</tr>
<tr>
<td>Type 1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other specific Types**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational Diabetes **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td>Not insulin Requiring Insulin requiring for control Insulin requiring for survival</td>
</tr>
</tbody>
</table>

* Even after presenting in ketoacidosis, these patients can briefly return to normoglycemia without requiring continuous therapy (i.e. "Honey moon" remission)

** In rare instances, patients in these categories (e.g. Vacor toxicity, type 1 diabetes presenting in pregnancy) may require insulin for survival

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)
TYPES OF DIABETES MELLITUS

1. TYPE 1 DIABETES MELLITUS:

The previously used terminology is insulin dependent diabetes mellitus (IDDM). These patients depend on insulin for survival. On withdrawal of insulin they develop hyperglycemia, ketoacidosis and coma. Type 1 diabetes has its onset most often in childhood and adolescence, although it may occur at any age. Though usually abrupt in onset, it can be protracted in its course (slow onset IDDM, LADA - Late onset Autoimmune Diabetes of Adult). The genetic factors, autoimmunity and environmental factors play a role in the causation and precipitating type 1 diabetes.

Type 1 diabetes is recognized to be due to autoimmune destruction of cells. Type 1A immune mediated is characterized by the presence of islet cell, GAD (Glutamic acid decarboxylase), IA-2, IA-2B or insulin auto antibodies that identify the autoimmune process that leads to cell destruction, in some subjects no evidence of autoimmunity is present; these cases are classified as Type 1B (idiopathic). Type 1A diabetics are prone to other autoimmune disorders such as Grave's disease, thyroiditis, autoimmune Addison's disease, ovarian failure, vitiligo, pernicious anemia etc.

There is a strong positive genetic association of type 1 diabetes with HLA -B8- DR and/or DR4. Recent research has shown that there is increased susceptibility to type 1 DM when the amino acid Asp 57 is absent in DQ B with the presence of Arg 52 in DQ A.
The absence or very poor response of glucagon stimulated ‘C’ peptide levels are diagnostic of type 1 diabetes as these patients have very low residual beta cell function (cell reserve <10%).

2. TYPE 2 DIABETES MELLITUS:

The previously used terminology is non-insulin dependent diabetes mellitus (NIDDM). Type 2 diabetes usually begins in the middle age or after 40 years. It is not uncommon to come across the development of diabetes in third decade itself in our country. The pathophysiological basis is a combination of impaired beta cell function, with marked increase in peripheral insulin resistance at receptor/post receptor levels and increased hepatic glucose output production. Their circulatory levels of insulin and C-peptide may be variable ranging from hyper to normo insulinemic levels in a majority of the subjects. Type 2 diabetes is further sub-classified into obese and non-obese types.

Coma is rare in type 2 diabetes, but may result from extreme hyperglycemia and hyperosmolarity; ketoacidosis can occur in fulminating illnesses due to acute increase in insulin requirements but "spontaneous" ketosis does not occur. Lactic acidosis is rare.

Given all credence to the latest classification based on etiology; for practical purposes, the classification of type 1 and type 2 diabetes for a clinician is mostly clinical with a key feature being proneness to ketosis and dependence on insulin. It also includes other clinical aspects like age and onset, family history of diabetes or autoimmune disease and presence or absence of obesity.
3. OTHER SPECIFIC TYPES

There are numerous reports from developing countries of specific presentation of diabetes that do not conform to the diagnostic criteria for classical type 1 and type 2 diabetes or the recognized forms of the disease. They are included in other specific type of diabetes in classification of Diabetes Mellitus. This is also called as secondary diabetes mellitus

A) GENETIC DEFECTS OF BETA CELL DYSFUNCTION: e.g. MODY 1 to 6

The development of type 2 diabetes below 25 years of age is classified as Maturity Onset Diabetes of the Young (MODY). They do not require insulin for control of diabetes for a varying period, from the time of detection. There are no immune or HLA markers as of type 1 diabetes. They do not have ICA (islet cell antibodies) and are not HLA DR3 heterozygote. It is generally inherited as autosomal dominant gene. MODY is rare in Caucasians, but commoner in blacks. MODY families have low susceptibility to micro and/or macro vascular complications, and show considerable heterogeneity. Glucokinase deficiency is a marker of MODY.

B) GENETIC DEFECTS IN INSULIN ACTION: e.g. Type A insulin resistance

Insulin resistance (Hyperinsulinism with various degrees of hyperglycemia) is associated with several congenital or acquired syndromes, like Leprechaunism, Lipoatrophy and Acanthosis Nigrigans.
Insulin resistance with Acanthosis Nigrigans is further subdivided into Type A (Hereditary), associated with genetic defects in insulin receptor number and function affecting young women and Type B (autoimmune) due to antibodies against insulin receptors affecting women who often have other features of generalized auto immune disease.

C) DISEASES OF EXOCRINE PANCREAS: e.g. Fibro calculus pancreatopathy.

Malnutrition related diabetes mellitus (MRDM) is a form of diabetes restricted to tropical countries. It has a spectrum of diagnostic criteria: Age of onset below 30 years, BMI < 19, a patient living in tropics with a frequent history of malnutrition in childhood, a stigma of present or past malnutrition, variable exocrine pancreatic deficiency, requiring high doses of insulin and lack of proneness to ketosis in the absence of stressful situation.

Malnutrition related Diabetes Mellitus comprises of two sub groups: a) Fibro calculous Pancreatic Diabetes (FCPD) and b) Protein Deficient Diabetes Mellitus (PDDM).

Protein deficient diabetes mellitus

This syndrome has been called by various other names, including protein deficient pancreatic diabetes and recently malnutrition modulated diabetes mellitus. Its pathogenesis is unknown. The syndrome is reported in young, malnourished individuals in the developing world, and differs from the usual clinical presentation of type 1 and type 2 diabetes in developed countries. The onset of
diabetes is early, usually before the age of 30 yrs. The affected have a low body mass index (BMI usually <17kg/m2), together with other clinical features of malnutrition and often growth retardation. Appropriate imaging shows no evidence of the structural pancreatic damage that characterizes FCPD, notably large calculi or ductal dilatation. These individuals require high doses of insulin (>1.5u/Kg/day) to achieve adequate glycaemic control, but do no develop ketoacidosis, even if insulin withdrawn.

*Fibrocalculous pancreatic diabetes*

FCPD occurs quite often in well nourished individuals, calling into doubt its specific association with malnutrition and thus its classification as a primary form of diabetes.

FCPD occurs in developing countries within the tropical belt. Its hallmark is chronic calculous pancreatopathy that is not due to alcoholism or other recognized causes of pancreatitis such as gall stone disease or hyperparathyroidism.

The pathogenesis of FCPD remains uncertain although nutritional environmental and genetic factors have been postulated. Malnutrition has been incriminated, but there is little hard evidence to support this association.

FCPD is no commoner in areas where malnutrition is most prevalent, and it is uncertain whether malnutrition is the cause or simply the consequences of uncontrolled diabetes in people with inadequate food intake. Sever malnutrition can affect glucose homeostasis – for example, patients with kwashiorkor (profound protein and energy
Dietary toxins have also been invoked in the etiology of FCPD. Mcmillan and Geevarghese first observed that geographical distribution of FCPD coincided with those parts of the world where cassava (Manihot esculenta) was served as a staple food. This led to the hypothesis that cyanide-generating glycosides from cassava (linamarin and lotusastralin) could damage the islet B cells and that cyanide is not detoxified in malnutrition. However, experimental evidence does not support this hypothesis; long term feeding of cassava to animals does not cause diabetes, while careful comparison of two rural populations in Tanzania confirmed that cassava consumption had no significant effect on either glucose tolerance or the prevalence of diabetes, even though plasma and urinary cyanide levels were raised.

FCPD is usually seen in young and malnourished adults, mostly in their twenties but not uncommonly in middle age; the condition is rare in children and adolescents. The degree of hyperglycemia varies from severe to mild, and hyperglycemia can occur with or without a tendency to ketosis. Gastrointestinal symptoms—notably recurrent abdominal pain and steatorrhoea—are a consequence of extensive pancreatic damage. The disease is associated with an increased risk of pancreatic carcinoma.

The Diagnosis of FCPD depends on the demonstration by plain radiography, ultrasound or computed tomography scanning of large multiple and intraductal pancreatic calculi. These calculi are strikingly...
different from the diffuse and finer calcification characteristics of alcohol induced chronic pancreatitis. Marked ductal dilatation and fibrosis are usual, but parenchymal inflammatory changes are uncommon. Exocrine pancreatic functions are invariably abnormal. The management of FCDP includes the conventional treatment of diabetes by insulin and/or OHA with oral pancreatic enzyme replacement to treat malabsorption and steatorrhoea, and analgesics to relieve pain. Surgery (e.g. Pancreateojejunostomy procedures) is sometimes required for severe and intractable pain.

Indian consensus is that malnutrition modulated diabetes mellitus does exist; whereas the International expert committee view is that while it appears that malnutrition may influence the expression of the other types, the evidence that diabetes can be directly caused by protein deficiency is not convincing. Therefore the class termed malnutrition related diabetes mellitus has been eliminated. Fibro Calculus Pancreatopathy has been reclassified as a disease of exocrine pancreas.
### Acute Pancreatitis

#### Table 7 Causes of Acute pancreatitis

<table>
<thead>
<tr>
<th>Common (75% of cases)</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol abuse</td>
<td>Drugs</td>
</tr>
<tr>
<td>Gallstone disease</td>
<td>Sulphonamides</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Tetracycline</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
</tr>
<tr>
<td></td>
<td>Didanosine</td>
</tr>
<tr>
<td></td>
<td>Oestrogen</td>
</tr>
<tr>
<td></td>
<td>Metabolic Disorders</td>
</tr>
<tr>
<td></td>
<td>Hypertriglyceridaemia</td>
</tr>
<tr>
<td></td>
<td>Hypercalcaemia</td>
</tr>
<tr>
<td></td>
<td>Diabetic Ketoacidosis</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Mumps, coxsackie and HIV</td>
</tr>
<tr>
<td></td>
<td>Viruses</td>
</tr>
<tr>
<td></td>
<td>Mycoplasma Pneumoniae</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Abdominal Injury</td>
</tr>
<tr>
<td></td>
<td>Surgery including ERCP</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td>Hereditary relapsing pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Pancreatic Cancer</td>
</tr>
<tr>
<td></td>
<td>Connective tissue diseases</td>
</tr>
<tr>
<td></td>
<td>Pancreas divisum</td>
</tr>
</tbody>
</table>

The classical symptoms is sudden onset of epigastric pain associated with nausea and vomiting, aggravated by food and partially relieved by sitting up and leaning forward. Various metabolic abnormalities may occur, including hyperglycemia, hypocalcaemia, hyperlipidemia, hypoalbuminemia, and coagulation disorders elevated serum levels of amylase and lipase point to the diagnosis, but these tests are not infallible; serum amylase for example is normal in up to 20% cases. CT or MRI shows edema and swelling of the pancrease with pancreatic necrosis, the gland does not show the normal enhancement on CT. Transient hyperglycemia occurs in 50-70% of patients with acute pancreatitis and glycosuria in about 30%. Interestingly, this is apparently due to raised glucagons levels (up to 10 times normal),
rather than to B-cell damage; indeed, insulin secretion is often increased.\textsuperscript{49,50} Blood glucose concentration exceeding 11.1mmol/L during the first 24 h indicates a poor prognosis.\textsuperscript{51} Generally though hyperglycemia is usually mild and resolves within a few days or weeks without requiring insulin treatment. Permanent diabetes is uncommon, developing in only 1-15\% of cases but in one - quarter of those with fulminant pancreatitis complicated by multiorgan failure\textsuperscript{52}.

Diabetic ketoacidosis may be accompanied by non-specific elevations of serum amylase and lipase.\textsuperscript{53} That generally parallel the severity of metabolic disturbances such as hyperglycemia, acidosis and dehydration\textsuperscript{54} However acute pancreatitis as diagnosed by CT scan of the abdomen, may affect up to 11\% of ketoacidosis patients usually with only mild or even no abdominal pain.\textsuperscript{51}

D) **ENDOCRINOPATHIES:**

Diabetes mellitus can co-exist with altered function of the pituitary, adrenal, thyroid glands and gonads. Specific endocrine disorders can have a major influence on metabolic control in patients with diabetes. Overt diabetes can occur in acromegalics (Growth hormone secreting adenomas) which improves with effective treatment. Growth hormone deficiency in insulin treated patients can lead to severe hypoglycemia. Autoimmune hypothyroidism, auto immune Addison’s can co-exist with diabetes. Diabetes occurring in patients with Cushing’s syndrome resolves with effective treatment. Upto 75 \% of patients with pheochromocytoma have glucose intolerance attributed to catecholamine mediated increase in hepatic glycogen breakdown. It can be observed from the above discussion that if there is an excess production of counter regulatory hormones like, catecholamines,
cortisol, and growth hormone from tumors of the endocrine gland, diabetic state ensues.

Poly glandular autoimmune syndrome (Schmidt’s Syndrome) is often inherited as autosomal recessive condition and it includes type 1 DM with autoimmune thyroiditis and adrenal failure.

E) DRUGS OR CHEMICAL INDUCED:

Certain drugs like glucocorticoids, ACTH, Thiazide diuretics, phenetoyin, pentamidine, Vacor (rodenticide) can cause hyperglycemia by various mechanisms.

Drug Induced Diabetes

Many commonly used drugs interfere with glucose homeostasis and can worsen glycaemic control in diabetic patients or provoke hyperglycemia in non-diabetic subjects.
### Table 8 Drug that cause or exacerbate hyperglycemia

<table>
<thead>
<tr>
<th>Potentially potent effects</th>
<th>Minor or no effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Oral contraceptive pills</td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td>Progesterone only pills</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Thiazides (low dosages)*</td>
</tr>
<tr>
<td>High dose oestrogen</td>
<td>Loop Diuretics</td>
</tr>
<tr>
<td>Levonorgestrel in combination pills</td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Thiazide diuretics(high Dosages)*</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>B2 Adrenoceptor antagonists</td>
<td>Alpha adrenoceptor antagonists</td>
</tr>
<tr>
<td>B2 adrenoceptor agonists</td>
<td>Growth hormone</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Somatostatin analogues</td>
</tr>
<tr>
<td>Ritodrine</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Indinavir, nelfinavir and others</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Pentamidine</td>
<td></td>
</tr>
<tr>
<td>Streptozocin</td>
<td></td>
</tr>
<tr>
<td>Diazoxide</td>
<td></td>
</tr>
<tr>
<td>Cyclosporin</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
</tr>
</tbody>
</table>

High and low dosage of thiazides correspond to $\geq 5$mg/day and $\leq 2.5$mg/day of bendrofumethiazide, respectively.

Somatostatin analogue may induce hyperglycemia in type 2 but not type 1 diabetes

**Glucocorticoids (steroid induced diabetes)**

Glucocorticoids were named for their hyperglycemic effects and have by far the most powerful adverse effect on glycemic control of all the commonly prescribed drugs. Data from General Practice Research
Database suggest that nearly 1% of the UK population may be using oral glucocorticoids at any time\textsuperscript{56}

Glucocorticoids worsen hyperglycemia in diabetic patients, but can also cause significant increase in blood glucose (and insulin) concentration in previously normoglycemic individual when given in high doses (i.e. equivalent to 30 mg/day or more of prednisolone).\textsuperscript{57} Impaired glucose tolerance or diabetes mellitus have been reported in 14-28% of subjects receiving long term glucocorticoids\textsuperscript{58,59}, and subjects who have an intrinsically low insulin response (e.g. in response to glucose loading) are particularly susceptible\textsuperscript{60}

Glucocorticoids reduce hepatic and peripheral tissue sensitivity to insulin through postreceptor mechanism. In adipocytes, dexamethasone inhibits the expression of the insulin-signalling intermediate protein, insulin receptor substrate 1 (IRS-1)\textsuperscript{61}, and this may contribute to insulin resistance. These effects may be partly offset by glucose-independent stimulation of insulin secretion.\textsuperscript{62}

All glucocorticoids cause dose dependent insulin resistance at dosages greater than the equivalent of 7.5 mg/day of prednisolone.\textsuperscript{59} The duration of exposure to glucocorticoids does not appear to be important, and hyperglycemia is generally reversible on withdrawing the drug.

Most problems have been reported with oral glucocorticoids, but those administered topically can also induce severe hyperglycemia, especially if given at high dosage over large areas of damaged skin and under occlusive dressings.\textsuperscript{63} Inhaled corticosteroids do not cause
significant hyperglycemia. There has, however been a single case report of deteriorating glycemic control in a patient with type 2 diabetes who was prescribed high dose fluticasone propionate.\textsuperscript{64} The hyperglycemic potency of glucocorticoids does not follow the hierarchy of their anti-inflammatory or immunosuppressive activities.\textsuperscript{65}

F) \textit{OTHER GENETIC SYNDROMES.}

About 2 \% of patients with Down's syndrome have diabetes, often insulin requiring type. Two thirds of women with Turners Syndrome and one quarter of patients with Kleinfelters Syndrome have diabetic glucose tolerance curve. Mild diabetes with Group I inherited insulin resistance syndromes can occur in Alstroms, Lawrence Moon Biedal and Prader Willi syndromes, and Dystrophia Myotonica. Severe diabetes requiring massive doses of insulin is associated with Group II inherited insulin resistance syndromes such as Leprechaunism, Rabson-Mendenhall syndrome and Lipodystrophic syndromes.

4. GESTATIONAL DIABETES MELLITUS (GDM):

Gestational diabetes mellitus is defined as glucose intolerance developing or recognized during pregnancy. In the post partum period they may revert back to normal, continue to have impaired glucose tolerance, or develop frank diabetes after a few years. Hence patients with GDM must undergo OGTT with 75 gm glucose six weeks after delivery for reclassification of their diabetic status and repeated after six months.
Gestational diabetes mellitus merits separate consideration by virtue of increased fetal risk associated with it and likelihood of developing diabetes in the future.

**IMPAIRED GLUCOSE TOLERANCE (IGT)**

IGT is a stage of impaired glucose regulation that is present in individuals whose glucose tolerance is above the conventional normal range but lower than the level considered diagnostic of diabetes. IGT is more frequent in obese than in non-obese persons and often is associated with hyperinsulinemia and insulin resistance. IGT represents a transient stage between normal glucose and Type 2 diabetes.

**IMPAIRED FASTING GLUCOSE (IFG)**

IFG is also a stage of impaired glucose homeostasis. Individuals whose fasting glucose levels were normal but below, those diagnostic for diabetes. Individuals with fasting plasma glucose concentrations of 100 to 125 mg/dl (5.6 to < 7.0 mmol/L) are now considered to have IFG.
DIAGNOSIS OF DIABETES MELLITUS

Diagnosis of diabetes mellitus based on urine sugar is unreliable. When the fasting plasma glucose is above 126mg% or random blood glucose more than 200-mg%, on more than one occasion the diagnosis of diabetes can safely be made. When in doubt, to diagnose diabetes mellitus, a standard glucose tolerance test is used. The WHO recommends specific test procedure and the criteria for the diagnosis of diabetes (Table-10).

ORAL GLUCOSE TOLERANCE TEST (OGTT)

The OGTT is recommended for diagnosis/exclusion of diabetes and is the only test for diagnosing Impaired Glucose Tolerance (IGT). The use of glycosuria (urinary glucose) as a diagnostic criterion for diabetes is obsolete and at the best warrants further investigation.

The OGTT is done in the morning after 10 - 16 hours of overnight fast (water may be taken) following at least three days of unrestricted diet (more than 150 gm of carbohydrates) to sensitize the beta cells of pancreas. During the test only water is drunk to alleviate the thirst. Smoking and all physical activity should be avoided.

TEST: A fasting blood sample should be taken before giving glucose load. The subject then drinks 75 Gms. of glucose in 250 - 300 ml of water. Children should receive glucose load at 1.75 gm/kg body weight to a maximum of 75 Gms. (The glucose load should be consumed over a period of five min). A further blood sample must be collected 2 hours after the load. The criteria for interpretation of OGTT
are the same regardless of the age of the subject. Blood samples must be collected into fluoride-oxalate tubes, which prevent the red cells from metabolizing glucose. The laboratory values are compared with those in Table - 9.

**IMPORTANCE OF IFG AND IGT**

There is no clear consensus (with current evidence) on whether IFG and IGT should be classified as diseases, but they clearly represent risk factors and risk markers for diabetes and CVD, respectively. Both IGT and IFG are similarly associated with an increased risk of diabetes, but IGT is more strongly associated with CVD outcomes. Risks are higher when IGT and IFG coexist. Lifestyle interventions are highly effective in delaying or preventing the onset of diabetes in people with IGT and may reduce CVD and total mortality, but the latter requires formal testing.

A. Diabetes is diagnosed if the fasting value \( \geq 126 \text{mg} \) or a 2-hour plasma glucose \( \geq 200 \text{mg} \).

B. Impaired Glucose Tolerance is present when the fasting level is \( \leq 126 \) and two-hour value is in the range of 140 - 200 mg/dl.

C. Impaired fasting glucose is present when the fasting level is \( \geq 100 \) and \( \leq 126 \) and the two-hour value is \( \leq 140 \text{mg/dl} \).

D. Glucose Tolerance is normal when the fasting and the 2-hour values are less than 100mg and 140mg respectively.
Table 9 Diagnostic values for oral glucose tolerance test (OGTT) for diabetes mellitus & other categories of hyperglycemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIABETES MELLITUS:</strong></td>
<td></td>
</tr>
<tr>
<td>Symptoms of Diabetes plus casual plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/L)</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>FPG ≥ 126 mg/dl (7.0 mmol/L)</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Two hour PG ≥ 200 mg/dL (11.1 mmol/L) during an OGTT as described by WHO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>• Casual is defined as any time of the day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia and unexplained weight loss</td>
<td></td>
</tr>
<tr>
<td>• Fasting is defined as no caloric intake for at least 8hr-12hrs</td>
<td></td>
</tr>
<tr>
<td>• 2-hr. PG is done using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water</td>
<td></td>
</tr>
<tr>
<td>• In the absence of unequivocal hyperglycemia with acute metabolic decompensation-testing must be repeated on separate day, by one of the three methods.</td>
<td></td>
</tr>
<tr>
<td><strong>IMPAIRED GLUCOSE TOLERANCE (IGT):</strong></td>
<td></td>
</tr>
<tr>
<td>Fasting value</td>
<td>&lt;100 mg/dl (&lt; 5.6 mmol/L)</td>
</tr>
<tr>
<td>2 hr. after 75 gm glucose load</td>
<td>140 - 200 mg/dl (7.8 - 11.1 mmol/L)</td>
</tr>
<tr>
<td><strong>IMPAIRED FASTING GLUCOSE (IFG):</strong></td>
<td></td>
</tr>
<tr>
<td>Fasting value</td>
<td>100 - 125 mg/dl (5.6 - 6.9 mmol/L)</td>
</tr>
<tr>
<td>2 hr. after 75 gm glucose load</td>
<td>&lt; 140 mg/dl (&lt; 7.8 mmol/L)</td>
</tr>
</tbody>
</table>
POINTS TO REMEMBER:

1. Do not make a diagnosis of diabetes in an asymptomatic person based on a single value it must be repeated.
2. Whole blood glucose values are lower than plasma values. Check which is being measured.
3. Capillary glucose values are about 1 mmol/l higher than venous levels after a glucose load or after meals.
4. In a same person the fasting blood glucose may be normal, due to suppression of hepatic glucose output and the post prandial blood glucose may be high because of poor meal stimulated insulin response.
5. Conversely fasting plasma glucose may be high due to uncontrolled hepatic glucose output in the fasting state, whereas good meal stimulated insulin response results in normal postprandial glucose (IFG).
6. Diagnosis of diabetes should not be made by the presence of glucose in the urine. In renal glycosuria, urine sugar occurs even when the plasma glucose is less than 180-mg%, because of low renal threshold. (Normally glycosuria occurs when the blood sugar is > 180 mg % which is the renal threshold for glucose.)
7. Diagnosis of Impaired Glucose Tolerance (IGT) requires Oral Glucose Tolerance Test (OGTT).
8. There may be severe hyperglycemia with OGTT, whereas plasma glucose with usual mixed meal may not be high. Hence, OGTT plasma glucose levels should not guide therapy.
TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS

Type 2 diabetes mellitus is the most prevalent form of diabetes, commonly seen in adults and is not considered as a pediatric disease. There is disturbing increase in cases of type 2 diabetes mellitus in children specifically in adolescents. It is a poorly understood entity and incompletely investigated on population basis.

CLINICAL CHARACTERISTICS OF TYPE 2 DIABETES MELLITUS IN YOUTH

1. Ethnicity in African-Americans, Hispanic, Pima Indians, and a recent report from India.
2. Insidious onset of age ≤ 15 years, characteristically around 13.5 years with majority of the patients in mid puberty.
3. There is a slight excess of female: male patients ranging from 1.6:1 to 3:1 in different studies.
4. Obesity is present in majority of the patients, with a BMI 85\textsuperscript{th} percent for age and sex in about 95% of the patients (BMI >32).
5. Acanthosis Nigricans is present in 60% to 95% of the patients.
6. A strong family history of type 2 diabetes (>95% of the patients). There is no autosomal dominant inheritance pattern thus distinguishing from MODY.
1. They have a significantly higher level of insulin and C-peptide (stimulated response of C-peptide ≥ 0.6 pmol/ml). They are less frequently ketonuric and have milder degree of acidosis.
2. Lack of evidence of autoimmune process (absence of GAD65 antibodies).
3. Response to treatment with oral antidiabetic drugs.

It is difficult to have a clear-cut demarcation between type 1 diabetes, MODY and type 2 diabetes in the young. Table -10 give some of their characteristic feature.

Table 10

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 1 Diabetes</th>
<th>MODY</th>
<th>Type 2 Diabetes in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>Peak at 5 &amp; 15 years</td>
<td>&lt;25 Years</td>
<td>Teenage years</td>
</tr>
<tr>
<td>Ethnic group</td>
<td>Caucasians</td>
<td>Caucasians</td>
<td>Hispanic, Asians,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>African American,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mexican- American,</td>
</tr>
<tr>
<td>M:F</td>
<td>1.1:1</td>
<td>1:1</td>
<td>1:1.5</td>
</tr>
<tr>
<td>Islet cell autoimmunity</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>HLA – DR3, DR4</td>
<td>Very common</td>
<td>No increased frequency</td>
<td>No increased frequency</td>
</tr>
<tr>
<td>DKA</td>
<td>Common</td>
<td>RARE</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Prevalence of obesity</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>≥ 90%</td>
</tr>
<tr>
<td>Mode of inheritance</td>
<td>Non Mendelian, generally sporadic</td>
<td>Autosomal Dominant</td>
<td>Non Mendelian, but strongly familial</td>
</tr>
<tr>
<td>Number of genes controlling inheritance</td>
<td>Polygenic</td>
<td>Monogenic</td>
<td>Polygenic</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Autoimmune beta cell destruction</td>
<td>Insulinopenia</td>
<td>Insulin resistance plus insulinopenia.</td>
</tr>
<tr>
<td>Long term course</td>
<td>Insulin dependent</td>
<td>Non Insulin dependent</td>
<td>Non Insulin dependent</td>
</tr>
</tbody>
</table>

Adapted from Winter et al ECNA, December 1999
MATURE-ONSET DIABETES OF THE YOUNG (MODY)

MODY is associated with beta cell dysfunction resulting from a specific mutation in a MODY related gene. The clinical features are early onset non-insulin-dependent diabetes with an autosomal dominant inheritance. The other features are genetic defects of beta cell function rather than insulin resistance. Subjects with MODY mutations need not be obese to develop diabetes, in contrast to subjects with childhood or early onset type 2 diabetes. A family is considered to have early onset diabetes if at least one, better two members of the family are diagnosed to have diabetes before the age of 25. MODY families have at least 3 or more generations affected. A young person with Acanthosis Nigricans, which is a marker of severe insulin resistance, is very unlikely to have MODY.

The mutations in six discrete genes have been shown to cause MODY: Hepatocyte Nuclear Factor-4 (HNF-4, MODY 1), Glucokinase (MODY 2), Hepatocyte Nuclear Factor-1 (HNF-1, MODY 3), Insulin Promoter Factor-1 (IPF-1, MODY 4), Hepatocyte Nuclear Factor-1 (HNF-1, MODY 5), and Neurogenic differentiation factor 1 (MODY 6). Maturity onset-diabetes is not that common. The molecular genetics testing helps in identification of certain specific forms of diabetes caused by single gene defect and is useful in determining the genetic etiology and helps in predicting the prognosis, treatment and eventually the prevention of diabetes within these families.
AETIOPATHOGENESIS OF DIABETES MELLITUS

The precise etiology of diabetes mellitus remains obscure in spite of the advances made in the knowledge with respect to various factors associated with the causation of diabetes mellitus. Genetic, epidemiological, immunological studies and chromosomal analysis have enabled us to link the available information to formulate a working hypothesis towards the aetiopathogenesis of diabetes.

AETIOPATHOGENESIS OF TYPE 1 DM

Type 1 DM has a high degree of prevalence in certain populations (e.g.) in Sweden, Finland) while relatively rare in others (e.g. in Japan, Cuba). Most often this type of diabetes occurs in subjects below 25 years though no age is exempt. Seasonal peaks in autumn and spring with a female preponderance and a temporal relationship to certain viral infections are implicated in the causation of type 1 DM. Genetic and autoimmunity play a determining role in the etiology of type 1 DM.

I. GENETIC FACTORS:

a) TWIN STUDIES:

About 10% of type 1 DM subjects have a sibling or parent with the disease. Such familial aggregation of cases prompted research workers to analyze the genetic factors involved in the etiology of type 1 DM. Studies of monozygotic twins have established about 30-50% concordance for type 1 DM i.e., among identical twins if one of them develops type 1 DM; the co-twin has a 30-50% chance of developing
the disease. These studies, while confirming the definite genetic
c ontribution, emphasize the additional contribution by the
e nvironmental factors as well, since a purely genetic disease would be
associated with a 100% concordance in monozygotic twins. Evidences
of genetic factors in the involvement of type 1 DM come from various
animals, human twins and family studies.

b) HISTOCOMPATABILITY ANTIGEN:

The short arm of chromosome 6 contains the major histocompatability
complex (MHC) genes. There are three classes of MHC genes on this
chromosome. The products of these genes in humans are referred to
as Human Leukocyte Antigen (HLA). The Class I molecules (HLA - A,
E, C, and B) are expressed on the surface of most nucleated cells,
whereas the Class II molecules (HLA-DR, DQ and DP) are expressed
only by macrophages, B lymphocytes, etc., and the Class III molecules
are the complement C4 and C2 genes, the properidien Bf gene and the
21-hydroxylase gene. The function of the HLA molecules is to present
the processed antigen which is recognized by the T-cell receptor.

Population studies have shown an association of type 1 DM with HLA -
B8 genes DR3-DQ2 and DR 4-DQ8. Those who possess DR3-DQ2 and
DR4-DQ8 are at 14 times higher risk of developing diabetes mellitus in
the Caucasians. The relative risk conferred by the heterozygous DR3-
DQ2/DR4-DQ8 is greater compared to the homozygous state of either
DR3 or DR4 individually. In the Caucasian population there is an
association with HLA - B 15. In Indian population there is no
association with HLA - B15. HLA studies have shown that certain
amino acids in the DQ alpha chain and DQ beta chain were positively
or negatively associated with type 1 DM in Caucasians. Aspartame at position 57 of DQ beta and non-Arg at position 52 of DQ alpha confers protection. However this is not true in Japanese and Chinese. Several non-HLA gene associations have been identified for type 1 DM. These include the hyper variable region near the insulin gene (on chromosome 11) and with polymorphism of the T-cell receptor beta chain. Till date 9 type 1 DM genes have been identified for the causation of disease.

The empiric risk of developing Type I diabetes in a general population is 0.4%. The empiric risk of developing Type I DM in the offspring of a diabetic father is 6.1%; in the offspring of a diabetic mother is 2%; in the offspring of diabetic father and mother is 3.6%; in a monozygotic twin the risk is 30 - 50 % and in a dizygotic twin 5%. Approximately 1 in 20 first-degree relatives of patients with Type I diabetes mellitus will develop this disorder.

C. INSULIN GENE:

Insulin gene is located in the short arm of chromosome 11. The changes in the nucleotide flanking the gene have been reported in type 1 DM.

II. IMMUNOLOGICAL FACTORS:

Studies of the immunological factors have contributed toward better understanding of the aetiopathogenesis of type 1 DM. Several evidences suggest that the humoral and cell mediated auto immune response leads to destruction of beta cells. Demonstration of
circulating antibodies to islet-cells, cell-mediated abnormalities in type 1 DM patients presenting with 'insulitis' (affecting 'diabetic' islets) all confirm the autoimmune pathogenic mechanism. The Islet Cell Antibodies (ICA) belonging to IgG class is directed against the cytoplasm of these cells. They are found in high titers in type 1 DM patients at the onset of the disease. In more than 80% of the cases the antibody levels decline over the years. The insulinopenia may be of varying degree depending upon the extent of beta cell mass destruction. About 80% to 90% of the beta cells are to be deranged by the autoimmune process before the clinical manifestation of diabetes. The ICA is demonstrated by conventional direct immune fluorescence (IFL). These auto antibodies react with the cytoplasm of glucagon ( ) and somatostatin ( ) cells as well as the beta ( ) cells of the pancreas. In a small proportion in which they persist, association of other organ specific auto antibodies are frequently encountered. In this sub-group of patients there is a female preponderance and a higher prevalence of HLA B8.

Islet Cell Surface Antibodies (ICSA) has also been detected. The ICSA show separate specificity to the , and cells. Recently a protein of molecular weight 64 kDa has been identified in human islet cells. This 64-kDa-auto antigen has been identified as Glutamic acid Decarboxylase (GAD 65). This enzyme facilitates the biosynthesis of the inhibitory neurotransmitter GABA. (Gamma Amino Butyric Acid). The GAD 65 antibodies are present in >80% of the newly diagnosed Caucasian type 1 DM patients and may even be detected several years prior to its clinical onset. GAD65 is beta cell specific unlike ICA, which is islet specific.
Insulin Auto Antibodies (IAA) to insulin molecule has been described recently in newly diagnosed type 1 DM. Their role is not clear but may appear before the onset of diabetes.

The infiltration of mononuclear cells in the islets of diabetic subjects at autopsy and experimental animals, and various studies analyzing the sub population of lymphocytes have highlighted the role of cell mediated immunity in the causation of diabetes. Lymphocytes from type 1 DM subjects have the capacity to kill cultured insulinoma cells. Even though the total T cell population is not altered significantly in type 1 DM subjects, the population of suppresser T cell is decreased.

III. VIRUSES / TOXINS:

Involvement of viruses in the causation of type 1 DM has been recognized. Epidemiological studies have linked viral infection with type 1 DM. Elevated titters of antibodies to Coxsackie B4 virus in some freshly detected type 1 DM subjects and association of type 1 DM with congenital rubella infection, induction of diabetic state in experimental animals by certain viral agents (Encephalomyocarditis virus, Mumps virus, Reovirus, Venezuelan equine encephalitis virus herpes virus and echo virus), form the basis of such conclusions.

Viruses may damage the beta cells by direct invasion or by triggering an auto immune response. They may also persist with beta cells and cause long-term interference with metabolic and secretory functions. While viruses do not produce type 1 DM in all infected individuals, it is tempting to speculate that in susceptible individuals these infective
agents trigger a host of immunological phenomenon resulting in cell death.

Besides viruses, chemical agents like pentamidine and Vacor (rodenticide) have been linked with the causation of type 1 DM in epidemiological studies.

**DIETARY FACTORS:**

Consumption of cow’s milk during early life may be a contributory environmental factor associated with type 1 DM. The bovine serum albumin (BSA) an antigen may enter in an intact form through the gut of neonates and stimulate an immune response directed against cells. This hypothesis has not been widely accepted. Another dietary factor linked to the causation of diabetes is the ‘nitrosamines’ found in smoked and cured meats.

To sum up type 1 DM is an autoimmune disease, which is triggered by a virus infection, in a genetically predisposed individual. In a HLA predisposed individual, viruses and other environmental agents may induce aberrant expression of the HLA antigens which can lead onto auto immune destruction of the beta cells. About 80 to 90% of the beta cell capacity must be lost to produce absolute deficiency of insulin and manifestation of the disease (Fig -2).

**HONEY MOON PHASE**

At the onset of the disease the beta cell response to secretagogues is poor. The exogenous insulin requirements are high. After the
correction of hyperglycemia the endogenous insulin secretary capacity recovers. With this recovery the requirement for exogenous insulin decreases. This is known as Honeymoon phase. This period may last for few months to years (as shown in Fig 3). Though there is decrease in need for insulin, follow up of the patient is necessary as at any time the disease may recur after a variable period with total destruction of beta cells and absolute deficiency of insulin occurs.

**Figure 2** Sequence of The Events In The Development Of Type 1 DM

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition )
AETIOPATHOGENESIS OF TYPE 2 DM

The role of genetic factors in the etiology of type 2 DM has been appreciated ever since the recognition of the disease. Studies of identical twins revealing 100% concordance for type 2 DM have highlighted the single dominant influence of genetic factors in the etiology of type 2 DM. This concordance was recorded independent of obesity and even when the index twin and co-twin lived in different environment. Earlier attempts to invoke a simple Mendalian type of inheritance, viz., autosomal dominant, autosomal recessive and sex-linked inheritance met variable results. It was only subsequently recognized that the diabetic genotype might be modified by other factors, which ultimately influence the phenotypic expression. Similarly attempts to quantify the risk in the inheritance of diabetes mellitus met with variable results.
Diabetic genotype is influenced by various other factors the predominant one being central obesity. Even though obesity per se does not produce diabetes mellitus, it nevertheless precipitates the disease in susceptible individuals. Epidemiological studies have established the significant contribution by other factors such as physical indolence, dietary habits (independent of obesity), viz., consumption of refined carbohydrates and reduced intake of fiber, urbanization with associated affluence and the stress of life, in the etiology of type 2 DM.

The current understanding of type 2 DM is that it is probably a heterogeneous in nature which involves triple abnormalities in the genesis of hyperglycemia, 1) impaired pancreatic insulin secretion, 2) peripheral resistance to insulin action occurring primarily in liver and muscle, and, 3) excessive hepatic glucose output. The classical glycemic profile of type 2 DM consists of elevated basal or fasting levels upon which postprandial glycemic excursions are superimposed. The hepatic glucose output is the principal factor for fasting hyperglycemia and the postprandial hyperglycemia in large part is determined by the peripheral glucose utilization (Insulin resistance).

1) IMPAIRED PANCREATIC INSULIN SECRETION:

The beta cell dysfunction in diabetics fall into two distinct types: a) The pulsatile insulin delivery is lost even when the glucose tolerance is normal and b) The loss of compensatory mechanisms, which include increase beta cell mass, quantitative insulin output and maximum secretory capacity.
a) **INSULIN SECRETION IN TYPE 2 DM:**

The normal fasting insulin level is between 5 and 15 U/ml. It may be low (< 5 U/ml) in subjects with high insulin sensitivity and elevated (> 15 U/ml) in insulin resistant subjects.

Normally insulin is secreted in a pulsatile fashion and also secreted in response to meals and or secretagogues. The pulsatile secretion is called ultradian oscillations. The ultradian pulses of insulin secretion occur 90 to 120 minutes and are exaggerated after the ingestion of food. Besides the ultradian pulsations, rapid oscillations of insulin level occur every 8 to 16 minutes in the beta cell. These rapid oscillatory insulin pulses are effective in inhibiting hepatic glucose output.

The insulin secretion following a glucose load shows a biphasic response. The first phase acute insulin response (AIR) is due to release of insulin stored in the granules, which suppresses the hepatic glucose output. This occurs within 4 to 5 minutes and returns to normal within 10 minutes. The second phase is in response to the ambient raise in the glucose level, which promotes disposal of glucose in peripheral tissues (Muscle and adipose tissue) (Fig - 4).

**Figure 4 Insulin Secretions in Non Diabetics And Diabetics**
(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition )
In type 2 DM subjects the ultradian oscillations of insulin delivery is no longer present and the first phase of insulin release is lost.

\[ b) \textit{BETA CELL DYSFUNCTION:} \]

The beta cell mass is mildly reduced especially when obesity is taken into account. Amyloid deposits are frequently observed in the islets. Morphologically islets appear normal and insulitis is never present. Amylin or the islet Amyloid polypeptide is a 37 amino acid protein normally produced by the beta cells and co-packaged with insulin in the secretary granules and co-secreted in the sinusoidal space. For reasons unknown this material tends to get accumulated extracellularray in close contact with beta cells and forms fibrils. Amylin has been reported to lower basal and insulin stimulated glycogen synthetase in the muscles and to inhibit glucose stimulated insulin secretion. These abnormalities of deficient insulin secretion and insulin action are similar to the pathogenic factors of type 2 DM.

There are evidences of impaired beta cell response to glucose (\textit{blindness of beta cells to glucose}) but acute insulin response to non-glucose stimulus like arginine, neurotransmitters and hormones persist.

\textbf{Insulin Secretory Abnormalities in Type 2 Diabetes Mellitus}

- Decreased glucose sensing
  - Impaired ability to respond to elevations and reductions during glucose infusion
  - Reduced or absent first-phase insulin secretion in response to intravenous glucose administration.
Reduced or absent early insulin secretory response to oral glucose
Alterations in the rapid oscillations of insulin secretion
Reduced effect of gastrointestinal hormones in potentiating glucose-mediated insulin secretion
Inadequate insulin secretion for the magnitude of hyperglycemia.

2) IMPAIRED PERIPHERAL ACTION OF INSULIN:

Numerous longitudinal and cross sectional studies have provided evidences that hyperinsulinemia antedates the development of type 2 DM. This insulin resistance can occur in various tissues, liver, muscle, splanchnic etc. After glucose ingestion insulin is released into the portal vein and is carried to the liver where it binds to its specific receptors on the hepatocytes and suppresses the hepatic glucose output. Failure of the liver to perceive this signal results in the increased hepatic glucose output and is manifested as raised blood glucose levels in type 2 DM.

In muscles the defect in action are 1) impaired insulin receptor tyrokinase activity, 2) diminished glucose transporters and 3) diminished glycogen synthatase and pyruvate dehydrogenase. These defect results in disturbances in major intracellular pathways of glucose disposal namely glycogen synthesis and glucose oxidation.

In type 2 DM subjects both receptor and post receptor defects have been shown to contribute to insulin resistance. Post binding defects are of three types a) impaired generation of insulin's second messenger b) diminished glucose transport into the cell and c) a post
glucose transport abnormality in some critical step involved in glucose utilization. In diabetic subjects with moderate to severe hyperglycemia post binding defects in insulin action are responsible for the insulin resistance. In subjects with impaired glucose tolerance the defect may be at insulin binding to its receptor.

3) INSULIN RESISTANCE AS A PRIMARY DEFECT:

Prospective studies have shown that hyperinsulinemia and insulin resistance precede the development of IGT. Impaired Glucose tolerance (IGT) represents a transient stage between normal glucose tolerance and development of type 2 diabetes. Cross sectional studies have shown that the insulin resistance is the inherited defect that initiates the diabetic event. The hyperglycemia to insulin resistance occurs in three phases (Table 11).

Table 11 Development of Insulin Resistance

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Phase</td>
<td>Plasma glucose remains normal despite demonstrable insulin resistance because the insulin levels are increased.</td>
</tr>
<tr>
<td>Second Phase</td>
<td>Insulin resistance tends to worsen so that post-prandial hyperglycemia develop despite elevated insulin concentration.</td>
</tr>
<tr>
<td>Third Phase</td>
<td>Insulin resistance does not change but declining insulin secretion caused fasting hyperglycemia.</td>
</tr>
</tbody>
</table>
Because of this insulin resistance the beta cells produce excess insulin. As the resistance progresses the muscle glucose uptake becomes impaired, but the insulin produced is sufficient to maintain the hepatic glucose output in the normal range (the fasting blood sugar is still normal).

**Figure 5 PATHOGENESIS OF TYPE 2 Diabetes**

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)

At this stage the time taken to achieve normoglycemia after the meal is the only defect noticed. Eventually as hyperglycemia becomes
sufficiently severe the compensatory hyperinsulinemia is no longer adequate to maintain the fasting plasma glucose in normal level. The development of fasting and post-prandial hyperglycemia stimulates the beta cell further. The resultant hyperinsulinemia leads to the down regulation of the receptor number and the post receptor events. This exacerbates the insulin resistance further and chronic hyperglycemia results; which is toxic (Glucotoxicity) to the beta cells and is responsible for the acquired defect of impaired insulin secretion (Fig–5). When the insulin becomes deficient the ‘glucose transporter’ system becomes severely impaired and the intracellular enzymatic steps involved in metabolism are depressed.

4) INSULIN SECRETARY DEFECT AS A PRIMARY EVENT:

In the evolution of the disease in those who are prone to diabetes the primary defect may be in the beta cell.

**Figure 6** Phase OG Insulin Secretion Defect

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)
Even when the blood glucose is normal the earliest abnormality noted is the loss of ultradian oscillation of insulin secretion. Some subjects may have decreased first phase insulin response (Fig 6).

This impairment of insulin secretion will lead to excessive and prolonged increase in plasma glucose concentrations. This increase in glucose concentration has a glucotoxicity effect and further reduces the insulin release from the beta cells. Though they have a diminished first phase of insulin secretion, the total amount of insulin secreted in response to a meal may actually be increased. The post prandial hyperinsulinemia may be sufficient to return the fasting plasma glucose levels to normal, but longer periods are required to restore euglycemia. This elevated insulin concentration will lead to the down regulation of the insulin receptors and the post receptor events in the insulin sensitive tissues and the emergence of insulin resistance.

Insulin resistance and insulin deficiency each may lead to or induce the other resulting in hyperglycemia (Fig -7).

Whether the primary defect initiating the glucose tolerance resides in the beta cell or in the peripheral tissues, development of insulin resistance will eventually ensue or become aggravated respectively. By the time the overt fasting hyperglycemia (>140mg/dl) develops both impaired insulin secretion and insulin resistance are present. Thus Hyperglycemia due to either of the primary abnormality may secondarily involve the other abnormality.
The sensitivity and maximum responsiveness to insulin are reduced (Insulin resistance) in the target tissues by prolonged elevation of the plasma glucose. Hyperglycemia is also toxic to the beta cells and further diminishes their capacity to respond to stimulation (Insulin deficiency). Hence hyperglycemia is not only the manifestation of diabetes but also its cause.
NORMAL HISTORY OF TYPE 2 DM

Normal glucose homeostasis is dependent on a finely balanced dynamic interaction between tissue sensitivity to insulin and insulin secretion. Insulin that is secreted in response to glucose suppresses the hepatic glucose production and promotes the uptake of glucose in the peripheral tissue to maintain euglycemia (Fig 8).

**Figure 8** Normal Regulation of Plasma Glucose

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)
A) THE FASTING GLUCOSE IS REGULATED BY

Hepatic glucose production is a primary factor determining fasting plasma glucose which depends on
- Fasting (basal) plasma insulin
- Hepatic sensitivity to insulin
- Fasting substrate availability

• In Type 2 Diabetes
  - Basal insulin secretion is impaired
  - Hepatic sensitivity to insulin is decreased

B) THE POSTPRANDIAL GLUCOSE IS REGULATED BY:
- Clearance of ingested glucose
- Suppression of hepatic glucose production
- Peripheral clearance of Glucose

• In impaired glucose tolerance or diabetes, these mechanisms are impaired by
  - Delayed and reduced insulin secretion
  - Lack of suppression of glucagon
  - Hepatic and Peripheral insulin resistance

The evolution of the disease process in type 2 DM requires the defects in both insulin secretion and insulin action. With the decline in insulin sensitivity, the endogenous insulin secretion increases to maintain normal fasting plasma glucose. As the disease progresses, the compensatory insulin secretion diminishes and the fasting plasma glucose rises (Fig – 9).
The current understanding is that type 2 DM is a heterogeneous disorder and that both insulin secretion and insulin sensitivity must be defective to get the full phenotypic expression of the disease. The contribution of these abnormalities varies considerably in the pathogenesis of hyperglycemia in individuals with Type 2 DM (Fig 10).
**Figure 10** Pathogenesis of Hyperglycemia In Type 2 DM

**Primary defects of type 2 DM and effects on target tissues**

![Diagram of pancreas, liver, and muscle showing pathogenesis of hyperglycemia in type 2 DM](Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)

**Figure 11** Stages of Type 2 DM in Relationship to Beta Cell Function

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)
The UKPDS has shown that type 2 diabetes is a progressive disease and at the time of diagnosis of type 2 DM almost 50% of the beta cell functions are lost (Fig 11).
NON MODIFIABLE RISK FACTORS

1. Genetics
2. Family history of diabetes
3. Age

GENETICS OF TYPE 2 DIABETES IN INDIANS

INTRODUCTION

Environmental factors certainly play a major role in the diabetes epidemic, this usually occurs on a background of genetic susceptibility. Indeed, there is a lot of evidence to suggest that genetic susceptibility plays a major role in the pathogenesis of type 2 diabetes. The ethnic diversity in prevalence of diabetes itself a pointer to genes playing a major role in diabetes although environmental factors may also well explain this.\textsuperscript{66,67} Secondly, the concordance rate of type 2 diabetes among identical twins varies between 60-90\%.\textsuperscript{68,69} Thirdly, several studies have shown associations between various genes and type 2 diabetes and the intermediate traits that precede diabetes namely insulin resistance and impaired insulin secretion.\textsuperscript{70-74} Finally, recent studies on whole genome scans have implicated numerous regions on many different chromosomes, which show susceptibility to type 2 diabetes.\textsuperscript{75,76} The simplest and easiest way of quantifying the role of genetic susceptibility in a complex disease like diabetes is to assess the risk of the relatives of affected individuals in developing the disease. Earlier studies have shown the risk for type 2 diabetes in relatives to be approximately 2.5-4 times higher than in those without
a family history of diabetes and they also tend to develop diabetes earlier.77

EVIDENCES FOR GENETIC PREDISPOSITION TO DIABETES IN INDIANS

Type 2 diabetes is a polygenic disorder, with many candidate genes identifies in different populations.

Sharp et al78 and Mohan et al79 first showed that insulin resistance and plasma insulin levels, are higher in Asian Indians compares to matched groups of Europeans. Though body mass index (BMI) an indicator of obesity is lower among Indians, for any given BMI, the waist to hip ratio was higher among Indians compared to other ethnic groups.80 Furthermore, at any BMI, Indians also had higher body fat; finally, even when matched for body fat, Indians had greater insulin resistance compared to other ethnic groups.81-83 These studies suggest that Indians seem to be genetically more prone to diabetes and insulin resistance.

Indians have a high genetic risk for diabetes. Racial predisposition is evident from the studies in migrant Indians.104-108,84 Asian Indian migrants living in different countries, have high rates of glucose intolerance compared with inhabitants of other racial origin.

It was confirmed by recent epidemiological studies that prevalence rates are very high in native Indians.85,86 This clearly indicates that Indians have a predilection to diabetes which could probably be due to genetic predisposition. Several novel genetic associations have been
recently reported with diabetes in Indians. This could at least partly explain the high prevalence of diabetes in Indians.

One factor contributing to insulin resistance is obesity and in Caucasians most people with type 2 diabetes are obese. Studies in Indian reveal that even a moderate degree of obesity can elicit insulin resistance when fat accumulates particularly in the intra-abdominal region (visceral fat). Individuals with abnormal fat distribution, characterized by a high waist to hip ratio or a high truncal to peripheral skin fold thickness ratio appear to be predisposed to developing insulin resistance. There is now a lot of data to suggest that Indians are more susceptible to developing truncal obesity, which might account for their propensity to insulin resistance. This tendency is reflected in reports of increased waist to hip ratios and increased truncal skin fold thickness in Asian Indians compared to other populations. This in turn leads to lower insulin sensitivity or increased insulin resistance and this is referred to as “Asian Indian Phenotype”.

Factors that determine the distribution of body fat are not known; the possibility that abnormal insulin action at the level of adipose tissue could promote the accumulation of truncal fat cannot be excluded. Studies on low birth weight and insulin resistance in Indian neonates have shown that newborn Indian babies have higher insulin level and greater adiposity compared to Caucasians. These studies underscore the importance of genetic susceptibility in Indian towards developing diabetes and insulin resistance.
It is evident that strong genetic factors contribute to the increased susceptibility of type 2 diabetes in Indians. Other than the candidate gene approach, genome wide linkage mapping for type 2 diabetes is needed to identify novel genes associated with the disease in Indians.

GENETIC DEFECTS IN MODY AND YOUNGER AGE AT ONSET OF DIABETES IN INDIANS

Many rare forms of defective glucose metabolism have been shown to be caused by gene defects involving the β-cell and the insulin receptor at a much earlier age. Of these the most common and important form is the maturity Onset Diabetes of the Young (MODY). MODY is a monogenic subtype of type 2 diabetes, characterised by an autosomal dominant inheritance, and an age of onset at 25 years or younger. MODY is primarily associated with insulin secretion defects and patients with MODY have normal insulin sensitivity and are in most cases lean. It is estimated that 2-5% of all patients with type 2 diabetes may have MODY. Studies by the senior author showed a high prevalence of MODY in south Indians (4.8%) (as defined at that time) besides reporting the insulin responses in them and beta-cell response in the offspring of MODY.

MODY is genetically heterogeneous and at present there are at least 6 different MODY forms, namely MODY 1, MODY 2, MODY 3, MODY 4, MODY 5, MODY 6. These are caused by mutations in the genes encoding hepatocyte nuclear factor-4α (HNF-4α), glucokinase, hepatocyte nuclear factor-1α (HNF-1α), insulin promoter factor (IPF-1), hepatocyte nuclear factor-1β (HNF-1β) and neuroD, respectively. MODY 1-3 seem to be the most common worldwide.
All of the known MODY genes have been considered as possible candidates for gene defects in late-onset type 2 diabetes mellitus also.

**FAMILY HISTORY OF DIABETES IN INDIANS**

Studies carried out in the 1980s in a group of 135 Asian Indian and 146 European diabetic patients attending a diabetic clinic in the UK showed that 45% of Asian Indians had a first degree relative with diabetes compared to 36% of the Europeans. Of greater interest was the excess of parental diabetes as 10% of Asian Indians compared to 1% of Europeans had two diabetic parents. Another study looked at the prevalence of diabetes among the offspring of two type 2 diabetic parents in India. This study showed that 60% of offspring had diabetes or impaired glucose tolerance. This was considerably higher than those reported for prevalence of diabetes in offspring of American or European diabetic parents.

Strong familial aggregation of the disease has been noted in the Indians. In India, nearly 75% of type 2 diabetic patients have first-degree family history of diabetes. The prevalence of diabetes increases with increasing family history of diabetes. The risk of the offspring developing diabetes with a parental history increases above 50% and it is around 40% if the proband has a diabetic sibling.

Familial aggregation of diabetes with a high prevalence among first-degree relatives and vertical transmission through more than two generations is commonly seen in Indians.
In the recent population-based study called Chennai Urban Population Study (CUPS) conducted on 1,262 individuals in Chennai in southern India, the prevalence of type 2 diabetes was higher among subjects who had positive family history of diabetes (18.2%) compared to those without (10.6%, \( p=0.0015 \)). Moreover, 9.3% of subjects with family history of diabetes had impaired glucose tolerance (IGT-a pre-diabetic stage) compared to 5.0% of subjects without a family history (\( p = 0.016 \)). The overall prevalence of glucose intolerance (diabetes + IGT) among subjects with two diabetic parents was significantly higher (55%) than those who had diabetic parent (22.1%, \( p=0.005 \)) or those with two non-diabetic patient (15.6%, \( p<0.0001 \)). The odds ratios of the risk for diabetes among subjects with one diabetic parent was 2.5 and this increased to 6.62 in subjects who had both parents affected by diabetes.\(^91\)

**AGE**

Indians develop diabetes at a very young age at least 10-15 years earlier than the white population.\(^{111}\) The NUDS study showed that more than 50% of diabetic cases developed the disorder before the age of 50 years,\(^{112}\) A recent analysis by the International Diabetes Epidemiology Group comparing the profile of type 2 diabetes in the European and Asian populations showed that Indians had the strongest age associated risk for diabetes among all the groups.\(^{113}\) In the developed Western countries diabetes generally occurs in individuals aged > 65 years. In the developing countries onset of diabetes occurs at a younger age (45-65 years).\(^{113}\) Studies from India have shown a much younger age at onset of diabetes compared to the Western population. The recent DECODA study has made a comparative
analysis of age at diagnosis of diabetes in different races.\textsuperscript{113} The overall effect of age on prevalence of diabetes differed considerably between ethnic groups even after correcting for other confounding factors such as BMI. The association between age and diabetes was higher in the Indian and the Maltese population compared to all other populations studies (Europeans, Chinese and Japanese).\textsuperscript{113} During an OGTT, in Indians the plasma glucose concentration rose with age and reached a peak at 60-69 years of age and then started to decline, but it continue to increase after 70 years of age in Europeans. At each age group the fasting and 2h plasma glucose were significantly higher for Indians than Chinese and Japanese populations. The age and sex specific prevalence and the peak prevalence of diabetes were higher in Indian and in Singapore cohorts than in Chinese and Japanese cohorts.\textsuperscript{113} A recent study from south India on the HNF 1 alpha gene polymorphism shows that those with the Val/Val genotype developed type 2 diabetes at least 11 years earlier than those with the Ala/Ala genotypes.\textsuperscript{114}

An early occurrence of diabetes in the population has severe economic impact as severe morbidity and early mortality occurs in the most productive years of life. The diabetic subjects live long enough to develop the debilitating vascular complications of diabetes.
MODIFIABLE RISK FACTORS

DEMOGRAPHIC AND ECONOMIC CHANGES

Important demographic and economic changes are occurring in India. The individual income and per capita expenditure have increased, and the annual gross domestic product has risen from 1.3% from 1960s-70s to 3.6% in the year 2000 in India. The life expectancy and the percentage of the elderly population have increased, which has lead to an increased proportion of elderly in the population. Increasing migration from villages to cities, urbanisation and mechanisation have increased. All these factors have brought forth adverse lifestyle changes, such as nutritional imbalance, physical inactivity, stress and increased consumption of alcohol and tobacco to a vast segment of the population.\textsuperscript{115}

DIETARY HABITS OF INDIA

The history of mankind has been linked with food since time immemorial. Basically all human life is based on the plant kingdom. Plants either themselves are the food of man or by supporting animal life indirectly contribute to man’s existence. Because food is basically needed, food habits are inculcated into the very fabric of a person’s being quite early in life. Culture and society determine food likings and these likings may or may not be similar to other. Thus, the food availability has becomes a focal point of discussion all though.
CHARACTERISTIC FEATURES OF A TRADITIONAL INDIAN DIET:

1. The Indian diet is mainly cereal pulse based lacto-vegetarian diet.
2. Bulk calories and protein come from whole grain cereals and pulses (legumes).
3. A small quantity of milk and freshly prepared Dahi (butter milk) is the usual source of animal protein.
4. Consumption of meat, fish and eggs is minimum. A certain set of the population totally avoided it.
5. Each meal consisted of mainly cereals, pulses with 1 or 2 cups of vegetables, condiments (ginger, garlic etc.) spices are freely used.
6. Majority of the people avoid preserved, processed and stored foods. Hand pounded rice, fresh vegetables; germinated, sprouted and fermented foods are used more frequently.

ADVANTAGES OF A TRADITIONAL INDIAN DIET:
1. Caloric content is limited.
2. More of complex CHO (cereals, pulses, vegetables and fruits)
3. Less of free sugar.
4. The amount of total and SAFA, cholesterol and animal protein is less.
5. Meal is rich in antioxidants and vitamins.
7. More of food bulk than caloric density.
8. Early satiety feeling.

Overall, each meal is more or less a balanced one
INFLUENCE OF URBANIZATION

Advances in civilization and rapid industrialization have not only changed our dietary pattern, but also has resulted in nutrient excesses. Added to these, the life expectancy has also gone up due to the availability of better health care facilities, thus producing the population more with nutrient excesses particularly in the developed countries. Rapid industrialisation also brought about the movement of population from rural to urban areas, joint family to nuclear family, active form of life to more sedentary jobs, from tension free to strenuous and stress oriented life and contentment to more ambitious life. Simultaneously there was rapid progression from illiteracy to literacy. All these factors cumulatively influenced the diet of pre-Industrialisation or agricultural era (mainly cereal – pulse rich and less fat “Low risk diet”) to the diet in of technological era “cereal pulse less, animal protein rich and fat rich diet” (high risk diet). Not only this affluent diet increased the prevalence of non-communicable chronic diseases of the European countries, but also influenced very much the dietary habits of developing countries too. In our country also, has been major change in the dietary habits in the post-independence era and has affected the nutrient composition of the diet very much both in rural and urban cities. Percentage of calories from cereals has come down with a concomitant increase in the consumption of fat. Gujarat has also witnessed this change very much particularly shifting from the cereal-pulse rich to cereal less and high fat diet.
DISTINCT FEATURES OF GUJARATI MEAL PATTERNS

1. Sugar and jaggery is added practically in all the food items.
2. Oil and Ghee are liberally used.
3. Pickle forms regular item in meals.
4. Various snacks and sweet dishes typical of Gujarat which are consumed by all the people of various regions of Gujarat.
5. Have sedentary lifestyle.

FAST FOOD SCENARIO IN INDIA

Fast foods have become a way of life for the young as well as the adult Indians and they are consumed by all clan of people in our country and thus have become part and parcel of life. Although no specific definition of fast food exists fast foods can be defined as foods which can be cooked easily (using pre-prepared food items eg. Dosa batter) and can be served in few minutes at serving centers. Such foods are available where they are needed and are accessible to those who have no opportunity to go home for their mid-day meal and snacks. Besides their convenience and employment potential the greatest factor in the favour of some of them is that they can meet most of the nutritional requirements within a very nominal cost. Fast food outlet is often referred to as a kitchen less restaurant as they employ pre-prepared foods that require little preparation, garnishing and portioning at the time of service.

It the West, the concept of fast foods grew out of necessity with both the parents of nuclear family working and having little time to cook at
home as well as to keep pace with the changing life style of the people which is becoming increasingly busy, mechanized and industrialized. The same has occurred in case of Indians where also fast food dominates the diets of the people today. The fast food establishments are coming up in India at an alarming rate especially the International food chain establishments. The foreign players see tremendous potential in the country’s voracious two hundred million strong middle class after the liberalization of the economy. The first to tackle the Indian palate was Pepsi Company Restaurants International which opened branches of its Kentucky Fried Chicken (KFC) in Bangalore & Delhi. Then it introduced Pizza Hut in all the metros. The next to follow was McDonalds & Dominos Pizza in Mumbai. And the best part is that all the foreign chains are adapting their menus to Indian tastes & preferences.

In a nutshell the great food rush is as a result of the change in Indian food habits & life styles. Moreover, the large, upwardly mobile population in the urban areas tends to eat out more often now for business or for leisure.

The urban Indian has picked up a fancy for tinned and tetra-packed food full of preservatives additives. Not only the consumption of Western foods has increased or that the west is the sole seller but we in India have an indigenous food industry here, churning out oily Chhole-Bhatura, Fiber-starved, Pao-Bhaji, Dosas, Idlies, and deep fried Bhajiyas dished out in dhabas and roadside lorries. Unfortunately, growing children with their new found thirst for coke as well as Indian fast foods and may-care eating habits bear the burnt of malnutrition.
A statement issued by the Brihanmumbai Municipal Council reveals two-thirds of Mumbai civic school students are mal-nourished and faint from hunger, suffer from low-weight, vit.A deficiency, dental problems and tuberculosis.

But the harshest indictment of our bad eating habits is the linking of diet and cancer. It is claimed that three to four million cancer cases could have been prevented by intake of healthy nutrition. Dietary snacking, nibbling, power lunching and food-fadding in turns seems to have made us to forget the normal physiology of eating. With National Statistics saying one-third of the World's mal-nourished children are in India, we have got to be a country of bad eaters-some as helpless victims of food shortage, others by choice. With the rise of the city and the consequent dissolution of age old family structures, the traditional dinner table which had a well structured, even religious aspect –is becoming pales. With the rise of the culture of eating out has come about the subversion of the established logic of appetite. Eating at home usually meant you ate a variety of foods at regular hours, assimilating more or less the required quota of essential nutrients. Now you do not eat when hunger beckons but rather eat when tongue tempts, or when company warrants which more often that not, means stuffing yourself with an overdose of fat, oil, salt sugar, food additives and preservatives at the expense of fiber, proteins, vitamins, and minerals. And at time when the body is probably enjoying metabolic siesta. The same is the case when eating at home also because of ready to eat mixes of various food products for example soups, noodles, idli, curries or fried products, etc. which are also high in preservatives, additives, sugars, oils etc. In the west as well as in the Indian scenario the food pattern have gone haywire culminating in
what the French food philosopher Cluade Frischler calls Nutritional Cacophergy.

Considering Indian fast food Samosas, Idli with Chutney, Dosas, bhajiyas, Pizzas, Burgers, Cutlets. Frankies, hotdog etc are consumed frequently by everyone. They all show a nutrient composition which is high in fat, low in fiber and low to moderate proteins.

The consumption pattern of fast foods amongst teenagers shows that deep fried foods like samosas, wada was more frequent in comparison of shallow fried foods like masala dosa, hotdog, noodles etc. also the consumption of baked food like pizza and pastries was found to be high.

Thus, increased consumption of these fast foods has profoundly produced adverse health effects particularly in increasing the incidence of various chronic degenerative diseases like diabetes. These adverse effects have been attributed to the metabolic aberrations in carbohydrates and liquid metabolisms affecting a shift in energy metabolism towards the retention side resulting in obesity. But one of the salient features of these fast foods is its ability in making the availability of glucose and triglycerides into the circulation when ingested.

Whether good or bad the fast foods are here to stay hence marking it a challenge for us incorporate nutrients in the possible way so as to make then nutritionally rich foods. Finally, when all of us know that these fast foods have become a routine dietary habit of us and it is up to us to consume these fast foods judiciously.
PREVENTION

Overall in the past two decades, there has been a sharp rise in the prevalence of all these chronic diseases in our country and undoubtedly going to cause a major health problem unless the remedial measures are planned in time. One of the ways to delay the progress of this chronic degenerative disease is to shift from the “Affluent diet” to “Preventable diet” consisting of more cereals and pulses (legumes), less fat, more green leafy vegetables and moderate consumption of sugars. The preventable diet mimics the traditional healthy low risk diet, the nutrient composition of which is normally noticed with the foods like dal - roti, idli - sambhar. Dal - rice, khichdi, bean, tocos etc.

Further, evidence indicates that a diet low in total and saturated fat, high in plant foods especially in green and yellow vegetables and citrus fruits and low in alcohol is consistent with a low risk of development of metabolic disorders. Such diets are usually high in starches and fibre as well as several vitamins and minerals including beta – carotene and vitamin A. Therefore, a diet that fulfills the above recommended nutrient intakes is characterized by frequent consumption of vegetables, fruits, cereals and legumes. Thus the traditional diet consumed by the global population has been a testimony to the very much lower risk of developing chronic degenerative diseases such as obesity, hypertension and diabetes Mellitus and other metabolic disorders.
PHYSICAL INACTIVITY AND SEDENTARY OCCUPATION

Another worrisome factor is physical inactivity of Indians. Only a few studies are available but consistently reveal that Indians are less physically active as compared to white Caucasians.\textsuperscript{116-119} For example, in United Kingdom, Indian, Pakistani and Bangladeshi men were 14\%, 30\% and 45\% less likely than the general population to meet the guidelines of physical activity, and these differences were more in women and other people.\textsuperscript{119}

Evidences are accruing to demonstrate that physical inactivity as an independent factor in triggering the epidemic of type 2 diabetes. The impact of physical inactivity is manifested more markedly in populations which had been accustomed to habitual heavy physical activity. Migration from rural areas to urban slums in metropolitan cities leads to obesity, glucose intolerance and dyslipidaemia.\textsuperscript{121,122} The risk of developing diabetes was more in subjects who followed a sedentary lifestyle.\textsuperscript{120,123} In Fiji, among Melansian and Indian men, the prevalence of diabetes was more than twice as high in those graded as sedentary or undertaking light activity as in those classified as performing moderate or heavy exercise.\textsuperscript{124}

Increasing urbanisation and mechanisation have further increased sedentary habits, which are also seen in young Indians. Interestingly, it is observed that substantial proportion of urban post-pubertal children and young adults in Delhi were sedentary.\textsuperscript{125} Mohan et al\textsuperscript{126} have shown that physical inactivity is associated with the components of the metabolic syndrome and CAD in this urban south-Indian population. Sedentary lifestyle may be critical for high tendency for
insulin resistance in Indians and remains to be comprehensively investigated.
The developing countries are undergoing rapid urbanisation and migration of population to urban areas. In the next 30 years a major redistribution of the population will occur and by the year 2030, 60% of the world’s population would be living in urban areas. According to the WHO estimates in the last 5 decades 2-5 fold increase in urban population have occurred in most of the South East Asian countries. In India, the percentage of urban population was 25.5% in 1990, 28.4%, in 2000 and it is expected to increase to 45.8% in 2030. A transitional to modern life urbanisation has produced several health hazards in many populations including the Asian Indians. Urbanisation is associated with increasing obesity, decreasing physical activity and other risk factors associated with diabetes development.

People migrating from rural areas to big cities with in India quickly acquire risk factors associated with urbanisation. They become physically inactive, take to smoking and alcohol, and their diets become imbalanced. High prevalence rates of T2DM, obesity, and insulin resistance have been reported in this intracountry migrant hypertension, atherogenic dyslipidaemia, hyperhomocysteinaemia, endothelial dysfunction population settled in urban area.127-133 Similar findings have been noted in urban slum population in Thailand.134 Importantly, nearly 20-25% of the urban population in metropolitan cities in India comprise of slum dwellers.

Impact of urbanisation on the prevalence of diabetes was evident from the two studies conducted in Chennai, India. In the first study, the prevalence of diabetes in a semi urban area was found to be 5.9% in
comparison with the prevalence of 2.4% in the rural and 11.6% in the urban population. The semi urban population remains 'rural' by their occupational status but had access to certain 'urban' facilities like transport and limited availability of household machines. These people led a more sedentary lifestyle in comparison with the rural population. The social and economic changes occurring in rural India have produced significant changes in the occupational, dietary and activity levels. Also, increasing number of people sought jobs involving less of manual labour and migrates to urban areas. Better transport facilities were available and physical activity levels were significantly reduced. Increased calorie consumption with more of fat and refined carbohydrates had also become common. Sedentary lifestyle and increasing rate of obesity were strongly associated with the increasing prevalence of glucose intolerance.
STRESS FACTORS

Impact of stress, both physical and mental, is very strong on diabetogenesis, especially in those with a strong genetic background. A clinic-based prospective study has clearly shown the effect of stress on diabetes.135

This is often seen after a MI or stroke, where raised blood sugar levels may be encountered for the first time. In people who have diabetes, the fight-or-flight response does not work well. Insulin is not always able to let the extra energy into the cells, so glucose piles up in the blood (ADA, 2007). Making things worse, many sources of stress are not short-term threats. For example, it can take many months to recover from surgery. Stress hormones that are designed to deal with short-term danger stay turned on for a long time. As a result, long-term stress can cause long-term high blood sugar levels. Many long-term sources of stress are mental. Like physical stress, mental stress can be short term from taking a test to getting stuck in a traffic jam. It can also be long term, from working for a demanding boss to take care of an aging parent. In mental stress, the body pumps out hormones to no avail. Physical stress, such as illness or injury, causes higher blood glucose levels in people with either Type of diabetes. Stress blocks the body from releasing insulin in people with Type 2 diabetes. The diagnosis of diabetes usually comes as a shock and is certainly a stressful time (Wijenaike, 2002; ADA, 2007).
In people who have diabetes, stress can alter blood sugar levels. It does this in two ways.

1. People under stress may not take good care of themselves. People who are anxious are under pressures and may lose appetite and skimp on eating, or reach for not-so healthy quick fixes like candy or chips and sometimes seek refuge in food and drink. This can take the form of chocolates, sweets and crisps, often in between meals. The intake of alcohol may be increased. Many people who are under stress turn to food as a source of 'comfort'. This pattern of 'comfort eating' can often play havoc with blood sugar level. Further anxiety leads to less exercise. The results can be disastrous for people with diabetes. They may forget, or not have time, to check their sugar levels or plan good meals.

2. Stress hormones may also alter blood sugar levels directly as it antagonizes the action of insulin.

While in most people glucose levels go up with mental stress, while in others can go down. The effects in people with Type 1 diabetes are more mixed. People with Type 1 diabetes may develop elevated blood glucose levels and ketoacidosis. Those with Type 2 diabetes usually gain weight and develop obesity and often blood sugar levels are raised (ADA, 2007).

Inflammatory signaling pathways can also become activated by metabolic stresses originating from inside the cell as well as by extracellular signaling molecules. It has been demonstrated that obesity overloads the functional capacity of the endoplasmic reticulum and...
that this endoplasmic reticulum stress leads to the activation of inflammatory signaling pathways and thus contributes to insulin resistance. Additionally, increased glucose metabolism can lead to a rise in mitochondrial production of reactive oxygen species. Reactive oxygen species production is elevated in obesity, which causes enhanced activation of inflammatory pathways (Wellen and Hotamisligil, 2005). Physical stress, such as illness or injury, causes higher blood sugar levels in people with either type of diabetes. For some people with diabetes, controlling stress with relaxation therapy seems to help. It is more likely to help people with Type 2 diabetes than people with Type 1 diabetes. Stress blocks the body from releasing insulin in people with Type 2 diabetes, so cutting stress may be more helpful for these people. People with Type 1 diabetes do not make insulin, so stress reduction does not have this effect. Reducing stress can help people with Type 1 diabetes take better care of them. Some people with Type 2 diabetes may also be more sensitive to some of the stress hormones. Relaxing can help by blunting this sensitivity. In people with Type 2 diabetes, mental stress often raises blood glucose levels. It is easy to find out whether mental stress affects glucose control. Many glucose meters have the capability to enter personal notes and data when one perform checks, or jot it down in a stress journal (Wijenaike, 2002). Once one begins recording stress levels, most people with diabetes figure out pretty quickly what makes his blood sugar to go up. People with diabetes should stay conscious of eating well and exercising regularly. It’s a good idea to check blood glucose levels more frequently when ill or under stress and to drink plenty of fluids as so as not to get dehydrated. Something else that affects peoples responses to stress coping style. Coping style is how a
person deals with stress. People who use them tend to have less blood sugar elevation in response to mental stress (ADA, 2007).

Hyperglycemia induces the overproduction of oxygen free radicals and consequently increases the protein oxidation and lipid oxidation. A significance difference in the mean plasma concentration of total antioxidant status was observed in diabetic patients. A statistically significant higher values of protein carbonyl groups and MDA as lipid peroxides were observed in diabetic patients with slight reduction in the synthesis of nitric oxide. It is interesting to note that there was a decrease in the antioxidant levels with corresponding increased protein and lipid oxidation. Decreased levels of proteins - albumin, transferrin, ceruloplasmin and heptoglobulins and variable GC globulin fractions in diabetes were found compared to normal healthy controls (Vadde and Jailkhani, 2007).
OBESITY

Obesity is a major public health problem worldwide. It has been well-known for centuries that obese suffer from ill health. Charaka, the Indian physician, about 2,000 years ago defined causes and consequences of obesity. Obesity was considered a result of surfeit, when the individual gorges on rich, sweet, cold and fatty food; enjoys sleeping during the day, refrains from manual work and suffers from genetic disorders. The eight handicaps faced by the obese included—shortened life, difficulty in movement and sexual intercourse, tiredness, body odour, copious sweating, ravenous hunger and severe thirst. He also noted that fat asymmetry impairs strength and shortens lifespan. This was indirect hint on increased incidence of diabetes among the asymmetrically obese.

Obesity is defined as "excess of body fat relative to weight". The obesity epidemic that started in the middle of last century has now established itself in north America and western Europe and there appears no abatement. In developing countries too the epidemic has taken deep roots and in many urban populations of low and middle income countries of Asia, Latin America and Africa there is a dual burden of obesity and malnutrition, often within the same families. In 1995, World Health Organisation (WHO) estimated that there were 250 million obese adults worldwide with body mass index (BMI)>30kg/m² and the numbers increased to more than 300 million in 2000 including 115 million in developing countries. The increase to 300 million occurred 25 years sooner than projected, since in 1998 WHO had projected that the number of obese persons worldwide would not reach 300 million until 2025. Obesity has also
emerged as an important cardiovascular risk factor.\textsuperscript{138,142,143} Both overweight and obesity are strongly associated with numerous cardiovascular risk factors, including elevated levels of total cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, fibrinogen, C-reactive protein (CRP) and insulin resistance or frank diabetes. It is also associated with low levels of high density lipoprotein (HDL) cholesterol. Many other biochemical abnormalities have been demonstrated including a plethora of hormonal changes and a marked increase in various pro-inflammatory markers.

It has been proposed that in developing countries obesity is the prime driver of cardiovascular risk factors and leads to escalating coronary heart disease epidemic in urban populations of such countries (Figure 12).\textsuperscript{136} Transition from an active rural to sedentary urban socioeconomic milieu leads to decrease in physical activity, increase in intake of calorie dense foods and leads to increase in obesity. The obesity may be either generalized those results in increased BMI or truncal/central/abdominal resulting in increased waist size and waist-hip ratio (WHR). These physical changes then translate into increased incidence of cardiovascular risk factors-high total and LDL cholesterol, low HDL cholesterol, high triglycerides and other lipid abnormalities hypertension and diabetes. These risk Factors usually cluster and lead to a heightened risk of atherosclerotic cardiovascular diseases.\textsuperscript{143}

FIGURE 12 Urbanization is the proximate coronary risk factor among developing countries of Asia and Africa. As populations move from rural to urban lifestyles there is change in dietary habits and physical activity resulting in population-wide increases in important coronary risk factors. These factors act conjointly with multiple thrombosis and
inflammatory risk factors in precipitating various manifestations of atherosclerosis.

**Figure 12** Urbanisation is the proximate ......

![Diagram showing the urbanisation process and its effects on health]

(Adopted from *Type 2 Diabetes in South Asians: Epidemiology, Risk Factors and Prevention under the Aegis of SASAT*)

**OBESITY AND CENTRAL OBESITY IN INDIA**

In India, the prevalence of overweight and obesity is on the last century focus of health care in India was on problems related to malnutrition and infections. However, with evolving epidemiological transition and demographic change, the problems of malnutrition have receded and phase of chronic degenerative diseases has taken over.
Increasing body weight and abnormal fat distribution are consequences of the changed socioeconomic circumstances.

CHILDHOOD-OBESITY

There has been a recent interest in life-course approach to obesity. Barker and his group have hypothesized that many adult diseases such as atherosclerotic cardiovascular disease, hypertension, diabetes, chronic lung diseases and central adiposity have roots in foetal development. Foetal malnutrition leads to faulty programming and endothelial dysfunction, lipid abnormalities, abnormal adipocyte distribution, pancreatic beta cell dysfunction and alveolar hypoplasia and result in their lifetime deficiency. As the child grows rapidly due to supportive environmental conditions, there is a mismatch of cellular demands and supply resulting in premature disease conditions of different kinds. There is evidence in India that the thrifty phenotype exists in rural populations and urban slums.

Childhood obesity is a new epidemic worldwide. In recent years due to burgeoning fast food industry in developed countries, the problem of obesity in children has emerged as a major problem and it has been estimated that more than 50% of children in USA and many western European countries are either overweight or obese. In the US, prevalence of individuals doubled among children 6 to 11 years of age between the second National Health and Nutrition Examination Surveys (NHANES) between 1976 and 1980 and the third NHANES conducted in 1999 and 2000. A similar trend has been observed in Japan and frequency of obese school children (>120% standard body
weight) aged 6-14 years increased from 5 to 10% between 1974 and 1993.150

In developing countries such as India, especially in urban populations, childhood obesity is emerging a major health problem.152 Studies from metropolitan cities in India have reported a high prevalence of obesity among affluent school children.153-160 On the other hand some studies reported a high prevalence of undernutrition among rural school children and children in urban slums.161-163 It can be said that children in developing countries presently suffer from double jeopardy of malnutrition-urban children are afflicted with problems of overnutrition while rural and slum children suffer from effects of undernutrition.161,164

EPIDEMIOLOGY OF OBESITY IN INDIA

India is currently experiencing a rapid epidemiological transition which has resulted in increased life expectancy and decreased mortality due to communicable diseases. As a consequence of industrialization and urbanisation, there has also been an increase in the standard of living, leading to a nutritional transition with consumption of diets that are energy dense and high in fat and content. Moreover, with changes in occupation from predominantly agriculture based manual labour jobs to sedentary office type jobs; there is a perceptible decrease in physical activity. This is the basis for the rapid weight gain and obesity seen in several parts of the subcontinent.

There is paucity on nationwide data on the prevalence of obesity. However, studies in different states of India provide some clues
regarding the magnitude of the health threat due to this problem. Table 12 provides the published data on obesity from different studies \(^{165-171}\) which shows that the prevalence of obesity ranges from 10 to 50%.

**Table 12** Prevalence of obesity in India

<table>
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<tr>
<th>Author</th>
<th>City/Centre</th>
<th>n</th>
<th>Prevalence of Obesity (%)</th>
<th>Male</th>
<th>Female</th>
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<tr>
<td>Dhurandhar et al, 1992(^{165})</td>
<td>Bombay</td>
<td>1784</td>
<td>10.7-53.1</td>
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<tr>
<td>Gopinath et al, 1994(^{166})</td>
<td>Delhi</td>
<td>13414</td>
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<td>Zarger et al, 2000(^{5})</td>
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<td>Gopalan, 1998(^{168})</td>
<td>Nutrition Foundation of India</td>
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<td>Survey, 1998(^{169})</td>
<td>Rural (n=142220)</td>
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<td>0.7</td>
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<td>Urban (n=35621)</td>
<td>0.4</td>
<td>0.7</td>
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<tr>
<td>National Family Health Survey,</td>
<td>-</td>
<td>-</td>
<td>2.2</td>
<td></td>
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<tr>
<td>2001(^{170})</td>
<td></td>
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<tr>
<td>Mohan et al, 2001(^{171})</td>
<td>Chennai Urban Population</td>
<td>1262</td>
<td>22.8</td>
<td>31.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td></td>
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<tr>
<td></td>
<td>Abdominal obesity</td>
<td>21.5</td>
<td>36.5</td>
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</tbody>
</table>

However, the only nationwide study is the national health survey on women and this revealed a low prevalence rate.\(^{170}\) According to the
Nutrition Foundation of India the prevalence of obesity is 1% for males and 4% for females in the slums while the corresponding figures for the middle socioeconomic class was 32.2% and 50% respectively.\textsuperscript{168}

In the Chennai Urban Population Study (CUPS),\textsuperscript{171-174} over 35% of the males in the middle-income group were obese compared to 13% in the low-income group. The corresponding figures for females were 33% and 24% respectively.\textsuperscript{171} Abdominal obesity among the middle income was 47.4% compared to 19.2% in the low-income group.

The rising prevalence of obesity has several health consequences as obesity is a predecessor for many related conditions like diabetes, dyslipidaemia, hypertension and coronary heart disease.

**ASIAN INDIAN (SOUTH ASIAN) PHENOTYPE**

For several years it has been recognized that south Asians (subjects originating in India, Pakistan, Srilanka, Bangladesh and Nepal) have certain unique clinical and biochemical characteristics that are collectively referred to as the “Asian Indian phenotype” (Figure 12) Despite relatively lower prevalence rates of obesity as defined by body mass index (weight in kg/height in square metres), they tend to have larger waist measurements and waist:hip ratios.\textsuperscript{175} and thus have a greater degree of central body obesity. This is associated with a characteristic metabolic profile with higher plasma insulin levels,\textsuperscript{176} a greater of degree of insulin resistance as measured by glucose clamp studies\textsuperscript{177} and a higher prevalence of diabetes.\textsuperscript{178}
Figure 12 Asian Indian phenotype

Greater ethnic/genetic susceptibility to type 2 diabetes

↑ Inflammatory markers, CRP

Lower Threshold for body mass index (BMI)

↑ Serum Insulin Levels/Insulin resistance

↑ Abdominal obesity and abdominal fat

↓ Levels of adiponectin

Increased prevalence of type 2 diabetes and coronary artery disease (CAD)

Characteristic dyslipidemia: ↓ HDL cholesterol and ↑ triglyceride & ↑ small dense LDL
Further, Indians also tend to have excess body fat and particularly abdominal and truncal adiposity. For any given waist circumference they also have increased body fat and moreover for any given body fat, they still have increased insulin resistance.\textsuperscript{179-181}

**PATTERN OF BODY FAT DISTRIBUTION**

It is now becoming increasingly clear that the regional distribution of fat plays a major contributory role for metabolic abnormalities. Research during the last two decades has suggested that the distribution of adiposity is important in understanding the association of obesity with disturbances in metabolism, particularly those of glucose and lipids. Abdominal adiposity assessed using waist circumference is considered to be more appropriate than generalized adiposity assessed by BMI.\textsuperscript{182-184} However, while the waist circumference gives us an overall indication of accumulation of total body fat in the abdomen, it does not distinguish between the different fat depots this is discussed in some detail below.

Over 65\% of the body is subcutaneous, nearly 20\% is abdominal and the rest is intramuscular, hepatic fat, etc. Abdominal fat plays a major role in metabolic abnormalities.\textsuperscript{185} Abdominal fat includes intra-abdominal fat (visceral) which constitutes approximately 80\% and the rest as subcutaneous fat. However, the proportion may vary greatly in different individuals.
OBESITY AND DIABETES

Several cross-sectional epidemiological studies suggest that obesity and abdominal obesity are strongly linked to diabetes.\textsuperscript{186-188} Indeed, obesity is considered to be the link between insulin resistance and metabolic abnormalities which includes diabetes, hypertension and dyslipidaemia, all of which are risk factors for coronary artery disease\textsuperscript{188} (Figure 13). Evidence for the link between obesity and diabetes, comes from the epidemiological and intervention studies with weight reduction as the main target. The Diabetes Prevention Programme demonstrated that a 7\% reduction in body weight by exercise and diet could prevent diabetes in subjects with impaired glucose tolerance by as much as 58\%.\textsuperscript{189} The Finnish Diabetes prevention study also showed similar findings.\textsuperscript{190} A study on Japanese women suggested that reducing the intra-abdominal fat to 60 cm\textsuperscript{2} was beneficial in reducing cardiovascular risk factors.\textsuperscript{191}

OBESITY AND DIABETES—INDIAN SCENARIO

In the Chennai Urban Population Study (CUPS), the prevalence of diabetes increased with in increase in quartiles of body mass index (BMI), the prevalence being 2.9\%, 8.1\%, 17.6\% and 19.5\% in the first, second, third and fourth quartile of BMI respectively. Prevalence of diabetes in subjects with abdominal obesity was significantly higher compared to those without abdominal obesity (27.8\% vs 9.0\%).
Figure 13 Adipose tissue – adverse effects

Adipose tissue
Accumulation

Adipocytokines

Inflammatory markers
TNF α, IL6 & CRP

↑FFA

Insulin Resistance

Diabetes

Dyslipidemia

Hypertension

Atherosclerosis
(CAD)

(Adopted from Type 2 Diabetes in South Asians: Epidemiology, Risk Factors and Prevention under the Aegis of SASAT)
The prevalence of impaired glucose tolerance (IGT) also with increase in quartiles of body mass index being 2.2%, 3.2%, 5.9% and 12.1% in the first, second, third and forth quartiles of BMI respectively and the increase was statistically significant (Trend chi square: 29.9, p<0.001). Prevalence of IGT in subjects with abdominal obesity (15.0%) was also significantly higher compared to subjects without abdominal obesity (2.6%). Body mass index showed a strong association with glucose intolerance both in Univariate and multiple logistic regression analysis. Moreover, even at lower BMI, categorized as low-risk according to WHO guidelines, the prevalence of diabetes was high among urban Indians.174

ADIPOSITY AND DIABETES

Fat storages in adipose tissue have been shown to be liked to insulin resistance and diabetes (Figure 13). Though studies have shown both total fat and visceral fat to be associated with diabetes, visceral fat is considered to be more important as it has been shown to have a strong correlation with glucose intolerance and insulin resistance.192,194 The visceral fat stored beneath the muscles and wrapped around the internal organs is considered to be the most 'atherogenic, 'diabetogenic, and 'hypertensiogenic, fat depot of the human body.192-194 However, this is still a debated issue with some authors suggesting that subcutaneous fat is more strongly associated with diabetes while others reported that visceral fat is a stronger risk factor for diabetes.195-197
VISCERAL FAT AND DIABETES

Three pathological mechanisms have been proposed to explain the association of visceral fat with diabetes. The first is based on the common soil hypothesis according to which visceral fat is simply a marker for some underlying genetic/environmental factors that lead to diabetes. The second mechanism suggests that visceral fat is uniquely deleterious because of its anatomical site with its direct venous drainage to the liver. Increased supply of FFAs to Liver increases hepatic insulin resistance. Finally visceral fat depot may produce metabolic markers and factors, which are directly involved in the pathological sequale of diabetes.

Cnop et al.\textsuperscript{197} in a cross-sectional study done on 174 individuals suggested that visceral fat was the best variable predicting insulin sensitivity which explained 54% of the variance in insulin sensitivity. Park et al, \textsuperscript{198} in a euglycaemic clamp study on nine young men suggested that insulin sensitivity correlated with both subcutaneous and visceral fat. Among Japanese, visceral fat was identified as a predictor of impaired glucose intolerance even after adjusting for total fat and subcutaneous fat.\textsuperscript{197, 198}

Metabolically, visceral fat is considered to be more active in producing free fatty acids (FFAS). Further pharmacological interventions support that visceral fat could be more active as interventions with insulin sensitizers like glitazones reduce visceral fat, but increase subcutaneous fat.\textsuperscript{199-202}
ASSOCIATION OF VISCERAL FAT WITH DIABETES—INDIAN SCENARIO

Very few studies in Indians have looked at visceral fat. A study in southern part of India suggested that visceral fat correlated with insulin secretion. Misra et al. showed a strong relation between subcutaneous fat with glucose disposal but this which was done using MRI which focused more on subcutaneous fat than on visceral fat. Anjana et al. studied visceral and subcutaneous fat in 82 type 2 diabetic and 82 age and sex matched non-diabetic subjects in the CURES study. Computed tomography (CT) was widely used to assess visceral fat and dual energy X-ray absorptiometry (DEXA) was used to assess the total and central abdominal fat.

It was found that diabetic subjects had significantly higher visceral fat (measured by CT) and central abdominal fat (measured by DEXA) compared to non-diabetic subjects. However, Subcutaneous abdominal fat, Visceral to subcutaneous abdominal fat and visceral to total fat ratio measured by CT showed no significant difference. Similarly with DEXA, total body fat and non-abdominal fat did not differ significantly between diabetic and non-diabetic subjects but abdominal fat was significantly greater in the diabetic group. Abdominal obesity indices as such waist and sagittal abdominal diameter showed a strong correlation with visceral fat and central abdominal fat both in diabetic and non-diabetic subjects. Logistic regression analysis revealed visceral fat (Odds ratio (OR): 1.011, p=0.004) and central abdominal fat (OR: 1.001, p=0.013) to be associated with diabetes even after adjusting for age and gender. However, subcutaneous abdominal fat did not show a significant association with diabetes.
ENDOCRINE ACTIVITY OF ADIPOSE TISSUE

Adipose tissue is considered as an endocrine organ which is the principle site for energy storage. Adipose tissue also influences the insulin action by release of FFA and by increased secretion of adipose-derived proteins. These adipose-derived proteins are pro-inflammatory peptides and have an adverse effect on glucose metabolism and insulin action (fig 14). The raised level of free fatty acids (FFA) – lipotoxicity, is implicated in inducing the acquired defect in beta cell function and progressive deterioration from IGT stage to diabetes. Experimentally also, the lipotoxicity effect has been proved. Islets culture with elevated levels of fatty acids develop beta cell dysfunction reminiscent of that in type 2 DM namely, lowered glucose-induced insulin release, impaired proinsulin synthesis and accelerated beta cell apoptosis. All these abnormalities are due to lower expression of IDX-1, (also called PDX-1) which is a key transcription factor for beta cell development, glucose metabolism and proinsulin synthesis.

An important concept is the recognition of adipose tissue as a metabolically active organ. It is not simply a storage depot for excess energy in the form of lipid, which undergoes lipolysis when energy intakes are low. Adipose tissue is active in maintaining an overall energy balance for human subjects in the face of excessive energy intakes and expenditures. The accumulation of lipid and development of adipose tissue triggers a release of several cytokines, adipocytokines, which act in the promotion of energy expenditure. These adipocytokines include leptin, tumour necrosis factor-alpha, monocyte chemoattractant protein, resistin, plasminogen activator inhibitor, angiotensinogen and interleukin-6. Adiponectin moves in the
opposite direction with a reduction in plasma levels with the accumulation of adipose tissue.

**Figure 14** Role of Adipocyte Secretion in Insulin Resistance

Together, these adipocytokines induce a complex set of responses which act in the protection of non-adipose tissues from excess energy releases, in the form of hyperglycaemia as one example, and promote energy balance through the dispensation of excess energy. This is an important function as the release of large amounts of excess energy can be detrimental to tissues. In general, energy release is highly regulated by control mechanisms.\(^{209}\)
However, significant variation occurs as a result of energy demands and pathologic conditions. The adipocytokines can dampen the detrimental effect of this excessive energy release.

TUMOR NECROSIS FACTOR (TNF)

TNF-alpha levels increase with the amount of adipose tissue. It is produced by both visceral and subcutaneous fat, but adipose tissue is not the only source of TNF-alpha. Immune and inflammatory cells produce TNF-alpha. It acts as a controller of inflammatory responses; it induces the synthesis and secretion of a wide range of cytokines involved in inflammation. In a similar manner, IL-6 is involved in the control of inflammatory responses. Only 30% of IL-6 is produced by adipose tissue and it is produced primarily by visceral fat. IL-6 and TNF-alpha levels are correlated with obesity and insulin resistance. TNF-alpha is associated, independent of insulin sensitivity with cardiovascular disease and endothelial dysfunction.

LEPTIN

Leptin is produced by adipocytes and is released into the circulation. It has several systemic effects, but most importantly influences the hypothalamus and induces a decrease in food intake, an increase in energy expenditure, an increase in glucose and fat metabolism and alters neuroendocrine function. Leptin levels increase in BMI above the ideal range. Obese individuals often have levels 3-4 times those of individuals with a more ideal weight. Leptin resistance may contribute toward these high levels and reduce the effectiveness of leptin in promoting energy balance. Interestingly, leptin is produced primarily
by subcutaneous fat, which may partially explain the higher levels in women than men. Gender and fat mass are the primary determinants of leptin levels.\textsuperscript{210}

Insulin resistance is another significant contributor to leptin levels.

RESISTIN

Resistin is a 10KDa adipose tissue-specific hormone. Resistin is also secreted by adipocyte. Resistin is named for its putative role in mediating insulin resistance in obesity. Its role and possible effect on insulin signaling is not yet elucidated. Resistin has inhibitory effect on hepatic rather than the peripheral insulin sensitivity.

Another adipocyte-produced cytokine is PAI-1. It has a positive correlation with BMI and obesity. Weight loss produces a reduction in the plasma levels of these cytokine. PAI-1 may have a role in the reduction of insulin sensitivity that accompanies of weight gain.

ADIPONECTIN

Adiponectin is a 30KDa adipose-specific secretory protein. Adiponectin is an adipocyte product that appears to ameliorate insulin resistance in both muscle and liver. Low circulating level of this hormone is found in obesity and insulin resistance. Decreased plasma level of the adiponectin contributes to pathogenesis of insulin resistance and type 2 DM.
ADIPONECTIN AND DIABETES IN INDIANS

Migrant Indian studies have documented that Indians have low levels of adiponectin, which is considered to play a major role in contributing to metabolic abnormalities. In CURES, adiponectin was estimated in 200 individuals with and without diabetes. Adiponectin values were significantly lower in diabetic subjects (males: 5.2 µg/ml vs 8.3 µg/ml, p=0.001, females: 7.6 µg/ml vs 11.1µg/ml, p<0.001) compared to non-diabetic subjects. Adiponectin clustered with metabolic abnormalities and showed a strong positive association with HDL cholesterol. A prospective study done in India also showed that lower adiponectin levels predicted future development of type 2 diabetes. It seems likely that lower adiponectin may at least in part explain the high risk for insulin resistance, diabetes and dyslipidaemia (particularly low HDL levels) among Indians.

INSULIN RESISTANCE IN OBESITY

Mechanisms of insulin resistance in obesity are multiple. Obesity adds to the genetic predisposition of insulin resistance in Type 2 DM. This most likely occurs through the production of some inhibitors of insulin action by the fat cell. These inhibitors might include free fatty acids (FFA), tumor necrosis factor – alpha (TNF – alpha), and the appetite – regulating hormone leptin. Tumor necrosis factor – alpha inhibits the insulin receptor kinase by increasing the serine phosphorylation of insulin receptor substrate type 1. Free fatty acids have been postulated to produce insulin resistance by several mechanism. FFA inhibits insulin stimulated glucose uptake at the level of glucose transport/phosphorylation. It also inhibits insulin stimulated glucose
synthesis and insulin stimulated glucose oxidation. There is an increased delivery of FFA's to the liver and this in turn results in accumulation of triglycerides and ultimate increase in hepatic glucose output (fig 15). The accumulation of triglycerides in muscles is the common link between insulin resistance and FFA in type 2 DM, obesity and syndrome X.

**Figure 15** Mechanism of Insulin Resistance Initiated by FFA

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)

**CONCLUSIONS**

Further studies in the identification of risk factors, including genetic factors, the endocrine activities of adipose tissue, the identification of mechanisms of obesity actions in diabetes, and the prevention of
diabetes by alterations in exercise and dietary intakes will lead to the
development of methods for the prevention of diabetes in the Indian
population. Thus, further research in these areas is needed and should
progress rapidly in the near future to aid the prevention of the
impending epidemic of diabetes and its associated diseases.
HYPERTENSION

INTRODUCTION

Hypertension and diabetes mellitus are interrelated diseases, which, if untreated, strongly predispose to atherosclerotic cardiovascular disease. Lifestyle and genetic factors are important in the genesis of both conditions. Diabetes mellitus and hypertension coexist three times more commonly than predicted by chance. Hypertension is twice as prevalent among diabetic patients when compared to the general population. Hyper tension occurs more frequently in persons with type 1 diabetes mellitus, than in those with type 2 diabetes mellitus. It is seen in almost all the patients who develop nephropathy. The prevalence of hypertension in type 2 diabetes increases with age, which is about 40-60% in the age range of 45 to 75 years. The development of type 2 DM is 2.5 times more likely in hypertensive patients than in normotensive persons within 5 years. In type 2 DM, hypertension antedates the diagnosis of diabetes by years and even decades, 8 times more frequently than the reverse. Hypertension is more prevalent in diabetic men than women before the age of 50 years, and reverse is true after the age of 50 years. In obese diabetic patients, who account for 90% of patients with type 2 DM, hypertension is more common than obese persons without diabetes. This connection is even stronger in those who have truncal obesity along with the “Dysmetabolic Syndrome” of insulin resistance.

ETIOLOGY OF HYPERTENSION IN DIABETES

1. Essential hypertension accounts for the majority of hypertension in persons with diabetes, particularly in those with type 2
diabetes, who constitute more than 90 percent of those with a dual diagnosis of diabetes and hypertension.

2. Diabetic nephropathy, which commonly occurs after 15 years of diabetes in one of three persons with type 1 diabetes and one of five persons with type 2 diabetes, appears to be another important cause of hypertension.

3. Dysmetabolic Syndrome X in which hypertension is associated with insulin resistance and glucose intolerance (including type 2 diabetes mellitus), a characteristic dyslipidemia (hypertriglyceridemia, low HDL cholesterol, high LDL, excess small, dense LDL particles), truncal obesity, procoagulant changes (elevated plasminogen activator inhibitor-I and fibrinogen) and hyperuricemia.

4. Secondary hypertension

a. Endocrine diseases causing both hypertension and diabetes eg. Cushing's syndrome, Conn's syndrome, pheochromocytoma, acromegaly

b. Hypertension due to diabetic complication: Besides diabetic nephropathy, repeated pyelonephritis can give rise to chronic pyelonephritis and end stage renal disease.

c. Drugs causing hypertension and diabetes eg. Oralcontraceptives, glucocorticoids.

d. Antihypertensive drugs causing diabetes: potassium losing diuretics eg. thiazides (especially chlorthalidone), beta-blockers, diazoxide
5. Isolated systolic hypertension due to accelerated atherosclerosis is an important feature in diabetes mellitus.

PREVALENCE OF HYPERTENSION IN INDIA

India leads the world with the largest number of diabetic subjects and is also projected to have the maximum number of cardiovascular deaths 15 years from now. Both these diseases are associated with hypertension, hence a thorough knowledge of the epidemiology of hypertension in India would be of great use in prevention of these diseases. Though hypertension is an ancient disease, reported centuries ago in India, there have been very few nationwide epidemiological studies on this disease. However, sporadic studies from different regions clearly suggest a rising prevalence in hypertension. In 1942, Chopra and Chopra reported on this problem for the first time in India on a large sample of 10,000 individuals. Studies by Vakil demonstrated prevalence of hypertension to be more among urban residents. A recent meta-analysis based on medline database, showed a rising prevalence of hypertension among Indians. Several studies have reported on the overall prevalence of hypertension in various regions of India which has been summarized in Table 24.1.

It is estimated that nearly 55 million Indians are currently affected by hypertension. Using a cut-off of 160/95 mm Hg for diagnosis of hypertension, studies conducted in 1950s in urban Indian populations revealed that the prevalence of hypertension ranged between 3.03 to 6.19%. Using the same criteria the prevalence increased to 6.43% and 10.9-12.8% in 1990. Based on the revised
diagnostic BP criteria of 140/90 mmHg, studies from Mumbai have reported a prevalence rate of 26.9-36.4%\textsuperscript{238,240} while in Jaipur, it was 36.9%.\textsuperscript{239}

Cross-sectional surveys conducted in women in different cities from five different regions of India showed that the prevalence of hypertension was in Thiruvananthapuram (30.7%) and Mumbai (28.0%, compared to Moradabad (22.6%), Nagpur (24.2%) and Calcutta (19.1%). The overall prevalence of hypertension in the five cities was 25.6%. Isolated diastolic hypertension was the most common form of hypertension (50.5%) reported in these five Indian cities.\textsuperscript{244}

The overall crude prevalence of hypertension (HTN) in CUPS was 21.1%.\textsuperscript{241} Prevalence of isolated systolic BP (SBP ≥ 140 and DBP < 90 mm Hg) and isolated diastolic BP (DBP ≥ 90 and SBP < 140 mm Hg) were 15.1% and 12.7% respectively.\textsuperscript{241} The prevalence of diabetes, obesity, CAD and peripheral vascular diseases were higher among the hypertensive individuals compared to normotensive group.\textsuperscript{241} The prevalence of hypertension in urban south Indians appears to be comparable to that reported in north India.

**RISK FACTORS FOR HYPERTENSION**

The common risk factors for hypertension includes family history of hypertension, increasing age, increased sodium intake, obesity, low birth weight, insulin resistance and lifestyle-related factors.\textsuperscript{245}
FAMILY HISTORY FOR HYPERTENSION

Clustering of hypertension within families has long been reported. The genetic contribution to the variability of blood pressure is estimated to range between 30-60%. A study on Australian children of age 9-18 years showed a clear influence of family history on the blood pressure. This study also revealed a stronger contribution from the father than from the mother. In the MONICA study, it was reported that subjects with both parents being hypertensive had a higher risk than those who had one hypertensive parent. Heritability of hypertension has been shown in various studies in the Western population. In the CUPS study the prevalence of hypertension among subjects whose parents had hypertension was significantly higher compared to subjects without family history of hypertension.

Familial aggregation points to the role of genes in hypertension although environmental factors cannot be excluded, e.g. excessive salt intake in some families. Various genes have been shown to be associated with hypertension, such as angiotensinogen, lipase, angiotensin converting enzyme, beta-2-adrenergic receptor and alpha 2-receptor genes. Though familial clustering has been well-documented for hypertension, it is considered to be an outcome of a strong gene-environment interaction as environmental factor, (e.g. increased salt intake ) and genetic disorders (e.g. obesity) can also cluster in families.
INCREASING AGE

Virtually all studies of blood pressure carried out in different populations including India have shown a rise of blood pressure with age in both men and women,\textsuperscript{255} and the rise is particularly seen in systolic blood pressure.\textsuperscript{256} Increasing age showed a strong association with the prevalence of hypertension in the CUPS study. Overall hypertension, isolated systolic hypertension as well as diastolic hypertension increased with increasing age (Table 24.2) the probable reason is that aging decreases arterial elasticity and this leads to metabolic alterations and changes in sympathetic nerve activity, which could result in elevated blood pressure.

SODIUM INTAKE

Numerous studies have shown the strong relationship between dietary salt intake and hypertension.\textsuperscript{257-260} In epidemiological surveys significant correlations between the level of salt intake and hypertension have been well-established.\textsuperscript{257-260} The strongest evidence arises from the INTERSALT study, which suggested that as the sodium intake increases the blood pressure increased.\textsuperscript{259} Impairment of renal dopaminergic response, impaired nitric oxide modulation and alteration in sympathetic activity have been suggested as the mechanisms linking salt intake and hypertension.\textsuperscript{260}

OBESITY

Obesity is considered to be a major risk factor for hypertension.\textsuperscript{261} Total 70\% of hypertension among males and 61\% among females was attributed to excess adiposity in the Framingham study,\textsuperscript{262} Kannel\textsuperscript{262}
reported that for every 4.5 Kg increase in body weight, systolic blood pressure increased by 4.5 mm Hg. The INTERSALT study also showed a strong association between body mass index and blood pressure. Furthermore, in a large cross-sectional study on 14,000 US residents aged between 45 to 64 years, blood pressure was found to be associated with body mass index and upper body obesity. Leptin and insulin resistance are considered to be the links between blood pressure and obesity.

LOW BIRTH WEIGHT

According to the Barker hypothesis, low birth weight (LBW) predisposes to adult onset metabolic diseases. Such an association has been well-documented for diseases like diabetes and to some extent for CAD. Observational studies have shown low birth weight to be associated with blood pressure. In contrast, Law et al showed that for every 1 kilogram rise in birth weight the systolic blood pressure decreased by 5.2 mm of Hg in 64 to 71-year-old subjects. The proposed mechanism is that LBW would lead to structural changes of blood vessels and kidneys, which can alter endothelial function and renal development resulting in hypertension. Evidence for this mechanism comes from a study, which showed that the elasticity of aorta is related to birth weight.

INSULIN RESISTANCE

Clustering of insulin resistance with hyperinsulinaemia, hypertension (HTN), glucose intolerance, increased triglycerides, decreased HDL cholesterol levels, central and overall obesity is termed as the insulin
resistance syndrome (IRS) or the metabolic syndrome. Reports suggest that IRS is associated with hypertension. Peripheral insulin resistance and hyperinsulinaemia have been shown to impair insulin-mediated renal sodium reabsorption, which may contribute to hypertension. Hyperinsulinaemia also results in vascular overactivity due to sympathetic. Increased Erythrocyte Na/Li counter transport has been reported in insulin resistant states associated with hypertension. Furthermore, insulin has been shown to reduce intracellular influx of calcium ions, which in turn increases vascular smooth muscle calcium efflux and circulating ionized calcium, which could be related to hypertension. In CUPS, “insulin resistance cluster” rather than insulin resistance per se showed a strong association with hypertension.

LIFESTYLE FACTORS

The epidemic of non-communicable disease like diabetes and hypertension has been attributed to the rapid epidemiological transition occurring in developing countries. Lifestyle changes like Westernised diets, with increased consumption of dietary fat and calories and sedentary lifestyle and decreased physical activity have led to shift in health burden from communicable diseases to non-communicable diseases. The influence of urbanisation on hypertension was clearly seen in the ‘CUPS’ study, where the prevalence of hypertension was 1.5 times higher among middle-income group compared to low-income group (14.9% vs 8.4%, p<0.001). The influence of physical activity was also computed in the CUPS, which showed prevalence of hypertension...
to be much higher among subjects with light activity compared to heavy physical activity.

Behavioural factors like smoking and alcohol use have also been reported to be associated with hypertension. A prospective study on 40,000 US women concluded that alcohol consumption is one of the strongest predictors for hypertension along with age and weight. Smoking seems to be associated with insulin resistance and induces endothelial dysfunction, which results in increased blood pressure. In fact these behavioural factors are associated with psychological factors like stress, hopelessness and depression.

**IMPORTANCE OF SYSTOLIC BLOOD PRESSURE**

Impressive evidence has accumulated to warrant greater attention to the importance of SBP as a major risk factor for CVDs. Changing patterns of BP occur with increasing age. The rise in SBP continues throughout life in contrast to DBP, which rises until approximately age 50, tends to level off over the next decade, and may remain the same or fall later in life.

Diastolic hypertension predominates before age 50, either alone or in combination with SBP elevation. The prevalence of systolic hypertension increases with age, and above 50 years of age, systolic hypertension represents the most common form of hypertension. DBP is a more potent cardiovascular risk factor than SBP until age 50; thereafter, SBP is more important.
Clinical trials have demonstrated that control of isolated systolic hypertension reduces total mortality, cardiovascular mortality, stroke, and HF events.\textsuperscript{285-287}

Both observational studies and clinical trial data suggest that poor SBP control is largely responsible for the unacceptably low rates of overall BP control.\textsuperscript{288,289}

In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) Trial, DBP control rates exceeded 90 percent, but SBP control rates were considerably less (60–70 percent).\textsuperscript{290,291}

Poor SBP control is at least in part related to physician attitudes. A survey of primary care physicians indicated that three-fourths of them failed to initiate antihypertensive therapy in older individuals with SBP of 140–159 mmHg, and most primary care physicians did not pursue control to <140 mmHg.\textsuperscript{292,293}

Most physicians have been taught that the diastolic pressure is more important than SBP and thus treat accordingly. Greater emphasis must clearly be placed on managing systolic hypertension. Otherwise, as the United States population becomes older, the toll of uncontrolled SBP will cause increased rates of CVDs and renal diseases.
HYPERTENSION AND DIABETIC COMPLICATIONS

An estimated 35 to 75 percent of diabetic complications can be attributed to hypertension. The macrovascular and microvascular complications of diabetes are increased further when hypertension accompanies diabetes. Patients who have both diabetes and hypertension have more renal disease and atherogenic risk factors, including dyslipidemia, hyperuricemia, elevated fibrinogen, and left ventricular hypertrophy. Hypertension contributes to the leading causes of morbidity and mortality in persons with diabetes, including coronary heart disease, stroke, peripheral vascular disease, lower extremity amputations, and end-stage renal disease. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that each 10 mm Hg decrease in SBP was associated with average reduction in rates of diabetes-related mortality by 15%; myocardial infarction by 11%; and the microvascular complication of retinopathy or nephropathy by 13%. The presence of microalbuminuria in type 1 DM precedes nephropathy and is also a marker for coronary artery disease. The progression to diabetic retinopathy is also hastened by hypertension. Therefore simultaneous control of BP and blood glucose is very important in patients with diabetes and hypertension for decreasing cardiovascular events and other diabetic risk and outcomes.

AWARENESS OF HYPERTENSION AND 'RULE OF HALVES' IN URBAN INDIA

Despite hypertension being one the foremost risk factors for CVD and overwhelming evidence that reduction of blood pressure has a great
Impact on the prevention of fatal and nonfatal CVD events, the management of hypertension has remained sub-optimal even developed countries. The level of control of hypertension in the community is assessed by the “Rule of halves” according to which half of the hypertensives remain undiagnosed, only half of those diagnosed are treated and only half of those treated actually have their blood pressure under control. Many studies have made an attempt to assess control of hypertension in the population using the “rule of halves”. The validity of this rule has, however, often been questioned. A Finnish study suggests that awareness of hypertension tends to be high and that rule of halves may not be valid in developed countries but may be still valid in developing countries. An Italian study, however, confirmed that rule of halves is valid in their population while a Belgian study suggested that the rule of halves was no longer valid in their population. In CUPS, more than 60% of the hypertensive were detected previously undiagnosed; 50% of the known hypertensive subjects received some kind of treatment and among them only 40% had their blood pressure under control. Though the level of treatment and control of hypertension are comparable with other studies, awareness seems to be very low among Indians showing that unfortunately the rule of halves is still valid in India.

SCREENING FOR HYPERTENSION IN DIABETES

All diabetic patients must be regularly screened for hypertension and vice versa. Obese hypertensives or those receiving antihypertensives that can raise blood glucose should be screened for diabetes at least once every year. If blood glucose is raised, these potentially
diabetogenic drugs should be changed, by which normoglycemia may be restored.

All diabetic patients with other cardiovascular risk factors such as nephropathy, obesity, dyslipidemia, smoking and poor glycemic control should also be checked frequently for hypertension.

GOAL FOR LEVELS OF BLOOD PRESSURE TO BE ACHIEVED

The NHLBI (JNC) and American Diabetes association (ADA) has recommended a goal BP of less than 130/80 mm Hg in patients with diabetes and hypertension. Data supporting this are found in the following studies:

1. The United Kingdom Prospective Diabetes Study (UKPDS) observed that near optimal control of hypertension (144/82 mm Hg) led to 44 percent fewer diabetes-related strokes, 37 percent fewer cases of microvascular disorders due to diabetes (particularly diabetic retinopathy) and 32 percent fewer diabetes-related deaths.

2. The results of the Hypertension Optimal Treatment (HOT) randomized trial showed that in patients with diabetes mellitus there was a 51% reduction (p=0.005) in major cardiovascular events in target Diastolic BP group less than 80 mm Hg compared with target group of less than 90 mm Hg.

3. A meta-analysis of multiple prospective randomized studies of more than 12 months duration reviewed the effect of drug treatment on morbidity and mortality in diabetic hypertensive
persons. This analysis concluded that antihypertensive treatment to less than 130/85 mm Hg reduces the risk for cardiovascular events\(^5\).

4. Subanalysis of the diabetic cohort in the Sys-Eur trial suggests that further reduction in diastolic blood pressure below 85 mm Hg is beneficial. While systolic blood pressure was reduced by a comparable amount in each group (22±16 mm Hg, nondiabetic vs 22.1±14 mm Hg, diabetic group), the risk reduction in mortality from CVD was 13% for the nondiabetic and 75% for the diabetic patients. Thus, the benefit conferred per mm Hg blood pressure reduction appears to be greater in persons with type 2 diabetes than in those with hypertension but no coexistent diabetes mellitus.

**ANTIHYPERTENSIVE PHARMACOLOGICAL THERAPY**

JNC 7 has recommended that hypertensive persons with target organ damage / clinical cardiovascular disease and / or diabetes should be promptly initiated on pharmacotherapy in order to protect the heart, brain, kidney and the vascular tree against arteriosclerotic damage, which is the main cause of mortality in types 1 & 2 diabetes mellitus.

**CONCLUSION**

Diabetes and hypertension frequently coexist and predispose to atherosclerotic cardiovascular disease and renal failure. There is a high prevalence of both diabetes and hypertension in the Indian population. This is attributed to the high prevalence of Dysmetabolic Syndrome X in Indians. Antihypertensive therapy must be promptly instituted in all
diabetic patients with any degree of high blood pressure. The target BP for diabetic patients is lower than in the remaining population of hypertensive. All major classes of antihypertensive drugs are appropriate to treat hypertension in diabetic patients, but ACE inhibitors are special.
DYSLIPIDEMIA

INTRODUCTION

Lipid disorders are not uncommon in diabetes. 50% of diabetic patients are dyslipidemic and abnormalities are more common in type 2 than in type 1 diabetes mellitus. They may arise from a lack (in type 1 diabetes) or a defect in the action (in type 2 diabetes) of insulin; in type 2 diabetes part of the problem may be a causally independent component of the ‘metabolic/dysmetabolic syndrome’. Besides, an individual with diabetes may also have some form of familial/genetic dyslipidaemia.

Whatever the mechanism, they contribute importantly to the considerable increases in the risk of atherosclerosis and consequent mortality in diabetes. In the Framingham study it was documented that the incidence of cardiovascular disease in diabetic men was twice that among non-diabetic men, and in diabetic women it was about three times.306 The absolute risk of cardiovascular death has been found to be much higher for diabetic than non-diabetic people in the large Multiple Risk Intervention Trial, irrespective of the presence of other risk factors.307

NATURE OF DYSLIPIDEMIA IN DIABETES

LIPID DISORDERS IN DIABETES

The lipid abnormalities associated with diabetes are better termed as ‘dyslipoproteinemia’ or ‘dyslipidemia’, rather than ‘hyperlipoproteinemia’ or ‘hyperlipidemia’, because there may be
changes in both the quantity and quality of the lipoproteins. The two main determinants of these changes are the type of diabetes and the degree of glycemic control.

DYSLIPIDEMIA IN TYPE 2 DIABETES

Dyslipidemia is more frequent in type 2 diabetes and is a major contributor to the high risk of CAD seen in this condition.

QUANTITATIVE CHANGES

The most frequent form of quantitative dyslipidemia is increased triglycerides.\textsuperscript{308-310} The United Kingdom Prospective Diabetes Study (UKPDS) has shown that the hypertriglyceridemia of the type 2 diabetes is already present at the time of diagnosis.\textsuperscript{311} In fact, this has been noted in the prediabetic phase as well.\textsuperscript{312} This is also influenced by the presence of other factors unrelated to hyperglycemia or insulin resistance, e.g., presence or absence of nephropathy, obesity, hypothyroidism, the frequent occurrence of genetically determined lipoprotein disorders (familial combined hyperlipidemia or familial hypertriglyceridemia), alcohol and estrogen usage.

The other quantitative dyslipidemia associated with type 2 diabetes is low HDL cholesterol concentration. In the multivariate analysis, the male diabetic had lower HDL-cholesterol levels than corresponding non-diabetic subjects after adjusting for other variables.\textsuperscript{313} UKPDS confirmed this and found the abnormalities more commonly in diabetic females.\textsuperscript{314} The Prospective Cardiovascular Munster (PROCAM) study in the German population also noted the prevalence of HDL cholesterol
in diabetic subjects. The same feature was over again noted in a Finnish population study. The future risk for CAD death in the study was found to be two fold to four fold higher in diabetic subjects with low HDL cholesterol than in diabetic patients without it. Other studies noted that it is the HDL2 sub-fraction which is specially depressed in the high-risk population with CAD in diabetes. The low HDL cholesterol may persist despite achievement of glycemic control.

Total and LDL cholesterol concentration in diabetics most often approach those in non-diabetic, especially on achievement of good metabolic control.

The similarity of plasma total cholesterol levels in type 2 diabetes and in those without diabetes should not lead one to conclude that cholesterol has no coronary risk effect in diabetics. The Multiple Risk Factor Intervention Trials has shown that the incidence of coronary mortality increases in a curvilinear manner with increasing concentrations of serum cholesterol both in those with and in those without diabetes. The two curves were similar in shape but differed, with the curve for those with diabetes being higher than the curve for those without. At any given serum cholesterol concentration, those with diabetes had a risk of CAD mortality between two and four times greater than those without diabetes. There may be several reasons for this. First, the level of cholesterol in serum reflects the level of all lipoproteins, not just LDL. Thus an elevation of serum cholesterol may, in part, indicate an increase in the triglyceride-rich lipoproteins as well. Second, there may be many non-lipoprotein atherogenic factors e.g. advanced glycation end products that might increase the risk in
diabetes. Third, LDL may be modified in a way that would make any given amount more atherogenic such as glycation and oxidation. Another aspect also needs mention. The LDL cholesterol concentration is usually calculated by Friedewald formula [LDL cholesterol= (total cholesterol- (HDL cholesterol + triglycerides/5)) (all concentrations in mg/dl). However, in diabetes the calculated LDL cholesterol correlates poorly with that actually determined by ultracentrifugation, probably because of changes in cholesterol:triglycerides ratio in VLDL.319

QUALITATIVE CHANGES

LDL distribution is tilted towards smaller and denser LDL3 particles (LDL B phenotype) which have greater atherogenic potential.320 Feingold et al found that normolipidemic men with diabetes have two-fold increase in the percentage of individuals with the LDL B phenotype compared with normolipidemic men without diabetes.321 In the Kaiser Permanents Women Twins Study, prevalence of LDL phenotype B has been found to be an integral feature of insulin resistance syndrome322 Conversely, subjects with predominance of small LDL had a greater than twofold increased risk of developing type 2 diabetes mellitus over a follow-up period of 3.5 years.323

HDL particle show enrichment in triglycerides, increased cholesterol to protein ratio and a selective reduction of apo AI. There is also increased glycosylation of apo AI and AII, which appears to accelerate HDL catabolism so that there is rapid clearance before they have circulated long enough to acquire sufficient cholesterol to become
HDL2. Glycosylation of HDL probably also impairs its ability to promote cholesterol efflux from cells in vitro. 

Lp (a) is of special interest in type 2 diabetes because of its known association with CAD. Studies have shown higher levels, no difference and even lower levels in type 2 diabetic. However, most of the studies on Lp (a) and type 2 diabetes are small and except for a few do not account for the apo (a) phenotype, which is a major determinant of Lp (a) concentration. The consensus appears to be that the diabetic state does not have any impact on Lp (a) concentration, though diabetic patients with CAD have been found to have higher Lp (a) concentration than those without CAD. A recent study from South India echoes the same conclusion that in diabetic population Lp(a) is an independent risk factor for CAD, though the level is not increased.

Diabetic subjects have been found to have greater glycation of LDL particles, which are more susceptible to oxidation. Increased oxidized LDL has also been found in diabetic subjects.

MECHANISM OF DYSLIPIDAEMIA IN TYPE 2 DIABETES

Insulin resistance, which is important in the genesis of type 2 diabetes itself, can also cause hypertriglyceridaemia and the preponderance of small dense LDL particles may be explained in terms of hypertriglyceridemia.
HYPERINSULINEMIA, DYSLIPIDEMIA AND CAD

It is common knowledge that insulin resistance and the compensatory hyperinsulinaemia (if pancreatic β-cells are competent) are associated with an atherogenic plasma lipid profile, comprising elevated triglycerides and depressed HDL cholesterol levels. A number of prospective studies, albeit in non-diabetic subjects, have also found plasma insulin to be an independent and statistically significant correlate of CAD. This naturally raises the important issue of the long-term safety of the use of insulin in type 2 diabetes, where hyperinsulinaemia is already believed to exist. However, administration of insulin to both insulin-dependent (i.e. insulinopenic) and non-insulin-dependent (i.e. hyperinsulinemic) diabetics (to control hyperglycemia) or indeed to non-diabetic subjects produces a decrease in serum triglycerides levels.\textsuperscript{334} Also, insulinoma is associated with low plasma concentrations of triglycerides.\textsuperscript{335} Hence direct role of Hyperinsulinemia in the genesis of hypertriglyceridemia has been questioned. It is insulin resistance rather than consequent hyperinsulinemia that may be consists as the cause of high triglyceridemia.

Moreover, in the UKPDS the intensive glycemic control group, many of whom were treated with insulin, far showing increased CAD mortality actually showed a non-significant 16% decrease.\textsuperscript{308}

DYSLIPIDEMIA IN TYPE 1 DIABETES
It differs from that in type 2 diabetes in two important respects:

a. It is closely related to the degree of glycemic control
b. Low HDL cholesterol is not a feature (in the absence of renal involvement)

In poorly controlled type 1 diabetics the characteristic lipid abnormality is increased triglycerides. This can be well explained by absolute deficiency of insulin. As expected the level normalizes with adequate insulinization.

In the Wisconsin Epidemiological Study on Diabetic Retinopathy (WESDR) the mean levels of total and HDL cholesterol were similar in type 1 diabetic subjects and age matched control population. In the DCCT population (n=1569), lipids and lipoproteins were similar to nondiabetic subjects participating in the Lipid Research Clinics Program.

In fact, type 1 diabetic subjects who are in good control tend to have normal (and sometimes even better than normal) levels of lipoproteins (lower levels of triglyceride and cholesterol and higher levels of HDL cholesterol). Regarding qualitative changes in plasma lipids it may be noted that LDL size is not different in type 1 diabetes mellitus compared to controls. However, type 1 diabetic subjects have an increased cholesterol to triglyceride ratio in VLDL particles which may not resolve with intensive insulin therapy.

Lp(a) levels have been variously reported as high or normal in type 1 diabetes.

Presence of nephropathy (even at the stage of microalbuminuria) adversely affects practically all aspects of lipid profile leading to
elevation of LDL cholesterol, VLDL triglycerides and reduction of HDL cholesterol, particularly HDL \textsuperscript{2}.\textsuperscript{341}

**DYSLIPIDEMIA IN 'MALNUTRITION RELATED DIABETES'**

WHO recognized malnutrition related diabetes mellitus as a separate type of diabetes in 1985. These patients tend to have rather low levels of cholesterol and triglycerides, which may partly explain their low rates of macrovascular disease. However, current view tends to be against identifying this as a separate class of diabetes.

**DIABETIC DYSLIPIDEMIA IN ASIAN INDIANS**

In an analysis in UKPDS cohort followed up for nine years, it was noted that the Asian Indian population cohort had lower total cholesterol, LDL cholesterol and HDL cholesterol, but higher triglyceride compared to the White Caucasian and Afro-Caribbean cohort. This probably signifies that the Asian Indians are more insulin resistant, a fact that has been proved in many other studies comprising multi-ethnic population.\textsuperscript{342}

During the follow-up period of nine years, the Asian Indians showed a similar decrease of total and LDL cholesterol as well as of triglyceride level compared to the WC and AC peer cohorts, but there was no significant change in HDL cholesterol level, which showed an upward trudge in the other groups. This was seen despite a less significant increase in body weight and marginal worsening of blood pressure and glycemic parameters amongst the cohorts. The lipid changes were not
related to the lipid lowering therapy because less than 2% of the population was receiving it.

CONCLUSION

Cardiovascular complication in 2 diabetics is pretty common, which has been documented in various large prospective trials. This is not decreased by strict glycemic control alone. Dyslipidemia in the form of increased triglyceride and decreased HDL cholesterol has been noted to be a common occurrence in type 2 diabetics. Increased LDL cholesterol has been implicated as the etiological agent in the causation of atherosclerotic vascular disease. In diabetics, apart from the genetic dyslipidemic phenotype, qualitative change in LDL cholesterol (LDL B phenotype and oxidized LDL) has also been implicated as the cause of increased incidence of cardiovascular complications. The decreased HDL cholesterol concentration also contributes to the increased incidence of cardiovascular disease. Insulin resistance and/or hyperinsulinemia has been implicated as the etiological phenomenon behind the increased triglyceride and decreased HDL cholesterol concentration. In type 1 diabetics, HDL cholesterol does not decreased and lipid disorder is closely related to degree of hyperglycemia. All type 2 diabetics should undergo annual lipid check up for cholesterol, triglyceride and HDL cholesterol. The treatment goals for diabetics with or without CAD is stricter compared to people without diabetes. The ADA recommendation for treatment of dyslipidemia in diabetics harps on LDL lowering.
DIABETES RISK SCORES

The recent epidemiological studies have thrown light on the peculiarities in the risk factors for diabetes in the Indian population. It has also helped to identify the modifiable risk factors such as obesity whereby preventive strategies could be evolved. Recently, risk scores have been developed specifically for the Indian population based on the risk assessments made in epidemiological studies. The risk score developed by Ramachandran et al is shown in Table 13. This simple score can be used in any clinic setting without any special investigation.

Table 13 Diabetes Risk Score

<table>
<thead>
<tr>
<th>Variables</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(30-44) yrs</td>
<td>10</td>
</tr>
<tr>
<td>Age (45-59) yrs</td>
<td>18</td>
</tr>
<tr>
<td>Age(&gt;59) yrs</td>
<td>19</td>
</tr>
<tr>
<td>FH – DM</td>
<td>7</td>
</tr>
<tr>
<td>BMI(&gt;=25)</td>
<td>7</td>
</tr>
<tr>
<td>Waist(M&gt;85, F&gt;80)</td>
<td>5</td>
</tr>
<tr>
<td>Sedentary Physical</td>
<td>4</td>
</tr>
<tr>
<td><strong>Maximum Score</strong></td>
<td><strong>42</strong></td>
</tr>
</tbody>
</table>

An ROC procedure showed a cutoff score of ≥21 having sensitivity and specificity close to 60%
METABOLIC SYNDROME

INTRODUCTION

In the developed countries the atherosclerosis risk factor model has moved away from the conventional tobacco-cholesterol risk model in the early parts of twentieth century to hypertension-diabetes model presently. On the other hand, in developing countries, such as India, both the models coexist—the tobacco-cholesterol model is important in rural and low socioeconomic status urban subjects, while in most urban regions of India and other parts of the developing world the hypertension-metabolic syndrome diabetes risk model has become pre-eminent.

In 1988, Gerald Reaven is generally credited with introduction of the concept of ‘Syndrome X’, a term used to denote the clustering of cardiovascular risk factors like central body obesity, hypertension, glucose intolerance, high triglycerides and low HDL cholesterol concentrations. The syndrome is however, much older, having been already observed in 1923 by Kylin, who described the clustering of hypertension, hyperglycaemia and gout as a syndrome.

Subsequently, several other metabolic abnormalities have been added to the syndrome, including obesity, microalbuminuria and abnormalities in fibrinolysis and coagulation. Several terms are used for the same entity namely; Syndrome X, Reaven’s syndrome, New World syndrome, CHAOS, Civilization syndrome, Deadly Quartet, Pluerimetabolic syndrome, Insulin resistance syndrome, Dysmetabolic syndrome and more recently the Metabolic syndrome.
The term 'Metabolic Syndrome (MS)’ currently is used to refer to the clustering of metabolic risk factors including abdominal obesity, atherogenic dyslipidaemia, hypertension, glucose intolerance and a prothrombotic proinflammatory state.\textsuperscript{352}

Several epidemiological studies have confirmed the occurrence of the metabolic syndrome in various ethnic groups including Caucasians, African Americans, Mexican Americans, Asian Indians, Chinese, Aboriginals, Polynesians and Micronesians. Lifestyle changes resulting from industrialization and migration to urban environments from rural settings, declining levels of physical activity, increased calorie intake with consequent rise in the rates of obesity have led to a huge increase in the numbers of people with metabolic syndrome particularly in developing countries.

Individuals with MS have two times higher risk for mortality due to myocardial infarction or stroke and three times as likely to develop, myocardial infarction or stroke compared to people without MS. Further they have a five-fold risk of developing type 2 diabetes (if not already present).\textsuperscript{353} MS has been indicated to be a risk factor and predictor for cardiovascular disease (CVD)\textsuperscript{354} and cardiovascular mortality.\textsuperscript{355}

**INSULIN RESISTANCE AND THE METABOLIC SYNDROME**

Insulin resistance is considered as the primary defect in the pathophysiologial mechanism underlying the development of the syndrome. The recent evidence suggests a possible role for inflammation and endothelial dysfunction in this process. The clustering of metabolic and
pro-thrombotic cardiovascular risk factors in the metabolic syndrome reflects genetic-environmental interactions which are also likely to influence the risk of developing athero-thrombotic vascular disease (figure 16).

**Figure 16** ‘Common Soil’ in the pathogenesis of the metabolic syndrome

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)
INSULIN RESISTANCE AND THE METABOLIC SYNDROME: EPIDEMIOLOGICAL DATA

Inordinately high prevalence of cardiovascular risk factors, their clustering, and high mortality due to CAD in south Asians was initially reported from UK in 1980s. Particularly abdominal obesity, hyperinsulinaemia and dyslipidaemia in south Asians were significantly more than British Caucasians.\textsuperscript{356-361}

Further, lower adiponectin levels in south Asians as compared to white Caucasians have been reported.\textsuperscript{362-364}

Most UK investigators have investigated south Asians consisting of Bangladeshis, Pakistanis and Asian Indians (predominantly Punjabis and Gujaratis).

As opposed to UK, research on migrant south Asians in USA has been carried out during last couple of years. Most studies are either hospital-based or convenience samples, and deal mostly with Asian Indians. As compared to white Caucasians, higher prevalence of T2DM, hypertriglyceridaemia, obesity and lower levels of high-destiny lipoprotein cholesterol (HDL-C) were seen in Asian Indian physicians and their relatives.\textsuperscript{365}

Diabetes among Indian Americans study, a population-based study among migrant Asian Indians in US showed high prevalence of hyperglycaemia (T2DM, 25%, impaired glucose tolerance 8%) and risk factors comprising metabolic syndrome. In particular, low HDL-C levels
and hypertriglyceridaemia were prevalent in both genders and abdominal obesity was particularly prevalent in women. Nearly 1/5th of subjects had 3 or more risk factors.\textsuperscript{366}

Overall, prevalence of the metabolic syndrome in migrant south Asians varies from 20-32\% (Table 14).

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study group</th>
<th>Geographical location</th>
<th>Definition of metabolic syndrome</th>
<th>Prevalence</th>
<th>Other observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tillin et al\textsuperscript{462}</td>
<td>South Asians vs. multiple ethnic groups</td>
<td>London, United Kingdom</td>
<td>WHO and NCEP</td>
<td>WHO: M,46%; F,31% NCEP: M,29%; F,32%</td>
<td>MS prevalence highest in south Asians, associated with CAD in men</td>
</tr>
<tr>
<td>Tan et al\textsuperscript{463}</td>
<td>Asian Indians vs. Chinese and Malays</td>
<td>Singapore</td>
<td>NCEP and modified NCEP\textsuperscript{b}</td>
<td>M:21.7%, F:19.3%</td>
<td>MS most common in Asian Indians</td>
</tr>
<tr>
<td>Misra et al\textsuperscript{464}</td>
<td>Asian Indians</td>
<td>Multiple sites, USA</td>
<td>NCEP</td>
<td>M:21 5%, F:19.2%</td>
<td>Low HDL-C particularly prevalent in women</td>
</tr>
<tr>
<td>Anand et al\textsuperscript{465}</td>
<td>South Asians vs. Chinese, Europeans, and native Indians</td>
<td>Multiple sites, Canada</td>
<td>NCEP</td>
<td>M: 23.4%, F:28.3%</td>
<td>People with MS had more severe atherosclerosis and increased PAI-1 levels</td>
</tr>
</tbody>
</table>

\textsuperscript{b} Includes modified criteria for waist circumference for Asian populations; WHO-World Health Organization; NCEP-National Cholesterol Education Programme, Adult Treatment Panel III; MS- The metabolic syndrome; CAD-Coronary heart disease; HDL-High density lipoprotein cholesterol; M-Male; F-Female; PAI-1 – Plasminogen activator inhibitor-1.
The prevalence of insulin resistance as measured by surrogate markers in Asian Indians residing in India ranges from 20 to 55%. The variations in the prevalence rates are due to considerable heterogeneity of the population and socioeconomic strata (SES) of the sample populations. The prevalence of insulin resistance is higher in the people belonging to high SES and urban population as compared to those belonging to low SES and rural population, respectively. Prevalence of the metabolic syndrome as defined by National Cholesterol Education Programme, Adult Treatment Panel III (NCEP, ATP III) and other criteria indicates ranges from ~11 to ~41%.

Interestingly, high prevalence of cardiovascular risk factors and the metabolic syndrome (~12%) have been recorded in intracountry rural-to-urban migrant population belonging to low SES residing in urban slums. Further, certain communities in India (e.g. Punjabi Bhatia community) have inordinately high tendency to have obesity, T2DM, and the metabolic syndrome.

While these studies show high prevalence of the metabolic syndrome in Asian Indians living in India, truly representative data from all regions of India are not available. Further, most investigators have not studied rural population which constitute ~70% of the population of India, and children and women.

The metabolic syndrome will likely increase further in the next several years, primarily because of the rapid increase in obesity. The health problems related to the metabolic syndrome will likely escalate dramatically.
AGE TRENDS

The prevalence of the metabolic syndrome is highly age dependent. A prevalence of 7 percent among adults 20–29 years of age rises to 40 percent or more among Americans over age 60.

CLINICAL IMPACT

The metabolic syndrome is associated in men with a fourfold increase in risk for fatal CAD, and a twofold greater risk of CVD and all-cause mortality, even after adjustment for age, LDL cholesterol, smoking, and family history of CAD. The metabolic syndrome is associated with increased CAD risk in women. Patients with the metabolic syndrome have a five- to ninefold increased risk of developing diabetes.

METABOLIC SYNDROME-A PREDICTOR OF CARDIOVASCULAR DISEASE

The relation of insulin resistance to cardiovascular risk, particularly to coronary artery disease (CAD) has been well-established in many prospective studies in the West. In 1,209 Finnish men and 42–60 years, the 10- year CVD risk was increased 2.1- and 2.5- fold with the ATPIII and WHO MS definitions, respectively. The same study found that the risk of death from CVD was increased by 2.63-2.96 times and the risk of death from may cause was increased 1.87-2.11 times with the presence of the MS. The MS alone predicted~25% of all new-onset CVD. The DECODE study reported that the presence of MS increased all-cause and CVD mortality by 1.2-2.8 times. In the WOSCOPS (West of Scotland Coronary Prevention Study), MS as
defined by ATPIII definition was associated with a 1.8-fold increase in CAD risk, but after adjusting for other risk factors, a more modest 1.3-fold increase was observed. In the Botnia study, in patients with MS, the relative risk of CAD was 2.96 (95% CI, 2.36-3.72; p<0.001) and cardiovascular mortality was significantly increased to 12%, compared with 2.2% in subjects without MS (p<0.001).

INSULIN RESISTANCE IN INDIAN CHILDREN

There are conflicting reports regarding insulin levels in south Asians neonates as compared to white Caucasians but higher magnitude of hyperinsulinaemia has been in 8-10 years old south Asian children as compared to British Caucasian children. In India, high prevalence of fasting hyperinsulinaemia has been reported by our group in the post-pubertal urban children and young adults, particularly girls. In a study on limited number of subjects in USA, young adult Asian Indians had the highest levels of post-prandial insulin and low insulin sensitivity as compared to four other ethnic groups. The relationship of adiposity and fasting hyperinsulinaemia was also stronger for pre-pubertal South Asian children as compared to white Caucasian children. A recent study from UK suggests that ethnic differences in insulin sensitivity between south Asians and white Caucasians could be explained by ethnic differences in body fat.
BODY FAT DISTRIBUTION OF INDIANS: RELATIONSHIP WITH INSULIN RESISTANCE AND OTHER CARDIOVASCULAR RISK FACTORS

EXCESS BODY FAT

The average value of body mass index (BMI) in south Asians is lower than that seen in white Caucasians. Mexican-Americans and Blacks. Value of BMI in Asian Indians, however, increases as they become affluent and urbanized.

Several distinctive features of body composition of south Asian have been recorded. Most investigators agree that south Asians have high percentage of body fat.\textsuperscript{389,390,392-401} For example; despite lower average BMI value, the migrant Asian Indians have higher percentage of body fat as compared to white Caucasians and Blacks (Table 15).\textsuperscript{389} Further, as compared to white Caucasians, Asian Indians also have lower muscle mass.\textsuperscript{391,402}

Table 15 Average values of various measures of obesity in south Asians/Asian Indians and other ethnic groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Asian Indians</th>
<th>Migrant*</th>
<th>White Caucasians</th>
<th>Blacks</th>
<th>Mexican Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rural</td>
<td>Urban slums</td>
<td>Urban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>19.6</td>
<td>20.9</td>
<td>22.4</td>
<td>24.7</td>
<td>26.3</td>
</tr>
<tr>
<td>Percentage of body fat</td>
<td>20.4</td>
<td>24.4</td>
<td>28.2</td>
<td>33.1</td>
<td>26.6</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>79.4</td>
<td>83.7</td>
<td>85.2</td>
<td>83.7</td>
<td>91.3</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.87</td>
<td>0.92</td>
<td>0.87</td>
<td>0.92</td>
<td>0.91</td>
</tr>
</tbody>
</table>
IMPACT OF BODY MASS INDEX ON THE RISK OF DEVELOPING COMMON CHRONIC DISEASES

Table 16 shows relative 10-year risk for diabetes, hypertension, heart disease, and stroke over the next decade among men initially free of disease stratified by baseline body mass index.

Table 16: Relative 10-year risk and baseline body mass index

<table>
<thead>
<tr>
<th>BMI</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Heart Disease</th>
<th>CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–21.9</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>22.0–24.9</td>
<td>1.8</td>
<td>1.5</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>5.6</td>
<td>2.4</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>30.0–34.9</td>
<td>18.2</td>
<td>3.8</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>&gt;35.0</td>
<td>41.2</td>
<td>4.2</td>
<td>2.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

BMI, body mass index; CVA, cerebrovascular accident


ABDOMINAL OBESITY

High prevalence of abdominal obesity is particularly characteristic of the south Asians and uniformly recorded by several investigators. Abdominal adiposity has also been reported among those with BMI < 25 kg/m². Further, although the average waist circumference in south Asians appears to be lower, abdominal adiposity is significantly more than white Caucasians.
TRUNCAL SUBCUTANEOUS FAT

A particularly distinctive body composition feature seen in South Asians is thick subcutaneous adipose tissue as highlighted by the investigators who used skinfold measurements in their investigations.\textsuperscript{418,419,420,421-424}

Higher insulin resistance in a BMI-matched Asian Indian men than white Caucasians in USA could only be explained by higher truncal skin folds in the former.\textsuperscript{425} Mishra also observed significant associations of truncal skin fold thickness with fasting hyperinsulinaemia in children and adolescent.\textsuperscript{426} Further, Mishra measured subcutaneous and intra-abdominal Fat with magnetic resonance imaging, insulin resistance as assessed by short insulin tolerance test correlated significantly to subcutaneous fat only and not intra-abdominal fat. Interestingly, thicker subcutaneous fat in Asian Indians has been recorded at birth, and associated with higher insulin levels when compared to British neonates.\textsuperscript{427}

Overall, investigators believe that thick truncal subcutaneous tissue is a particular distinctive features of obesity phenotype of Indians and important correlate of insulin resistance seen in this ethnic group.

INDIANS ARE METABOLICALLY OBESE

Indians can be classified as metabolically obese,\textsuperscript{428} i.e. they have multiple metabolic derangements but are ‘non-obese’ by conventional BMI standards. These ‘non-obese’ people usually have high body fat, abdominal adiposity and specifically in south Asians, thick truncal
subcutaneous fat. These body composition characteristics individually, or in combination contribute to insulin resistance, dyslipidaemia, hyperglycaemia, and excess procoagulant factors in Indians.429-437

RELATIONSHIP OF INSULIN RESISTANCE TO C-REACTIVE PROTEIN IN INDIANS

C-reactive protein (CRP) is a marker of sub-clinical inflammation. High levels of CRP have been shown to predict CAD 438 and T2DM.439,440 Investigators from developed countries have shown that CRP levels correlate to insulin resistance and the metabolic syndrome.441-444

Table 17 Associations of insulin resistance and other cardiovascular risk factors in Indians

<table>
<thead>
<tr>
<th>Factors with evidence of positive association</th>
<th>Factors with weak/no evidence of association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess body fat</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>Intramyocellular triglycerides</td>
</tr>
<tr>
<td>High truncal subcutaneous fat</td>
<td>Leptin</td>
</tr>
<tr>
<td>Low birth weight</td>
<td></td>
</tr>
<tr>
<td>High levels of procoagulant factors</td>
<td></td>
</tr>
</tbody>
</table>

A complex interplay of genetic, metabolic and environmental risk factors resulting in insulin resistance, the metabolic syndrome, T2DM and CAD are shown in Figure 17.
OVERVIEW OF METABOLIC SYNDROME

Over the past two decades, there has been a striking increase in the number of people with MS in developing countries. However, precise figures of its prevalence are generally not available, as there is no internationally agreed definition for the syndrome. Different definitions of MS have been laid down by the World Health Organization (WHO), European Group for the study of Insulin Resistance (EGIR), National Cholesterol Education Programme and Adult Treatment Panel III (NCEP-ATPIII) and recently by the International Diabetes Federation (IDF) (Table 18).
Table 18 Definitions of the metabolic syndrome

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Obesity Body mass index</td>
<td>Not used for diagnosis</td>
<td>Not used for diagnosis</td>
<td>&gt;= 30 kg/m²</td>
</tr>
<tr>
<td>2</td>
<td>Abdominal Obesity</td>
<td>Waist Circumference Males &gt;= 90cm Females &gt;=80 cm</td>
<td>Waist Circumference Males &gt;= 102 Females&gt;= 88</td>
<td>Waist to Hip ratio Males &gt;0.90 Female &gt; 0.85</td>
</tr>
<tr>
<td>3</td>
<td>Blood pressure</td>
<td>SBP &gt;=130 and/or DBP &gt;= 85 or on medication</td>
<td>SBP &gt;= 130 and/or DBP &gt;=85 or on medication</td>
<td>SBP &gt;=140 and/or DBP&gt;=90 or on medication</td>
</tr>
<tr>
<td>4</td>
<td>FPG</td>
<td>&gt;=5.6mmol or preexisting diabetes</td>
<td>&gt;=6.1mmol or on medication for diabetes</td>
<td>Diabetes, impaired glucose tolerance or insulin resistance</td>
</tr>
<tr>
<td>5</td>
<td>Microalbuminuria</td>
<td>Not used for Diagnosis</td>
<td>Not used for Diagnosis</td>
<td>Urinary albumin excretion rate &gt;=20mcg/min</td>
</tr>
<tr>
<td>6</td>
<td>TG</td>
<td>&gt;=1.7 mmol/L</td>
<td>&gt;=1 7 mmol/L</td>
<td>TG&gt;=1.7mmol/L And/or HDL-C &lt;0.91 mmol/L (Male), &lt;1.01 mmol/L (Female)</td>
</tr>
<tr>
<td>7</td>
<td>HDL</td>
<td>Males&lt;1.04mmol/L Female&lt;1.3mmol/L</td>
<td>Males&lt;1.04mmol/L Female&lt;1.3mmol/L</td>
<td>Diabetes, impaired glucose tolerance or insulin resistance plus any tow or more risk factors</td>
</tr>
</tbody>
</table>

While most definitions agree on essential components, i.e. glucose intolerance, obesity, hypertension and dyslipidaemia, they differ in the cut-points for criteria of each component of the cluster and the way of combining them to define MS. The definition used in the WHO report, centres on diabetes and insulin resistance, whereas, the ATPIII guidelines gives equal weightage to abdominal obesity, hypertension, hyperglycaemia, hypertriglyceridaemia and low HDL cholesterol.

The NCEP,ATP III definition of the metabolic syndrome is based on simple clinical and biochemical parameters, which could be measured
in any clinic or a simple laboratory. Other available definitions of the metabolic syndrome include measures which are expensive and difficult to analyse; fasting hyperinsulinaemia, microalbuminuria, etc.

Many investigators feel that NCEP, ATP III definition of the metabolic syndrome is not optimal for identification of risk for T2DM or CAD, and does not identify the metabolic syndrome correctly in Indians. Most important limitation is the cut-off points of waist circumference (men ≥ 102 cm and women, ≥ 88cm) for diagnosis of abdominal obesity are not applicable for Indians. Waist circumferences-morbidity correlation studies in Asian Indians, and other Asian ethnic groups show that waist circumference cut-off points should be lower.449,450

The International Diabetes Federation has revised the guidelines to remedy the ethnic group based disparities in the original classification (Table 19).451

The consensus was that metabolic syndrome as defined the US National Cholesterol Education Programme was a pragmatic approach and it was agreed that other definitions unnecessarily highlight diabetes and insulin resistance. Central obesity as assessed by waist circumference was agreed as essential because of the strong evidence linking waist size with multiple metabolic syndrome components.

This definition included three major modifications as compared to NCEP, ATP III definition; (a) Central obesity has been made a mandatory variable, (b) The cut-offs of waist circumference have been lowered (male 94 cm, Female 80 cm), and made ethnicity-specific (e.g. for south Asians: male 90 cm, female 80 cm) and made ethnicity-specific (e.g. for south Asian: male 90 cm, female 80 cm)
and (c) Cut-off for fasting plasma glucose has been lowered to 100 mg/dl.\textsuperscript{452} (Table 19). Although this new definition will miss substantial number of subjects with impaired glucose tolerance it retains the simplicity of the US National Cholesterol Education Programme's definition. A recent population based study in south Indians compared the prevalence of metabolic syndrome using WHO, ATPIII and IDF definitions, the prevalence of metabolic syndrome were 23.2%, 18.3% and 25.8% respectively.\textsuperscript{453}

**Table 19** International Diabetes Federation metabolic syndrome definition (revised 2005)

<table>
<thead>
<tr>
<th>Central obesity according to the waist circumference</th>
<th>Ethic specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus any two of following four risk factors</td>
<td>South Asians: Men $\geq$ 90 cm; Women $\geq$ 80 cm</td>
</tr>
<tr>
<td></td>
<td>Europids: Men $\geq$ 94 cm; Women $\geq$ 80 cm</td>
</tr>
<tr>
<td></td>
<td>Chinese: Men $\geq$ 90 cm; Women $\geq$ 80 cm</td>
</tr>
<tr>
<td></td>
<td>Japanese: Men $\geq$ 85 cm; Women $\geq$ 90 cm</td>
</tr>
<tr>
<td></td>
<td>South and central Americans: as South Asians</td>
</tr>
<tr>
<td>Raised triglycerides</td>
<td>$&gt;150$ mg/dl</td>
</tr>
<tr>
<td>Reduced HDL cholesterol</td>
<td>$&lt;40$ mg/dl in men</td>
</tr>
<tr>
<td></td>
<td>$&lt;50$ mg/dl in women</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>Systolic $&gt;130$ mm Hg</td>
</tr>
<tr>
<td></td>
<td>Diastolic $&gt;85$ mm Hg</td>
</tr>
<tr>
<td></td>
<td>Treatment of previously diagnosed hypertension</td>
</tr>
<tr>
<td>Raised fasting plasma glucose</td>
<td>$&gt;100$ mg/dl</td>
</tr>
<tr>
<td></td>
<td>Previously diagnosed type 2 diabetes</td>
</tr>
</tbody>
</table>

Although the prevalence of MS varies according to the definition used, the WHO and ATPIII definitions appear to identify people at increased risk for developing cardiovascular disease and all-cause mortality and for developing diabetes. There are few reports on prevalence of MS
using all three definitions and none from India which currently has the largest number of people in the world with diabetes.\textsuperscript{454}

**DEFINITIONS IN CHILDREN**

There is lack of consensus regarding the criteria and appropriate cut-off points for various components of the metabolic syndrome in children and adolescents. Investigators have used percentile-based cut-off points, and other modifications of NCEP, ATP III criteria for defining the metabolic syndrome in children.\textsuperscript{455,456}

**STUDIES ON METABOLIC SYNDROME IN INDIANS**

There is scarcity in data on the prevalence of MS in Indians; the few available studies are based on ATPIII criteria and one study using EGIR criteria. An earlier study in urban Indian adults aged 20-75 years, reported a prevalence of MS to be 1.1\% using NCEP definition.\textsuperscript{457} The age-adjusted prevalence of MS based on ATPIII criteria in Jaipur (urban north Indian population) was 24.9\%.\textsuperscript{458} Using EGIR criteria, the Chennai Urban Population Study (CUPS), reported an overall prevalence of MS to be 11.2\% with a significant difference between the middle income (18.7\%) and low income groups (6.5\%).\textsuperscript{459}

Singapore National Health Survey, revealed a higher prevalence of MS among the Asian Indians (28.8\%), compared to Malays (24.2\%) and Chinese (14.8\%).\textsuperscript{460} Prevalence rates of MS reported in Indians in Singapore are similar to that observed in the CURES study. The NHANES III in the US shows an age-adjusted prevalence of MS of 23.7\% as defined by ATPIII criteria.\textsuperscript{461}
TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

INTRODUCTION

Until very recently, Type 2 Diabetes has been thought to be a rare occurrence in children and adolescents. However, in the mid-1990s, investigators began to observe an increasing incidence of Type 2 diabetes worldwide.\textsuperscript{466} This is particularly the case in the USA\textsuperscript{467} but has also been reported in other countries such as Canada, Japan, Austria, the United Kingdom and Germany.\textsuperscript{466, 468-470}

This Observation followed a striking increase in both the prevalence and the degree of obesity in Children and adolescents in many populations.\textsuperscript{471} Overweight is at present the most common health problem facing children in both developed and developing countries. In some countries, the prevalence of obesity in childhood and adolescence has become higher than that of allergic disorders including both asthma and eczema. Worldwide, approximately 22 million children the age of 5 years are overweight and the prevalence of overweight in the young is increasing.\textsuperscript{472}

Type 2 diabetes is a serious and costly disease. The chronic complications of diabetes include accelerated development of cardiovascular disease, end-stage renal disease, loss of visual acuity and limb amputations. All of these complications contribute to the excess morbidity and mortality in individuals with diabetes. Superimposed on this disturbing picture in recent reports of the emerging problem of Type 2 diabetes in children and adolescents.
If the incidence and prevalence of Type 2 diabetes in children are increasing and if this increase cannot be reversed, our society will face major challenges. That is, the burden of diabetes and its complications will affect many more individuals than currently anticipated. And the cost of diabetes to our society will cause us to consume enormous resources.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

Type 2 diabetes is a complex metabolic disorder of heterogeneous aetiology with social, behavioural and environmental risk factors unmasking the effects of genetic susceptibility. There is a strong hereditary (probably multigenic) component to the disease, with the role of genetic determinants illustrated when differences in the prevalence of Type 2 diabetes in various racial groups are considered. The recent increase observed in diabetes prevalence are too quick to be the result of increased gene pool, emphasizing the importance of environmental factors.

Puberty appears to play a role in the development of Type 2 diabetes in children. During puberty, there is increased resistance to the action of insulin, resulting in hyperinsulinaemia. After puberty, basal and stimulated insulin responses decline. Hyperinsulinaemic-euglycaemic clamp studies demonstrate that insulin-mediated glucose disposal is on average 30 per cent lower in adolescents between Tanner stage II and IV compared with prepubertal children and with young adults. Increased growth hormone secretion in puberty is suggested to be responsible for the insulin resistance during puberty. Given this
information, it is not surprising that the age at presentation of Type 2 diabetes in children coincides with the usual age of mid-puberty.

The adverse effect of obesity on glucose metabolism is evident early in childhood. Obese children are hyperinsulinaemic and have approximately 40% lower insulin-stimulated glucose metabolism compared with non-obese children. Furthermore, the inverse relationship between insulin sensitivity and abdominal fat is stronger for visceral than for subcutaneous fat. In a seven-year longitudinal study of African-American and white young adults 18 years and older, the strongest predictor for increases in both insulin and glucose concentration was an increase in weight.\textsuperscript{466}

Racial differences in insulin sensitivity are also evident in childhood. African-American 7- to 11-year-old children have significantly higher insulin levels than age-matched white children. These data suggest that minority children may have a genetic predisposition to insulin resistance, which may increase their risk for Type 2 diabetes.

**EPIDEMIOLOGY OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS**

The limited amount of information about the epidemiology of Type 2 diabetes in children is in large part due to the relatively recent recognition of its emergence in this age group. In United States and in Canada Type 2 Diabetes in adolescents was found especially in specific ethnic subgroups. Being highest in pima Indians (22.3/1000 in 10-14-year-old children).\textsuperscript{467} The estimated prevalence of diabetes (all types) in adolescents has been estimated in the Third National Health and
Nutrition Examination survey (NHANES) to be 0.41 per cent and that of impaired fasting glucose 1.76 per cent. Recently, Sinha et al. investigated a multiethnic American cohort of 167 obese children and adolescents and found Impaired Glucose tolerance in more than 20% of the subjects and silent Type 2 diabetes in four subjects.\textsuperscript{474} Finally, in case series, Type 2 Diabetes constituted an increasing percentage of incident paediatric cases of newly diagnosed diabetes, with fewer than 4% reported before the 1990s and up to 45% in recent studies.\textsuperscript{467}

The emergence of type 2 diabetes in children is not limited to North America. In a screening study of diabetes by using an oral glucose tolerance test in cohort of 520 overweight children and adolescents of Caucasian origin between 9 and 20 years, in eight children (1.5%) diagnosis of diabetes Type 2 was suggested.\textsuperscript{470} The overall prevalence of elevated blood glucose levels was 7%. 4% of these patients had impaired fasting blood glucose and 2% of the patients showed an impaired glucose tolerance. Based on these data, it could be speculated that up to 15 000 overweight children suffering from Type 2 diabetes might be expected in Germany due to approximately 1 million obese children and adolescents. In contrast to this, only 130 children with Type 2 diabetes are documented in the standardized evaluation program 'dpv', which is used by most paediatric diabetologists in Germany.

**TYPE 2 DIABETES IN CHILDREN – INDIAN SCENARIO**

Recent studies in migrants in UK and USA,\textsuperscript{475} studies in India\textsuperscript{476} and Japanese\textsuperscript{477} show a rising trend in type 2 diabetes in children and adolescents. Overweight in childhood is a forerunner of overweight in
adulthood. The association of obesity with metabolic diseases such as diabetes and cardiovascular diseases is well-known. Reports of increasing overweight among children in urban India indicate that the epidemic of diabetes could become worse with the increasing epidemic of obesity now seen even among children. In a study in urban southern India, the prevalence of overweight was 17.8% among boys and 15.8% among girls aged 14-19 years.476 There was a strong association of overweight with lack of physical activity and higher socioeconomic group. Studies from India show fairly high prevalence of maturity-onset diabetes in the young (MODY) and also type 2 diabetes in children. With the emerging epidemic of diabetes and obesity, the prevalence of diabetes in children will also increase.

CLINICAL PRESENTATION OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

Obesity is the hallmark of Type 2 diabetes. Most children with Type 2 diabetes are overweight or obese at diagnosis and present with glucosuria without ketonuria, absent or mild polyuria and polydipsia and little or no weight loss. Currently. Children with Type 2 diabetes are usually diagnosed over the age of 10 years and are in middle to late puberty.

In the mildest Type 2 diabetes form, the diagnosis is made in an asymptomatic child during a routing medical check-up by detection of glucosuria and subsequent hyperglycaemia. One-third of patients are diagnosed by urine analysis during physical examination.473 In its severest form, the child presents with evidence of severe insulin deficiency polyuria. Polydipsia and weight loss. Up to 33% in particular
ethnic groups have ketonuria at diagnosis and 5-25% ketoacidosis at presentation. With this clinical picture, often the distinction from Type 1 diabetes is not possible until months later when insulin requirements decline and a non-insulin dependent course develops without dependence on insulin for survival.

Children with Type 2 diabetes usually have a family of Type 2 diabetes and those of non-European ancestry (Americans of African, Hispanic Asian and American Indian descent) are disproportionately represented. Of the patients, 74-100% have a first- or second-degree relative with type 2 diabetes of note diabetes in the parent or other relative may not be recognized until the child is diagnosed.

Acanthosis nigricans and polycystic ovarian syndrome (PCOS) disorders associated with insulin resistance and obesity are common in youth with Type 2 diabetes. Acanthosis is a cutaneous finding characterized by velvety hyper pigmented patches most prominent in the intertrigenous area, and is present in up to 90% of children with Type 2 diabetes. It is recognized more frequently in darker-skinned obese individuals. PCOS is a reproductive disorder characterized by hyperandrogenism and chronic anovulation. Lipid disorders and hypertension also occur in children with Type 2 diabetes.

**DIFFERENTIAL DIAGNOSIS OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS**

Individuals with Type 2 diabetes may have clinical presentations indistinguishable from those of patients with other types of diabetes. This is relevant because as the number of children with Type 2
diabetes increases it becomes increasingly important to classify their diabetes correctly so that appropriate therapy may be instituted.

Typically, children with type 1 diabetes are not overweight and have recent weight loss, polyuria, and polydipsia (see Table 20). They usually have a short duration of symptoms and frequently have ketosis; 30% have ketoacidosis at presentation. After metabolic stabilization, they may have an initial period of diminished insulin requirement, after which they require insulin for survival. Of children with Type 1 diabetes, 5% have a first-or second-degree relative with the same disease.

Children with idiopathic Type 1 diabetes may be difficult to distinguish from those with Type 2 diabetes. The majority of those described with idiopathic Type 1 diabetes has what has been termed atypical diabetes mellitus and are African-American. Their family history is positive for early-onset diabetes in many relatives in multiple generations. Insulin may not be required for survival after the resolution of the acute metabolic deterioration. Metabolic control, however, is poor without insulin therapy, and ketoacidosis may occur.

Maturity-onset diabetes of the young (MODY) is another rare form of diabetes in children, which includes several disorders caused by monogenic defects in beta cell function. MODY 2 (defect in glucokinase) and MODY 3 (defect in HNF1α) are the most frequent types of MODY. Patients with MODY have a dominant genetic trait, usually are nonobese and have low fasting insulin levels. Recent studies suggest that the clinical presentation of MODY is broad,
ranging from asymptomatic hyperglycaemia to a severe acute presentation. MODY has been reported in all races/ethnicities.

Table 20 Clinical characteristics of Type 1, Type 2 and MODY diabetes mellitus.

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Type 1 diabetes m.</th>
<th>Type 2 diabetes m.</th>
<th>MODY diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age when diagnosis is established</td>
<td>Preschool-adolescents</td>
<td>&gt;10 years</td>
<td>MODY 2: youth MODY 3: adolescents</td>
</tr>
<tr>
<td>Obesity</td>
<td>uncommon</td>
<td>common</td>
<td>uncommon</td>
</tr>
<tr>
<td>Gender</td>
<td>Male=female</td>
<td>Female&gt;male</td>
<td>Male=female</td>
</tr>
<tr>
<td>Relatives</td>
<td>5% Type 1 d.m.</td>
<td>75-100% Type 2 d.m.</td>
<td>100% MODY</td>
</tr>
<tr>
<td>Population</td>
<td>Predominantly Caucasian</td>
<td>Predominantly Americans of African, Hispanic, Asian and American Indian origin</td>
<td></td>
</tr>
<tr>
<td>Beta-cell autoantibodies</td>
<td>85-98%</td>
<td>uncommon</td>
<td>uncommon</td>
</tr>
<tr>
<td>Insulin, C-peptide</td>
<td>low</td>
<td>high</td>
<td>Low</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>frequently</td>
<td>&lt;33%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Associated disorders</td>
<td>Autoimmune disorders (thyroid, adrenal, vitiligo), celiac disease</td>
<td>Acanthosis nigricans PCOS Metabolic syndrome</td>
<td></td>
</tr>
</tbody>
</table>

These gene abnormalities are thought to be rare, and molecular diagnostic testing, currently only available in research laboratories, is required for specific classification. Until such testing becomes commonplace, children with MODY should be classified as having the type of diabetes that best fits their clinical picture.

**DIAGNOSTIC CRITERIA OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS**

Diagnostic Criteria of Type 2 Diabetes Mellitus in Children and Adolescents are the criteria for the diagnosis of diabetes recommended by WHO.
In most patients with diabetes, classification can be made reliably on the basis of clinical presentation and course. In the unusual circumstance that requires a specification to be made, another test may be necessary, such as fasting insulin or C-peptide determination and, occasionally, beta cell autoantibody measurements (see figure 18). To achieve a high degree of sensitivity, a combination of tests is required, which greatly increases the cost of classification. In the future, these tests may be standardized, more reliable and less expensive.

**Figure 18** Flow sheet for classification of diabetes in children and adolescents.

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)

Individuals with type 2 diabetes usually do not have autoantibodies to beta cell proteins; fasting insulin and C-peptide levels are elevated,
although not as elevated as might be expected for the degree of hyperglycaemia. Specific autoantibodies to insulin, to GAD-II or to tyrosine phosphatase insulin antibodies (IA)-2 and IA-2b are found at presentation in 85-98% of individuals with immune-mediated Type 1 diabetes. Type 1 diabetes mellitus also has a strong HLA association; however, HLA typing is not a useful diagnostic tool. Endogenous fasting insulin and C-peptide is low in Type 1 diabetes, with little or no increase after oral or intravenous glucose administration. Specific laboratory evaluation to classify diabetes in children should only be used by diabetologists with paediatric expertise and only when a definitive classification is clinically required.

COMPLICATIONS TO TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

The chronic complications of diabetes in adults include macrovascular disease such as accelerated development of cardiovascular disease leading to stroke and myocardial infarction and microvascular disease such as retinopathy, nephropathy and neuropathy leading to end-stage renal disease, loss of visual acuity and limb amputations. All of these complications contribute to the excess morbidity and mortality in individuals with diabetes.

They are only a few data concerning complications of Type 2 diabetes mellitus in childhood. Assessing trial data from adults and extrapolating to outcomes in children is fraught with difficulties. The largest follow-up study of Type 2 diabetes mellitus in adults was the UK Prospective Diabetes Study (UKPDS), which followed 5012 patients for a median of 10 years. Clearly outcomes in terms of absolute
numbers are non-informative in children, One would not expect myocardial infarction rates to be similar in teenagers to those of median age 65 years, even if their glycaemic control were similar. On the other hand, the relative rates of events across quintiles of glycaemia are likely to be informative. The pathological process caused by hyperglycaemia is likely to be similar. It would be perverse to suggest that these relative risks did not apply to children, and the conclusion must therefore be that diagnosis and aggressive control of glycaemia is a mandatory requirement if we are to reduce the burden of endpoints. Moreover, since the risk is logarithmic we should be especially assiduous in reducing glycaemia in those in the upper ranges of HbA1c.

One notable outcome of the UKPDS analysis was the observation that the accrual of endpoints was a time-dependent process. At higher level of HbA1c the effects become even more marked. Such observations have particular implications for onset of diabetes in childhood.

We know little about the onset and progress of macrovascular disease in children with Type 2 diabetes mellitus. Arteriosclerosis is a time-dependent phenomenon, and thus absolute time from diagnosis to developing pathological cardiovascular lesion may be many years in that sense these children may be protected by age since they do not have pre-existing age-related cardiovascular disease. However, it is almost certain that they will develop an excess cardiovascular morbidity early in life.
Microvascular disease is the hallmark of hyperglycaemia diagnosed at a young age. Data from Japanese, Pima Indian children show the presence of microvascular diabetic complications already at diagnosis and follow-up. In Japanese children, incipient retinopathy was detected in 36% of the cases at the time of diagnosis, and in 39% of the cases at 2 years follow-up. Among Pima Indian children, 22% had microalbuminuria. And at follow-up between 20 and 29 years of age 60% had microalbuminuria and 17% already had macroalbuminuria.

**SCREENING FOR TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS**

Most of the European Caucasian children and adolescents with Type 2 diabetes and one-third of the American children were asymptomatic at diagnosis. According to this, the prevalence in a screening study in Germany of obese children was much higher than the prevalence rate reported in the standardized documentation system of diabetes in Germany. Type 2 diabetes mellitus is characterized by absence of symptoms early in the disease. It is likely that, as with adults, undiagnosed Type 2 diabetes mellitus is a common condition in childhood. Screening of diabetes in high-risk populations is necessary since unrecognized hyperglycaemia would undoubtedly contribute to both microvascular and macrovascular risk in later life. Screening studies demonstrated Type 2 diabetes mellitus in approximately 1% of obese Caucasian children in Germany and in 4% of screened obese adolescent in particular ethnic groups in the USA.

Consistent with the recommendations for screening in adults, only children at substantial risk for the presence or the development of
Type 2 diabetes mellitus should be tested. Acknowledging the clinical presentation of Type 2 diabetes mellitus and that there are insufficient data to make definite recommendations, testing seems meaningful in overweight children and adolescents at onset of puberty in high-risk patients who display (1) a family history of Type 2 diabetes mellitus in first and second-degree relatives or (2) signs of insulin resistance (acanthosis nigricans) or (3) conditions associated with insulin resistance (hypertension, dyslipidaemia, polycystic ovary syndrome) or (4) belong to a particular ethnic group (American Indians, African-Americans, Hispanics, Asians) and (5) in extremely obese children (see Table 21). Testing should be performed every two years starting at the age of 10 years or at onset of puberty if it occurs at a younger age.466

Table 21 Criteria for testing of Type 2 diabetes in children and adolescents (adapted from reference 1)

<table>
<thead>
<tr>
<th>Overweight (BMI&gt;90th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus</td>
</tr>
<tr>
<td>One of the following risk factors:</td>
</tr>
<tr>
<td>o Family history of Type 2 diabetes in first- or second-degree relative</td>
</tr>
<tr>
<td>o Race/ethnicity (Asian, American Indian, Africa-American, Hispanic)</td>
</tr>
<tr>
<td>o Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidaemia, PCOS)</td>
</tr>
<tr>
<td>o Extreme obesity (BMI&gt;99.5 percentile)</td>
</tr>
</tbody>
</table>
Requirements for testing an asymptomatic group include the availability of a test that is sensitive (few false negatives) and accurate with acceptable specificity (minimal number of false positives). HbA1c is not a useful screening tool, since one-third of the asymptomatic children with Type 2 diabetes mellitus demonstrated normal values. Since fasting blood glucose failed to diagnose diabetes in one-quarter of children with Type 2 diabetes in the European cohort, the oral glucose tolerance test seems to be a better screening tool even if fasting glucose is preferred because of its lower costs and greater convenience.

**TREATMENT OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS**

Behaviour modification strategies for changing lifestyle, sedentary behaviour and decreasing high-calorie high-fat food choice should be implemented. Lifestyle changes cannot be imposed. They need to be accepted and indeed come from self-motivation. This self-motivation depends on education about glycaemia, blood pressure, lipids and the reasons for attention to good metabolic control. Adherence may be difficult, but the gains are immense. The families of those with the condition should be counseled, and siblings engaged in the education programmes.

Referral to a dietician with knowledge and experience in nutritional management of children with diabetes is necessary. Dietary recommendations should be culturally appropriate, sensitive to the family resources and provided to all caregivers. Encouraging healthy eating habits by the entire family is important.
Obesity has its own psychological consequences in children, sometimes leading to a positive feedback into comfort eating. Breaking such a cycle can be a huge challenge, and may need repeated reinforcement, much educational input to the children and their parents and the provision of exercise facilities and training courses in appropriate eating patterns.

Monitoring and Treatment of Complications of Type 2 Diabetes Mellitus in Children and Adolescents

Since microvascular complications of Type 2 diabetes mellitus such as retinopathy and nephropathy already occur in children, dilated eye examination should be performed. Screening for microalbuminuria should also be performed yearly. It is unclear whether foot examinations are important in children. Other than testing for and treating elevated blood pressure and lipid abnormalities. Studies to detect macrovascular disease are probably not indicated, although there are no data in this age group.

Careful control of hypertension in children is critical. ACE inhibitors are the agents of choice in children with microalbuminuria. If normotension is not achieved, combination therapy with α-blockers, calcium antagonists or low-dose diuretics may be needed.
PREVENTION OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

The financial and societal consequences of the emerging epidemic of Type 2 diabetes are substantial and demand an urgent public health response. Emphasis must be placed upon preventive behaviors and early detection. Prevention of Type 2 diabetes means prevention of obesity in childhood. The effect of weight loss on comorbid conditions and, most importantly, on the development of Type 2 diabetes has been unequivocally proven.\textsuperscript{480-483} As prevention should start very early in life, perhaps even before birth, a population and community approach for prevention of obesity in childhood and hence Type 2 diabetes mellitus in childhood and adolescence seems to be the most promising and reasonable treatment strategy available at present. However, primary prevention has proven to be difficult or impossible in most societies. A multidisciplinary team approach is needed to develop and secure preventive strategies. Good nutrition and modest exercise for pregnant women as well as monitoring of intrauterine growth of the foetus are mandatory. After birth, rapid weight gain should be avoided and the principles of good nutrition and physical activity be taught at all ages. Breast-feeding should be strongly recommended. Children’s food can be influenced by early intervention and guidance. In fact, teacher training of school meals and physical education are effective in reducing risk factors for obesity.\textsuperscript{472}

The cost-effectiveness of group and mixed family-based treatments for childhood obesity has been tested and proven for motivated families. Therefore, family-based, behavioural treatment for obesity is also effective in preventing Type 2 diabetes mellitus and is also extremely
cost effective. In unmotivated families, treatment remains difficult and frustrating for the patient and family, as well as for the multidisciplinary team caring for the obese child.

To prevent the development of Type 2 diabetes and its life-shortening sequelae, early detection of impaired glucose regulation may represent an appropriate strategy, as subjects with impaired glucose tolerance are at increased risk of developing this disease. Recent intervention studies have convincingly demonstrated that adoption of a healthy lifestyle characterized by healthy eating, regular physical activity and subsequent modest weight loss can prevent the progression of impaired glucose tolerance to clinical diabetes.

**CONCLUSIONS**

Type 2 diabetes mellitus is rare in childhood and adolescence, but recent reports indicate an increasing prevalence around the world, possibly due to increasing prevalence of obesity in children and adolescents. This is particularly the case in the USA but has also been reported in other countries in Asia and Europe. It is becoming increasingly clear that overweight children with clinical signs of insulin resistance (acanthosis nigricans, dyslipidaemia, hypertension, PCOS) or relatives with Type 2 diabetes mellitus or of particular ethnic populations (Asian, American-Indian, African-Americans, Hispanics) above the age of 10 years should be screened for the presence of impaired glucose tolerance or overt Type 2 diabetes. Prevention and treatment of Type 2 diabetes mellitus should become one of the prime targets of public health intervention programmes. Much more attention should be given to the prevention and development of preventive
strategies early in life. Finally, and most importantly, public awareness of the increasing health burden and economic dimension of the childhood obesity epidemic is of importance. Physicians should make the public aware of both the childhood obesity epidemic and its serious consequences, not least Type 2 diabetes mellitus.
COMPLICATIONS OF DIABETES

DIABETIC NEPHROPATHY

Diabetic nephropathy is the leading cause of end-stage renal disease worldwide.\textsuperscript{487}

About 20 – 30\% of the patients with type 1 and type 2 diabetes develop evidence of nephropathy, but in type 2 diabetes, a considerably smaller fraction of them progress to ESRD. However because of the much greater prevalence of type 2 diabetes, such a fraction constitutes over half of those diabetic patients undergoing treatment for ESRD. The situation is much the same in India.

The incidence of diabetic nephropathy in type 2 diabetes varies considerably among different ethnic population. Native Americans, Hispanics and Afro Americans have a much higher risk of developing ESRD than non Hispanic whites with type 2 diabetes. The Pima Indians have the highest prevalence of diabetic nephropathy in the World. There are no population based data on the prevalence of diabetic nephropathy in India, but the published data reveal that the microalbuminuria – the early marker of diabetic nephropathy is more common in type 2 Indian diabetics living abroad compared to Europeans.

In India the prevalence of microalbuminuria varies from 19.7 to 28.5\% of unselected type 2 diabetics. Whereas the prevalence of diabetic nephropathy in type 2 diabetics is reported to be 5 – 9\% from various Indian studies.
A study involving 4837 patients with chronic renal insufficiency in India showed that diabetes was the cause of renal insufficiency in more than 30% of them.\textsuperscript{488} The economic burden and psychological consequences to the individual patients, not to mention the cost to the concerned nations, can easily be imagined.

India has the largest number of diabetic patients in the world.\textsuperscript{489} Diabetes in Indian differs in several respects from that in Caucasians. The onset is at an earlier age\textsuperscript{490} and the relationship to obesity is not as strong as in Caucasians.\textsuperscript{491} The sheer number of diabetes patients in the country, combined with the early age at which they develop the disease and hence its complications, implies that diabetic complications including nephropathy will emerge as a major public health problem in India, affecting individuals in the productive age group.

**DEFINITIONS AND STAGES**

Diabetic nephropathy has conventionally been described as proteinuria of 500 mg or more per day, in association with an elevated blood pressure and relentless fall in glomerular filtration rate (GFR), usually in the presence of coexisting diabetic retinopathy. However, it has long been known that diabetic nephropathy in type 1 diabetes passes through a series of well-defined stage (Figure 19 & Table 22). To an extent, the same stages hold good for type 2 diabetes also (Figure 19 & Table 22). However, in type 2 diabetes, renal disease is often well-established at diagnosis of diabetes and the progression to end-stage renal disease occurs faster.


Table 22 Stages of diabetic nephropathy in type 1 and type 2 diabetes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histological changes</th>
<th>Functional changes</th>
<th>24 hrs protein excretion</th>
<th>Clinical Diagnosis</th>
<th>Duration from onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Glomerular Hypertrophy Enlarged Kidney</td>
<td>Increase in glomerular filtration rate</td>
<td>&lt;100 mg/day</td>
<td>Clinically silent</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>II</td>
<td>Continued Hypertrophy</td>
<td>Increase in Glomerular Filtration rate</td>
<td>&lt;100 mg/day</td>
<td>Clinically silent</td>
<td>1.5-5 yrs</td>
</tr>
<tr>
<td>III</td>
<td>Basement membrane thickening Messangial Expansion</td>
<td>Increase in albumin excretion rate Increase in Blood Pressure</td>
<td>Varies from 150-750 mg/day</td>
<td>Microalbuminuria</td>
<td>5-15 yrs</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse nodular Gomerulosclerosis</td>
<td>Further increase in albumin excretion rate Decrease in glomerular filtration rate</td>
<td>&gt;1000 mg / day</td>
<td>Overt Proteinuria</td>
<td>10-20 yrs</td>
</tr>
<tr>
<td>V</td>
<td>Glomerular Closure</td>
<td>Glomerular filtration rate &lt;15 ml/min Complication like retinopathy might occur</td>
<td>&gt;1000 mg/day</td>
<td>End-Stage renal disease</td>
<td>20-23 yrs</td>
</tr>
</tbody>
</table>

The stage of microalbuminuria deserves special mention. Microalbuminuria refers to that level of urinary albumin excretion which cannot be detected using conventional dipsticks and which requires specialised techniques for detection.
Persistent microalbuminuria is the earliest sign of diabetic kidney disease. Definitions for microalbuminuria and clinical albuminuria are given in Table 23. Aggressive intervention at this stage can retard or even reverse the progression of kidney disease. Moreover, microalbuminuria has also been found to be an independent predictor of cardiovascular morbidity and mortality.\textsuperscript{492}

**Table 23 Definition of Microalbuminuria**

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Normoalbuminuria</th>
<th>Microalbuminuria</th>
<th>Clinical Albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin Excretion Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hrs collection</td>
<td>&lt;30mg/24hr</td>
<td>30-300mg/24hr</td>
<td>&gt;300mg/24hr</td>
</tr>
<tr>
<td>Timed Collection</td>
<td>&lt;20mcg/min</td>
<td>20-200mcg/min</td>
<td>&gt;200mcg/min</td>
</tr>
<tr>
<td>Spot Collection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin to Creatinine ratio</td>
<td>&lt;30mcg/mg of creatinine</td>
<td>30-300mcg/mg of creatinine</td>
<td>&gt;300mcg/mg of creatinine</td>
</tr>
</tbody>
</table>
EPIDEMIOLOGY

The prevalence of diabetic nephropathy varies widely from country and even among various ethnic groups in a particular country, ranging from 7-9% in the White UK population\textsuperscript{493} to 42% in Nauruans\textsuperscript{494}. The varying rates of prevalence reported by different researchers may also reflect the differing criteria employed to define diabetic nephropathy.

The predominant evidence from immigrant studies seems to support the premise that persons of south Asian ethnic origin are more susceptible to develop certain complications of diabetes, including but not limited to nephropathy. This observation was made initially by Allawi et al\textsuperscript{495} in the UK and later confirmed by Feehally and colleagues\textsuperscript{496}. Essentially similar conclusions were drawn by Shaw et al\textsuperscript{497} and Stewart et al\textsuperscript{498} in their studies on multi-ethnic populations in the Netherlands and Australia, respectively. However, studies on another multi-ethnic population in Singapore failed to show increased susceptibility of south Asians to diabetic nephropathy\textsuperscript{499}.

However, we have little information on the prevalence of diabetic nephropathy from India, which is home to the largest number of diabetic subjects in the world. Moreover, all the data mentioned below are derived from clinic-based studies, which do not portray the full picture. (Table\textsuperscript{24}). Viswanathan et al in 1991, reported the prevalence rate of microalbuminuria to be 28.5\% in a cohort of 316 type 2 diabetes patients\textsuperscript{500}. In the same Year, Gupta et al noted microalbuminuria to be present in 26.6\% of type 2 diabetes patients studied by him in a clinic in north India\textsuperscript{501}. John et al, working in a teaching hospital in south India noted prevalence rates of 8.9\% and 19.7\% for diabetic nephropathy and microalbuminuria, respectively\textsuperscript{502}. 
Table 24 Prevalence of diabetic nephropathy in Indians - studies from the Indian subcontinent.

<table>
<thead>
<tr>
<th>Authors (Reference)</th>
<th>Prevalance of microalbuminuria(%)</th>
<th>Prevalance of Proteinuria(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viswanathan et al 500</td>
<td>28.5</td>
<td>-</td>
</tr>
<tr>
<td>Gupta et al 501</td>
<td>26.6</td>
<td>-</td>
</tr>
<tr>
<td>John et al 502</td>
<td>19.7</td>
<td>8.9</td>
</tr>
<tr>
<td>Varghese et al 503</td>
<td>36.3</td>
<td>-</td>
</tr>
<tr>
<td>Mohan et al 504</td>
<td>-</td>
<td>6.9</td>
</tr>
<tr>
<td>Shiea et al 505</td>
<td>20.2</td>
<td>-</td>
</tr>
<tr>
<td>Ahmedoni et al 506</td>
<td>34.0</td>
<td>-</td>
</tr>
<tr>
<td>Weerasurya et al 507</td>
<td>29.0</td>
<td>-</td>
</tr>
</tbody>
</table>

Mohan et al, working in a diabetes centre in south India, observed a prevalence rate of 36.3% for microalbuminuria and 6.9% for macroproteinuria among type 2 diabetic subjects. In neighbouring Pakistan, Shera et al in 2004 found that 20.2% of diabetic subjects had elevated urinary albumin excretion levels. More recently, in 2005, Ahmedani et al published the result of a multicentre study in Karachi in which 34% of diabetes patients were found to have microalbuminuria. In Sri Lanka, Weerasuriya et al reported that 29% of newly diagnosed diabetic subjects already had some elevation in urinary albumin excretion.

From the available data, it appears that the prevalence of diabetic nephropathy and its predecessor, namely, microalbuminuria, among south Asians in their native countries is similar to that noted in other ethnic groups throughout the world. However, firm conclusion on this matter will have to await publication of full-scale population based studies.
RISK FACTORS

FAMILIAL/GENETIC FACTORS

Even after exclusion the influence of all the known risk factors, there remains a subset of patients who have an increased susceptibility to diabetic nephropathy. In some of the studies familial clustering of diabetic nephropathy has been reported, which postulate that inherited factors may play a role in determining the susceptibility to diabetic nephropathy. Familial predisposition of raised arterial blood pressure has been said to be a contributory factor in some patients.

The cell membrane cation transport system namely the red cell sodium-lithium counter transport is genetically determined. The elevated rate of transport found in hypertensives, in proteinuric diabetes, and the associated lipid abnormalities in them point to the involvement of genetically mediated pathway in diabetic nephropathy. Sodium-lithium counter transport plays a crucial role in the control of renal resorption of sodium and thus in the regulation of blood pressure. Environmental changes due to diabetes leads on to dysregulation of the counter transport activity. In susceptible individuals, it induces cell hypertrophy and hyperplasia contributing to glomerular hypertrophy and mesangial expansion. The altered sodium balance leads to hypertension, which is transmitted to glomerular capillaries. This increases the GFR and may be responsible for the permeability properties generating proteinuria.

Vijay et al have drawn attention the familial clustering of kidney disease in type 2 diabetes in south India. This has led to the
concept of genetic susceptibility in the pathogenesis of diabetic nephropathy. However, Shaw et al failed to find evidence of similar familial clustering of nephropathy in south Asian type 2 diabetic patients living in the Netherlands.\textsuperscript{497}

**Figure 20** Interplay of genetics and risk factors

![Diagram of Interplay of Genetics and Risk Factors](Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)

There is no consensus as to whether there is one major gene effect or several minor ones; current evidence favours the latter. Small effects of several polymorphisms in various genes have been identified. Considering the central role of the Renin-Angiotensin-Aldosterone System (RAS) in the pathogenesis of diabetic nephropathy, most of the studies so far have looked at the genes representing the proteins in this cascade.

ACE polymorphisms are risk factors for initiation of diabetic nephropathy. In Japanese population there is higher incidence of DD genotype in type 2 DM patients with declining renal functions. Thus there is interplay of genetic factors and other risk factors depicted in Fig – 20 in the causation of nephropathy. Several studies have noted that the D allele of the Angiotensin Converting Enzyme (ACE) gene is
associated with faster loss of renal function. There is little data from India regarding the genetics of diabetic nephropathy in this region. A study by Vijay et al showed a positive association between the D allele of the ACE gene and diabetic proteinuria in type 2 diabetic subjects in south India,\textsuperscript{510} which is in keeping with the findings in other populations. Further population-based studies are essential to uncover other polymorphisms which may be of significance in predisposing to diabetic nephropathy in this population.

DURATION OF DIABETES:

During the first five years of diabetes, nephropathy is rare. The incidence reaches a peak by 15\textsuperscript{th} year and declines thereafter. Nephropathy is rare to develop after 25 years of diabetes. Patients diagnosed as diabetics after the age of 50 years have higher prevalence and degree of microalbuminuria than those diagnosed before the age of 40.

HYPERTENSION:

In the background of normoalbuminuria if there is hypertension, then it is likely that the patient has two co-existent diseases, namely diabetes mellitus and essential hypertension. If there is no hypertension, the patient with normoalbuminuria remains normotensive despite an additional decade of diabetes. With the development of incipient nephropathy there is a gradual elevation of blood pressure. The progression of early nephropathy is related to blood pressure. Hypertension is a definitive risk factor for the development of diabetic nephropathy. In type 1 diabetes presence of
hypertension suggests renal involvement. With the progression of renal disease the incidence of hypertension increases and by the time of overt nephropathy hypertension is usually always present.

In a diabetic with renal involvement, the blood pressure either remains normal throughout (A in fig. 21) or rises progressively (B in fig. 21).

**Figure 21**

*STAGES OF DIABETIC NEPHROPATHY*

<table>
<thead>
<tr>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macro Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Micro Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A. Subgroup in which blood pressure remains normal.
B. Pattern of change in blood pressure in subgroup in which hypertension develops

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)

A stage of "micro-hypertension" with the onset of Incipient diabetic nephropathy (stage III) is recognized to emphasize the deleterious role of marginally elevated blood pressure on renal function that is, above normal (120/80) but below (140/90) the well-defined hypertensive range. The blood pressure increases at the rate of 4% per year during this stage. Macro-hypertension develops with the onset of persistent proteinuria (stage IV). The blood pressure is said to increase at the rate of 8% per year during stage IV.
RENAL HYPERTROPHY & HYPERFILTRATION:

When the hyperfiltration is pronounced (GFR >150ml/min corrected to 1.73 m² body surface) for many years there is increased risk for diabetic nephropathy. The GFR is higher than normal in the stage of glomerular hypertrophy and hyperfiltration. It can be as high as 150 ml/min. It slowly starts falling during stages II and III, when it remains within the so called, normal range. With the onset of persistent proteinuria of Stage IV, GFR progressively falls at a rate of about 1.2 ml per minute per month culminating in ESRD in a matter of months to years when left untreated (Fig 22). Meticulous care can help to lower the rate of decline in renal function from a fall in GFR of 1.2 ml per minute per month to 0.2 ml per minute per month. Some authors recommend renal biopsies to follow up the patients, to evaluate the basement membrane thickening, mesangial expansion and occluded glomeruli. In established diabetic nephropathy increased renal size persists despite decrease in GFR or intensive insulin therapy. High protein intake induces some degree of hyperfiltration in normal man. Hence, high protein diet of more than 0.8 g/kg of ideal body weight is a risk factor for diabetic nephropathy.
HYPERGLYCEMIA:

GFR is positively correlated to HbA1c. Patients with HbA1c levels of < 7% are at lower risk of nephropathy. DCCT and UKPDS have clearly demonstrated that intensive glucose control resulted in a reduction in progression of diabetic nephropathy. Raised urinary albumin excretion is also associated with HbA1c in patients with 'incipient nephropathy'. The rate of progression of nephropathy is correlated with metabolic control.

SMOKING:

Smoking causes vasoconstriction, platelet dysfunction and coagulation abnormalities which can accelerate the vascular damage. Smoking is also an independent risk factor for essential hypertension.
Some studies have identified male sex, dyslipidaemia, and pre-existing retinopathy as risk factors for microalbuminuria. Some of these risk factors are modifiable (Table 25).

<table>
<thead>
<tr>
<th>Table 25: Risk factors for diabetic nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modifiable</td>
</tr>
<tr>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
</tbody>
</table>

A clinic-based study conducted by Mohan et al found age, duration of diabetes, diastolic blood pressure, HbA1c and fasting plasma glucose levels to risk factors for microalbuminuria. Gupta et al reported HbA1c to be associated with microalbuminuria, John et al reported male sex, older age, longer duration of diabetes, poor glycaemic control and raised blood pressure as risk factors for microalbuminuria, while Vijay et al reported duration of diabetes, systolic and diastolic blood pressure, age of the patient and serum creatinine to be associated with protenuria.

**FUNCTIONAL CHANGES IN DIABETIC NEPHROPATHY:**

Three cardinal functional changes characterize the natural history of diabetic nephropathy. They are i) Changes in glomerular filtration rate (GFR) ii) proteinuria and albuminuria, and iii) changes in arterial pressure. A study of these functional changes will be made easy if one understands the five stages of diabetic nephropathy. (Table - 26)
STAGE 1: (STAGE OF HYPERFUNCTION AND HYPERTROPHY)
This stage is characterized by large kidneys and glomerular hyperfiltration and hypertrophy. The basement membrane mesangium is in normal. The GFR is > 150 ml/min with normal blood pressure. The urinary albumin excretion may be increased.

STAGE 2: (SILENT STAGE)
In the silent stage the blood pressure and UAE are normal. But structural lesions like increased basement membrane thickening and mesangial expansion may be present. This situation may last for years. In periods of metabolic stress or during exercise there is raise in albumin excretion rate.

Table 26 STAGES OF DIABETIC NEPHROPATHY

<table>
<thead>
<tr>
<th>Stage</th>
<th>Designation</th>
<th>Glomerular Filtration Rate</th>
<th>Urinary Albumin Excretion</th>
<th>Blood Pressure</th>
<th>Main Structural Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hyperfunction / hypertrophy</td>
<td>May be increased</td>
<td>May be increased</td>
<td>Usually normal</td>
<td>Hypertrophy, increased kidney volume</td>
</tr>
<tr>
<td>II</td>
<td>Normalbuminuria</td>
<td>Normal / increased</td>
<td>Normal</td>
<td>Normal</td>
<td>Increasing basement membrane thickness and mesangium expansion</td>
</tr>
<tr>
<td>III</td>
<td>Incipient diabetic nephropathy</td>
<td>Normal / increased</td>
<td>20 - 200µg / min (microalbuminuria)</td>
<td>Increasing ~ 3mmHg / year</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Overt diabetic nephropathy</td>
<td>Decreasing</td>
<td>&gt; 200 µg / min (macroalbuminuria)</td>
<td>Usually frank</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>End stage renal failure</td>
<td>&lt; 20 ml / min</td>
<td>Macroalbuminuria, often decreasing due to glomerular occlusion</td>
<td>Hypertension</td>
<td></td>
</tr>
</tbody>
</table>

180
STAGE 3: (STAGE OF INCIPIENT DIABETIC NEPHROPATHY)
The patients in this stage are at risk to develop overt nephropathy if left untreated. There is persistent microalbuminuria and hypertension.

STAGE 4: (STAGE OF OVERT DIABETIC NEPHROPATHY)
This stage is characterized by proteinuria, hypertension and a fall in GFR.

STAGE 5: (STAGE OF ESRD)
End stage of renal failure is characterized by uremia, with generalized enthroned closure and very low GFR.

PROTEINURIA AND ALBUMINURIA:

The normal Albumin excretion per day is less than 30 mg/day and the Albumin excretion rate (AER) is 1-12 μg/minute. One of the earliest signs of renal involvement in diabetes is an increase in albumin excretion (30-300 mg/day). Albumin excretion rate varies from 20-200 μg/minute.

This stage is referred to as the "micro-albuminuric" stage which is albustix-negative. The clinical importance of micro-albuminuria is that it signifies definite renal involvement in the diabetic. Its therapeutic importance lies in the fact that it is reversible by tight glycemic control. With further progression of diabetic nephropathy, persistent albuminuria is referred to as "macro-albuminuria" heralding the onset of clinical diabetic nephropathy. At this stage, 24 hour urinary albumin excretion is >300 mg/day, and AER is >200μg/minute. Macro-albuminuria is albustix positive. (Fig.23)
Figure 23 Abnormalities in Albumin/Protein Excretion

Normal proteinuria is less than 150 mg/day and albumin constitutes 11% of this. During microproteinuric stage the protein excretion is 150-500 mg/day out of which albumin constitutes 22%. Macroproteinuria denotes protein excretion of more than 500 mg/day out of which 50% is albumin (Table 27).

Table 27

<table>
<thead>
<tr>
<th>Albumin Excretion Rate (AER)</th>
<th>Normo</th>
<th>Micro</th>
<th>Macro(Clinical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/day</td>
<td>&lt;30</td>
<td>30-300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>µg/min</td>
<td>&lt;20</td>
<td>20-200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Urinary Protein Excretion n</td>
<td>&lt;150</td>
<td>150-500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Urinary Albumin/Protein %</td>
<td>11%</td>
<td>22%</td>
<td>50%</td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Albusix -</td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Over 90% of diabetics with renal damage have retinopathy. Absence
of the latter is reason to suspect other causes for the kidney disorder, rather than diabetes mellitus (Table - 28). Neuropathy is common in uraemic diabetic. Autonomic neuropathy of the urinary bladder is an important co-existent complication that contraindicates renal transplantation. Uraemic diabetic differs from a non-diabetic with chronic renal insufficiency due to another cause in the co-incident vasculopathy, especially retinopathy, coronary artery disease, peripheral vascular disease, etc., that limit rehabilitation.

Table 28

<table>
<thead>
<tr>
<th>Clinical features of Diabetic Nephropathy</th>
<th>Suspect other renal diseases in diabetic patients for nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Proteinuria is the hallmark</td>
<td>1. Absence of albuminuria</td>
</tr>
<tr>
<td>2. Fluid retention</td>
<td>2. Absence of retinopathy</td>
</tr>
<tr>
<td>3. Hypertension: &quot;Diabetic Hypertension&quot;</td>
<td>3. Diabetes duration &lt; 5 years</td>
</tr>
<tr>
<td>4. Retinopathy</td>
<td>4. Rapidly increasing serum creatinine</td>
</tr>
<tr>
<td>5. Neuropathy</td>
<td>5. Presence of active urinary sediments</td>
</tr>
<tr>
<td>6. Arterial disease</td>
<td></td>
</tr>
</tbody>
</table>

NATURAL HISTORY

After a variable duration of diabetes, a diabetic develops microproteinuria that is intermittent to start with. Later it becomes persistent. This is followed by intermittent macroproteinuria that soon becomes persistent. Microproteinuria and intermittent macroproteinuria are reversible by tight glycemic control. Once persistent macroproteinuria develops, the future course of diabetic nephropathy is one of progressive decline in renal function. Multi-system involvement, particularly of the heart, worsens the prognosis. Hence, advent of persistent macro-proteinuria is said to signal the onset of "malignant angiopathy" in the diabetic.
Only 28% of diabetics live for 10 years beyond the onset of "Clinical Proteinuria". A rise above normal in BUN/Creatinine (azotemia) indicates a residual creatinine clearance of 25-30 ml/min. In other words, azotemia is a marker for the loss of at least 75% of kidney reserve. Subsequent loss of renal function follows an exponential course over a mean of 3 Yr. Two years prior to the development of ESRD, the diabetic often experiences an accelerated progression of diabetic retinopathy, diabetic neuropathy and hypertension. The natural history of diabetic nephropathy in type 2 diabetes is ill-defined. (Fig 24)

**Figure 24** Natural history of diabetic nephropathy

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)
Type 1DM patients with nephropathy often die of uremia, while Type 2 DM patients with nephropathy die more often of myocardial infarction. Nephropathy is exceptional in survivors of more than 40 years of diabetes

**PRIMARY PREVENTION OF DIABETIC NEPHROPATHY**

Primary prevention involves intervention before Stage 1 – Hyperfiltration – Hyperperfusion develops. (Fig – 25)

1. Early diagnosis of diabetes mellitus and strict control of blood glucose from the very beginning.

2. Control of hypertension

3. Lipid control

4. Dietary protein of acceptable quantity

5. Identification of high risk group such as those with i) family history of hypertension, ii) a red cell marker, viz., sodium/lithium exchange system activity
Diabetes and hypertension are frequent concomitant diseases with microalbuminuria acting as the early triple indicator of increased risk.

Diabetic patient with microalbuminuria and proteinuria have a particularly poor prognosis, especially when accompanied by renal disease.

Since no specific treatment is available which can completely reverse established diabetic nephropathy, it becomes important to prevent diabetic patients from developing nephropathy in the first place. Preventive strategies involves the control of hyperglycaemia, hypertension and hyperlipidaemia and the avoidance of smoking. Evidence suggests that lowering of high (or even normal) blood
pressure reduces microalbuminuria and slows the decline in glomerular filtration rate. Therefore, the presence of diabetes, both Type 1 diabetes and Type 2 diabetes, in patient with mild hypertension is an indication to begin antihypertensive treatment. In these patients, particular attention should be paid to glucose levels and accompanying disorders of lipid metabolism.\textsuperscript{512}

Once microalbuminuria has set in, the use of ACE inhibitors or ARBs can help to prevent its progression to overt nephropathy. The role of glycaemic control in this setting is less clear-cut. The blood pressure should be maintained below 125/75 mm Hg, using a combination of anti-hypertensive agents if necessary. Insults to the kidney in the form of dehydration and administration of nephrotoxic agents should be avoided.

**SCREENING FOR MICROALBUMINURIA**

Several guidelines on microalbuminuria and prevention of diabetic nephropathy emphasize the importance of early treatment before the glomerular filtration rate declines. Therefore, early screening for microalbuminuria using the albumin-creatinine ratio is recommended. The best defined urine sample to use is the first morning urine. This urine sample can be brought to the clinic for measurement of albumin-creatinine ratio or can be screened for albumin with the newly developed stix. An increased albumin-creatinine ratio found on several occasions gives good evidence for abnormal albuminuria, but may be further confirmed by measuring overnight urine collection. Screening should be carried out at yearly or 6 month intervals. Note that confounding factors (such as heavy exercise, urinary tract infection,
acute illness, cardiac failure or metabolic decompensation) increase microalbuminuria, and patients should be screened for associated abnormalities, such as retinopathy, cardiovascular disease and dyslipidaemia.

**SUMMARY**

Hyperglycaemia is an important contributor to complications, including nephropathy. In order to obtain the best possible glycaemic control throughout the course of diabetes, it is important to diagnose renal disease early on by screening for microalbuminuria. Blood pressure elevation is also an important factor and normalizing blood pressure throughout the course of Type 2 diabetes is, of course, essential.

Studies show that treatment with ACE inhibitors can prevent the development of microalbuminuria (e.g. the Benedict study). Many studies also show that micro-albuminuria can be reduced by antihypertensive treatment, especially with ACE inhibitors, but also with other agents. Usually ACE inhibitors are the best in the treatment process.

The effect on strong end-points in microalbuminuric patients is difficult to ascertain because of the long follow-up needed. However, the HOPE study suggested a positive effect in microalbuminuric diabetic patients on strong end-points. New studies using angiotensin receptor blockers show a positive effect in patients with proteinuria and Type 2 diabetes on the progression of renal disease.
Thus, ACE inhibitors seem to be important in preventing cardiovascular disease and mortality, and angiotensin receptor blockers (ARBs) are important in preventing or postponing ESRD. Patients with diabetic renal disease need effective antihypertensive treatment on top of ACE inhibition using diuretic treatment and beta-blocker treatment as well as calcium blockers with prolonged action. Dyslipidaemia should be treated carefully although there are no clinical studies that suggest that the renal outcome is better with statins or other lipid-lowering agents. All general risk factors should be treated and patients should be urged to stop smoking, lose weight and exercise a low-sodium diet. The role of protein reduction is less clear and it is even weak in patients with other types of renal disease.

CONCLUSIONS

Diabetic nephropathy is the leading cause of end-stage renal disease worldwide. Available data from India, which has the largest diabetic population in the world, show that the prevalence of diabetic nephropathy in this region is not drastically different from that in the Western world. Considering the vast numbers involved, this translates into a huge economic and social burden for the countries of this region. Fortunately, though, diabetic nephropathy can be prevented by screening and early diagnosis and control of all the known risk factors. True primary prevention, however, would depend on prevention of development of diabetes per se in the huge populations at risk in this region.
NEUROPATHY

Diabetic Neuropathy is heterogeneous in its clinical presentation. Diabetic peripheral neuropathies are a variety of syndromes which affect sensory, autonomic and motor nerve function. The commonest form, distal symmetric sensory polyneuropathy can affect virtually every tissue of the body and greatest source of morbidity and mortality in diabetes patients.\textsuperscript{514} It is a major risk factor for foot ulceration, which may eventually lead to lower limb amputation. More often the condition poses a therapeutic challenge to the attending physician.

PREVALENCE OF NEUROPATHY

Population-based studies of neuropathy (inflammation and degeneration of peripheral nerves) in persons with diabetes indicate that neuropathy is a common complication of type 1 diabetes mellitus and type 2 diabetes mellitus, with 60%-70% of patients affected. The reported prevalence of diabetic neuropathy varies from less than 5 to 60%.\textsuperscript{515} It is estimated from a comprehensive collection of epidemiologic studies that the prevalence of neuropathy in diabetes patients is approximately 30% in hospital patients and 20% in community patients.\textsuperscript{516} The overall annual incidence of neuropathy was \textasciitilde2\% in the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT).\textsuperscript{517} Few studies have been done to study the prevalence of neuropathy in newly diagnosed diabetes. A commonly cited study in 1977 reported that roughly 7\% of patients had neuropathy upon diagnosis of diabetes, and the incidence approached 50\% for patients with diabetes for more than 25\,years.\textsuperscript{518} However, it is impossible to accurately
approximate the true prevalence of diabetic neuropathy, because the criteria for diagnosis vary, epidemiologic studies are limited to patients receiving medical care, and diabetes remains undiagnosed in a large population of diabetes patients.\textsuperscript{519} Therefore, the frightening statistic that diabetic neuropathy is implicated in 50-75\% of non-traumatic amputations is merely an exclamation point in the overall impact.\textsuperscript{514}

**RISK FACTORS FOR NEUROPATHY**

Risk factors associated with diabetic peripheral neuropathy need to be identified so that interventions can be devised. The primary risk factor for diabetic neuropathy is hyperglycemia.\textsuperscript{516} As noted above, the annual incidence of diabetic neuropathy in the DCCT was approximately 2\% in conventionally treated patients, but that rate dropped to 0.56\% in intensively treated type 1 diabetes mellitus patients.\textsuperscript{517} The UKPDS failed to support a similar correlation between the incidence of neuropathy and glycemic control in type 2 diabetes patients, but the progression of diabetic neuropathy is dependent on glycemic control in both type 1 and 2 diabetes patients, and the pathologies are considered similar.\textsuperscript{516,517,520} The duration of diabetes also increases the risk of neuropathy, but the association between duration and prevalence may depend in part upon patient age, which itself is a risk factor.\textsuperscript{516,521} Cigarette smoking, alcohol consumption, hypertension, height, and hypercholesterolemia are all considered independent risk factors for diabetic neuropathy.\textsuperscript{516,521,522}
CLASSIFICATION

Simple classification of diabetic neuropathy.

<table>
<thead>
<tr>
<th>Mononeuropathies Neuropathy</th>
<th>Polyneuropathies</th>
<th>Autonomic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated</td>
<td>Sensory -- Acute</td>
<td>Para Sympathetic</td>
</tr>
<tr>
<td>Cranial</td>
<td>- Chronic sensorimotor</td>
<td>Sympathetic</td>
</tr>
<tr>
<td>Truncal</td>
<td>Proximal</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>Truncal Motor</td>
<td></td>
</tr>
</tbody>
</table>

DIABETIC POLYNEUROPATHIES

Distal symmetrical polyneuropathy is the most common type of neuropathy, followed by carpal tunnel syndrome, other mononeuropathies, and autonomic neuropathy. The frequency distribution for neuropathies is similar in Type 1 and Type 2 diabetes. However, severe distal neuropathy is more common in Type 1 diabetes.

Subclinical neuropathy is much more common than clinical neuropathy. Subclinical neuropathy is defined by an abnormal electrodiagnostic test, quantitative sensory threshold, or autonomic function test in the absence of clinical signs and symptoms. Clinical neuropathy is defined as symptoms and signs together, or as symptoms or signs alone plus abnormal test results.

ACUTE SENSORY NEUROPATHY

Acute sensory neuropathy is relatively rapid in onset with symptoms frequently of severe burning pain and associated weight loss. Sensory
signs are often mild and motor abnormalities are unusual. Sensory symptoms include burning discomfort in the feet, severe hyperesthesia, and painful paresthesias with sudden sharp stabbing shock like sensation in the lower limbs with nocturnal exacerbation. Patients may even be unable to tolerate the contact of their bed sheets and own clothes. The condition is associated with severe reactive depression. Objective neurological examinations may just reveal patchy sensory loss in the feet. This condition has a male predilection. This condition described in detail by Archer is akin to the acute neuropathic Cachexia described by Ellenberg. They may not have other diabetic complications though impotence is not uncommon. Electrophysiological abnormalities are minor. Complete recovery usually occurs within one year of treatment following control of blood glucose. Recurrences of symptoms do not usually occur.

CHRONIC SENSORY MOTOR NEUROPATHY

Chronic sensory motor neuropathy is gradual and insidious in onset, with burning pain and paresthesias, numbness of varying intensity. Weight loss is unusual. Numbness, hyperesthesia, pins and needles, burning pains, itching, tingling and altered temperature sensation are experienced. Another frequent presentation is unpleasant sensation on the lateral aspect of the thighs aggravated by contact with clothes (allodynia), burning and tingling sensation (meralgia paraesthetica). The painful-painless leg is frequently encountered. These patients have glove and stocking sensory loss, often with signs of motor dysfunction with small muscle wasting and diminished or absent reflexes. The diagnosis requires exclusion of other causes of peripheral nerve disease. There is increased prevalence of associated micro vascular diabetic complications. Electrophysiological
studies show abnormalities in motor and sensory nerves. Symptoms may be intermittent or persist for years. Gradual improvement in symptoms with long standing sensory motor neuropathy does not necessarily indicate structural improvement. The persisting residual symptoms may be due to loss of small fiber function leaving the patient numb, with insensitive foot which is prone for painless injury.

Table 29 Stages of diabetic peripheral sensory neuropathy

<table>
<thead>
<tr>
<th>Stage of neuropathy</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neuropathy</td>
<td>No symptoms or signs</td>
</tr>
<tr>
<td>Clinical neuropathy</td>
<td>Burning, shooting, stabbing pain ± pins and needles; increased at night; absent sensation to several modalities; reduced / absent reflexes</td>
</tr>
<tr>
<td>Chronic painful</td>
<td></td>
</tr>
<tr>
<td>Acute painful</td>
<td>Severe symptoms as above (hyperesthesia common); may follow initiation of insulin in poorly controlled diabetes; signs minor or absent</td>
</tr>
<tr>
<td>Painless with complete/</td>
<td>Numbness/deadness of feet or no symptoms; painless injury; reduced/absent sensation; reduced thermal sensitivity; absent reflexes</td>
</tr>
<tr>
<td>Partial sensory loss</td>
<td></td>
</tr>
<tr>
<td>Late complications</td>
<td>Foot lesions; neuropathic deformity; nontraumatic amputation</td>
</tr>
</tbody>
</table>

PROXIMAL MOTOR NEUROPATHY

The term proximal myopathy is used synonymously with diabetic amyotropy, motor myopathy, sub acute proximal diabetic neuropathy, and femoral neuropathy. Males are affected more often than females, more often in the sixth decade of life in type 2 DM. The clinical picture
is that of acute or sub acute pain with weakness, and atrophy of pelvic girdle musculature. The iliopsoas, quadriceps and the adductors of the thigh, are almost always involved in every patient. Wasting is a prominent feature associated with weakness and loss of knee jerk. The onset is usually abrupt with unilateral aching pains initially later involving both the thighs within a period of few months. Sensory symptoms and signs of neuropathy are commonly present in the form of paresthesias. There is evidence to suggest involvement of multiple nerve roots and motor nerves. Weight loss is frequently marked and is regained during recovery. Recovery with tight glycemic control is possible in patients with proximal motor neuropathies. Differentiation from neoplastic infiltration of lumbosacral plexus and lumbar nerve root disease is very important.

DISTAL SENSORIMOTOR NEUROPATHY

Small fibre neuropathy occurs as an early complication of diabetes mellitus with varying degrees of pain and sensory loss. Small fibre neuropathy is clinically characterized by pain. There is dissociated pattern of pain and temperature deficit with preserved vibration sense, tendon reflexes and power. Some patients with small fibre neuropathy may develop severe acrodystrophic changes with foot ulceration—referred to as "pseudo syringomyelic" form of diabetic neuropathy. Sensations mediated by large fibres (position, vibration sense and muscle power) are spared with intact tendon reflexes. Autonomic nervous system dysfunction is associated, and male patients frequently have impotence.
In contrast to small fibre neuropathy, patients with large fibres neuropathy have muscle weakness, loss of vibration sense and impaired tendon reflexes. When these defects are combined with proprioceptive deficit in the toes and feet, a "Pseudo tabetic" gait ataxia may result. Most often this type of neuropathy coexists with diabetic retinopathy or nephropathy (Table - 30).

**Table 30 Clinical features of distal sensorimotor diabetic neuropathy**

<table>
<thead>
<tr>
<th>Large fiber type</th>
<th>Small fiber type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsteady gait</td>
<td>Pain predominates</td>
</tr>
<tr>
<td>Absent reflexes</td>
<td>Variable reflexes</td>
</tr>
<tr>
<td>Decreased vibration / position sense</td>
<td>Variable position / vibration sense</td>
</tr>
<tr>
<td>Charcot’s joints possible</td>
<td>Variable presence of Charcot’s joints</td>
</tr>
<tr>
<td>Mimics posterior column lesions</td>
<td>Ultimately leads to sensory loss</td>
</tr>
</tbody>
</table>

**AUTONOMIC NEUROPATHY**

This is usually accompanied by peripheral neuropathic disturbances. Conventionally diagnosis of autonomic neuropathy is based on simple tests using cardiovascular reflexes like heart rate changes during deep breathing, standing, Valsalva maneuver and blood pressure response to standing and sustained handgrip (Table-31). Tests involving parasympathetic nerves show abnormalities earlier than those involving sympathetic. Loss of sweating in the feet and impotence may precede abnormal cardiovascular test. *Diabetic with autonomic neuropathy are prone for sudden death from painless myocardial infarction and cardio-respiratory arrest.* Generally symptoms due to autonomic neuropathy include postural hypotension, gustatory sweating, diarrhea, unawareness of
hypoglycemia; bladder dysfunction impaired temperature regulation and altered sweating.

**Table 31** Symptoms of diabetic autonomic neuropathy

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Postural hypotension, Painless myocardial infarction, Resting tachycardia, Loss of heart rate variation</td>
</tr>
<tr>
<td>Gastro-Intestinal</td>
<td>Impaired esophageal motility, Gastric atony, Diarrhea, Colonic atony, Enlarged gall bladder</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Bladder dysfunction, Impotence, Retrograde ejaculation, Loss of testicular sensation</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Respiratory arrest</td>
</tr>
<tr>
<td>Pupillary Abnormalities</td>
<td>Reduced resting diameter, Delayed or absent response to light, Diminished Hippus</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>Loss of skin vasomotor responses, Peripheral vascular changes, Osteopathy, Charcot’s arthropathy, Dependent Edema</td>
</tr>
<tr>
<td>Sudomotor</td>
<td>Diabetic anhydrosis, Gustatory sweating</td>
</tr>
<tr>
<td>Hypoglycemia unawareness</td>
<td>Decreased catecholamine release with loss of warning symptoms of hypoglycemia, Decreased pancreatic glucagon and pancreatic polypeptide release</td>
</tr>
</tbody>
</table>

Delayed gastric emptying, marked retention and patulous pylorus (Gastro paresis diabeticorum), disorder of esophageal motility, bladder paralysis resulting in urinary retention with superimposed infection, and sexual dysfunction contribute significantly to the morbidity in subjects with autonomic neuropathy. Pupillary abnormalities namely a reduction in the resting pupil size, loss of spontaneous oscillations (Hippus), loss of light reflex and occasionally
loss of accommodation reflex are observed (Table – 31). Very rarely a true Argyll-Robertson pupil is seen.
DIABETIC RETINOPATHY IN INDIA

MAGNITUDE OF THE PROBLEM

Diabetic retinopathy (DR) is today the major cause of blindness in the industrialised western world. In India, it was the 17th cause of blindness a couple of decades ago but today diabetes related blindness has rapidly ascended to the sixth position.\textsuperscript{523}

Blindness is 25 times more common in diabetics than non-diabetics. In India with the epidemic increase in diabetes mellitus diabetic retinopathy is-fast becoming a burden leading to morbidity among the earning age group.

Several epidemiological studies have provided valuable information on the prevalence of DR in the Western countries; however, there are very few reports on the prevalence of retinopathy both from the population and clinic cohort from developing countries like India. Lack of data from the Indian subcontinent may be because of logistic and economic reasons as retinal cameras are expensive and the total lack of awareness in the past that diabetic retinopathy should be documented. With the advent of advanced and cheaper techniques like digital retinal photography, documentation has improved, and treatment more successful.

In urban Indian population-based studies suggests that the prevalence of DR is lower compared to other ethnic groups. However, given the large number of diabetic subjects in India (31.7 million), even with the lower prevalence rates (17.6%), this would translate to over 5.6 million subjects with DR.
CLASSIFICATION OF DIABETIC RETINOPATHY

Diabetic retinopathy can be basically classified into two major types:

I. Non-Proliferative or Background Diabetic Retinopathy or
II. Proliferative or Advanced Retinopathy

I. NON-PROLIFERATIVE RETINOPATHY: This can be further subdivided into:

a) Non-Proliferative Retinopathy without Macular Involvement which includes microaneurysms, haemorrhages and/or hard exudates within the major temporal vascular arcades or elsewhere on the retina.

b) Non-Proliferative Retinopathy with Macular Involvement or (Maculopathy) includes haemorrhages and/or hard exudates within one disc diameter of the macula, with or without visual loss. Maculopathy can be of two forms:

I. Exudative Maculopathy when oedema, haemorrhages and/or hard exudates develop in the macula.
II. Ischaemic Maculopathy indicates widespread capillary closure affecting the macula.

c) Pre-Proliferative Retinopathy is an intermediary stage characterised by venous irregularities (beading, loops and reduplication) and/or multiple haemorrhages and/or multiple cotton wool spots and/or intra retinal microvascular abnormalities (IRMA) and extensive capillary dropouts.

This stage indicates widespread retinal ischaemia and hence the possibility of progression to new vessel formation on the retina within a short period of time (usually within two years).
II. PROLIFERATIVE DIABETIC RETINOPATHY new vessels on the optic disc and elsewhere on the retina, preretinal haemorrhages and fibrosis on the surface of the retina.

The new vessels grow into the vitreous. They are very friable and bleed producing a vitreous haemorrhage,

PREVALENCE OF DIABETIC RETINOPATHY-THE INDIAN SCENARIO

Few epidemiological studies have been conducted on the prevalence of DR in urban and rural population. To assess the magnitude of the disease, one must screen for the prevalence of DR in the population. Most of the studies are clinic-based studies, which have a referral bias. In India population based-studies have had several limitations: a) limited to self-reported diabetic subjects (i.e. newly detected diabetes not included); b) small sample sizes; c) standardized methods of documentation-like stereo colour photography of retina not done; and d) standardized methods of grading of DR not used. These limitations underscore the need for large population-based studies involving a representative sample of the population including both self-reported and newly diagnosed diabetic subjects, by using standard documentation techniques and grading system.

Although there is an explosion of diabetes with 31.7 million diabetic individuals in India, the propensity to develop DR is lower in south India compared to the other populations (Table 32). This may be due to the fact that Indians develop type 2 diabetes at an earlier age than the Western population and hence may have more resistance to the development of retinopathy at a younger age. However, when
corrected for age (i.e. >40 years) also the prevalence is 18.6% which is significantly lower than the reported prevalence of DR in other populations, extrapolated into actual numbers assuming a prevalence of 17.6%,\textsuperscript{524} it translates into 5.6 million subjects with diabetic retinopathy, which is a health care burden. Inherent ethnic difference in the Indians susceptibility to DR may be one aspect. Another reason may be the type of diet which although rich in carbohydrates includes more vegetables, less fat and perhaps antioxidants and anti-inflammatory agents like Haldi (curcumin). This is called as turmeric, a condiment, which is used in the preparation of curry.

The prevalence of DR in a cohort of 6,792 type 2 diabetic patients attending a diabetes centre at Chennai in south India (1996) screened using a combination of retinal photography and clinical examination by retinal specialists was 34.1%. This included 30.8% with NPDR, 3.4% with PDR and 6.4% had maculopathy.\textsuperscript{531} However, as this is a tertiary care centre where patients are referred for specific problems, a referral bias exists. To overcome this bias the CURES (Chennai Urban Rural Epidemiology Study) eye study was conducted. In phase 1, in the urban component of CURES, 26,001 individuals were screened by a systematic sampling technique from 46 out of 155 corporation wards representative of the various social tiers in Chennai. Individuals aged 20 years were screened for diabetes using capillary fasting blood glucose.\textsuperscript{532}

In Phase 2, detailed retinal evaluation was performed in all the known diabetic subjects (n=1529). In addition, subjects with fasting capillary blood glucose levels in the diabetic range based on the ADA fasting criteria FBS > 110 mg, underwent Oral Glucose Tolerance Test
(OGTT). Of the 1,529 known diabetic subjects, 1,382 (90.4%) participated in the study in addition to 354 newly detected diabetic subjects. All the subjects underwent four-field stereo colour photography and retinopathy was assessed by ETDRS grading of the colour fundus photographs. The CURES eye study-1 is the first population-based study, which used four-field stereo retinal photographs and ETDRS grading to document DR in the Indian population. Finally 1,715 subjects (known diabetes-1,364; newly detected diabetes-351) whose eyes could be photographed were included in the study. The overall prevalence of DR in urban population in this study was 17.6%. This study clearly demonstrates that prevalence of DR is lower when compared to other populations. The prevalence of retinopathy varied from 29-50% in other countries as shown in Table 32.

Among the known diabetic subjects, 20.8% had DR while 5.1% of newly detected diabetic subjects had DR. Known diabetic subjects had higher frequency of all the grades of retinopathy compared to newly detected cases. Prevalence of Diabetic Macular Edema (DME) in the total diabetic population was 5.0% while among the known diabetic subjects it was 6.3% and 1.1% among the newly diagnosed diabetic subjects.
Table 32 Prevalence rates of diabetic retinopathy in different populations

<table>
<thead>
<tr>
<th>Prevalence rates of diabetic retinopathy in different populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population studies</td>
</tr>
<tr>
<td>Chennai Urban Rural Epidemiology study</td>
</tr>
<tr>
<td>Los Angeles Latino Eye study</td>
</tr>
<tr>
<td>The Liverpool Diabetic Eye study</td>
</tr>
<tr>
<td>Blue Mountains Eye study</td>
</tr>
<tr>
<td>Taiwan</td>
</tr>
<tr>
<td>Beaver Dam Eye study</td>
</tr>
<tr>
<td>Wisconsin Epidemiologic Study of Diabetic Retinopathy</td>
</tr>
</tbody>
</table>

In another study, 10 years after the diagnosis, 67 per cent of patients had retinopathy and 10 per cent had proliferative diabetic retinopathy. 533

In a study by Stratton et al, in Type 2 (non-insulin-dependent) diabetes patients, 37 per cent of whom already had retinopathy at diagnosis. 534

Diabetic retinopathy may be present even at the time of diagnosis of type 2 diabetes due to the insidious onset of this disease. Earlier
studies have reported on prevalence of the DR at the time of diagnosis in clinic population. Rema et al.\textsuperscript{535} in a study of 438 consecutive newly diagnosed type 2 diabetic patients, reported that 7.3\% already had diabetic retinopathy, detected by four-field retinal colour photography at the time of diagnosis of diabetes. This prevalence was higher compared to 5.1\% in the population-based study because of the bias component in clinical studies. In studies conducted in USA, the prevalence of retinopathy at the time of diagnosis of type 2 diabetes varied from 10-21\%\textsuperscript{536-538} however, in the UKPDS\textsuperscript{539} the prevalence of diabetic retinopathy at the time of diagnosis of diabetes was 35\%, which was phenomenally higher than other studies. Studies done in Australia in the newly detected diabetes\textsuperscript{536} showed a prevalence rate of 9.9\%, which is consistent with the prevalence in India.

Table 33 summarises results of recent population based studies, which shows the prevalence of the DR in urban India.\textsuperscript{524,525,532,535-542} In a population-based study conducted at Hyderabad, the overall prevalence of DR in self-reported diabetic subjects was 22.4\%.\textsuperscript{540} A marginally higher prevalence of DR (26.8\%) was reported among self-reported diabetic subjects aged 50 years and older from Palakkad.\textsuperscript{542} The limitations of these studies were that DR was diagnosed by ophthalmoscopy and was also among self-reported diabetic subjects.

In Chennai Urban Population Study (CUPS), a population-based study conducted in Chennai, involving two residential areas representing the lower and middle income group, overall prevalence of DR was 19\%, which included 17.5\% with NPDR and 1.5\% with PDR. The prevalence of DR in the middle-income group was 21.1\% compared to 14.3\% in the low-income group.\textsuperscript{541} Interestingly the prevalence of diabetes was
higher in middle-income group (12.4%) compared to lower socioeconomic strata (6.5%). This is inconsistent with the Western population studies where diabetes is higher among the lower economic strata. This study was conducted using four-field stereo colour photography and included both known and newly detected diabetic individuals using WHO criteria.

Table 33 Prevalence of diabetic retinopathy in urban India

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Place/State</th>
<th>Diabetic Subjects/ Total Screened</th>
<th>Method of Screening</th>
<th>Prevalence%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall (%)</td>
<td>KD (%)</td>
<td>NDD (%)</td>
</tr>
<tr>
<td>Chennai Urban Rural Epidemiology Study 2005 542</td>
<td>Chennai/Tamilnadu</td>
<td>1715/26001</td>
<td>Stereo colour retinal photography and modified ETDRS grading</td>
<td>17.6</td>
</tr>
<tr>
<td>Palakkad Eye Disease 2002 542</td>
<td>Palakkad/Kerala</td>
<td>260/5212</td>
<td>Questionnaire Slit lamp biomicroscopy/direct ophthalmoscopy and indirect ophthalmoscopy (20 D lens)</td>
<td>-</td>
</tr>
<tr>
<td>Chennai Urban Population Study 2000 541</td>
<td>Chennai/Tamil Nadu</td>
<td>152/1262</td>
<td>Stereo colour retinal photography and modified ETDRS grading</td>
<td>19.0</td>
</tr>
<tr>
<td>Andhra Pradesh Eye Disease study 1999 540</td>
<td>Hyderabad/Andhra Pradesh</td>
<td>124/1399</td>
<td>Slit Lamp biomicroscopy and (78 D lens)/indirect ophthalmoscopy (20 D lens)</td>
<td>-</td>
</tr>
</tbody>
</table>
Patients who have had Type 1 (insulin-dependent) diabetes mellitus for less than 5 years rarely show evidence of sight-threatening diabetic retinopathy, although some background diabetic retinopathy is already present.\textsuperscript{544,545}

There is paucity of data as to the prevalence of diabetic retinopathy in Insulin Dependant Diabetes Mellitus (IDDM) in India as a registry for prevalence of IDDM is only recently being set up in the county. An earlier study done in a clinic-based population reported an overall prevalence of 14%. NPDR was observed in 6%, while 4% had macular edema and 4% had PDR.\textsuperscript{546}

To compare the prevalence of diabetes and its complications in young subjects between different Asian countries a study called Asian Young Diabetes Research (ASDIAB) Study was initiated. This study was done in 724 young diabetic subjects of age 12-40 years with duration of diabetes < 12 months in 7 centers of four Asian countries. It was interesting to note that the prevalence of DR was significantly lower in young Indians compared to other ethnic group like Malays and Chinese.\textsuperscript{547} All the participants underwent four-field stereo colour photography at onset and at the end of 6 years thereafter and DR was diagnosed using modified ETDRS grading system. In this study the fasting C-peptide and glucagons stimulated C-peptide levels were highest among the Indians compared to the other subgroups. Perhaps this could be one of the reasons for lower prevalence DR in young Indians, when compared to young diabetic subjects in other Asian countries or a genuine genetic variation between Indians and other ethnic groups.
DETERMINANTS OF DIABETIC RETINOPATHY

Various risk factors have been associated with DR in epidemiological surveys. The onset and progression of DR may be influenced by many factors including duration of disease, sex, degree of glycaemic control, blood pressure, pregnancy and renal disease.

Virtually all studies carried out in different parts of India have shown an increased prevalence of DR as the duration of diabetes increased.\textsuperscript{524,540-542} Dandona et al\textsuperscript{540} reported that 87.5\% of those with > 15 years duration of diabetes had DR compared with 18.9\% of those who had < 15 years duration. As the study was done only in known diabetic subjects, it may reflect a bias. In the CURES eye study where known and newly diagnosed subjects were studied, severity of retinopathy proportionally increased with longer duration of diabetes, however, only 41.8\% had DR after 15 years of diabetes. In addition, it has been demonstrated that for every five year increase in duration of diabetes, the risk for increased by 1.89 times.\textsuperscript{524}

In a large clinic-based study conducted in south India, it was shown that NPDR and PDR increased as the duration of diabetes increased. In this study, in type 2 diabetic subjects with 20 years or more duration of diabetes, 73\% had NPDR and 11.9\% had PDR.\textsuperscript{531} Although the exact duration of diabetes of type 2 diabetes is difficult to determine, the approximate duration could be calculated from the known onset of diabetes. In type 1 diabetic individuals the duration of diabetes is accurate because of the severity of the disease. In the WESDR, approximately 97.5\% of type 1 diabetic patients had retinopathy after
15 years duration of diabetes. PDR the vision threatening form was present in 25% after 15 years of duration.554,548

There was a male preponderance in relation to DR as shown in clinic (sex ratio – 2:1)535 and in the population-based data from CURES (males-21.3% vs females-14.6%)524 and the Hyderabad study.540 A study done in the Joslin clinic patients in US, showed increased prevalence of DR in females compared to males in the older-onset group, although PDR was present equally in both sexes.549

The risk of developing DR was higher with uncontrolled blood sugar as indicated by the glycated haemoglobin (HbA1c) in the CURES eye study. For every 2% elevation of HbA1c, the risk for DR increased by a factor of 1.7.524 There is strong evidence to suggest that the prevalence of DR is influenced by the level of HbA1c as shown in the CUPS study.541 In subjects with HbA1c ≤7% the prevalence of retinopathy was 12% as compared to 40.7% when HbA1c levels were > 10%. In the 14-year progression of retinopathy study (WESDR), increased risk of PDR was associated with more severe baseline retinopathy and higher HbA1c in type 1 diabetic subjects.550 The DCCT551 demonstrated that intensive control of blood glucose in the primary-prevention cohort reduced the adjusted mean risk for the development of retinopathy by 76% as compared with conventional therapy. In the secondary-intervention cohort, intensive therapy reduced the risk of eye complications for example by 54% for development of DR, decreased progression of NPDR to PDR or severe NPDR by 47% and the need for laser therapy by 56%. the risk reduction in age complications for every 1% decrease in HbA1c in the UKPDS552 was 19%. In the Indian context, Rema et al553 have shown
that visual outcome of laser photocoagulation was also dependent on the degree of glycaemic control as demonstrated in a study on 261 eyes with PDR, who underwent pan retinal photocoagulation.

Hypertension, an established risk factor for retinopathy has been hypothesized, to damage the retina capillary endothelial cells by increase in sheer stress of the blood flow. The possible mechanisms by which hypertension may affect DR are haemodynamic (impaired autoregulation and hyperperfusion) and secondly through VEGF (Vascular Endothelial Growth Factor). It has been observed that hypertension independent of hyperglycaemia upregulates the VEGF expression in retinal endothelial cells and ocular fluids.

Various clinic and population-based studies have shown an association between hypertension and the presence and severity of retinopathy in people with diabetes. Hypertension was significantly associated with PDR in a south Indian clinic cohort. In the CURES eye study presence of hypertension was not a confounding factor, however, uncontrolled hypertension did influence the progression of DR. In the United Kingdom Prospective Diabetes Study, over half of the patients had high blood pressure or were receiving antihypertensive treatment. Tight control of the blood pressure, aiming at below 150/90, had a significant beneficial effect, reducing the incidence of retinopathy and its progression to photocoagulation. For every 10 mm reduction in the systolic blood pressure there was an 11 per cent reduction in the need for laser treatment. The effect was similar whether beta blocker or angiotensin-converting enzyme inhibitor was used.
Dyslipidaemia, independent of glycaemia, has also been shown to be associated with an increased risk of developing retinopathy although the results have not been consistent. An association of diabetic macular edema in type 2 diabetic subjects with increased LDL levels has been shown in an earlier study.\textsuperscript{556} Other studies have demonstrated that decreasing dietary polyunsaturated fats may have an association with shrinkage of exudates and a treatment apt to lower plasma lipid levels reduced the risk the size of perimacular hard exudates. It has also been shown that in type 2 diabetics there was an increase in the lipid peroxidation in plasma and this is accentuated in patients with diabetic complications.\textsuperscript{557} The role of oxidant stress in the causation of DR is increasingly being recognised.\textsuperscript{558,559} Increased erythrocyte glutathionylated Hb (HbSSG) level with decreased glutathione (GSH) was shown to be associated with DR indicating that the increased oxidative stress may be one of the implicating factors in the pathogenesis of DR.\textsuperscript{566} Recently in the CURES eye study, an association of DR was seen with total cholesterol and serum triglycerides. This significance was maintained ever after adjusting for age, as age by itself is a significant risk factor for hyperlipidaemia. Diabetic Macular Edema also showed a strong correlation with high LDL levels in the study.\textsuperscript{561}

Pregnancy can affect pre-existing ocular conditions such as diabetic retinopathy due to hormonal changes.\textsuperscript{562} There is a paucity of epidemiological data as to the role of pregnancy as a risk factor for DR in Indians. Studies conducted in Western population report that progression of all stages of DR can occur in pregnant women with uncontrolled diabetes mellitus. A case control study reported that incidence of PDR in pregnant diabetic individuals was 3 times higher
than in non-pregnant diabetic women.\textsuperscript{563} Fetal loss is more in the presence of retinopathy and the rate increases with increasing severity of retinopathy. In women who begin a pregnancy without retinopathy, the risk of developing nonproliferative diabetic retinopathy has been reported to be about 10 per cent. Further, those with nonproliferative diabetic retinopathy at the onset of pregnancy and those who have or who develop systemic hypertension tend to show progression.\textsuperscript{583}

About four per cent of pregnant women who have nonproliferative diabetic retinopathy progress to PDR.\textsuperscript{583}

Renal disease as evidenced by proteinuria, elevated blood urea nitrogen and elevated blood creatinine is a reliable predictor of presence of retinopathy.\textsuperscript{584}

Even patients who have microalbuminuria are at high risk of developing retinopathy.\textsuperscript{585}

Many studies have reported an association between DR and nephropathy. Microalbuminuria has been associated with the presence of retinopathy in persons with diabetes and with the presence of proliferative disease in younger-onset individuals and hence may be a marker for the risk of developing proliferative retinopathy.\textsuperscript{564} Studies from north India\textsuperscript{565,566} have suggested a correlation between DR and microalbuminuria. Mohan et al\textsuperscript{567} reported that the prevalence of proliferative retinopathy was significantly higher in type 2 south Indian diabetic patients with macroproteinuria (35%) compared with those with microproteinuria (4%). Proteinuria was present in 29.2% of the subjects with DR in the CURES eye study.\textsuperscript{524} Other studies have shown a higher prevalence of DR from 75 to 86% in diabetic subjects with
nephropathy. The varying prevalence rates may be due to the different methods used for documenting DR.

There may be progression of diabetic retinopathy after cataract surgery, however, this can be treated effectively by laser photocoagulation preserving the sight of the diabetic individuals. In the Palakkad Eye Disease Survey, which looked at visual impairment and blindness in the population reported that cataract (27.8%) and refractive errors (38.9%) were the major causes for visual disability among subjects with diabetes. In another study done in 223 eyes of 184 type 2 diabetic subjects after cataract extraction. 44% showed progression of DR and 8.0% developed DR for the first time. This emphasises the need of routine retinal documentation and detecting DR before cataract extraction. Laser photocoagulation done in sight threatening DR helps in the best visual outcomes after cataract extraction.

Recent studies in Western population have shown that DR is associated with atherosclerotic endpoints, severity of DR type 1 diabetes was associated with increased odds of cardiovascular disease and greater mortality in all age groups in a 20-year incidence study. The CURES study, which assessed the association of intima-media thickness (IMT) and arterial stiffness (AI) with diabetic retinopathy in 590 south Indian population demonstrated that IMT and AI showed a significant association with diabetic retinopathy, even after adjusting for age, duration of diabetes, HbA1c, serum cholesterol, serum triglycerides, and microalbuminuria. This association suggests that common pathogenic mechanisms might predispose to diabetic micro- and macroangiopathy.
It has been observed that subjects with DR are likely to be on insulin therapy. In the CURES eye study 46.8% of type 2 diabetic subjects on insulin treatment exhibited DR as compared to 20% on oral hypoglycaemic agents\textsuperscript{524} and in the Andhra Pradesh Eye Disease Study 70% of the subjects on insulin therapy had DR compared to 20.2% on oral hypoglycaemics.\textsuperscript{540} This suggests that there is an association of DR with type therapy although it can be perhaps explained by the fact that subjects with DR may have been preferentially treated with insulin.

There is substantial evidence that good diabetes control is important to prevent diabetic retinopathy, however, some patients develop DR despite good control and others escape retinopathy despite poor control. This suggests the role of genetic factors in susceptibility to retinopathy.\textsuperscript{576} Various studies have identified that there is strong familial and genetic predisposition for the development of DR\textsuperscript{577-579} To study whether there was a familial clustering among subjects with or without DR and their siblings, Rema et al\textsuperscript{578} studied 322 type 2 diabetic families. The risk of developing DR was 3.5 times higher for siblings of probands with DR.

**SCREENING FOR DIABETIC RETINOPATHY**

Life long evaluation for retinopathy by retinal screening is a mandatory strategy, as individuals with DR may not have symptoms.\textsuperscript{580} It is only with the combined effort of diabetologists and ophthalmologists that implementation of a screening programme for diabetic retinopathy is possible in our country. Efficient, objective
methods are available to detect high risk lesions and blindness can be prevented if appropriate laser treatment is instituted early.

WHO SHOULD DO THE SCREENING?

Ideally, screening for diabetic retinal disease should be clone by an ophthalmologist trained for this purpose. When this is not feasible, screening should be the primary responsibility of the doctor in charge of the diabetic patient. This has been endorsed by the 1990 convention on Diabetic Retinopathy by diabetologists and ophthalmologists of Europe.

WHEN TO SCREEN?

It is mandatory that every patient should have a fundus examination at the time of diagnosis of diabetes. This is because, in Type 2 DM patients, retinopathy could be present even at the time of diagnosis of diabetes, due to the insidious nature of this disease and the long asymptomatic period.

If the retina is normal, the follow-up examination should be done on an annual basis, but more frequently if lesions of diabetic retinopathy are already present.

In Type 1 DM patients, the retina should be first examined at the time of puberty or within five years after the diagnosis of diabetes whichever is earlier and annually thereafter. If diabetic retinopathy is complicated by an intercurrent illness or renal disease, more frequent examinations should be done.
The fundi should also be examined if patient's complain of visual symptoms such as impaired central vision, distorted vision or seeing black floaters which may be caused by a vitreous haemorrhage.

Regular examination of the retina of the people with diabetes is simply part of good clinical care in the same way that screening of feet helps to minimize amputation rates. Although often characterized as a free-standing screening exercise with the single aim of detecting those who require laser therapy, retinal screening informs the setting of clinical targets for blood pressure and blood glucose control in individual patients. From the point of view of the patient, it is important that feet, eyes, blood pressure and injection sites are examined annually. The organization of retinal screening is therefore inextricably linked with organization of the rest of clinical care in any one locality.

The single most important characteristic of a successful system is population coverage.

HOW TO SCREEN?

The retina may be examined by ophthalmoscopy and slit lamp biomicroscopy using 78 D lens, or by using retinal photography. It has been shown that seven-standard field stereoscopic 30° fundus photography is the gold standard for assessing DR, however, digital colour photography have now replaced this cumbersome mode of screening.

FOLLOW UP PROTOCOL: The recommended follow up Schedule for diabetic retinopathy is as follows:
Table 34

<table>
<thead>
<tr>
<th>Retinopathy level</th>
<th>Follow-up Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Mild NPDR, no macular edema</td>
<td>12 months</td>
</tr>
<tr>
<td>2) Moderate NPDR, no macular edema</td>
<td>6-8 months</td>
</tr>
<tr>
<td>3) Mild or moderate NPDR with macular edema</td>
<td>4-6 months</td>
</tr>
<tr>
<td>4) Mild or moderate NPDR with CSME</td>
<td>2-4 months</td>
</tr>
<tr>
<td>5) Severe NPDR, no macular edema</td>
<td>3-4 months</td>
</tr>
<tr>
<td>6) All cases of very severe, NPDR, non-high-risk PDR, high risk PDR without macular edema and severe NPDR with either macular edema or CSME</td>
<td>2-3 months</td>
</tr>
<tr>
<td>7) High risk PDR with macular edema or CSME</td>
<td>1-2 months</td>
</tr>
</tbody>
</table>

EFFECT OF SCREENING UPON RATES OF BLINDNESS

A decrease of more than one-third in the incidence of blindness in patients with diabetes in Stockholm country has been reported over a 15 year period of regular screening.

In Newcastle district the rates of blindness and partial sight are now less than one-third of those reported in the surveys prior to 1997, confirming that objectives of the St. Vincent declarations are being achieved. However, a more dramatic observation is that in 1986 there were six people under the age of 25 years registered blind due to diabetes. By 2000, the youngest person blind due to diabetes was 35 years of age. Clearly change in blood pressure and blood glucose therapy have contributed to this change, but it is likely that systematic screening has played the largest part.
MANAGEMENT

Treatment must be appropriately timed and rigorous to prevent diabetes-related visual disability. Visual impairment does not occur in DR, when treatment is most effective hence, preventing visual loss due to DR relies on early detection of the disease by retinal examination. The advent of laser photocoagulation has dramatically changed the management of DR in the last few decades. Several laser photocoagulation procedures like focal and scatter treatment have proven benefits for reducing the progression of diabetic retinopathy, and in some cases, improved the visual acuity. In a study conducted in 261 eyes of 160 type 2 diabetic subjects with PDR who underwent Pan Retinal Photocoagulation (PRP), 73% eyes maintained ≥ 6/9 at 1-year follow-up. Visual acuity at baseline, duration of diabetes and proteinuria played a significant role in determining the post-PRP visual acuity. Gupta et al retrospectively evaluating 96 eyes for the effect of various risk factors on the final visual outcome after laser photocoagulation for Clinically Significant Macular Edema (CSME) in diabetic retinopathy reported that advanced age of the patient, severity of CSME and poor baseline visual acuity were found to be significantly associated with poor visual outcome.

OTHER COMPLICATIONS OF THE EYE:

The other non-retinal complications affecting the eye are the involvement of cornea, iris and lens. The cornea is susceptible to injury and is slower in healing in a diabetic. The abrasions and ulcerations take a longer time to heal. The reduction in corneal sensitivity is symmetrical and is due to diffuse polyneuropathy of the fifth cranial
nerve and its branches. The reduction in corneal sensitivity can be a potential for corneal complications due to contact lens in diabetic patients who wear contact lens. Careful contact lens selection and constant use of artificial tear drops help to overcome this condition. Glycogen can get deposited in the epithelial cells of iris and can lead to depigmentation of the epithelial layer of iris. Rarely there can be new blood vessel growth on the iris, usually observed at the papillary border resembling a cluster of grapes, rubeosis iridis. Rubeosis can progress and a fine network of vessels may grow over the filtration angle of eye. This glaucoma requires aggressive treatment, the prevalence of open-angle glaucoma is 1.4 times more common in diabetic patients, and the prevalence increases with age and duration of diabetes.

Diabetes can have reversible cataracts related to poor metabolic control. The diabetic cataracts are usually bilateral, characterized by dense bands of white sub capsular spots, snow flake in appearance or fine needle shaped opacities. It is more common in earlier onset diabetics.

A condition called ‘anterior optic neuropathy’ is encountered in type 1 DM patients. Extra-ocular palsies are also not uncommon in a diabetic.
DIABETIC FOOT PROBLEMS: INDIAN SCENARIO

The impact of diabetes is staggering. Serious and costly complications such as heart disease, kidney failure and blindness are among the complications that affect individuals with diabetes. However, foot complications take the greatest toll and are the most expensive of all the complications. Approximately 40 to 72% of all lower extremity amputations are related to diabetes.

The diabetic foot is thus a serious issue of great economic and social importance.

DIABETIC FOOT

The global term ‘diabetic foot’ is used to refer to a variety of pathologic conditions that may affect the feet of people with diabetes. A number of facts attest to the importance of diabetic foot disease:

- Diabetic foot infection is a common cause for hospital admission among diabetic patients in India. This could be attributed to several sociocultural practices such as barefoot walking, inadequate facilities for diabetes care and education and poor socioeconomic conditions.\textsuperscript{586}
- Recurrence rates for ulcers in neuropathic subjects were estimated at 52% in a study carried out in 374 patients.\textsuperscript{587}
- In a study from southern India, it was found that patients without foot problems spent 9.3% of their total income, while patients with foot problem had to spend 32.3% of their total income towards treatment.\textsuperscript{588}
- In India, there is a poor awareness regarding the need for foot care among diabetic patients.\textsuperscript{589}
EPIDEMIOLOGY AND ECONOMIC ASPECTS

Foot ulceration is common in both type 1 and type 2 diabetes and occurs in every part of the world. The most recent epidemiological data are from the western USA, where the cumulative incidence of foot ulcers in a population of nearly 9000 diabetic patients was 5.8% over three years of observation. In India, the prevalence of diabetic foot ulcers in the clinic population is 3.6%.

**Epidemiology of the diabetic foot**
- Approximately 40-60% of all (non)-traumatic amputations on the lower limb are performed on patients with diabetes.
- 85% of diabetes-related lower extremity amputations are preceded by a foot ulcer.
- Four out of five ulcers in diabetic subjects are precipitated by external trauma.
- The prevalence of foot ulcer is four to ten percent of the diabetic population.

<table>
<thead>
<tr>
<th>Factors associated with foot ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous ulcer/amputation</td>
</tr>
<tr>
<td>Neuropathy</td>
</tr>
<tr>
<td>Sensorimotor</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Poor footwear</td>
</tr>
<tr>
<td>Walking barefoot</td>
</tr>
<tr>
<td>Falls/accidents</td>
</tr>
<tr>
<td>Objects inside shoes</td>
</tr>
<tr>
<td>Biomechanics</td>
</tr>
<tr>
<td>Limited joint mobility</td>
</tr>
<tr>
<td>Bony prominences</td>
</tr>
<tr>
<td>Foot deformity/osteoarthropathy</td>
</tr>
<tr>
<td>Callus</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Socio-economic status</td>
</tr>
<tr>
<td>Low social position</td>
</tr>
<tr>
<td>Poor access to healthcare</td>
</tr>
<tr>
<td>Non-compliance/neglect</td>
</tr>
<tr>
<td>Poor education</td>
</tr>
</tbody>
</table>
SOCIAL AND ECONOMIC FACTORS

Diabetic foot complications are expensive due to prolonged hospitalization, rehabilitation and increased need for home-care and social services. Given the high cost of diabetic ulcer and amputations to both the individual and society, the relatively low cost interventions of foot-care are likely to be cost effective in most societies. Information regarding the long term prognosis of diabetic foot ulcer is scarce.

PATHOPHYSIOLOGY OF FOOT ULCERATION

Neuropathy (sensory, motor and autonomic) is the most important cause of diabetic ulcer. In addition to purely neuropathic and purely ischemic ulcerations, there is a mixed group of neuro-ischemic ulcers.

SENSORIMOTOR NEUROPATHY

Chronic sensitomotor peripheral neuropathy is the most common long-term complication in diabetes. Sensory neuropathy, motor neuropathy and autonomic neuropathy are the three components of peripheral neuropathy that act conjointly in initiation and perpetuation of diabetic foot ulcers. Loss of pain and thermal sensation renders the foot vulnerable to trauma due to mechanical, chemical and thermal factors, leading to ulcerations. Loss of proprioception and muscle atrophy due to motor neuropathy, result in foot deformities. The resultant alteration in the configuration with new pressure points leads to callous formation and subsequent ulceration. Autonomic neuropathy
sympathetic dysfunction) with absent sweating and dry, fissured skin offering portals of entry for infection are important contributory factors for foot ulcer. Sympathetic dysfunction increases the blood flow with ‘arterio-venous shunting’ leading to warm foot. The insensitive foot due to the shunting is warm and gives a false impression to the patients that the circulation is intact.

Combination of neuropathy and trauma results in tissue breakdown. The atrophy of the intrinsic muscle of the foot, predominantly plantar flexors of the toes alters the flexor / extensor balance at the metatarsophalangeal joints and causes clawing of the toes and prominence of the metatarsal heads. Alterations of foot shape results in increased plantar pressure. A majority of wounds on insensitive foot are not caused by accidental injury or ischemia but from continuous pressure. Often moderate stress as occurring during locomotion on the same part of the insensitive foot leads to calus formation and ulcer. The presence of calus may exacerbate the problem both acting as a foreign body and by increasing the plantar pressure. The neuropathy and the pathophysiology of the diabetic foot is depicted in the Fig – 26.
In a normal as well as in insensitive feet, walking briskly is accompanied by progressive hyperemia over points of maximum stress. Thermography helps to outline the temperature contrast of progressive inflammation from such a process. In subjects with insensitive feet, the thermo graphic pattern shows hyperemia at sites of old scar, thereby inferring that these subjects have been stressing that particular area more than optimally, due to absence of pain and as a result of motor neuropathy. Similarly, in-shoe foot prints help to detect the points of persistent and maximum stress on the feet which probably could be alleviated by proper footwear.
The classical peripheral neuropathy of diabetes mellitus is often bilateral and symmetrical. The sensory component predominates, with patients complaining of pain and paraesthesia while on objective examination there is blunting of pain and temperature sensation - 'the painful painless leg'. The sensory disturbances generally appear early in the distal portions of the lower extremities, eventually progressing to a stock and glove distribution. Involvement of large sensory and motor fibres impairs light touch and proprioception and causes weakness of intrinsic muscles of the feet with alteration of pressure points (Fig - 27).

**Figure 27** Prediction of foot ulcers vs. Neuroarthropathy

<table>
<thead>
<tr>
<th>C–fiber dysfunction</th>
<th>Large fiber dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of pain and warm thermal perception</td>
<td>Loss of vibration and position sense</td>
</tr>
<tr>
<td>Wasted interossei, hammer toes, dry scaly feet, decreased blood flow</td>
<td>Equinus, Warm feet, Increased blood flow, osteopenia</td>
</tr>
<tr>
<td>Ulcer</td>
<td>Neuroarthropathy</td>
</tr>
</tbody>
</table>

( Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)

It has been estimated that upto 50% of older type 2 diabetic patients have evidence of sensory loss on clinical examination and must
therefore be considered at risk of insensitive foot injury. The most challenging patients are those who develop sensory loss with no symptoms, who are difficult to convince that they are at risk of foot ulcer and are consequently difficult to motivate regarding regular foot self-care.  

<table>
<thead>
<tr>
<th>Diabetic neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Sensorimotor and peripheral sympathetic neuropathies are major risk factors for diabetic foot ulcers.</td>
</tr>
<tr>
<td>▪ Neuropathy cannot be diagnosed by history alone; a careful foot examination is mandatory.</td>
</tr>
<tr>
<td>▪ Up to 50% of type 2 diabetic patients have significant neuropathy and &quot;at-risk&quot; feet.</td>
</tr>
</tbody>
</table>

PERIPHERAL VASCULAR DISEASE AND DIABETES IN INDIANS

Peripheral Vascular Disease (PVD) is defined as disease of any blood vessel that is not part of the heart or brain. If it affects the arteries it is termed as Peripheral Arterial Disease (PAD). The most common form of PVD reported, is that observed in the lower extremities, which is also termed as the Lower Extremity Arterial Disease (LEAD). LEAD occurs due to the decreased arterial perfusion to the lower extremities. PVD manifests due to insufficient, arterial perfusion as a result of increased deposits of fatty material (atheroma) in arteries of the legs along with either emboli or thrombi. PVD rarely exhibits an acute onset; it manifests a more chronic progression with or without symptoms.

Peripheral Vascular Disease (PVD) is a major cause of morbidity and mortality especially in the elder population. Furthermore PVD can have a substantial economic impact on the individual, family and society due to limb loss as this disease can result in both direct and indirect costs. It can also decrease the quality of life. Finally PVD is a manifestation of atherosclerosis, it could also be a predictor of fatal
atherosclerotic events like myocardial infarction and stroke. Due to its asymptomatic and insidious nature, PVD does not get the importance it deserves both among patients and among the physicians unlike CAD or stroke which are more dramatic in their presentation.

The peripheral vascular disease occurring in diabetic subjects is multisegmental with a predilection for vessels below the level of the popliteal artery; often the pathology is bilateral. These features are in marked contrast to those encountered in the non-diabetic population. Not uncommonly, the collateral vessels are also involved, with the result that gangrene occurs in patchy areas of the foot and toes, in contrast to the extensive gangrene occurring in the non-diabetic subjects.

Patients may present with intermittent claudication, nocturnal pain and rest pain, the latter two being relieved by dependency. Nocturnal pain is a form of ischaemic neuritis that precedes rest pain. During sleep, the circulation predominantly caters to that splanchnic area, resulting in diminished perfusion of the lower extremities; the consequent ischaemic neuritis becomes intense and disturbs and patient from his sleep. The patient attempts to gain relief by standing, dangling the feet or occasionally walking a few steps; the resultant increase in cardiac output improves tissue perfusion, affording relief from pain. Failure of intervention at the stages of nocturnal and rest pain ultimately results in tissue necrosis and gangrene, necessitating amputation.

On examination of an ischaemic limb, the feet are cold with absent pulses, blanching on elevation with delayed venous filling. The skin appears shiny with loss of hair and thickened nails.
Features of the Ischemic foot

- Painful lesions: dry black gangrene either confined to a toe or the heel, or extensive and superinfected
- Cold feet that become pale on elevation and cyanosed on depression
- Thin atrophic feet; thickened nails; sparse hair
- Peripheral pulses weak or absent
- Slow venous filling
- Vascular investigations: ischemia
- Normal or slightly reduced reflexes and sensation.

On the other hand, the neuropathic foot will be warm and veins will be prominent on the dorsum of the foot due to arterio-venous shunts resulting from autonomic neuropathy.

The vascular laboratory provides essential additional information which serves to initiate measures in the management of peripheral vascular disease. The ankle and toe pressures, ankle-brachial systolic pressure ratio (ischemic index), the wave pattern of flow, are some of the indices routinely used in the assessment. The normal ankles to brachial systolic blood pressure is $>1.0$ and values $<0.6$ usually indicate significant arterial stenosis in the leg. The Doppler ultrasound stethoscope identifies pulse waves in the peripheral vessels. An ankle pressure of less than 70 mm Hg is associated with poor healing of ulcers while a pressure of more than 100 mm Hg is associated with good prognosis. Similarly, a toe pressure of less than 20 mm Hg has been found to be associated with increased failure of distal amputation, while more than 40 mm Hg is associated with good prognosis.
However, the outcome of non-invasive vascular studies should not be allowed to influence clinical judgment on site selection for amputation, because falsely high segmental systolic pressures could be obtained with a rigid calcified lower extremity artery. In fact, the importance of pulsatile wave forms on arterial impedance Plethysmography are more reliable parameters of prevailing vascularity.

Sophisticated techniques are now available for vascular assessment in predicting healing of amputation and ulcers. Skin blood flow calculated from xenon-133 clearance, a micro-invasive procedure and transcutaneous oxymetry are some of those techniques. Cutaneous blood flow of more than 2.6 ml/100 g/min has been associated with good healing. However, all the above indices may fail to predict healing accurately because the state of the local wound dominates the outcome. For example, a severe infection can dampen the beneficial effects of the marginal blood flow or occasionally even a good blood flow.

**Table 35 Foot Ulcer Risk Factors and Relevant Measurement Techniques**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Screening method</th>
<th>Abnormal result indicating increased risk of foot ulceration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>Clinical examinations</td>
<td>Absent ankle reflexes or sensory loss</td>
</tr>
<tr>
<td></td>
<td>Pressure perception threshold</td>
<td>Insensitivity to a 10-gram monofilament on the plantar surface of the foot</td>
</tr>
<tr>
<td></td>
<td>Vibration perception threshold</td>
<td>Greater than 25V at the greater toe</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Clinical examinations</td>
<td>Less than 2/4 palpable foot/ankle pulses</td>
</tr>
<tr>
<td></td>
<td>Doppler pressures</td>
<td>Systolic ankle pressure less than 90% of brachial pressure</td>
</tr>
<tr>
<td>Previous foot lesion</td>
<td>History</td>
<td>History of ulcer or amputation</td>
</tr>
</tbody>
</table>
Neuropathy is the starter, vasculopathy is the chaser and the infection is the perpetuator of the diabetic foot ulcer. The screening procedures are given in the table-35.

CAUSATIVE FACTORS

In India, very few studies have explored the risk factors for PVD. The Causative factors for PVD reported in Western studies include age and duration of diabetes. Several studies have indicated that hypertension and cigarette smoking, two classic risk factors for coronary disease, are also operative for peripheral vascular disease (PVD).\textsuperscript{598}

PERIPHERAL VASCULAR DISEASE AND DIABETES

Peripheral vascular disease is the most important factor related to outcome of a diabetic foot ulcer.
Peripheral vascular disease can often be recognized by simple clinical examination: color and temperature of the skin, palpation of pedal pulses, ankle blood pressure measurement.
The probability of a diabetic foot ulcer healing can be estimated using noninvasive vascular tests. Ankle and occasionally toe blood pressure readings may be falsely elevated due to medial sclerosis.
Rest pain due to ischemia may be absent in diabetic patients (probably) due to peripheral neuropathy.
Micro-angiopathy should never be accepted as the primary cause of an ulcer.
Conservative approaches should involve a walking program (if no ulcer or gangrene is present), appropriate foot wear, cessation of smoking and aggressive treatment of hypertension and dyslipidemia.

Patency rates and limb salvage rates after revascularization do not differ between diabetic and non-diabetic patient; therefore, diabetes is not a reason to withhold this treatment.

PREVALENCE OF PVD AMONG DIABETIC SUBJECTS

Most of the epidemiological studies on PVD were conducted in the 1970-1990s. PVD is considered to be a very common condition affecting 12-20% of Americans aged >65 years. The Höorn study in the Netherlands documented a prevalence of 7.3% in Caucasians in the age group 50-74 years,599 while the Edinburgh Artery Study reported a prevalence of 18% in a Scottish group of age>55 years.600 The prevalence of PVD has been shown to be higher among diabetic subjects compared to age and sex matched non-diabetic subjects.601 Earlier studies from USA, UK, Greece, and the Netherlands have clearly shown that diabetic subjects have a higher risk for PVD compared to non-diabetic subjects.599,600,602-604

PREVALENCE OF PVD IN INDIA

The overall prevalence of PVD among Indians is considerably lower compared to Western patients. A prospective study among 613 type 2 diabetic patients from Tanzania, Germany and India was conducted to determine the differences in underlying risk factors and clinical presentation of foot problems.605 It was reported that PVD was
frequent in Germany while in Tanzania and India it was far less common probably due to younger patient populations, shorter diabetes duration, lower proportions of smokers and ethnicity related factors.

POPULATION-BASED STUDIES

Prevalence of PVD in newly diagnosed diabetic subjects was 3.5% compared to 7.8% in known diabetic subjects. The overall prevalence of PVD in Indians is lower than that reported in Western studies (Table 36).

Table 36 Prevalance of PVD in various population based studies

<table>
<thead>
<tr>
<th>References</th>
<th>Country</th>
<th>Age Group</th>
<th>Prevalance of PVD NGT</th>
<th>Prevalance of PVD DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beach et al</td>
<td>USA</td>
<td>50-70</td>
<td>3.0%</td>
<td>22.0%</td>
</tr>
<tr>
<td>Katsilambros</td>
<td>Greece</td>
<td>All age groups</td>
<td>42. %</td>
<td></td>
</tr>
<tr>
<td>Beks et al</td>
<td>Netherlands</td>
<td>50-74</td>
<td></td>
<td>NDM: 15.1% KDM: 20.9%</td>
</tr>
<tr>
<td>Mohan et al</td>
<td>India</td>
<td>≥20</td>
<td>3.5%</td>
<td>NDM: 3.5% KDM: 11.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50</td>
<td>6.7%</td>
<td>NDM: 6.7% KDM: 9.1%</td>
</tr>
</tbody>
</table>

This lower prevalence of PVD is most likely due to the lower age of the population and the lower age at onset of type 2 diabetes in Indians. As the population ages one can expect the prevalence of PVD to substantially increase even in India. A lesser prevalence of PVD and yet higher prevalence of amputation rate among Indians is due to progressive infection.

HOSPITAL-BASED STUDIES

A couple of hospital-based studies have reported the prevalence of PVD in type 2 diabetic patients. In a study conducted in 3,010 type 2
diabetic subjects, 4.0% had PVD, these included 15.1% with gangrene and 17.6% who had undergone amputations. In another hospital-based study on 4,941 subjects, the prevalence of PVD was 3.9%. There was a slight female excess in PVD patients. PVD increased with increase in duration of diabetes. A hospital-based study from Bikaner in north-west India, recruited 4,067 type 2 diabetic patients. PVD was diagnosed using Doppler. The study showed that among diabetic the prevalence of PVD was 24.6%. This study also describes the various risk factors associated with PVD.

ASSESSMENT OF PVD

The simplest screening test for PVD is palpation of peripheral pulses and this is the usual clinical tool to assess occlusive arteries in peripheries. Absence of posterior, tibial, popliteal, or femoral pulses on peripheral examination are clinically significant and indicate significant occlusive disease. Sometimes it is difficult to interpret the significance of diminished peripheral pulses when symptoms are not present. Measurement of the ankle-brachial index (ABI), which represents the systolic blood pressure at the posterior tibial or dorsalis pedal level compared with brachial blood pressure, can be used to define clinically significant occlusive disease. However, at time in diabetic patients with arterial wall calcification, pressure measurements may be falsely elevated.

PVD is associated for increased morbidity and mortality, its early recognition is of great important. Angiography is considered to be the gold standard for diagnosis of PVD, but this technique is an invasive procedure requiring expertise, use of contrast agent, and it is
expensive. Color Duplex Ultrasound (CDU) and Continuous Waveform Doppler (CWD) (peripheral Doppler) can be used as alternatives, keeping in mind their limitations. Extensive studies have been done on the reliability, reproducibility, sensitivity and specificity of CDU. Several studies have documented that CDU is reliable in detecting and locating stenosis and plaques in peripheral arteries\textsuperscript{611-614} and for detection of peripheral embolisation\textsuperscript{614}

**DYSLIPIDAEMIA AND PVD**

There is a strong association of hyperlipidaemia with peripheral vascular disease. In the Bikaner study, regression analysis revealed low HDL and high LDL cholesterol to be associated with PVD in north Indian diabetic subjects\textsuperscript{609}. The ratio of LDL-cholesterol to HDL-cholesterol probably assumes greater significance in the diabetic population because the protective effect of a high HDL-cholesterol is nullified by a concomitant increase in LDL-cholesterol fraction.

**PVD AS A MARKER FOR OTHER ATHEROSCLEROTIC DISEASES**

Several studies in Western countries have shown PVD to be a significant of coronary artery and cerebrovascular disease\textsuperscript{615,616}. However, there are no studies assessing the predictive role of PVD for other microvascular disease in Indians. This is very important because of differences between the prevalence rates of rates of CAD and PVD in Asian Indians.

Prevalence of PVD in Indians are substantially lower compared to other ethnic groups, in contrast CAD is very abnormally high. While CAD occurs with increased prevalence and at a younger age (premature
CAD), PVD appears to show the opposite trend, i.e., lower prevalence and occurrence at older age groups. This suggests that the pathogenic mechanisms for CAD and PVD could be different.

CONCLUSIONS

The prevalence of PVD seems to be significantly lower in Indians compared to other ethnic groups. However, even this low prevalence could be a matter of concern as 6% (prevalence of PVD) of the total diabetic population in India (32 million) would represent a huge decrease burden. Moreover, as the population ages one can expect the prevalence of PVD to substantially increase. This calls for early detection to avoid morbidity and mortality due to PVD. Awareness among physicians and patients must be improved to overcome the economic and health burden due to PVD in India.

PLANTAR PRESSURE

Based on many studies linking high barefoot pressure to ulceration, it makes sense to measure barefoot plantar pressure in all patients with loss of protective sensation. The best study that defines risk is that of Armstrong et al. They suggested that a pressure of 750 kPa provides the best level of discrimination between low-risk and high-risk patients. They do point out, however, that the higher the pressure, the higher the risk, and there is no clearly safe pressure. Therapeutic footwear is course an option that can be utilized to deal with all the abnormalities that cause high pressure.
LIMITED JOINT MOBILITY

Glycosylation of collagen in tendons and ligaments results in limited motion of joints found in feet. Limited joint mobility (LJM) contributes to the abnormal mechanics in the diabetic foot. Diabetic subjects often have limitations in the range of motion of feet that are rigid, firm and dry. LJM is associated with an increased foot pressure and greater chances of foot ulceration.

In a prospective study, LJM and the foot pressure were measured in 345 subjects of whom 295 had diabetes and the remaining 50 were non-diabetic controls. The diabetic patients were those with neuropathy and without neuropathy. In this study, it was reported that the joint mobility at the ankle and at the big toe was significantly reduced in the diabetic patients when compared with control. Among the diabetic patients those with neuropathy and those with history of foot ulcer had significantly lesser joint mobility. LJM and increased foot pressure appears to be important determinants of foot ulcerations in south Indian diabetic patients.

FOOTWEAR

People with intact sensation respond to repetitive stress that occurs during walking either by shifting the pressure to another part of the foot, by modifying the foot meets the ground, by resting or by checking their shoes for problems. Lack of feeling makes shoe-fitting assistance essential.
QUALITIES OF GOOD FOOTWEAR

The footwear for diabetic should:
- Relieve areas of foot pressure
- Prevent ulcers in insensate foot
- Fit the foot correctly
- Give grip while walking
- Improve gait
- Accommodate, stabilise and support deformities
- Provide relief of pain as well as protect the foot.

BIOMECHANICS AND FOOTWEAR

Biomechanical abnormalities are frequently a consequence of diabetic neuropathy and lead to abnormal plantar foot pressure. A combination of foot deformity and neuropathy increases the risk of ulcer. Pressure relief is essential for the prevention and healing of an ulcer, as abnormal foot pressures lead to plantar ulceration. Shoes and inserts should be inspected frequently and replaced when necessary. A patient should never return to footwear which has caused ulceration. Appropriate footwear (adapted to high pressures, deformities, and/or lesions present in the foot) has been associated with significantly fewer recurrences and development of ulceration.

The effectiveness of therapeutic footwear has been reported in a recent study conducted at Diabetes Research Centre, Chennai. The

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foot pressure was measured in 241 diabetic patients who had previous foot ulceration. Among 241, 191 wore therapeutic footwear using a combination of insole materials and 50 wore their usual footwear. Reulceration occurred after 9 months in 33% of patients who resumed wearing their own footwear, compared to 4% of those who wore therapeutic footwear. This study also reported that the patients included in the therapeutic group showed a relatively decreased foot pressure while those who used the non-therapeutic footwear showed an increase in foot pressure. Use of therapeutic footwear was therefore recommended in order to reduce ulceration and consequently the amputation rate in the diabetic population.

THE DIABETIC FOOT ULCER: OUTCOME AND MANAGEMENT

In diabetes, healing of foot ulcer is limited by multiple factors and therefore requires a multifactorial approach. Control of infection, treatment of vascular disease, pressure relief and wound management are essential components of the multifactorial treatment of foot ulcers. Type, site and cause of the ulcer must be considered in choosing treatment strategies. Topical wound management is adjunctive to systematic and surgical treatment. Continuity of care and lifelong observation of the diabetic foot at risk are essential both in management and prevention of foot ulcers.
INFECTION

Frequent and severe infection in diabetic subjects is facilitated by vascular insufficiency. A normal individual responds to infection by increasing the blood supply to the site, as blood supply has to be increased 12-15 times to maintain the viability of the skin. If this increased demand cannot be met, the skin breaks down and tissue necrosis results. Necrosed tissue is a good nidus for organisms to thrive.

Most of the diabetic foot infections are caused by multiple organisms, including anaerobes. Bacteriodes are the commonest group of pathogens isolated in culture. Soft tissue gas formation has been encountered in diabetic subjects and the capacity for gas formation is exhibited not only by the coliform group (aerobic and anaerobic gram negative rods) but also by streptococci and staphylococci. Osteomyelitis is observed in some of the diabetic foot lesions.

Many diabetic foot ulcers tend to be neglected because patients are asymptotic. Osteomyelitis should be suspected when a non-healing ulcer overlies a bony prominence. It should however be distinguished from diabetic osteopathy, occurring as a result of denervation (Fig-27).

The radiological hallmark of diabetic osteopathy is the characteristically pointed distal metatarsal called ‘the peppermint stick sign’. The distribution of diabetic osteopathy is multifocal and bilateral; besides, the condition is associated with normal leukocyte count and ESR. However, the distinction between osteomyelitis and
osteopathy is often made on clinical grounds and radiology.

<table>
<thead>
<tr>
<th>Diabetic foot infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Infection in a diabetic foot is limb-threatening and must be treated empirically and aggressively.</td>
</tr>
<tr>
<td>- Signs and symptoms of infection (fever, increased white blood count, elevated CRP) may often be absent in diabetic patients with infected foot ulcers.</td>
</tr>
<tr>
<td>- A superficial infection is usually caused by Gram-positive bacteria, whereas deep infections are often polymicrobial, involving anaerobic and Gram-negative bacteria.</td>
</tr>
<tr>
<td>- In acute deep foot infection, surgical removal of infected tissue is essential.</td>
</tr>
<tr>
<td>- A multidisciplinary approach providing debridement, meticulous wound care, adequate vascular supply, metabolic control, empirical antimicrobial treatment and relief of pressure is essential in the treatment of foot infection.</td>
</tr>
</tbody>
</table>

NEURO-OSTEOARTHROPATHY

Neuro-osteoarthropathy should be suspected in any hot, erythematous and swollen foot and the patient should be referred to a specialist diabetic foot team.

Differentiation from infection is important to prevent misdiagnosis and possible amputation.

The aim of treatment with foot contact casting and limitation of activity is prevention of severe deformity.

Features of the neuropathic foot

- Disproportion between lesions and absence of pain.
- Keratosis, cracks, ulcers and plantar ulcers.
- Deformity of foot and toes; amyotrophy
- Loss of sense of touch, pain and vibration; loss of tendon reflexes
- Warm dry feet, venous congestion; edema
- Pulses present; no evidence of ischemia on investigation.
AMPUTATIONS IN DIABETIC PATIENTS

As the number of limbs salvaged by arterial reconstruction and foot revisions increases, the number of minor amputations and thereby the number of deformed feet requiring special shoe and orthotic fitting is also increasing.

Minor amputations may be indicated to remove gangrene, e.g. after revascularization for ischemia, as a part of a debridement for foot infection, or for correction of foot deformities.

As patients who have undergone a major amputation have a high risk of subsequent contralateral amputation, a surveillance program for the remaining foot is crucial.

Although healing may take several months, minor amputations do not significantly compromise the ability to walk, but may result in progressive deformity.

When considering major amputation, the option of revascularization should first be considered.

Arterial perfusion at the level of amputation should be assessed when an amputation is performed. Glycemic control and nutritional status should be optimized.

A non-healing ulcer is not an indication for a major amputation.

Limited resection with open wound management is beneficial in foot infection and can preserve weight-bearing areas.

PATIENT EDUCATION

These include giving detailed foot care recommendations, requesting patient commitment to self-care, demonstrating and practicing foot
care procedures and communicating a persistent message that foot complications can be avoided by self-care.

A number of studies have shown the beneficial effects of foot care education. In a study by Barth et al, it was shown that patients who were on intensive educational group showed greater reduction in the number of foot problems requiring treatment, in comparison with the patients in the conventional group. In an Amputation Prevention Initiative in south India, it was shown that strategies like intensive management and foot care education were helpful in preventing recurrent problems and surgery. Type 2 diabetic patients with high-risk foot were selected for the study. Ulcers present during the recruitment had healed in 81% subjects who followed the advice, whereas among the non-adherent subjects, complete healing occurred only in 49%. A significantly larger proportion of subjects who did not follow the advice developed newer problems (26%) and required surgical procedures (13%) when compared with those who followed the advice (7%, 3% respectively).

Since the ‘diabetic foot’ is the sequel of interaction of a multitude of factors, intervention must be directed towards correction of all the causative factors.

**HOW TO PREVENT FOOT PROBLEMS**

Foot examination should be performed in diabetic patients at least once a year and more frequently in those patients at high risk of foot ulceration.
Identification of patients at risk of ulceration is the most important aspect of amputation prevention.
Education, an integral part of prevention, should be simple and repetitive.
Education should be targeted at both healthcare providers and patients.

CONCLUSIONS

People with diabetes need to take special care of their feet. Neuropathy and blood vessel disease both increase the risk of foot ulcers. Because of the loss of sensation caused by neuropathy, sores or injuries to the foot may not be noticed and may become ulcerated. Routine annual foot screening facilitates early interventions to reduce the incidence of the most common precipitating events including injury and foot-related trauma to the insensitive foot. The key elements of preventive care include: annual examination of the feet by healthcare providers to determine risk factors for ulceration, subsequent examination of high-risk feet at each patient visit, patient education about daily self-care of the feet and careful glucose management.

ORGANIZATION OF FOOT CARE

Effective organization requires systems and guidelines for education, screening, risk reduction, treatment and auditing. There is strong evidence that the institution of a multidisciplinary foot-care team reduces amputation rates. The specialist foot-care team must not only treat patients, but must also work in the primary care setting.
Make each patient a respected member of the team- you cannot succeed without their help.

**CORONARY ARTERY DISEASE AND DIABETES**

**INTRODUCTION**

Type 2 diabetes, one of the top five causes for mortality presently affects more than 170 million individuals worldwide. Diabetes is not a mixture of several metabolic abnormalities; it also affects the vascular tree resulting in multiple micro- and macrovascular complications. Premature cardiovascular morbidity and mortality is reported to be more common in diabetic subjects. All these make diabetes an expensive disease. Over 8% of total health care expenditure in many countries is attributed to diabetes and over 80% of death in diabetic subjects are due to cardiovascular disease, of which 2/3rd are due to coronary Artery disease (CAD). It is estimated that in the year 2000, 2.9 million deaths were due to diabetes, which is nearly 5% of the total deaths reported worldwide. The scenario is even worse in developing countries, particularly India.

**EPIDEMIOLOGY OF DIABETES AND CAD-INDIAN SCENARIO**

Indians also have three times higher risk of developing CAD compared to Chinese and are 20 times more likely to die due to CAD compared to native black or white South Africans. The SHARE study demonstrated that south Asians had higher prevalence of cardiovascular disease compared to Europeans and Chinese living in Canada. Moreover, Indians also tend to develop CAD two to three decades earlier compared to Europeans. This predilection for CAD among Indians was reported fifty years ago, which was confirmed
later by several studies.632,633 In India, approximately 2.78 million deaths are due to cardiovascular disease, of which over 50% is due to CAD, making CAD the number one killer disease in our country.634 Prevalence of CAD in Indians has been shown to be escalating in alarming proportions in the few decades. The prevalence of heart disease in 1950s was 1.05%; this increased to 9.7% in 1990 and to 11.0% by 2000 in urban populations635.636 (Table 37) In the Jaipur Heart Watch-2 study conducted in 2002, prevalence of CAD was reported to be 8.2%.637 This rising trend in CAD will shortly make India, the leader in CAD death rates also.638 Thus India faces the dangerous dual epidemic of diabetes and CAD and in many respects, the aetio-pathogenesis of both conditions may be similar.

**Table 37 Prevalence of CAD in Urban and Rural India**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age Group (Years)</th>
<th>Place</th>
<th>Sample size</th>
<th>CHD(%) ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathur KS</td>
<td>1960</td>
<td>30–70</td>
<td>Agra</td>
<td>1046</td>
<td>1.05 ± 0.3</td>
</tr>
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<td>Padmavathi</td>
<td>1962</td>
<td>30–70</td>
<td>Delhi</td>
<td>1642</td>
<td>1.04 ± 0.3</td>
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<tr>
<td>Savoruthi SG</td>
<td>1968</td>
<td>30–70</td>
<td>Chandigarh</td>
<td>2030</td>
<td>6.60 ± 0.6</td>
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<tr>
<td>Gupta SP</td>
<td>1975</td>
<td>30–70</td>
<td>Rohtak</td>
<td>1407</td>
<td>3.63 ± 0.5</td>
</tr>
<tr>
<td>Chaddha SL</td>
<td>1950</td>
<td>25–64</td>
<td>Delhi</td>
<td>13723</td>
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<td>Reddy KS</td>
<td>1994</td>
<td>35–64</td>
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<tr>
<td>Gupta R</td>
<td>1995</td>
<td>20–80</td>
<td>Jaipur</td>
<td>2212</td>
<td>7.59 ± 0.6</td>
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<tr>
<td>Singh R B</td>
<td>1995</td>
<td>20–70</td>
<td>Morababad</td>
<td>152</td>
<td>8.55 ± 2.3</td>
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<tr>
<td>Begom TR</td>
<td>1995</td>
<td>20–70</td>
<td>Trivandrum</td>
<td>506</td>
<td>12.65 ± 1.5</td>
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<td>Mohan V</td>
<td>2001</td>
<td>≥20</td>
<td>Chennai</td>
<td>1262</td>
<td>11</td>
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<tr>
<td>Gupta R</td>
<td>2002</td>
<td>≥20</td>
<td>Jaipur</td>
<td>1123</td>
<td>7.30</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age Group (Years)</th>
<th>Place</th>
<th>Sample size</th>
<th>CHD(%) ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dewan BD</td>
<td>1974</td>
<td>30–70</td>
<td>Haryana</td>
<td>1506</td>
<td>2.06 ± 0.4</td>
</tr>
<tr>
<td>Japoo UN</td>
<td>1988</td>
<td>30–70</td>
<td>Vadodara</td>
<td>2433</td>
<td>1.69 ± 0.3</td>
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<tr>
<td>Katty VR</td>
<td>1993</td>
<td>≥25–65</td>
<td>Kerala</td>
<td>1130</td>
<td>7.43 ± 0.8</td>
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<td>Wander GS</td>
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<td>30–70</td>
<td>Punjab</td>
<td>1100</td>
<td>3.09 ± 0.5</td>
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<tr>
<td>Gupta R</td>
<td>1994</td>
<td>20–80</td>
<td>Rajasthan</td>
<td>8148</td>
<td>3.53 ± 0.3</td>
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<tr>
<td>Singh RB</td>
<td>1995</td>
<td>20–80</td>
<td>U P</td>
<td>162</td>
<td>3.09 ± 1.4</td>
</tr>
</tbody>
</table>
The risk for CAD among diabetic subjects is remarkably higher compared to non-diabetic subjects. The risk for death due to CAD in diabetic subjects with one prior myocardial infarction (MI) is similar to that seen in a non-diabetic subjects with an earlier MI, while the risk is tripled in diabetic subjects with known MI. The life expectancy of a diabetic patient is reduced by 30% compared to non-diabetic subjects which translates to 8 years loss of life years in diabetic subjects. Further, the protective female gender effect in pre-menopausal women is abolished in diabetic females. The Chennai Urban Population Study (CUPS), 11% of the total population had CAD and the age-standardized prevalence (standardized to the 1991 census of Chennai) was 9.0%. 1.2% had
documented myocardial infarction, 1.3% had Q wave changes, 1.5% had ST segment and 7.0% T wave abnormalities. The overall figure of 11% of CAD in the population represents a ten-fold increase in prevalence of CAD in urban India during the last 40 years.\textsuperscript{636} The prevalence of CAD was higher among diabetic subjects (21.4%) (Known diabetes 25.3% and newly diagnosed diabetes-13.1%) compared to 14.9% among subjects with impaired glucose tolerance (IGT) and 9.1% among subjects with normal glucose tolerance.\textsuperscript{636} Prevalence of Known myocardial infarction was three times higher in subjects with diabetes compared those without. At every age point, subjects with diabetes and impaired glucose tolerance had higher prevalence of CAD compared subjects with normal glucose tolerance. The risk for CAD thus seems to increase even at the stage of impaired glucose tolerance.

**Mortality Due to CAD in Diabetic Subjects**

Mortality among diabetic subjects with CAD is higher than in non-diabetic subjects.\textsuperscript{639} Studies have also shown that the myocardial infarction in diabetic subjects is more extensive and recurrence is more common in them compared to non-diabetic subjects. Furthermore, the prognosis after a clinical event is worse in diabetic subjects compared to non-diabetic subjects.\textsuperscript{641} A review on diabetes and atherosclerosis showed that the metabolic abnormalities due to diabetes predispose to vascular changes, which in turn lead to atherosclerotic end-points.\textsuperscript{645} Very high risk for CAD among diabetic subjects lead the American Associations to label diabetes as a cardiovascular risk equivalent.\textsuperscript{646}
The Chennai Urban Population Study (CUPS), mortality due to cardiovascular (52.9% vs 24.2%, p=0.042) and renal causes (23.5% vs 6.1%, p=0.072) were higher among diabetic, compared to non-diabetic subjects. The hazards ratio for diabetics for mortality due to cardiac vascular disease was 7.8 (95% CI: 3.0 - 20.2, p<0.001). Another interesting observation is that out of the total of 1,070 subjects, who had baseline information on coronary artery disease, recurrence of coronary artery disease was observed in 4.2%, and all these occurred in diabetic subjects.647

RISK FACTORS FOR CAD

Several risk factors have been identified for CAD in the general population, which includes aging, smoking, strong family history of CAD and diabetes. The INTERHEART study involving 15,152 cases and 14,820 controls from 52 countries revealed nine risk factors for CAD, which includes abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, decreased consumption of fruits and vegetables, excess alcohol intake and physical inactivity.648 Usual metabolic abnormalities like hyperglycaemia, hypertension and hyperlipidaemia complicate atherosclerosis in diabetes. Studies have demonstrated that atherosclerosis manifests earlier among diabetic subjects.

Additionally newer risk factors are also involved in this phenomenon and some of them discussed below:
METABOLIC CLUSTER AND CAD

Several epidemiological studies have shown that metabolic cluster contributes to CAD. Insulin Resistance plays a central role in metabolic abnormalities as it clusters with hyper insulinaemia, hypertension (HTN), glucose intolerance, increased triglyceride, decreased HDL cholesterol levels, central and overall obesity. This was first identified by Reaven and termed as ‘Syndrome X’ which was later renamed as the metabolic syndrome or the insulin resistance syndrome (IRS).649 This syndrome has been recognized as a major risk factor for coronary artery disease (CAD).650,651

Studies by Laasko et al652 and Meigs et al653 have shown using factor analysis that the metabolic abnormalities cluster and result in CAD. The CUPS study using factor analysis, showed that the components of metabolic syndrome-insulin resistance (HOMA IR), obesity, hyperglycaemia and hypertriglyceridaemia clustered in native Indian population and this cluster is associated with hypertension.654 An earlier study conducted on 654 non-diabetic subjects aged ≥ 40 years also showed similar results. The insulin resistance factor was found to cluster with hypertension through obesity indices.655 In CUPS, CAD also showed a strong association with components of metabolic abnormalities which includes hyperglycaemia, hypertension and dyslipidaemia.656,657

In CURES, they looked at the association of CAD with metabolic syndrome defined by three different criteria, the World Health Organisation (WHO), Adult Treatment Panel (ATPIII) and International
Diabetes Federation (IDF) criteria. Prevalence of CAD was higher among subjects with metabolic syndrome irrespective of whichever definition was used. However, metabolic syndrome defined using WHO criteria had highest odds ratio for CAD compared to other definitions. This could probably be due to inclusion of insulin resistance in the WHO criteria of metabolic syndrome.

INFLAMMATORY MARKERS

Several studies have shown an association between inflammatory markers with diabetes. Chronic low grade inflammation is considered to play a contributory role in both diabetes and CAD. Inflammation has been documented to be increased even during the insulin resistance stage which continues during the diabetes stage and eventually results in CAD. Inflammatory changes could also take place near the rupture of the plaque, leading to instability of the fibrous tissue in the plaque, thus facilitating the risk of chronic thrombosis. Studies on proinflammatory markers have revealed that cytokines like tumour necrosis factor-α (TNF-α), C-reactive protein (CRP) and interleukin-6 (IL-6) are strongly associated with CAD. Recent studies suggest that CRP plays a key role in mediating insulin resistance and coronary artery disease.

Studies conducted in UK has shown that CRP levels are higher in migrant Indians compared to other ethnic groups. This is suggested as one of the reasons for the high prevalence of heart disease among Indians. CRP also has a strong association with cardiovascular risk factors, like obesity, insulin resistance and lipids. A study on children also suggested that Asian Indian children had higher
CRP levels compared to Europeans. However, there have been very few studies on native Indians with one study showing that CRP correlated significantly with body fat.

Mohan et al included non-diabetic subjects without CAD, diabetic subjects with and without CAD, CRP levels were higher among diabetic subjects with and without CAD compared to non-diabetic subjects without coronary artery disease. CRP showed a strong association with CAD, even after adjusting for age and gender, and the association was abolished when body fat was added into the model. A review on the relevance of CRP in young individuals associates high CRP in Indians with excess body fat, subcutaneous fat and physical inactivity.

**FIBRINOLYTIC MARKERS**

Insulin resistance not only clusters with classic cardiovascular risk factors like hypertension and dyslipidaemia, but also with several disorders of coagulation and fibrinolysis. Patients with insulin resistance syndrome and diabetes mellitus tend to have increased plasminogen activator inhibitor (PAI-1) levels. The later have been shown to be associated with a number of atherosclerotic risk factors. Decreased fibrinolysis, increased PAI-1 levels, increased t-PA and increased fibrinogen levels are now considered to be part of the metabolic syndrome. Proinsulin and insulin induce production of PAI-1 in experimental models. In one of the studies on diabetic and non-diabetic subjects with CAD have shown fibrinogen and PAI-1 levels to be associated with angiographically proven CAD and the
relative odds ratios for CAD also increased with increase in quartiles of fibrinogen and plasminogen activator inhibitor.\textsuperscript{669}

**OTHER ATHEROGENIC MARKERS**

**SMALL DENSE LDL**
In diabetic subjects, LDL tends to get modified due to hyperglycaemia and other oxidation stress and metabolic abnormalities. A study in Birmingham, USA revealed that migrant Indians have higher small dense LDL compared to their white counterparts.\textsuperscript{670} In a study in south Indians, small dense LDL levels were higher in diabetic patients and even higher in diabetics with CAD.\textsuperscript{671} Small dense LDL is considered to be more prone to oxidation and conformational changes.\textsuperscript{672}

**OXIDISED LDL (OX-LDL)**
Some studies have shown the oxidisability of LDL to be associated with early structural changes.\textsuperscript{673} Oxidatively modified LDL, has reduced clearance by its receptors, triggering immunological changes resulting in atherosclerosis.\textsuperscript{674} OX-LDL is found in monocyte-derived macrophages in atherosclerotic lesion but not in normal arteries.\textsuperscript{675} It has also been suggested that OX-LDL induces smooth muscle cell proliferation.\textsuperscript{676} An earlier study from south India\textsuperscript{677} has shown an increase in antibodies to oxidised LDL in Indians with CAD. In a recent study Deepa et al had shown that oxidised LDL increases with increase in severity of glucose intolerance and it also exhibited a strong association with IMT.\textsuperscript{678}
LIFESTYLE FACTORS AND CAD

India is facing a rapid epidemiological transition which has led to transition in nutrition and lifestyle. Increased consumption of energy dense fast foods combined with sedentary lifestyles has increased the prevalence of diseases like diabetes and CAD. Several studies have shown an increase in the prevalence of cardiovascular risk factors in urban areas compared to rural areas. In the CUPS study, proportion of subjects with diabetes and hypercholesterolaemia were higher among middle-income group compared to low-income group. In the same study they also analysed the association of CAD with physical activity. When heavy grade activity was taken as reference, the odds ratio for CAD in the light grade activity was 2.42 (95% confidence interval: 1.40-4.24, p=0.011) for CAD. There is increasing evidence that with changes in lifestyle prevention of CAD is possible, further, the DPP and DPS studies have clearly documented that diabetes also can be prevented by exercise and weight loss.

PROGNOSIS AND COURSE OF CAD IN DIABETIC PATIENTS

Mortality after acute myocardial infarction in diabetic versus non-diabetic patients is already greatly increased during hospital stay. As an example, a retrospective study by Yudkin and colleagues demonstrated a hospital mortality of 24.7 per cent in 380 non-diabetic (patients defined by normal HbA1c values) after infarction versus 42.2 per cent in diabetic patients, which is almost doubled.
Medium- and long-term survival is also decreased in diabetic patients with coronary heart disease. In the aforementioned Finnish observation trial by Heffner et al. only a little more than half of the patients with Type 2 diabetes survived the 7 year observation time after myocardial infarction.\textsuperscript{687}

Similar results were seen in the diabetes subgroup analysis of the placebo arms of the statin intervention trials, such as the 4S-trial.\textsuperscript{688}

In the OASIS trial, which was conducted in six different countries, male patients with diabetes mellitus admitted due to unstable angina or non-Q-wave infarction showed a 1.5-fold increased mortality in the following 2 years compared with non-diabetic patients. In female diabetic patients the 2 year mortality rate was even twice as high.\textsuperscript{689}

Coronary heart disease in diabetic patients shows significantly more frequently a multi-vessel disease pattern with diffuse coronary sclerosis than in non-diabetic patients. Acute coronary syndrome in diabetic patients leads more often to impaired left ventricular function. The occurrence of cardiac dysrhythmias also seems to be higher. The primary size of infarction, however, does not differ significantly.\textsuperscript{690}

\textbf{CONCLUSIONS}

Overall, Indians seems to be more predisposed to both diabetes and CAD. This is due to lifestyle changes with increased consumption of high energy dense foods and decreased physical activity. By adopting lifestyle changes, more of these risk factors can be modified and thereby both diabetes and CAD are potentially preventable.
SEXUAL DYSFUNCTION

Sexual function is a complex blend of anatomic, neurologic, metabolic, endocrine and psychic factors more than any other human activity. Alterations in any one of the factors can result in sexual dysfunction. Though the exact prevalence of sexual dysfunction in general population is not known, the consensus is that this problem is not uncommon in male diabetic subjects. Amongst the systemic diseases, diabetes is unique in this regard. The prevalence of erectile dysfunction in male diabetic subjects varies between 30 to 70%, the average being 50% and increases as age advances. Sexual dysfunction in a male diabetic subject may occur at an early age and could be the presenting symptom of diabetes.

ETIOLOGY

Causes of erectile failure may be enumerated as metabolic, psychogenic, endocrine, neurological, and vascular and drug induced or mixed Figure 29. The organic causes are the commonest, comprising about 85% of the cases, psychological problems account for about 10% and in the remaining 5%, the cause is not known. Failure to attain penile erection due to organic causes puts a man into strain and repeated unsuccessful attempts leads to psychological stress and the vicious cycle perpetuates. In any sexual dysfunction, psychogenic cause always exists and male diabetic subjects are no exception to this.
METABOLIC

Among the organic causes of erectile failure diabetes is the most important. The impact of diabetes and associated factors on sexual function is given in Fig - 30.

PATHOGENESIS

Pathogenesis of erectile dysfunction is multifactorial. Neuropathy, accelerated atherosclerosis and alterations in the corporal tissues, smooth muscle degeneration, abnormal collagen deposition and endothelial dysfunction have all been implicated. Increased oxidative stress, glycation, protein kinase C activity and aldose reductase may also be causative factors.
HORMONAL CAUSES

The role of hormonal disturbances leading to diabetic erectile failure is yet to be settled. There are differing opinions on this etiology causing sexual dysfunction as testosterone levels and its response to HCG stimulation were found to be normal in many instances. Testicular biopsy studies showed more abnormalities when compared with non-diabetic controls and hence the concept of "Diabetic testes". In a study conducted at Govt. General Hospital, Madras on male diabetic subjects with erectile failure there were reduction in urinary testosterone levels and concomitant reduction in Leydig cell distribution in testicular biopsies.
SPERMATOGENESIS

Alterations in spermatogenesis appear closely associated with metabolic disturbances and to the presence of autonomic neuropathy. Damage to seminal vesicles is seen. Alterations in the sexual behavior and reduction in the weight of secondary sex glands is observed in diabetic animals. In these animals production of androgens and disturbance in spermatogenesis occurs as a result of altered gonadotropin pulsatility.

NEUROGENIC CAUSES

Increased incidence of erectile failure in a male diabetic subject seems to be primarily a result of diabetic autonomic neuropathy. This observation was substantiated by bladder function studies. The pelvic parasympathetic nerves (Nervi erigentes) that lead to erection also innervate the bladder and involvement of those nerves is demonstrated by the abnormal cystometrogram.

Autonomic neuropathy assessment in male diabetic subjects with erectile failure revealed greater involvement of parasympathetic nerves and hence it is not surprising that erectile erectile failure is the common sexual dysfunction in a male diabetic subject.

VASCULAR CAUSES

Both macro and micro-vascular complications of diabetes may confound the clinical picture of diabetic erectile failure. Severe vascular lesions involving the distal aorta and iliac arteries as in Leriche’s syndrome may also result in erectile failure. Small blood
vessel disease (micro-angiopathy) may further interfere with normal penile function. Whether neuropathy in a male diabetic subject can influence vascular lesions with subsequent production of erectile failure is still subjudice. Invariably male diabetic patients with arterial occlusive disease secondary to arterioscleroses do also have corporal veno occlusive dysfunction due to pan cavernosal alteration in corporal tissue compliance.

DRUG INDUCED ERECTILE FAILURE

Since diabetic subjects receive a number of drugs for control of diabetes and its complications, they may suffer from the side effects of these drugs. Some of these drugs (methyl dopa, reserpine, atenolol, clonidine, pindolol, prazocin, verapamil and guanathidine) may cause erectile failure in a male diabetic subject. Withdrawal of these drugs may restore potency.

PSYCHOGENIC OR ORGANIC

The foremost is to distinguish between psychogenic and organic causes of erectile failure.

Table 38 Some factors that help to differentiate psychological from organic causes of erectile failure

<table>
<thead>
<tr>
<th>More likely to be:</th>
<th>Psychological</th>
<th>Organic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td>Gradual</td>
</tr>
<tr>
<td>Permanence</td>
<td>Intermittent or partial</td>
<td>Permanent and total</td>
</tr>
<tr>
<td>Spontaneous erections (nocturnal or on waking etc.)</td>
<td>Sometimes</td>
<td>Never</td>
</tr>
<tr>
<td>Psychological problems</td>
<td>May be overt</td>
<td>May be secondary</td>
</tr>
<tr>
<td>Organic causes</td>
<td>None apparent</td>
<td>May be apparent</td>
</tr>
</tbody>
</table>
In psychogenic erectile failure the onset is abrupt, libido is diminished and nocturnal and special situation erection is present. A few factors that may help to differentiate is given in Table – 38.

**SEXUAL PROBLEMS IN DIABETIC WOMEN**

The equivalent of impotence in a woman is absence of vaginal lubrication during intercourse. They may also suffer from fatigue, depression, changes in perimenstrual blood glucose control, vaginitis, decreased sexual desire and an increased time to reach orgasm. A distinct clinical entity ‘Clitoral neuropathy’ has been reported. This is usually mistaken for candidial vaginitis since it produces paresthesias over the genitalia.

It is quite easy to manage most of the sexual problems in female diabetic subjects. Systematic clinical approach in diagnosis is all that is required. A lubricant like K.Y. Jelly additionally during intercourse helps overcome dry coitus.

Adequate control of diabetes and prompt treatment of candidial vaginitis relieves dyspareunia and orgasmic dysfunction. Strict metabolic control and neurovitamins help overcome clitoral neuropathy in diabetic women.

In conclusion, both women and men with diabetes are at increased risk for sexual dysfunction. In men, sexual dysfunction is related to somatic and psychological factors, whereas in women with diabetes, psychological factors are more predominant.
Increased incidence of erectile failure in a male diabetic subject seems to be primarily a result of diabetic autonomic neuropathy. Both macro and micro-vascular complications of diabetes may confound the clinical picture of diabetic erectile failure. Since diabetic subjects receive a number of drugs for control of diabetes and its complications, they may suffer from the side effects of these drugs. History and physical examination may indicate the probable cause of erectile failure.

A diabetic subject presenting with sexual dysfunction requires utmost sympathy and deft handling. The patient and the spouse should be educated on the effects of the chronic disease on the sexual function and further counseled to adapt well to the new situation. The future for these unfortunate men is not all that gloomy as the treatment choice ranges from oral medications to injections, from psychological therapy to surgery and from external devices to internal ones.
SKIN DISEASES AND DIABETES

INTRODUCTION

Cutaneous disorders associated with diabetes mellitus (DM) are thought to occur in about 30% of patients during the course of their disease, but a recent study has documented prevalence rate of skin diseases to be 60% in (unselected) diabetic subjects consecutively attending an outpatient clinic. The cutaneous signs of diabetes are the manifestations of multiple factors, Abnormal carbohydrate metabolism, other altered metabolic pathways, atherosclerosis, microangiopathy, neuron degeneration, and impaired host mechanisms all play a role. Cutaneous manifestations generally appear subsequent to the development of diabetes, but may be the first presenting sign or even precede the diagnosis by many years.

The cutaneous findings can be classified into four major groups: (1) skin diseases associated with diabetes, such as necrobiosis lipoidica, diabetic dermopathy, and diabetic bullae; (2) cutaneous infections; (3) cutaneous manifestations of diabetic complications, such as neuropathic foot ulcers; and (4) skin reactions to diabetic treatment. Diabetic bullae, limited joint mobility and waxy skin and diabetic dermopathy are virtually diagnostic of diabetes. For all these recognition is the key to treatment and prevention.
## Table 39 Diabetes Mellitus and Skin Manifestations

<table>
<thead>
<tr>
<th>Necrobiotic disorders</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrobiosis lipoidica diabeticorum</td>
<td>Diabetic bullae</td>
</tr>
<tr>
<td>Disseminated granuloma annulare</td>
<td>Genital prunus</td>
</tr>
<tr>
<td><strong>Vascular changes</strong></td>
<td>Acanthosis nigricans</td>
</tr>
<tr>
<td>Diabetic dermopathy</td>
<td>Skin tags</td>
</tr>
<tr>
<td>Diabetic foot</td>
<td>Vitiligo</td>
</tr>
<tr>
<td><strong>Changes in collagen and skin constituents</strong></td>
<td>Perforating dermatoses</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Lichen planus</td>
</tr>
<tr>
<td>Dupuytren’s contracture</td>
<td>Nail disorders</td>
</tr>
<tr>
<td>Limited joint morbility and waxy skin</td>
<td>Hair disorders</td>
</tr>
<tr>
<td>Infections</td>
<td><strong>Metabolic disorders</strong></td>
</tr>
<tr>
<td>Bacterial</td>
<td>Eruptive and other xanthomata</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>Carotinemia</td>
</tr>
<tr>
<td>Erythrasma</td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td>Dermatophytosis</td>
<td>Hemochromatosis</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td>Rare syndromes</td>
</tr>
<tr>
<td>Trophic ulcer</td>
<td>Werner’s syndrome</td>
</tr>
<tr>
<td>Pathological gustatory sweating</td>
<td>Partial lipodystrophy</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Glucagonoma</td>
</tr>
<tr>
<td><strong>Reactions to antidiabetic drugs</strong></td>
<td></td>
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<tr>
<td>Sulfonylureas</td>
<td></td>
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<tr>
<td>Biguanides</td>
<td></td>
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<tr>
<td>Insulin</td>
<td></td>
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</tbody>
</table>

Skin Markers of Diabetes Mellitus (Tables 39 and 40)

**Necrobiosis Lipoidica Diabeticorum**

*Rare*

*Best known skin lesion associated with diabetes*

*Unknown etiology*

*Not related to diabetic status or duration*

*Usually pretibial site*

*A therapeutic challenge*
Necrobiosis lipoidica diabeticorum (NLD) is relatively rare, even in diabetic patients, in whom it has been reported to occur in 0.3-1.6%. Only 11-65% of patients with NLD have diabetes at the time of cutaneous diagnosis. Of those without diabetes, approximately 90% eventually develop diabetes, have abnormal glucose tolerance, or report one or both parents with diabetes. Consequently, nondiabetic patients with NLD should be evaluated and followed for development of diabetes.

NLD occurs three times more commonly in female than in male patients and is associated with both T1DM and T2DM. The lesion is uncommonly observed in blacks or orientals. The average age of onset is 34 years.

The fully developed clinical appearance is diagnostic: non-scaling plaques with yellow atrophic centers, surface telangiectasia, and a violaceous or erythematous border that may be raised. The lesion may vary in size from a papule less than a centimeter to larger plaques several centimeters in dimension. Multiple or bilateral lesions are found in the majority of cases. Whereas most lesions of NLD present on the pretibial and medial malleoli, about 15% of lesions are found elsewhere including the hands, forearms, abdomen, face or scalp. When NLD occurs in areas other than lower extremities the patient is less likely to have diabetes. Ulceration is reported in about one third of leg lesions: mostly in large ones following minor trauma.
Table 40  Virtually Diagnostic Markers of Diabetes Mellitus

1. Diabetic bullae
2. Syndrome of limited joint mobility and waxy skin.
3. Diabetic dermopathy

NLD can usually be diagnosed by a dermatologist on clinical appearance alone. If the diagnosis is not certain, a biopsy will reveal the characteristic changes of granulomatous inflammation and degeneration in collagen and elastic fibers associated with altered extracellular matrix deposition. The pathogenesis of NLD is still not clearly understood. However, diabetic microangiopathy associated with neuropathy may contribute to the necrobiosis of collagen.

NLD has not as yet been demonstrated to have any consistent relationship to diabetic control. About 20% of patients show spontaneous regression of the lesions

GRANULOMA ANNULARE

• Association with diabetes not clear
• Benign
• Asymptomatic
• Self limiting dermatosis

Granuloma annulare (GA) was first described by Fox in 1895. It is an inflammatory disease of unknown etiology characterized clinically by dermal papules and plaques and histologically by collagen
degeneration and granulomatous inflammation. Clinically, the well recognized subtypes of GA are localized, generalized, subcutaneous and perforating GA. The localized form consists typically of skin coloured or pink papules in an annular configuration on the distal upper and lower extremities particularly overlying bony prominences. They are asymptomatic and nearly three quarters of all cases will resolve spontaneously. Generalized GA typically involves the arms, chest, abdomen and thighs with sparing of the face. Spontaneous resolution is much less common than in localized GA. The disseminated form can appear and disappear rapidly. There is also a perforating form which can be associated with diabetes.\textsuperscript{702}

All forms of GA share common histological features and the histopathological similarity to necrobiosis lipoidica would imply a shared etiology and both conditions may coexist in the same patient. Pathogenesis of GA may involve a cell mediated immune mechanism. An analysis of 100 cases of generalized GA showed an association with diabetes in 21\% of cases (as compared with 9\% of localized GA). In another series of some 1100 patients approximately 120 were reported to have coexistent diabetes and GA.\textsuperscript{702}

**DIABETIC DERMOPATHY (SHIN SPOTS, PIGMENTED PRETIBIAL PATCHES)**

- Most common cutaneous finding
- Asymptomatic
- Pretibial location
- Cutaneous sign of microvascular disease
In 1964, Melin\textsuperscript{703} and later Bindley\textsuperscript{704} described the existence of atrophic hyperpigmented 5-12mm lesions occurring on the pretibial area of the lower legs. Affecting 7% to 70% of diabetic subjects predominantly men over the age of 50, diabetic dermopathy, also known as shin spots and pigmented pretibial papules, is considered the most common cutaneous manifestation of DM.\textsuperscript{696,705} Diabetic dermopathy, however, is not pathognomonic of diabetes because 20% of nondiabetic persons may develop similar lesions.

They are usually bilateral, but are not symmetrically distributed. They are asymptomatic and often are overlooked by patient and physician alike.\textsuperscript{706,707}

These lesions appear to be consistent with post traumatic atrophy and post inflammatory hyperpigmentation in poorly vascularized skin. When several are present, they may be a cutaneous sign of microvascular disease in other tissues. Their presence in patients seen for other conditions should prompt an evaluation for diabetes mellitus. The frequency of these lesions increases with the duration of diabetes and severity of diabetes. The genesis of shin spots is unclear.

The frequency of changes over bony prominences suggests that trauma may be a modifying factor, especially in diabetic patients with neuropathy. Evidences also exist for and against the role of microangiopathy.

The lesions of diabetic dermopathy may resolve spontaneously, even as new lesions arise. Treatment should focus on the patient’s diabetes. No treatment for these non ulcerated lesions is required except for protection from trauma.\textsuperscript{696}
DIABETIC BULLAE

- Clinically distinct diabetic marker
- Occur suddenly
- Acral distribution
- Resolve spontaneously
- Unknown etiology
- In longstanding diabetes
- Retinopathy in 75%

The sudden spontaneous appearance of one or more tense blisters, generally on the acral portions of the body is a rare, but specific even in diabetes. Since its first description in 1930 only about 100 cases of this condition have appeared in the published literature. In a recent study 2212 patients have been described over a period of 8 years emphasizing the fact that it is not as uncommon as believed to be.

Approximately 0.5% of diabetic patients develop diabetic bullae or bullosis diabeticorum. The characteristic history is the appearance of multiple, painless, bullae varying in size from half to several centimeters and occurring spontaneously without antecedent trauma, often overnight. Location is variable with reports of involvement of the fingers, toes, hands, feet, arms and rarely the trunk.

However, they are more commonly seen on the distal extremities, particularly on the feet and lower legs. They contain clear sterile fluid with eosinophilic material and a few polymorphs and occur on a non-inflamed base. The lesions dry up to form a dark or black crust. Most patients are with longstanding diabetes with peripheral neuropathy and nephropathy. Coexistent retinopathy occurs in 75% of
patients. The age group of affected patients varied from 17-79 years. Males are more commonly affected than females with a ratio of approximately 2:1.24. The abnormalities of carbohydrate metabolism are not proportionate to the clinical presentation. There have been a few reports of diabetic bullae leading to the diagnosis of DM.710

The etiology of diabetic bullae is unknown, but does not seem to be immunologically mediated. The bullae heal spontaneously in 2 to 5 weeks but may recur in the same or new anatomic locations.696 If large and symptomatic, the bullae can be aspirated with an intact blister root providing a physiologic wound covering.

**DIABETIC THICK SKIN**

Three forms of diabetic thick skin have been identified. First, diabetics in general have an asymptomatic, often unnoticed, but measurable increase in skin thickness. Second the diabetic hand syndrome (syndrome of limited joint mobility, cheiroarthropathy, waxy skin and stiff joints, scleroderma-like syndrome, and diabetic sclerodactyly) consists of scleroderma-like skin changes in the fingers with limited joint mobility. Third, diabetic scleredema is distinct from the self resolving scleredema adultorum of Buschke seen in children after a streptococcal infection.

Quantitative estimations of skin thickness have been determined by microscopic measurement, caliper measurement, ultrasonography, and radiologic investigation. Normally, skin thickness varies based on body site, age and sex. Typically, the skin thickens until adulthood then decreases in thickness after age 20. Several groups have found an
increase in skin thickness of the forearm in T1DM in comparison with age and sex-matched nondiabetic controls.696

LIMITED JOINT MOBILITY (DIABETIC HAND SYNDROME)

- Collagen disease seen only in diabetes
- Limitation of joint mobility
- Thickness and waxiness of skin
- Asymptomatic
- Harbinger of microvascular disease

Rosenbloom and Frias711 first described in 1974 a clinical syndrome consisting of two major components: limitation of mobility, primarily of the joints of the hands and thickening and stiffness of the skin most marked on the dorsa of the fingers. Limited joint mobility (LJM) is the earliest clinically apparent long term complication of diabetes in children and adolescents. It occurs in all forms of diabetes, classical type 1, non autoimmune type 1 and type 2 DM.712 LJM may be the harbinger of a subset of young people who are at 400-600% greater risk for developing retinopathy, nephropathy, neuropathy and hypertension.713

The abnormal waxiness and thickness of the skin appears in about one third of patients with LJM. More predictable in the severe cases although at times evident without joint involvement. Clinical clues that the skin on the dorsum of the fingers is thickened include pebbled or rough skin (Huntlev’s papules) which are multiple grouped minute papules on the extensor surfaces of the fingers, on or near the knuckles or periungual areas.696

Joint stiffness begins in the metacarpophalangeal and proximal interphalangeal joints of the fifth finger and extends medially. The
distal interphalangeal joints and larger joints may also be involved, most commonly the wrist and the elbow, but also the ankles, cervical and thoracolumbar spine. The limitation of movement initially involves active and later passive extension. Flexion limitations may occur in the end stage. The limitation is painless, unresponsive to physical therapy and non disabling. Apart from periarticular thickening radiographs of the joints reveal no intrinsic abnormality.\textsuperscript{714}

Limited joint mobility can be demonstrated by inability to flatten the hand on a tabletop and by failure of palmar approximation (the prayer sign. The patient places the hands together in prayer position with the forearm parallel to the floor. Normal placement allows for juxtaposition of all the fingers as well as the palm. Staging of LJM is useful for patient follow up and in reporting relationships to other complications and control criteria.

The Brink Starkman\textsuperscript{713} classification is as follows:
\begin{itemize}
  \item a. Stage 0 no abnormality
  \item b. Stage I skin thickening without contractures
  \item c. Stage II bilateral fifth finger contracture
  \item d. Stage III other fingers involved bilaterally
  \item e. Stage IV fingers plus wrist involvement
  \item f. Stage V fingers, wrist and other joint involvement
\end{itemize}

Although contractures of the joints seem related to duration of hyperglycemia particularly in those with insulin dependence, it is probable that if a patient is to develop this complication, he does so by the end of the first decade of disease. There is less agreement as to the relationship of the syndrome to diabetes control.
SCLERODEMA DIABETICORUM

- Poorly controlled obese T2DM
- Associated with retinopathy
- Extensive skin involvement
- Resistant to treatment

Scleredema diabeticorum (SD) is a diffuse non-pitting induration of the skin with loss of skin markings occurring in 2.5% to 14% of obese diabetics\textsuperscript{705}, most of them who are poorly controlled and in need of insulin. Conversely, 94% of adult patients with scleredema have diabetes. The thickened skin in scleredema pits if pressure is applied forcefully for 30 seconds may display a peau d’orange appearance usually with a modest erythematous tinge. Although usually asymptomatic, neck discomfort and back pain may accompany severe cases of this chronic disorder. If the deltoid area is involved, patients may experience a decreased range of motion of the upper extremity\textsuperscript{711}

SD shares certain characteristics with scleredema adultorum of Buschke but also has distinct differences. Like the classic type, the condition often involves the nape of the neck, upper chest, back, and arms, with occasional extension to the face and abdomen.\textsuperscript{705} The cutaneous problem is not only generally more widespread than in the classic type, but also has little tendency to resolution. There is usually no prodromal infection. For SD there seems to be a moderate correlation with microangiopathy (retinopathy).\textsuperscript{707}

DUPUYTREN’S CONTRACTURE

Long standing diabetes

Male predominance

Older patients
Greater occurrence of retinopathy

Dupuytren’s contracture (DC) typically affects the third and fourth fingers and is characterised by palmar fascial thickening or nodules. It is recognized in 1-13% of middle aged or elderly normal individuals.\textsuperscript{715} The prevalence of DC in diabetes varies from 1.6-63% in different series, but patients with diabetes and DC tend to be older with long standing disease. There is a genetic predisposition and an increased frequency in diabetic, epileptic and alcoholic persons. Although diabetic subjects are more prone to DC the clinical picture and course of the disease is indistinguishable from other patients with this disorder. There is a male predominance with the onset delayed in women.

Retinopathy occurs significantly more frequently in those patients who have DC than in those without.\textsuperscript{715} Presence of either LJM or DC may be associated with the presence of microangiopathy.

**CUTANEOUS INFECTIONS**

- Recurrent genital candidiasis
- Carbuncle
- Extensive erythrasma
- Rhinocerebral mucormycosis

Skin infections occur in 20% to 50% of those with diabetes.\textsuperscript{695,697} Poor diabetes control might be the cause or the consequence of the concurrent infection. The infectious disorders can be of fungal or less commonly bacterial origin.\textsuperscript{695} Factors that would render a diabetic patient more susceptible to increased morbidity from skin infections include uncontrolled hyperglycemia, ketoacidosis, abnormal
microcirculation, peripheral vessel disease, diabetic neuropathy, decreased phagocytosis and killing activity, impaired leucocyte adherence, delayed chemotaxis, an impaired T-cell mediated immune response, a dry skin, hypohidrosis and trauma.\textsuperscript{716,705}

Diabetic subjects have an increased incidence of infections due to Candida albicans, Corvnebacterium minutissimurn and soft tissue infections of the lower extremities. They are also more susceptible to some rare infections including rhinocerebral mucormycosis, malignant pseudoniononas

**CANDIDA INFECTIONS**

Little controversy exists about the association of Candida albicans infection especially of the female genitalia, which occurs with greater severity and frequency in poorly controlled diabetes. The presence of pruritus vulvae and the coexistence of culture proven candida in a non pregnant woman can alert clinicians to the onset of diabetes. It is marked by leucorrhea, intertriginous erythema with scaling, satellite papules, pustules and superficial erosions.

Lesions may also occur in places such as the corners of the mouth (perl—che), axilla, inframammary region, groin, abdominal or other skin fold. Angular stomatitis may be caused by increased concentration of salivary glucose.\textsuperscript{710} Balanitis, balanoposthitis, and phimosis may be less common than candida infections in women, but are presenting manifestations of diabetes in uncircumcised men.\textsuperscript{717} Purulent drainage may indicate a secondary bacterial involvement. Less common than paronychia, another site of candidal infection of the hands is of the web space between the middle and fourth fingers
(erosiointerdigitale blastomycetica) or between the fourth and fifth toes due to occlusion and retention of moisture.

A classic cutaneous complication in childhood diabetes and occasionally in diabetic adults, candidiasis presents as white, curd like patches (thrush) on the buccal mucosa and tongue.

**BACTERIAL INFECTIONS**

Common bacterial infections of the diabetic skin usually caused by staphylococcus aureus and - hemolytic streptococci, include impetigo, folliculitis, furunculosis, carbuncle, ecthyma, cellulitis and erysipelas; these can be more severe and widespread.

Carbuncle characteristically occurs as an extremely painful lesion at the nape of the neck, the back or thighs. Fever and malaise are often present and the patient may appear quite ill. The involved area is red, swollen and multiple pustules soon appear on the surface draining externally around multiple hair follicles. The lesion heals leaving a permanent scar, it is imperative to assess all patients for diabetes. In diabetes, erysipelas of the legs is often complicated by bullous lesions leading to diabetic gangrene and necrotizing fasciitis. Although infection due to staphylococcus is apparently no more frequent in well controlled diabetics, it remains good practice to exclude this disease in any patient with recurring or resistant furunculosis or folliculitis.

Extensive erythrasma, caused by gram positive Corynebacterium minutissimum, occurs with increased frequency in elderly, obese patients with diabetes. Clinically, it is manifested by tan-red, fine, scaly patches in intertriginous areas.
Fatal in over 50% of patients, 25 malignant otitis externa caused by Pseudomonas aeruginosa, especially in elderly diabetic men can progress to chondritis, osteomyelitis and bacterial meningitis.

**PHYCOMYCETES INFECTIONS**

Hyperglycemia can allow usually nonpathogenic organisms to establish an infection in traumatized skin occasionally resulting in gangrene and loss of limb. Patients with diabetes who have leg ulcers or non healing surgical wounds may have a complicating phycomycete infection. This infection should be suspected when leg ulcers or post traumatic lesions do not respond to therapy.

Patients with uncontrolled diabetes and ketosis may be predisposed to deep fungal infections or rhinocerebral mucormycosis of the turbinates, septum, palate, maxillary and ethmoid sinuses.

**MISCELLANEOUS**

**ACANTHOSIS NIGRICANS**

Cutaneous marker of insulin resistance

In acanthosis nigricans (AN) velvety, hyperpigmented (brown, yellow or grey) thickened plaques are seen in body folds such as the axilla, under the breasts, neck and the groin. Other locations include the, umbilicus, areolae, submammar regions, and hands (tripe hands). Although, it may be familial and benign, it has long been recognized as a cutaneous marker for a heterogenous group of endocrine disorders that are characterized by insulin resistance viz., obesity, diabetes and polycystic ovarian disease.
In a study of 223 patients with AN, nearly 50% of patients in their fifth decade had type 2 DM, whereas only 4 of the 99 patients under age 29 had developed diabetes. Impaired glucose tolerance without a diagnosis of DM, however, was present in a larger proportion of the younger patients. Because AN can also be seen as a complication of carcinoma (particularly of the stomach), secondary to medications, such as rucotinic acid or corticosteroids, and in various other endocrinopathies, work up becomes necessary to rule out other underlying disorders.

Insulin resistance contributes significantly to the pathogenesis of Type 2 DM and has been implicated as the common denominator of most causes of AN whether by way of genetic defects of the insulin receptor or defects of post receptor functions, antibodies or by obesity. Insulin resistant diabetes has been associated with AN in various syndromes including total lipodystrophy. There is no correlation between the severity of insulin resistance and AN.

SKIN TAGS (ACHROCHORDI, SOFT FIBROMAS)

Common in obesity and elderly women

Not a reliable diabetic marker

Skin tags (ST) are small, soft, pedunculated, often pigmented lesions, usually occurring on the eyelids, neck and axillae. The condition is very common; particularly in middle aged and elderly women. In obesity ST are both commoner and more numerous. Though some reports suggest association of diabetes with skin tags, at present there is insufficient evidence to regard skin tags as a reliable diabetic marker.
PERFORATING DERMATOSES

Patients with renal failure and/or type 1 DM or type 2 DM often have an acquired perforating dermatoses of the skin characterized by hyperkeratotic papules (2-10 mm diameter) with transepidermal elimination of degenerated material, such as collagen and elastin. Lesions occur primarily on the legs, but may also be found on the trunk and face. They are often very itchy with little tenderness and spontaneous resolution.

XANTHOMAS

Eruptive xanthomas are firm, non tender, itchy, skin coloured or yellow papules (1-4 mm) often surrounded by an erythematous rim. Knees, elbows, back and buttocks are commonly involved. They appear suddenly in crops in less than 0.1% diabetic patients with poor control and raised triglyceride levels. Often presenting as a Koebner phenomenon, the lesions may be tender. Polyphagia in uncontrolled diabetes accelerates formation of very low density lipoprotein and increases chylomicrons.

Other chronic diseases such as chronic biliary cirrhosis, nephrotic syndrome, chronic renal failure, myxedema, chronic pancreatitis and glycogen storage disease may show secondary eruptive xanthomata. Xanthomas and diabetes are also associated with hemochromatosis and total lipodystrophy. When carbohydrate and lipid metabolism is controlled, the lesions tend to resolve.

Multiple xanthomas may coalesce and form tuberous xanthomas. Tendon xanthomata are more persistent, tender on pressure and often seen over the pressure areas such as knees, elbows and Achilles’
tendon. They occur more frequently with hypercholesterolemia. Xanthelasma may be associated with hypercholesterolemia.

VITILIGO

Many theories exist to explain the cause of vitiligo. Genetic, autoimmune melanocytic self destruction, as well as abnormal neurogenic stimuli play an important etiological role.

There is an increased association of vitiligo with other endocrinopathies, specifically those associated with a proven or presumed autoimmune etiology. Vitiligo has been reported in T2 DM as well as T1 DM making it difficult to advance autoimmune and genetic factors as the only explanation for their coexistence. Vitiligo may precede the onset of clinically evident diabetes and also occurs more frequently in families of diabetic patients.

There appears to be no difference in the clinical course of vitiligo even if associated diabetes is well controlled.

RUBEOSIS FACEI

Although difficult to quantify, flushed face of rubeosis facei has been reported in 3% to 59% of diabetic subjects. Blond and red haired persons appear more erythematous because of reduced cutaneous melanin to obscure the erythema. The red color may be caused by microangiopathy, increased solar sensitivity, or dehydration. Tighter glucose control might improve the appearance.
LICHEN PLANUS

Numerous reports have studied the association of diabetes and lichen planus, especially oral lichen planus. The prevalence of decreased glucose tolerance in patients with oral lichen planus varies widely between 1.6% and 85%. Fewer studies have examined the frequency of lichen planus in known cases of diabetes. Although most reports do not differentiate the types of diabetes, the reported rate varies from 0.55 to 5.76% of patients having clinical and less often histologic evidence of oral lichen planus.

An increased incidence of diabetes and abnormal glucose tolerance has been claimed in patients with lichen planus but as yet there is no unequivocal evidence in favour of this association.

PRURITUS

Generalized pruritus is not associated specifically with diabetes, but if it occurs dry skin is commonly the cause and suitable emollients should be prescribed. When pruritus is present, it is usually localized. Localized anogenital pruritus (pruritus vulvae and halanitis) may be the presenting symptom of diabetes.

NAIL CHANGES

Subtle yet valuable indicator of systemic disease

Paronychia

Periungual telangiectasia

Yellow nails
No nail changes are truly pathognomonic for diabetes, many do suggest that it be ruled out. Paronychia may result in partial or total matrix destruction followed by permanent abnormality of the nail plate. A greenish black discoloration may appear as a result of pseudomonas colonization.

Hypertrophic thickening, darkening and surface irregularity (onychauxis) may be due to vascular insufficiency. Venous dilatation in the cutaneous microcirculation is an excellent indicator of functional microangiopathy and of long term control of the diabetic. Yellow discoloration of the nails may develop from many causes. In diabetes yellow nails probably represent glycosylation end products.\textsuperscript{723}

HAIR DISORDERS

Diffuse thinning of the scalp hair is not unusual in uncontrolled diabetes and fine lanugo hairs on the back and arm may be seen in undernourished diabetic patients.

Achard-Thiers syndrome consists of obesity, hirsutism principally of the face, hypertension and diabetes.

Generalized hypertrichosis can be seen in the Lawrence-Seip syndrome.\textsuperscript{724}

HEMOCHROMATOSIS

Hemochromatosjs is a clinical disorder referred to as “bronze diabetes” with chief components being diabetes, hepatic cirrhosis, hyperpigmentation of the skin, cardiomyopathy, arthritis and hypogonadism. Abnormal glucose tolerance is found in 60-80%.\textsuperscript{725}
KAPOSI’S SARCOMA

Kaposi’s sarcoma seen in AIDS patients bears no relation to diabetes. Diabetes mellitus has been reported with greater than expected Frequency in Kaposi’s sarcoma.726

YELOW SKIN

Upto 10% of diabetic patients may show some yellow discoloration of the skin.721 The cause of yellow skin remains in dispute. Possibilities include elevated serum carotene and one or more glycosylation end products which are noted to be yellow.707

PORPHYRIA CUTANEA TARDA

Diabetes mellitus has been found associated with porphyria in 8-22% of cases.727 There is a higher association with men.

The cutaneous manifestations include bullae on light-exposed areas, excessive skin fragility, hypertrichosis, melanosis. scarring, alopecia and scleroderma like plaques.

WERNER’S SYNDROME

In this hereditary disorder of connective tissue, insulin resistant diabetes is found in at least one third of the cases.

Premature ageing affects many tissues and the disease is heralded in the first or second decade by premature greying of the hair and alopecia.728
GLUCAGONOMA

At the time of presentation, patients with the glucagonoma syndrome have a triad of symptoms including glucose intolerance, normocytic normochromic anemia and a distinctive eruption termed necrolytic migratory erythema. The dermatological component may precede other evidence of its existence, sometimes by several years.

Clinically, there is a polymorphous, erythematous eruption with a peripheral scale. It waxes and wanes in a 7-14 day generalized cycle. Superficial vesiculation leads to erosions and necrosis, characteristically in the perioral area, around the genitals and in the anal orifice.

Systemic accompaniments include weight loss, weakness, diarrhoea, anemia and mild non ketotic diabetes. A beefy red tongue, angular cheilitis, and nail hypertrophy also may be present.

SUMMARY

The cutaneous manifestations in diabetes mellitus are due to multiple factors like metabolic disturbances, chronic degenerative changes and complications due to therapy. Diabetic patients are more prone to develop bacterial, fungal and viral infections. Patients with recurrent furuncles or carbuncle should always be investigated for diabetes. Monilial balanoposthitis and vulvo-vaginitis as well as extensive ring worm infections are common amongst diabetic subjects. Pruritus vulvae is quite frequent in diabetic females.

Eruptive xanthomas are a characteristic, but uncommon complication of diabetes with associated hypertriglyceridemia. The lesions come in crops and regress when hyperlipidemia is controlled.
Necrobiosis lipoidica is the most specific, but very rare manifestation of diabetes. Majority of the patients either have diabetes or develop diabetes later or have first degree relatives with diabetes. Diabetic dermopathy is the most common dermatosis associated with diabetes. Diabetic bullae are pathognomonic of diabetes. They are painless, non-inflammatory bullae, and commonly appear spontaneously on the feet and hands. Granuloma annulare is another uncommon disorder and disseminated and diffuse granuloma annulare has strong association with diabetes.

Patients with various dermatoses like acanthosis nigricans, generalized vitiligo, perforating dermatoses, skin, tags, generalized pruritus and knuckle pebbles also need to be screened for diabetes.
INFECTIONS AND DIABETES MELLITUS

It is commonly believed that people with diabetes are more susceptible to infection. After the advent of Insulin and various antibiotics the mortality in diabetes due to infections has been reduced to a great extent. However the morbidity due to infections still remains high. Poorly controlled diabetics are particularly susceptible to infections of urinary tract, respiratory tract, soft tissues and skin. Trivial infections may progress rapidly due to lowered immunological resistance. Certain rare fungal infections are also associated with diabetes.

IMPACT OF DIABETES MELLITUS ON SEPSIS

There are various factors which influence resistance to infections. Hyperglycemia per se can alter leukocyte functions. Plasma glucose of more than 200 mg% has been shown to impair phagocytosis. Insulin is needed for normal metabolism of glucose to provide energy for phagocytosis and to destroy microorganisms. Hence the consequences of Insulin lack are defective diapedesis, leukocyte adherence, phagocytosis, enzyme activity (superoxide, myeloperoxide lysozyme) and bactericidal activity. All these defects are correctable with insulin therapy. Diminished chemotaxis may be genetically determined and associated with HLA B8 DR W3. This defect has been shown to occur in non-diabetic relatives and twins of type 1 diabetes.

A few studies have shown decreased production of antibodies against staphylococcal toxins in diabetic patients. Recent theory is that glycosylation of immunoglobulin in poorly controlled diabetics, makes them more susceptible to infections.
Complications of diabetes can predispose to infections. Microangiopathy results in impaired tissue perfusion which delays healing. The antibiotics fail to reach the site of infection. Peripheral neuropathy predisposes to foot trauma and secondary infection supervenes. These infected ulcers fail to heal due to associated poor peripheral circulation. Autonomic neuropathy results in bladder dysfunction and stasis which predisposes to urinary tract infections. Glycosuria and repeated catheterization are additional risk factors.

Frequent hospitalization increases the risk of nosocomial infections. Additional high risk groups are those on pumps, patients receiving steroids for renal transplant and patients with ketoacidosis. In DKA serum free iron is elevated by ketone bodies and this favors growth of various bacteria and fungi.

**Table 41** Factors Exacerbating Infections in The Diabetic

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dehydration</td>
</tr>
<tr>
<td>2.</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>3.</td>
<td>Impaired polymorpho-nuclear leukocyte function</td>
</tr>
<tr>
<td>4.</td>
<td>Vascular insufficiency</td>
</tr>
<tr>
<td>5.</td>
<td>Humoral factors: Defective or inadequate gamma globulin, complement, antibody formation</td>
</tr>
<tr>
<td>6.</td>
<td>Neuropathy</td>
</tr>
</tbody>
</table>

**SKIN AND SOFT TISSUE INFECTIONS**

Thirty percent of type 1 Diabetes is staphylococcal carriers compared with 10% of type 2 Diabetes and normal persons. Gram negative wound infections are three times more frequent in diabetics than non-diabetics. However it has been shown that blood sugars more than 400 mg% inhibit gram negative organisms.
Necrotizing cellulitis is caused by aerobic and anaerobic organisms (Clostridium and enterobacteriaceae). Necrotizing fascitis is an extensive necrosis of skin and subcutaneous tissues. It is more common in extremities and perineum. In adult males scrotal skin involvement is described as Fournier's gangrene. Vascular insufficiency and tissue hypoxia create favorable conditions for these infections. Bacteremia and endotoxic shock may result in high mortality.

**INFECTIONS ASSOCIATED WITH DIABETES MELLITUS**

1. **Proven association**
   - a. Bacteriuria in females: 4 fold increase
   - b. Tuberculosis: 3-16 fold increase
   - c. Malignant otitis externa: 100%
   - d. Necrotizing cellulitis: 75%
   - e. Emphysematous cystitis: 80%
   - f. Emphysematous Pyelonephritis: 72%
   - g. Acute papillary necrosis: 57%
   - h. Emphysematous cholecystitis: 38%
   - i. Peri nephric abscess: 36%

2. **Probable association**
   - a. Acute necrotizing periodnitis
   - b. Cellulitis of hand or foot
   - c. Gram negative pneumonia (Klebsiella)
   - d. Foot ulcer related infections
   - e. Fungal urinary tract infections

3. **Possible association**
   - a. Staphylococcal pneumonia
   - b. Liver abscess
   - c. Bacteremia: Staphylococcal, Group B streptococcal
   - d. Mucocutaneous candidiasis
   - e. Osteomyelitis
   - f. Fournier's gangrene
   - g. Cryptococcosis, histoplasmosis, blastomycosis coccidiomycosis
   - h. Carbuncles and boils

4. **Proven no association**
   - a. Hepatitis B
   - b. Bacteriuria males
   - c. Pneumococcal pneumonia
Post operative wound infections are due to invasions from the colonized bacteria which are facultative pathogens. The following are the various carrier states in diabetics.

<table>
<thead>
<tr>
<th>a. Staphylococcus</th>
<th>Skin, nose throat</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Klebsiella</td>
<td>Throat flora</td>
</tr>
<tr>
<td>c. Aspergillus</td>
<td>Sputum</td>
</tr>
<tr>
<td>d. Candida</td>
<td>Skin, mouth, vulva</td>
</tr>
</tbody>
</table>

Bacteria due to group B streptococcal infections are common in diabetes. It originates frequently from the urinary tract or from foot ulcers. In 80% of cases E coli has been identified which originates from the urinary tract.

Dental sepsis is common in diabetics. Gingivitis and Pyorrhea result in loss of teeth at an early age. Blepharitis, styes and dacryocystitis are also associated with diabetes.

**URINARY TRACT INFECTIONS**

Asymptomatic bacteriuria is more common in diabetic women than non-diabetic women. Upper urinary tract infections also occur. Emphysematous Pyelonephritis is a necrotizing infection characterized by gas production in or around the kidneys. Over 70% of reported cases have occurred in diabetic patients. E coli are causative in 50% of cases, the remainder being caused by other gram negative bacilli. Survival is higher in patients managed with antibiotics plus surgery (67%) than with antibiotic therapy alone (30%).

Emphysematous cystitis is less severe and is caused by E.coli and Klebsiella. Plain X-ray shows gas in the bladder region. These bacteria utilize glucose found in the urine in the bladder, hence urine
sugar monitoring in these patients show falsely low values.

Over 50% of cases with papillary necrosis have diabetes. E.coli and other enteric organisms are causative. Ischemia and infection results in necrosis of the renal papilla. Patient presents with abdominal colic, hematuria and features of acute renal shut down. Urine shows necrotic debris. Retrograde pyelogram shows ring shadows. Renal scan is helpful.

Diabetes is present in one third of patients with peri-nephric abscess. E.coli and staphylococci are usually responsible. Patient presents with fever, chills and joint pain. Ultrasound is diagnostic. Mortality is 23% despite therapy.

Symptomatic urinary infections are frequent precipitants of ketoacidosis. Bacteriuria may be associated with worsening of diabetic nephropathy. Asymptomatic Bacteriuria (colony count of $10^5$ per field) is also significant in pregnant diabetics and after renal transplant. In both these conditions it should be looked for routinely. Early diagnosis and adequate therapy are mandatory. Genital infections like balanoposthitis and vulvo-vaginitis give a diagnostic clue to screen for diabetes.

**FOOT INFECTIONS**

Foot infections are common in diabetics. Infection may develop in the nail bed, beneath plantar callouses, or in ulcers. The infection may extend into deeper soft tissues, bones or joints. Osteomyelitis of foot bones is common. Web space fungal infection can co-exist. Pain may
not be prominent in patients with neuropathy. Bacteremia complicates severe foot infections. In diabetic patients, infection can spread so rapidly that a delay of one or two days can make the difference between saving a limb and amputation. Prevention of cross infection is important when treating foot infections.

**PULMONARY INFECTIONS**

Bacterial Pneumonia is frequently caused by staphylococcus, Klebsiella or E coli. Tuberculosis has higher incidence in diabetes. Involvement of lower lobes is common. Diabetes reactivates latent tuberculosis. X-ray must be taken once a year in all diabetics. Tuberculosis must be suspected if there is an increase in insulin requirement associated with weight loss.

**GASTRO INTESTINAL INFECTIONS**

Gastro intestinal infections range from diarrhea (blind loop syndrome) to emphysematous cholecystitis. The latter is due to mixed aerobic and anaerobic infections. Clostridia and E coli have been isolated from bile cultures. Staphylococcus, Streptococcus and Pseudomonas have also been implicated. Males are commoner (M: F = 3:1); one third of patients with emphysematous cholecystitis are diabetic. X-ray reveals gas in and around the gall bladder. In any diabetic with right upper quadrant pain, nausea and vomiting, sequential abdominal X-rays for 4 days are essential. Gangrene and perforation of gall bladder are fatal complications.
Amebic liver abscess is commoner in males. Female diabetics are more prone than non diabetics. Pregnant diabetics are also at risk.

**MALIGNANT OTITIS EXTERNA**

Occurs exclusively in diabetics, typically in the type 2 DM. Severe ear pain, discharge and painful induration around the ear occur. Facial palsy occurs in 50% of patients in whom prognosis is poor. Pseudomonas aeruginosa is the causative organism. Coliforms may also be associated. Vasculitis and rapid spread of infection to CNS are characteristic. Fever and leukocytosis are not present. Inspection of ear reveals polypoid mass of granulation tissue. Culture of the discharge is diagnostic. This infection may occur in diabetics with good control indicating that microangiopathy is the prime predisposing factor. Despite antibiotics and surgical debridement the mortality is high.

**FUNGAL INFECTIONS**

Mucocutaneous candidiasis is more frequent in diabetics. Vulvovaginitis of candidial origin must be looked for in diabetic females with pruritis vulvae. A colony count of 10,000/cc is significant. Esophageal candidiasis has been noted in diabetics. Diabetes is present in 10-20% of patients with cryptococcal infections.

Rhino cerebral Mucormycosis is found more specifically in diabetic ketoacidosis. Ketosis results in increased serum free iron which helps fungal growth. The patient presents with painful proptosis, black necrotic nasal turbinates and bloody nasal discharge. The fungus
lodges in nasal and paranasal sinuses and invades the CNS via cribiform plate. Meningitis and cavernous sinus thrombosis can result. Scraping of turbinates reveals the hyphae microscopically which are diagnostic. The mortality is 90%.

EFFECTS OF INFECTIONS ON DIABETES

Viral insulitis (mumps and coxsackie) are implicated in the etiology of type 1 DM.

Secondary infections in a diabetic can aggravate hyperglycemia and precipitate ketoacidosis (Hyperglycemia ketosis syndrome). This syndrome should be controlled by supplemental regular Insulin (additional 20% of total daily dose). Insulin resistance may be encountered in chronic infections. When there is an unexplained increase in Insulin requirements, occult infection must be looked for.

Rarely hypoglycemia can result from gram-negative septicemia and Pseudomonas infections where gluconeogenesis is inhibited by the bacterial toxins.

PREVENTION OF INFECTIONS

Glycemic control is the most important. Patient education regarding dental hygiene, foot care, sterilization technique for self Insulin injection is essential. Early surgical debridement and prophylactic antibiotics are useful. Pneumococcal vaccines and immunoglobulin are not routinely recommended. Early diagnosis and supplemental doses of regular Insulin is useful to prevent implementing keto acidosis.
Sepsis can precipitate ketoacidosis and set up the vicious cycle of sepsis-ketosis-sepsis. Hence prompt attention is needed.
Ketoacidosis is one of the most serious acute metabolic complications of diabetes. Ketoacidosis continues to be an important cause of morbidity and mortality in patients with diabetes in spite of major advances in understanding their pathogenesis, diagnosis and treatment. Even in the experienced center the mortality due to ketoacidosis is around 5%. In the United States, >150 000 children have diabetes mellitus, and 21 000 are diagnosed annually. Over the past 40 years, the incidence of type 1 diabetes in children has been increasing worldwide by 3% to 5% per year. In addition, recent reports have suggested that type 2 diabetes in youth has become more common. Diabetic ketoacidosis (DKA), the metabolic outcome of very low levels of effective insulin action, can be a life-threatening complication present in 15% to 67% of youth at the time of diagnosis. Despite the high morbidity and cost of DKA at diagnosis of diabetes, there are no recent estimates of its prevalence in the US population. Although predictors of DKA in children with established type 1 diabetes have been studied, little is known about predictors of DKA that precede diagnosis. Previous studies have suggested that DKA at the diagnosis of diabetes is more frequent in younger patients, in populations with lower socioeconomic status, and in countries with a lower incidence of type 1 diabetes where diabetes awareness is low. Type 2 diabetes may also present with DKA, but the prevalence and predictors of such a severe presentation of type 2 diabetes in youth have not been systematically studied.
PATHOPHYSIOLOGY OF DIABETIC KETOACIDOSIS

In a non-diabetic when the blood glucose levels are allowed to exceed 250 mg%, the plasma insulin concentration also increases more than 50 IU/ml. This concomitant normal increase in insulin for this prevailing blood glucose does not occur in a diabetic. A diabetic need not have absolute deficiency of insulin to develop ketoacidosis. Even when there is relative insulin deficiency ketoacidosis can occur. The term absolute insulin deficiency indicates plasma insulin concentration < 10 IU/ml and relative insulin deficiency indicates plasma insulin concentration between 10 and 50 IU/ml, when the plasma glucose concentration exceeds 250mg%. Absolute insulin deficiency or withdrawal of insulin in type 1 diabetics will result in metabolic catastrophe. A similar effect will also occur in type 2 diabetics, with relative insulin deficiency in clinical situation wherein there is increased elaboration of counter regulatory hormones like catecholamines, glucagons, cortisol and growth hormone (Figure 31).

Figure 31 Role of Insulin and Counter Hormones in Ketoacidosis

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)
Whenever there is lack of insulin the scenario is dominated by the catabolic effect of these counter regulatory hormones. There will be increased production of glucose by glycogenolysis and gluconeogenesis with impaired glucose uptake by the peripheral tissues resulting in hyperglycemia. The two prime glucose producing organs are liver and kidney since they possess glucose synthesizing enzymes, most important being Pyruvate carboxylase and Phosphoenol pyruvate carboxy kinase. The activities of these two enzymes are increased by glucagon and cortisol. Pyruvate and lactate from Glycolytic pathway, amino acid from muscles and glycerol from adipose tissue constitute the glucose precursors for gluconeogenesis. The cumulative effect of these “fuel, enzyme and hormone” interaction is severe hyperglycemia. At the same time, insulin lack and counter – hormones excess activate the hormone sensitive lipase leading to increased lipolysis. Consequently there is an increase in the release of FFA. FFA is the substrate for ketogenesis  

**Figure 32** Hormones of Gluconeogenesis

![](image)

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)
In the liver cell, FFA can either be esterified into triglyceride (Fuel storage) in the cytosol or can be oxidized to acetyl CoA, the substrate for ketone production (fuel utilization) in the mitochondria (Fig 33).

The entry to FFA into mitochondria is dependent on the activity of the enzyme Carnitine acyl transferase (CAT), present on the outer surface of the inner mitochondrial membrane. Malonyl CoA, the first intermediate along the pathway of fat synthesis from Acetyl CoA is a potent inhibitor of CAT. Low insulin and high glucagon levels in DKA inhibit glycolysis, thus resulting in low Malonyl CoA production. CAT activity is therefore enhanced resulting in a shift in hepatic metabolism of FFA from synthesis of triglyceride to generation of ketone bodies (Fig.33). In addition, Acetyl CoA carboxylase, the enzyme converting Acetyl CoA to Malonyl CoA is inhibited by Glucagon and this also helps to increase the activity of CAT system.

**Figure 33 Fate of FFA**

![Figure 33 Fate of FFA](image)

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)

The end result of these changes in the hepatic metabolism is a rapid increase in the - oxidation of fatty acids to Acetyl CoA. The Acetyl CoA is converted to Acet - acetyl CoA and metabolized further to a)
Acetoacetate (AA) b) - hydroxybutyrate (BB) and c) Acetone (A) [all of them constitute the 'ketone bodies']

The ketone bodies so formed leave the hepatocytes because they cannot be used in the liver, which lacks enzyme thiokinase. They are diverted to be used elsewhere (brain and skeletal muscle). Insulin deficiency impairs the ability of peripheral tissues to take up and metabolize ketone bodies.

**SUMMARY OF THE PATHOPHYSIOLOGY OF DIABETIC KETOACIDOSIS**

Increased glycogenolysis and gluconeogenesis (from the glucogenesis substrates pyruvate, lactate, and amino acids from muscle protein breakdown and glycerol from adipose tissues) at the liver and kidney resulting in marked hyperglycemia.

Insulin lack and counter hormone excess activate the hormone sensitive lipase leading to increased lipolysis. The free fatty acids thus released are taken to the liver and serve as substrates for ketogenesis. Low insulin and high glucagon levels of DKA result in low malonyl Coenzyme A production at the liver cell leading to reduced entry of free fatty acids into mitochondria.

The end result of these changes is the rapid increase in the beta oxidation of free fatty acids to acetyl CoA and later acetoacetate, beta hydroxy butyrate and acetone (ketone bodies).
Brain and skeletal muscle can metabolize ketone bodies to a certain extent but due to insulin deficiency, impairs the ability of peripheral tissues to take up ketones, plasma levels of ketones are elevated. Acetoacetic acid and beta hydroxy butyrate are strong acids and are fully dissociated at body pH consuming the body buffers and result in acidosis.

Marked hyperglycemia causes osmotic diuresis with loss of water and electrolytes. Increased extra cellular osmolarity shifts water from cells resulting in cellular dehydration.

**PATHOGENESIS SIMPLIFIED**

Normal metabolic homeostasis results from a balance between the anabolic effect of insulin and the catabolic effects of the counter regulatory hormones i.e., glucagon, catecholamines, growth hormones and cortisol on the metabolic fuels (glucose, fats and proteins). In DKA there is insulin deficiency coupled with concomitant elevation of counter-regulatory hormones. Whenever insulin lack occurs, the scenario is dominated by the catabolic effects of the counter regulatory hormones (Fig 32). This hormonal imbalance promotes glycolysis, gluconeogenesis, and glycogenolysis and inhibits peripheral utilization of glucose by muscles and adipose tissue. Simultaneously there is accelerated protein breakdown and lipolysis. All these results in hyperglycemia, increase free fatty acids, glycerol, amino acids (alanine and glutamine) and lactate. The oxidation of excess free fatty acids in the liver results in increased production of ketone bodies namely – acetoacetate, beta hydroxy butyrate and acetone. Normally these are utilized by the peripheral tissues like cardiac and skeletal muscles. But when there is excess production, it results in hyperketonaemia thereby
causing acidosis, 5 - 15 mmol/L of ketone bodies (normal ketone level - < 0.2 mmol/L) and an increased anion gap, 14 - 15 mmol/L (normal 12 ± 2 meq/L). Thus the hormone-metabolic disturbance results in severe and sustained hyperglycemia, ketonemia, aminoacidemia and lipaemia.

**Table 42** Metabolic Abnormalities and Clinical Correlates of DKA

<table>
<thead>
<tr>
<th>METABOLIC ABNORMALITIES</th>
<th>CLINICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Carbohydrate Metabolism</td>
<td>1. Diminished uptake of glucose by tissues such as muscle, adipose tissue and liver</td>
</tr>
<tr>
<td></td>
<td>2. Overproduction of glucose (via glycogenolysis and gluconeogenesis) by the liver</td>
</tr>
<tr>
<td>B) Protein Metabolism</td>
<td>1. Diminished uptake of amino acids and diminished synthesis of protein</td>
</tr>
<tr>
<td></td>
<td>2. Increased proteolysis</td>
</tr>
<tr>
<td>C) Fat Metabolism</td>
<td>1. Increased lipolysis</td>
</tr>
<tr>
<td></td>
<td>2. Decreased lipogenesis</td>
</tr>
<tr>
<td></td>
<td>3. Increased production of triglycerides</td>
</tr>
<tr>
<td></td>
<td>4. Decreased removal of triglycerides</td>
</tr>
</tbody>
</table>

300
The consequence of hyperglycemia and heavy glycosuria is osmotic diuresis, water and electrolyte loss, producing severe dehydration, hypotension and shock (Fig 34). The metabolic abnormalities and clinical correlates of DKA are shown in Table 42.
SPECTRUM OF PRESENTATION

A diabetic can present with high blood sugar with ketones in the urine and can still be ambulant called as “ambulant ketosis”; can have acidosis and can still be conscious – “diabetic ketosis”; or can present in a stuporous state – “diabetic ketoacidosis” or in an unconscious state – “diabetic ketoacidotic coma”.

PRECIPITATING CAUSES

The most important precipitating cause is the infection followed by omission of insulin. In 20% of cases no cause can be ascertained. In type 2 DM patients any stress situations (acute myocardial infarction, cerebrovascular accident, surgery, trauma etc.,) or infections can precipitate diabetic ketoacidosis. Diabetic ketoacidosis may be an initial presenting feature of type 1 DM.

CLINICAL PRESENTATION

DKA may be the presenting feature in 10% of patients with undiagnosed diabetes. A similar proportion of case may be spontaneous without any extraneous causes. The onset of DKA is insidious occurring over hours or days. Polyuria and polydipsia are manifestations of osmotic diuresis secondary to hyperglycemia (Table - 43). This is a unique situation where the dehydration is associated with polyuria in the initial stage. Weakness, lethargy and myalgia are relatively non-specific symptoms. The gastro – intestinal and respiratory symptoms, however, are specifically related to DKA. The abdominal events center around the transpyloric plane (L1). The abdominal pain can be quite severe and mistaken for acute abdomen
and the patient operated upon. The pain is related to ketosis and is due to pooling of fluid in the intestinal tract. Ileus results from temporary autonomic neuropathy, electrolyte disturbances and hyperglucagonaemia. Vomiting in a diabetic is an ominous sign and may point to an impending metabolic derangement. It is related to the level of glycerol in circulation. Acidosis induces deep and hurried breathing (Kussmaul's breathing). Dyspnoea is the ventilatory response to metabolic acidosis due to the rise in the hydrogen ion concentration. In children the presentation feature may be pain abdomen, hyperventilation, dehydration or altered consciousness. These conditions may be mistaken for surgical abdomen, bronchopneumonia, gastroenteritis or meningitis.

Table 43 Symptoms of DKA

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyuria</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>Nausea</td>
</tr>
<tr>
<td>Weakness</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Lethargy</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Myalgia</td>
<td>&quot;Dyspnoea&quot;</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
</tbody>
</table>

SIGNS

The signs of DKA are listed in table 44. The most sensitive sign of dehydration, which is really due to intravascular volume depletion, is a change in the way in which the neck veins fill. When a normally hydrated subject lies entirely horizontally (i.e. without a pillow), the neck veins fill from below – upwards to a point near the angle of the mandible. If the vein is not filled from below or is filled to less than one half of the distance to the angle of the mandible, the intravascular volume is significantly reduced.
The only other reliable sign of intravascular volume depletion is a fall of systolic blood pressure by 20mm Hg or more when the patient moves from a lying to a sitting or standing position. It must be kept in mind, that diabetics with autonomic dysfunction may manifest orthostatic changes in blood pressure in the absence of any fluid loss.

**Table 44 signs of DKA**

<table>
<thead>
<tr>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperpnoea (Kussmaul's respiration)</td>
</tr>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Acetone breath</td>
</tr>
<tr>
<td>&quot;Dehydration&quot; (intravascular volume depletion)</td>
</tr>
<tr>
<td>Hyporeflexia</td>
</tr>
<tr>
<td>&quot;Acute abdomen&quot;</td>
</tr>
<tr>
<td>Stupor – Coma</td>
</tr>
<tr>
<td>Hypotonia</td>
</tr>
<tr>
<td>In coordinated ocular movements</td>
</tr>
</tbody>
</table>

Soft eye balls and poor skin turgor are seen only with profound dehydration. The deterioration in the level of consciousness is proportional to the plasma osmolality (Table – 45). Hypothermia is due to reduced oxygen and fuel consumption. Even though infection is one of the important causes of diabetic ketoacidosis they may not be febrile.

**Table 45 Plasma Osmolality and The Level of Consciousness**

<table>
<thead>
<tr>
<th>Plasma Osmolality</th>
<th>Level of consciousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>324 mOsm/Kg</td>
<td>Drowsy</td>
</tr>
<tr>
<td>340 mOsm/Kg</td>
<td>Semi – coma</td>
</tr>
<tr>
<td>370 mOsm/Kg</td>
<td>Coma</td>
</tr>
</tbody>
</table>

The normal osmolality is 285 milli osmoles/kg. Serum osmolality can be estimated by using the formula:

\[
\text{Osmolality} = 2(\text{Na} + \text{K}) + \left(\frac{\text{Glucose (mg)}}{18} + \frac{\text{Urea (mg)}}{6}\right)
\]
DISCUSSION

In a study, conducted in USA, the prevalence of DKA at the time of diagnosis was 25.5%. Prevalence decreased significantly with age from 37.3% in children aged 0 to 4 years to 14.7% in those aged 15 to 19 years. Prevalence did not differ significantly by gender or race/ethnicity. As expected, DKA at diagnosis occurred significantly more often in patients with type 1 diabetes than in those with type 2.

The major finding in this large, population-based study is that a substantial percentage (29.4%) of youth in the United States who are currently being diagnosed with type 1 diabetes present with potentially life-threatening ketoacidosis. This estimate is similar to those reported 10 to 20 years ago from several European countries. Although we found that low socioeconomic status, insufficient health insurance, and lower parental education were independently associated with the risk of DKA, they also found that >20% of children from the most affluent families have DKA at diagnosis. This high prevalence of DKA at diagnosis of diabetes among US youth suggests that efforts aiming at preventing this frequent severe complication of diabetes are warranted. Comparisons with previous studies in the United States and elsewhere suggest that the risk of DKA at diagnosis has not improved decisively over the past 20 years. In Colorado, over the past 23 years, the proportion of children with type 1 diabetes who have presented with DKA at the time of diagnosis has decreased only modestly, from 38% in 1978–1982 to 29% in 1998–2001. On the other hand, the incidence of type 1 diabetes in youth is doubling every 2 decades, and several studies have reported increasing rates of type 2 diabetes in youth, especially in nonwhite ethnic groups.
Although the rates of DKA are somewhat lower, with more youth with diabetes, in the absence of community efforts to increase public awareness of the early symptoms of diabetes, DKA is likely to remain a major cause of morbidity and health care expenditures in youth.

Currently, there are few population-based epidemiologic data on the prevalence and predictors of DKA at the time of presentation of type 2 diabetes in youth. In this study, using a large number of patients with type 2 disease from several settings and geographic areas, they found that 9.7% of youth with type 2 diabetes presented with DKA. This finding is consistent with previous reports. DKA in adults occurs in those with ketosis-prone diabetes and particularly in nonwhite persons with type 2 diabetes. Finding suggests that DKA at diagnosis should not be used to exclude the diagnosis of type 2 diabetes, at least in patients <20 years of age. Their data confirm previous reports suggesting that lack of insurance and less favorable health insurance are associated with more severe onset of diabetes in youth. They did not find any significant differences in the prevalence of DKA among different racial and ethnic groups in univariate and multivariate analyses. This is consistent with a previous report on predictors of recurrent DKA in the US youth with type 1 diabetes, where rates were similar in Hispanics and non-Hispanic whites. In contrast, young Asian children in the United Kingdom had 8 times the risk of presenting in DKA as did non-Asian children of the same age.

In developed countries, earlier studies have suggested that as many as 1% of children used to die at the diagnosis of diabetes.

In light of the increasing incidence of diabetes in the United States and worldwide, a high index of suspicion on the part of parents and health
care providers may reduce the cost of initial diabetes care. Early recognition of the classical triad of polydipsia, polyuria, and polyphagia with weight loss (present also in many cases of type 2 diabetes before diagnosis) is essential, as is awareness of the variable presenting symptoms, for example, vomiting or rapid breathing in a young child. An intensive community intervention to raise awareness of the signs and symptoms of childhood diabetes among school teachers and primary care providers in a region of Italy was found to reduce the prevalence of DKA at diagnosis of type 1 disease from 83% to 13%.755 In the United States, the Diabetes Autoimmunity Study in Youth, an observational study following children at high risk for type 1 diabetes by periodic testing for diabetes autoantibodies, levels of hemoglobin A1c, and random blood glucose, demonstrated that the clinical course of diabetes is milder in youth diagnosed without DKA.756 Children followed by the Diabetes Autoimmunity Study in the Young were rarely hospitalized and did not develop DKA at diagnosis of diabetes, in contrast to community control subjects with and without a family history of diabetes. They also had nearly normal hemoglobin A1c values at diagnosis, with significantly lower requirements for insulin in the first year of illness. This milder clinical course at diagnosis may have very important long-term implications because near-euglycemic control at onset occurring spontaneously757 or achieved by intensive insulin treatment758 has been shown to preserve the secretion of insulin. Residual endogenous insulin secretion, as shown by the Diabetes Control and Complications Trial, predicted a 65% lower risk of severe hypoglycemia759 and a 50% lower risk of the progression of diabetic retinopathy.760
CONCLUSION

They found that 29.4% of those with type 1 diabetes and 9.7% of those with type 2 were diagnosed with DKA. Young and poor children were disproportionately affected, but DKA occurred even in affluent and well educated families. The prevalence of DKA at the diagnosis of diabetes continues to be high. Increased public awareness and greater medical alertness concerning the symptoms and signs of diabetes are warranted. Improved access to care may additionally reduce the severity and costs of initial diabetes treatment in youth.

PREVENTION

Diabetic ketoacidosis can be an initial presentation of diabetes in a child. Family physician has to be alert when a child presents with evidence of dehydration or hyperventilation or drowsiness or with polyuria, and polydipsia. During infection insulin requirement may be high. Insulin should never be stopped even if the child refuses to take the usual diet. A palatable diet may be given along with insulin with adequate fluid intake. If the child is not able to retain fluid it is advisable to hospitalize.
DIABETES AND PREGNANCY

INTRODUCTION

The prevalence of diabetes is increasing globally and India is no exception. The 1997 WHO estimates of the prevalence of diabetes in adults showed an expected total rise of > 120% from 135 million in 1995 to 300 million in 2025. These numbers also include GDM, and should alert physicians to the need to direct special attention to this population, especially in developing countries.\textsuperscript{761}

GESTATIONAL DIABETES MELLITUS (GDM)

Gestational Diabetes Mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy.\textsuperscript{762} The definition applies irrespective of whether or not insulin is used for treatment or the condition persists after pregnancy. It does not exclude the possibility that glucose intolerance may have antedated the present pregnancy. GDM results from sluggish first phase insulin release and in addition to excessive resistance to action of insulin on glucose utilization due to placental hormones (Placental lactogen, progestin, prolactin and cortisol).

PREVALENCE

As of today we have no current national data regarding the occurrence of abnormal glucose tolerance in the pregnant women. The routine screening for glucose intolerance during pregnancy is not done in maternity hospitals maintained by the Government, municipality or
local bodies that care for the majority of the pregnant women in our country.

A study by Seshiah et al\textsuperscript{763} reported a prevalence of 17.7\% in the urban population.

Subsequent to the observation of the high prevalence of GDM in one centre, a multicentre study was initiated in different parts of the country in 2002 - 2003 taking only the 2 hr 75 gm post glucose value of $\geq 140\text{mg/dl}$ as diagnostic criteria for GDM. Almost a similar prevalence of 15\% was obtained in another govt. maternity hospital affiliated to Madras Medical College in the city of Chennai. This trend of high prevalence of GDM was also found in other parts of the country, 15\% in Trivandrum, 21\% in Always, 12\% in Bangalore, 18.8\% in Erode and 17.5\% in Ludhiana. The total number of pregnant women screened in these centres was 3674 and an overall GDM prevalence of 16.55\% was observed. This study documented a definite increasing trend in the prevalence of GDM compared to that of 2\% in 1982\textsuperscript{764} and 7.62\% in 1991.\textsuperscript{765} This trend is also seen in other countries. For example in Australia at one hospital where the same testing procedure and diagnostic criteria have been used for more than 2 decades, the prevalence has more than doubled.\textsuperscript{766}

A recent national survey reported the prevalence of IGT in the age group of 20-29 years and 30-39 years as 12.2\% and 15.3\% respectively.\textsuperscript{767} No gender difference was seen in the prevalence of IGT.\textsuperscript{767} Further for a given population and ethnicity the risk of diabetes and pregnancy, mirrors that of the underlying frequency of type 2 DM in the general population.\textsuperscript{768} Seshiah et al also observed that the
prevalence of GDM is closer if not similar to the prevalence rate of IGT in our population. With this huge population of reproductive age in India, a significant segment of women with abnormal glucose tolerance during pregnancy needs cognizance. Their attempt and outcome of the screening for glucose intolerance during pregnancy has given an insight for the phenomenal increase in the prevalence of diabetes in India. This view is substantiated by the observation of Dabelea et al on Pima Indians. The gestational diabetes mellitus has a far reaching consequence in predisposing the offsprings to glucose intolerance has been documented in Pima Indians. The children born in 1965 to women with gestational diabetes were followed up till 2000. By the time they reached 35 years, more than half of the group had diabetes.769 Hence as a policy to identify GDM and its consequences on the infant a 75 gm OGTT has been recommended to all women in the population during the third trimester of pregnancy.769

In India, both undernutrition and overnutrition exist during pregnancy. There are two reported studies in India which are related to size at birth to future risk of type 2 diabetes. In Mysore, low birth weight did not increase the risk of diabetes but babies who were short and fat (higher body mass index, BMI) at birth were at increased risk.770 Fall et al speculate that the rise in type 2 diabetes in Indian urban populations may have been triggered by mild obesity in mothers, leading to glucose intolerance during pregnancy, macrosomic changes in the fetus and insulin deficiency in adult life.770 Yet another study by Yajnik et al attributes high prevalence of type 2 DM and IGT in Indian people may be linked to poor fetal growth.771 Same author also suggests that type 2 DM in India may be programmed in fetal life, hence diabetes prevention will have to start in early life (in utero) and
continue in later life. The importance is that the intrauterine milieu, whether one of nutritional deprivation or one of nutritional plenty, results in changes in pancreatic development and peripheral response to insulin that may lead to adult-onset GDM and type 2 DM.

**SCREENING AND DIAGNOSIS**

<table>
<thead>
<tr>
<th>Table 46 Indications For Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH RISK FOR GDM</strong></td>
</tr>
<tr>
<td>* Family History of diabetes</td>
</tr>
<tr>
<td>* Glucose in second fasting urine sample</td>
</tr>
<tr>
<td>* History of unexplained Perinatal loss</td>
</tr>
<tr>
<td>* History of Large for Gestational age infant</td>
</tr>
<tr>
<td>low prevalence of GDM</td>
</tr>
<tr>
<td>* History of Congenitally malformed infant</td>
</tr>
<tr>
<td>* Maternal obesity</td>
</tr>
</tbody>
</table>

ADA RECOMMENDS TWO STEP APPROACHES

1) One Step Approach

Diagnostic oral glucose tolerance test without prior plasma or serum glucose screening

2) Two Step Approach

An initial screening by measuring plasma glucose one hour after 50g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT. When the two-step approach is employed, a glucose threshold value > 140mg/dl (7.8mmol/L)
identifies approximately 80% of women with GDM, and the yield is further increased to 90% by using a cutoff of > 130mg/dl (7.2mmol/L).

CARPENTER AND COUSTAN DIAGNOSTIC CRITERIA

The American Diabetes Association has adopted Carpenter and Coustan criteria given in Table – 47.

Table 47 Diagnosis of GDM

<table>
<thead>
<tr>
<th>100 g OGTT</th>
<th>75g OGTT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting</strong></td>
<td>95 mg/dl (5.3mmol/L)</td>
</tr>
<tr>
<td>1 - hr</td>
<td>180mg/dl (10mmol/L)</td>
</tr>
<tr>
<td>2 - hr</td>
<td>155mg/dl (8.6mmol/L)</td>
</tr>
<tr>
<td>3 - hr</td>
<td>140mg/dl (7.8mmol/L)</td>
</tr>
</tbody>
</table>

Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis.

WHO Criteria: A Standard OGTT should be performed after over night fasting by giving 75g of glucose. Plasma glucose is measured at fasting and after 2 hours. Pregnant women who meet WHO criteria for IGT (2 hr PG > 140 mg/dl are classified as having gestational diabetes mellitus (GDM) (Table – 48).

Table 48 WHO Criteria (Plasma Glucose)

<table>
<thead>
<tr>
<th></th>
<th>FPG (mg/dl)</th>
<th>2h PG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT</td>
<td>&lt; 126</td>
<td>140-200</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&gt; 126</td>
<td>&gt; 200</td>
</tr>
</tbody>
</table>

If the screen has fasting plasma glucose more than 126 mg and/or 2hr post glucose more than 200 mg, probably she has been having
undetected diabetes prior to conception (pre gestational diabetes) and confirmed by A1c estimation.

RECOMMENDATIONS

American Diabetes Association suggests selective screening for GDM. Selective screening is applicable for women belonging to ethnic group with the low prevalence of GDM, whereas ethnically Indian women are more prone to develop glucose intolerance during pregnancy and have eleven fold increased risk compared to White Caucasians necessitating Universal Screening during pregnancy. It is important to detect these GDM cases because if unrecognized, pregnancy may end in perinatal death and fetal wastage.

The hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was initiated on April 1, 1999. The objective of the study is to clarify unanswered questions on associations of maternal glycemia, less severe than overt diabetes mellitus, with risks of adverse pregnancy outcome. The glucose tolerance is assessed by a 75g OGTT at 24 – 32 weeks of gestation. The primary outcomes to be assessed in relation to maternal glycemia are caesarian delivery, increased fetal size (macrosomia / LGA / obesity), neonatal morbidity (hypoglycemia), and fetal hyperinsulinism. The study is of five years duration.774 Till the results of this study are available, a uniform policy of adopting WHO screening and diagnostic criteria is recommended for the following reasons.

1. GDM diagnosis based on two hour 75 g OGTT defined by either WHO or ADA criteria predicts adverse pregnancy outcome.775
2. The criteria recommended by WHO is simple and cost effective and is practiced in many centers.

3. Further assuming that effective treatment is available, WHO criteria of 2 hr PPG ≥140 mg/dl identifying a large number of cases may have a greater potential for prevention.

4. One step procedure of WHO serves dual purpose of both screening and diagnosis.

Seshiah et al favours one step procedure recommended by WHO for screening instead of two step procedure using preliminary screening with 50 gm one hr test.776

**A SINGLE TEST PROCEDURE TO DIAGNOSE GESTATIONAL DIABETES MELLITUS**

American Diabetes Association (ADA) recommends selective screening to detect GDM. This policy may not be applicable for population belonging to the ethnic group with high prevalence of GDM.777 Further, compared to selective screening recommended by ADA, universal screening for GDM detects more cases and improves maternal and offspring prognosis.778 Women with a history of GDM are at an increased risk of future diabetes predominantly type 2 diabetes as are their children.779 Thus GDM women are an ideal group for the primary prevention of diabetes.780 This implies that universal screening for detection and care of women with GDM may be considered as mandatory, and for this we need a simple and acceptable test procedure.
The importance of any screening procedure is not only to identify women with GDM but also to exclude NGT women. ADA recommends 50 g of oral glucose for screening without regard to time of the last meal and the PG of 140 mg/dl 1 h after the glucose load as a positive screen test. In them, the diagnosis of GDM needs confirmation by 100 g OGTT. This two-step procedure is cumbersome and also the phenomenon of no show occurs since the woman has to visit the antenatal clinic twice. However, the one-step procedure of WHO serves the dual purpose of both screening and diagnosis of GDM. But the disadvantage with this procedure is that the pregnant woman has to come to the antenatal clinic or laboratory in a fasting state. In this context a procedure that does not impose any restriction would be ideal for universal screening. The test performed should be able to diagnose GDM, as they walk into the antenatal clinic or laboratory irrespective of their last meal timings.

A normal glucose tolerant woman would be able to maintain euglycemia despite glucose challenge due to adequate insulin response. Whereas in a woman with GDM who has impaired insulin secretion, her glycemic level increases with a meal and with glucose challenge, the glycemic excursion is expected to exaggerate. This cascading effect is advantageous as this would not result in false positive diagnosis of GDM. Performing the test procedure in the non-fasting state is rational as glucose concentrations during the glucose tolerance are affected little by the time since the last meal.

Seshiah et al and Pettitt et al. observed that WHO criteria based on the glucose concentration 2 h after 75 g of load administered to non-fasting women correctly identified subjects with GDM. The non-
fasting 2 h post-75 g glucose concentration strongly predicts adverse outcome for the mother and her offspring.\textsuperscript{788}

The 75 g of glucose challenge though larger than the 50 g recommended by ADA, the difference in the glycemic load is not expected to result in a higher glycemic excursion in NGT subjects.\textsuperscript{787} Further, ADA also permits both 100 and 75 g OGTT for diagnosis of GDM. Though the glucose loads are different, the cut off values (FPG 95 mg/dl, 1-h PG 180 mg/dl, 2-h PG 155 mg/dl) for diagnosis of GDM are the same implying that the quantity of glucose load has little influence on the PG levels in a normal person, whereas in a metabolically deranged state like GDM, both 50 and 75 g glucose load would unmask the glucose intolerance. The advantage of 75-g GCT is that there is no necessity to repeat OGTT; however, for 50-g glucose challenge it is.

The 75-g GCT performed irrespective of the last meal timing is a patient-friendly approach. Diagnosis of GDM may be established or excluded by this simple procedure. Women found to have NGT in the first visit may need to undergo GCT in the subsequent visits of all trimesters. This one-step diagnostic procedure is easy to perform, cost effective and causes least disturbance in a pregnant woman’s routine activities.
CONSEQUENCES OF THE CHANGES IN FUEL METABOLISM DURING PREGNANCY ON THE FETAL DEVELOPMENT:

Consequences of the changes in fuel metabolism during pregnancy on the fetal development revolve around 'maternal hyperglycemia and fetal hyperinsulinemia' (Fig - 35).

Figure 35 Model of Maternal Gestational Diabetes, Fetal Hyperinsulinemia and Infant Outcome
(Modified Pedersen Hypothesis)

Pregnancy is considered as tissue culture experiment implicating that placenta and fetus develop in an incubation medium that is totally derived from maternal fuels consisting of glucose, amino acids and
lipids. The fuels travel the placenta by facilitated diffusion and active transport and enter the fetal circulation (Fig- 36).

**Figure 36** Schematic representation of maternal – fetal nutrient transport in humans

<table>
<thead>
<tr>
<th>Mother</th>
<th>Placenta</th>
<th>Fetus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td></td>
<td>Glucose</td>
</tr>
<tr>
<td>Amino acids</td>
<td></td>
<td>Amino acids</td>
</tr>
<tr>
<td>Ketones</td>
<td></td>
<td>Ketones</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td>Fatty acids</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Adopted from Handbook on Diabetes Mellitus by Dr. V. Seshiah 4th edition)

These processes are regulated by insulin and hence any disturbance in the secretion and action of insulin will influence the whole nutrient composition to which fetus is exposed and may lead to fetal hyperinsulinemia. The abnormal mixture of maternal nutrients gain access to the developing fetus and modify phenotype gene expression in newly forming cells and thereby causing permanent short and long term effects upon the offsprings. Accordingly the fetal and neonatal complications occur when the fetus is exposed to the abnormal fuel mixture during different periods of gestation (Table - 49).

**Table 49** Fetal Problems Associated with Maternal Hyperglycemia by Trimester

<table>
<thead>
<tr>
<th>FIRST TRIMESTER</th>
<th>SECOND TRIMESTER</th>
<th>THIRD TRIMESTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformations</td>
<td>Hypertrophic</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Growth Retardation</td>
<td>Cardiomyopathy</td>
<td>Hypocalcaemia</td>
</tr>
<tr>
<td>Fetal Wastage</td>
<td>Polyhydramnios</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>Erythraemia</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td></td>
<td>Placental insufficiency</td>
<td>Macrosomia</td>
</tr>
<tr>
<td></td>
<td>Preeclampsia</td>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td></td>
<td>Fetal loss</td>
<td>Intrauterine death</td>
</tr>
<tr>
<td></td>
<td>Low IQ</td>
<td></td>
</tr>
</tbody>
</table>

319
In the first trimester, the exposure to abnormal mixed nutrients during organogenesis (first 6 - 8 weeks of gestation) may cause spontaneous miscarriage, intrauterine growth retardation and malformations (Table 50).

Table 50 Types And Timing Of Malformations In Infants Of Diabetic Mothers

<table>
<thead>
<tr>
<th>TYPE OF ANOMALY</th>
<th>TIMING OF LESION (WEEKS POSTCONCEPTION)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal</td>
<td></td>
</tr>
<tr>
<td>Caudal regression</td>
<td>3</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>6</td>
</tr>
<tr>
<td>Neural</td>
<td></td>
</tr>
<tr>
<td>Anencephaly</td>
<td>4</td>
</tr>
<tr>
<td>Myelocele Hydrocephalus</td>
<td>4</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Dextrocardia</td>
<td>4</td>
</tr>
<tr>
<td>Conus arterosus defects</td>
<td>5</td>
</tr>
<tr>
<td>Ventricular septal defects</td>
<td>6</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Renal agenesis/hypoplasia</td>
<td>6</td>
</tr>
</tbody>
</table>

Most evidence from human pregnancies point to the maternal metabolic abnormalities as the most important cause for the increased risk of malformations in diabetic pregnancies.

If this fuel mediated teratogenesis is to be avoided, then excellent control of maternal metabolism must commence before conception and must be maintained during the first eight weeks, a critical period when many women may not be aware that they are pregnant. Preventive medicine necessarily starts before conception reflecting the importance
of pre-pregnancy counseling. Supplementation with folic acid, myoinositol and antioxidants may play a role in the prevention of malformations and lower the ratio from 7.5 to 0.8%.

Hyperglycemia, during the second trimester when the formation and the development of brain cells takes place, alters the behavioral, intellectual and psychological pattern in childhood. Insulin is detectable in the fetal pancreas as early as 9\textsuperscript{th} week after conception. B cell growth and replication are regulated by nutritional insulin secretogogues such as glucose, mannose and essential amino acids. Human studies have shown an increase in pancreatic fetal cell mass and insulin secretion in fetuses of poorly controlled diabetic women of 16\textsuperscript{th} week of gestation and both abnormalities increase throughout second trimester until 26\textsuperscript{th} week of gestation. This priming of B cell in mid gestation may account for the persistence of fetal hyperinsulinemia throughout the pregnancy and the risk of accelerated fetal growth even when mother achieves a good metabolic control in lateral pregnancy.

Maternal hyperglycemia in the third trimester causes proliferation of fetal adipocytes, muscle cells and pancreatic beta cells and neuroendocrine systems and they form the base for macrosomia and for the development of obesity, IGT and type 2 diabetes in later life. Still birth in diabetic pregnancies is still unexplained, although both maternal hyperglycemia and fetal macrosomia are associated. Mechanism implicated are fetal hypoxia, acidosis, hyperkalemia leading to dysrhythmias and placental dysfunction and competition for essential nutrients. In an unexplained stillbirth, the possibility of undiagnosed GDM must be considered and at autopsy the fetus may have islet cell
hyperplasia (in the absence of rhesus problem) and increased interstitial tissue in the testis or lutenization of the theca interna of the ovary.

NEONATAL COMPLICATIONS

HYPOGLYCEMIA

Due to the endogenous hyperinsulinemia and suppression of endogenous glucose production, the Infant of the Diabetic Mother (IDM) is at increased risk of hypoglycemia at 1 to 3 hours after birth. About 50% of the hypoglycemic babies may remain asymptomatic. Twitching of the limbs, hypotonia, tachypnoea and rarely seizures in severe hypoglycemia are the clinical presentations. Hypoglycemia is defined as blood sugar level less than 30 mg/dl in any infant regardless of gestational age.

The factor mainly protective against fetal hypoglycemia is the optimal control of maternal hyperglycemia especially during the third trimester and during labor. It has been shown that a mean maternal plasma glucose > 105 mg/dl during the last four hours of labor in a diabetic mother leads to a higher incidence of neonatal hypoglycemia.

HYPOCALCEMIA

About 25% of the IDMs may present with serum Calcium of < 7 mg/dl and this may remain mostly asymptomatic and is usually detectable during the 2nd or 3rd day of the birth. Asphyxia and prematurity, operating through elevated Cortisol, induces Vitamin D antagonism at the intestinal level. Respiratory distress and fetal metabolic acidosis
may result in calcium being shifted from intracellular to extra cellular pools and reversal of this shift during correction of the acidotic event may produce hypocalcaemia. Hypomagnesemia may coexist and may require correction.

RESPIRATORY DISTRESS SYNDROME (RDS)

Observed in about 5% of IDM. In vitro studies indicate that insulin antagonizes the stimulatory effects of cortisol on fibroblasts to induce the synthesis of Fibroblast-Pneumonocyte Factor (FPF), which in turn inhibits type II cells and Phosphatidyl Choline production. Measurement of Phosphatidyl glycerol alone or in combination with the lecithin phosphatidyl choline may be a more reliable indicator of lung maturity in diabetic pregnancies than the Lecithin: Sphingomyelin ratio alone. Prophylactic steroids to accelerate the lung maturity may be indicated if the L: S ratio is < than 2:1. Such obstetric situations, requiring steroids or Beta sympathomimetics drugs (E.g. Salbutamol) may worsen the diabetic control and calls for frequent monitoring of blood sugar and correction with soluble insulin.

POLYCYTHEMIA

Relatively common in IDM. This is mostly due to the hypoxic stimulus by the placental insufficiency and elevated Glycohemoglobin. Over transfusion from the large placenta of diabetic pregnancy may also contribute. The resultant hyper viscosity may induce congestive heart failure and vascular thrombosis accounting for the increased risk of renal vein thrombosis in these infants.
HYPERBILIRUBINEMIA

This common abnormality is due to increased bilirubin production and decreased life span of the RBCs with glycosylated cell membranes. Hepatic conjugation of bilirubin may be impaired due to an immature liver.

MACROSOMIA

Neonates weighing more than 4 kg are considered to be macrosomic.

The Indian consensus is that newborn baby’s weight $\geq$ 3.5 kg should be considered as macrosomia. Macrosomic babies have considerable greater shoulder / head and chest/head differences and are prone to shoulder dystocia. Fetal hyperinsulinemia per se is accompanied by excessive transfer of nutrients to the fetus and external somatic growth. This phenomenon usually manifest around 28\textsuperscript{th} week gestation. The fetal insulin has a central role in fetal growth and development approximately around the last 10 weeks of gestation. Meticulous control of maternal metabolism (substrate concentration) tends to normalize the fetal growth to a certain extent. The reduction in size at birth is partly attributed to reduced amount of adipose tissue, which normally accumulates during the last 8 – 10 weeks of gestation.
CONSEQUENCES OF DIABETES ON THE PREGNANT MOTHER

Complications of diabetes in pregnancy occur almost exclusively in pregestational diabetic women.

HYPOGLYCEMIA

Hypoglycemia may occur in the first trimester of the pregnancy. This is due to combination of physiological adaptation, attempt for strict control and the nausea of early pregnancy.

DIABETIC KETOACIDOSIS

As pregnancy has some features of starvation state, ketoacidosis is a real hazard. DKA has deleterious effect on the fetus.

RETINOPATHY

Background diabetic retinopathy (BDR) can develop or worsen during pregnancy. It is not a risk for vision and usually regresses post partum. If BDR is already present, may progress to proliferative diabetic retinopathy (PDR). It is essential to perform periodic ophthalmic examination and in a few photocoagulations may be necessary. The pregnant women in poor glycemic control and with hypertension are at an increased risk of developing PDR. These risks can be minimized by instituting pre conception control of diabetes and hypertension.
NEPHROPATHY

The risk of worsening diabetic nephropathy depends on baseline renal function and the degree of hypertension. Diabetic women with microalbuminuria may develop albuminuria during pregnancy with regression post partum. Some among them are likely to develop preeclamptic symptoms. If the initial renal function is impaired in pregnancy, almost 50% of them are likely to show further decline in renal function.

HYPERTENSION

The safe and effective anti hypertensive drug during pregnancy is methyldopa. The other alternate drugs are diltiazem, clonidine and Prazosin. Better to avoid beta-blockers due to possible association with fetal growth retardation. Angiotensin inhibitors should never be used due to potential damage to the fetal kidneys.

DIABETIC GASTROPATHY

This condition severely exacerbates nausea and vomiting. The drug such as cisapride or mosapride may give relief.

POLYHYDRAMNIOS

This occurs in poorly controlled diabetic mothers attributed to increased glucose content in the amniotic fluid, creating an osmotic pressure that equilibrates in the presence of an increased volume of amniotic fluid.
FUTURE RISK OF DIABETES

A considerable proportion about 30% of women with GDM will progress to type 2 DM in the 2 to 20 years after pregnancy. The risk factors for progression are:

- The degree of glucose tolerance during and after pregnancy;
- Elevated fasting plasma glucose > 105 mg,
- Need for insulin therapy during pregnancy,
- Obesity and choice of contraception.

Abnormal glucose tolerance during pregnancy is not only associated with increasing pregnancy morbidity but also increases the likelihood of subsequent diabetes in the mother. Maternal hyperglycemia has a direct effect on the development of fetal Beta cell mass and is associated with increased susceptibility to the development of obesity and diabetes in the offspring (Fig – 37).

This effect on the offspring is independent of other genetic factors. As such GDM has implications beyond the index pregnancy, identifying two generations at risk of future diabetes.779 Hence, detection and care of women with GDM becomes necessary in the strategy for the primary prevention of diabetes.780
The primary prevention is likely to reverse or halt this trend. For this the need is to focus at the intrauterine environment as the "preventive medicine starts before birth". Intrauterine exposure to hyperglycemia during the critical period of fetal development programmes the development of pancreas negatively and affects the insulin secretory function.\textsuperscript{790}

**FOLLOW UP OF GDM**

GDM may be viewed as:

1. An unidentified preexisting disease, or
2. The unmasking of a compensated metabolic abnormality by the added stress of pregnancy, or
3. A direct consequence of the altered maternal metabolism stemming from the changing hormonal milieu.
Gestational diabetes (GDM) is a strong indicator of future diabetes. It is a major health hazard in women as it adversely affects both maternal and fetal outcomes of the pregnancy unless a tight glycaemic control is maintained.

Gestational diabetic women require follow up and Glucose tolerance test is repeated after 6 weeks and if necessary after 6 months to determine whether the glucose tolerance has returned to normal. A small proportion of gestational diabetic women may continue to have glucose intolerance.

GDM reoccurs approximately in 50% of subsequent pregnancies. It was reported that 34% of Danish women with previous diet-treated GDM had abnormal glucose tolerance 11 to 12 years after pregnancy compared with 5% in a control group.791

The future risk of developing diabetes for a gestational diabetic is two fold, if she becomes overweight but maintaining ideal weight approximately halves the risk. The requirement of insulin in addition to diet to maintain euglycemia during the index pregnancy is also predictive of future diabetes.

In conclusion the scope of Diabetes and pregnancy encompasses not only a known diabetic marching through pregnancy (pre gestational Diabetes mellitus) but also any form of abnormal glucose tolerance developing during gestation. A known diabetic marching through pregnancy represents only the tip of the diabetic pregnancy iceberg.
The abnormal glucose tolerance of any etiology, during pregnancy, is associated with the following:

- A high risk of a poor outcome like miscarriages, stillbirth,
- Neonates with heavy birth weight,
- Hypotrophic infants, and small for dates,
- Children with lethal or handicapping congenital malformations which will be morally and socially demanding.

The pregnant mother may also develop hydramnios, toxemia, recurrent urinary tract infections etc. The maternal health and fetal outcome depends upon the care by the committed team of diabetologists, obstetricians and neonatologists. A short term intensive care gives a long term pay off in the primary prevention of obesity, IGT and diabetes, as the preventive medicine starts before birth.

**CONCLUSION**

Universal screening for glucose intolerance during pregnancy is essential as Indian women have high prevalence of diabetes and their relative risk of developing GDM is 11.3 times compared to white women. Asian women are ethnically more prone to develop glucose intolerance compared to other ethnic groups. GDM based on 2hr 75gm OGTT defined by WHO predicts adverse pregnancy outcome and warrants treatment. A 2 hr 75 gm post plasma glucose ≥ 140mg/dl serves both as screening and diagnostic criteria besides being a simple and economical one step procedure. As the routine screening for glucose intolerance during pregnancy is not done, probably the undiagnosed glucose intolerance that has been occurring in the past has resulted in the increased prevalence of diabetes in India. The
timely action taken now in screening all pregnant women for glucose intolerance, achieving euglycemia in them and ensuring adequate nutrition may prevent in all probability, India becoming diabetes capital of the World.

'No single period in human development provides a greater potential than pregnancy for long range pay off via relatively short range period of enlightened metabolic manipulation' - Norbert Frienkel.
COSTS OF TREATING DIABETES

The world Health Organisation estimates that 2.5 to 15% of annual health budgets are spent on diabetes related illness. If the predictions of diabetes prevalence are fulfilled then the health care expenditure being spent in 2025 will go even higher with high prevalence countries spending nearly 40% of their budget.\textsuperscript{794} The costs involved in the care and management of diabetes are quite considerable, for both the individual and the health care system as well. The nature of the disorder is such that it not only involves a direct cost which is borne by the affected individual, his or her family and health care authorities but also an indirect and intangible costs which holds a substantial proportion of health costs. An estimate of the direct costs of diabetes has been made as early as 1997 by the American Diabetes Association (ADA), and was estimated as US $ 44 billion per year.\textsuperscript{795}

The cost of diabetes is differentiated between direct costs, indirect costs and intangible costs.

\textbf{Direct costs} to individuals and their families include medical care, drugs and other supplies in addition to other personal costs such as increased payments for health and insurances. Direct costs to the health care sector include hospital services, physician services, lab tests and the daily management of diabetes. Hospital inpatient costs for the treatment of complications are the largest single contributor to direct health care costs. The medical costs incurred by a person with diabetes are two to five times higher than those who are without diabetes.
Indirect costs are the result of lost production as a consequence of time off from work, inability to work because of disability, premature retirement and even premature mortality because of complications. Indirect costs may be even greater than direct costs of diabetes and ADA estimates were at US $ 54 billion.\textsuperscript{796}

Intangible costs are the ones that reduces the quality of life after the onset of the disease ranging from pain, anxiety, stress to the influence in the personal relationship and leisure time activities.

<table>
<thead>
<tr>
<th>Direct costs</th>
<th>Indirect costs</th>
<th>Intangible cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation</td>
<td>Time off from work</td>
<td>Pain</td>
</tr>
<tr>
<td>Investigations</td>
<td>Disability payment</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Treatment-</td>
<td>Premature retirement</td>
<td>Depression</td>
</tr>
<tr>
<td>- Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Premature mortality</td>
<td>Stress to the influence in the personal relationship</td>
</tr>
<tr>
<td>Costs of Treating Complications</td>
<td></td>
<td>Loss of enjoyment &amp; leisure time activities</td>
</tr>
</tbody>
</table>

**SOCIO ECONOMIC FACTORS IN TREATING DIABETES IN INDIA**

The need to prioritize distribution of limited resources in India has resulted in a public health-care system that tends to concentrate on the care of people with acute illness. Diabetes care provided in government health centers is free or of low cost. However, given the limited funds and infrastructure for chronic progressive conditions like diabetes, the quality of care suffers: public hospitals and clinics are crowded and ill-equipped. Insurance cover and cost-reimbursement for treatment in the private sector is marginal or nonexistent; here too the infrastructure for chronic care is limited. The lack of adequate facilities and financial capacity indirectly worsens long-term prognosis.
Prevailing poverty and illiteracy, and the lack of health education exacerbate this problem. Many sociological factors determine the long-term outcome of health conditions: the ability of people to access treatment is dependent on their proximity to health facilities, the resources necessary to travel to these, and even knowledge of their existence.797

THE WIDER CONSEQUENCES - LONG-TERM CONSEQUENCES

An illness affecting the wage-earning member of a family often also has a significant effect on others. In the absence of protection during illness or bad times through an effective social-security system, many people in India rely on the physical and financial support of their family in order to overcome medical crises or other social problems. As a result, children and adolescents may be forced to start work prematurely and at low wages – significantly reducing their education and negatively impacting their long-term earning capability.

EXCESS COSTS

People with diabetes use more health-care resources than those who do not have the disease. This excess expenditure is related to the high cost of treatment for late-developing diabetes complications, such as eye damage (retinopathy) or kidney failure (nephropathy), as well as indirect costs resulting from lost work days or unrealized economic opportunity.
FACTORS INFLUENCING COSTS OF CARE: LATE VS EARLY DIAGNOSIS

Diabetes is often diagnosed late – perhaps too late: 50% of people with diabetes even in developed countries have complications at diagnosis. Untreated or improperly managed diabetes leads to serious and often life-threatening complications. Complications requiring multiple therapies and prolonged hospitalization are responsible for most of the diabetes-related direct costs. Among people with diabetes who are hospitalized, the average annual direct costs are more than double those for people with diabetes who are not hospitalized. Complications are also responsible for indirect costs in terms of productivity loss and absenteeism.

EDUCATION

Many socio-economic factors affect the time of diagnosis and thus the outcome of diabetes. Consequently they also affect the costs. The level of education appears to be important. Whether this is related to greater understanding of the condition and therefore greater commitment to self-care, or whether it is a reflection of a better socio-economic status and therefore better access to medical care (or both), is difficult to say. Diagnosis can be delayed by 3-7 years in the less-educated and uneducated sections of the population. In the CODI study, the age of diagnosis was directly related to the level of education: college-educated people were on average diagnosed 7 years before people with no literacy.
Despite a longer average duration of diabetes, those with a college education had a considerably lower rate of diabetes complications (45% complication-free) compared with people with low or no literacy (20% complication-free).

UNEMPLOYMENT

Type 2 diabetes produces few symptoms and acutely is not life threatening. Often, weakness and tiredness are the only manifestations of the condition. While it is common for inactive unemployed people to ignore these symptoms (consciously or otherwise), those who are working are more likely to notice the signs as these influence the capacity to work. In the CODI study, compared to working people in urban areas, people in lower-income groups were diagnosed on average 4 years later – as were people living in remote rural areas. People who are aware of diabetes before diagnosis or those with a family member with diabetes may be diagnosed earlier.

COMPLICATIONS

The factors that influence delay in diagnosis also determine the rate of complications. Place of residence seems to play an indirect role: people with diabetes living in the semi urban or rural areas have higher rates of complications – despite less duration of diabetes – than those in urban settings. This would appear to reflect delayed diagnosis and the availability of less-than-optimum or indeed the total lack of care. A similar trend is noted with regard to employment and socioeconomic status. Employed and working people with diabetes have fewer complications compared to those not working or those in rural areas.
engaged in agricultural labour. Among people with similar diabetes duration, larger proportions from the higher socio-economic strata are free of or have fewer diabetes complications (54% complication free; 8% with three complications), compared to the lower socioeconomic group (22% complication free; 26% with three complications). As might be expected, education appears to play a role in the development of diabetes complications. For people with a similar duration of diabetes, 45% of those who finished higher education had no complications, compared to 20% for the no-literacy group. While awareness alone cannot overcome the socioeconomic barriers to health, within the same socio-economic groups, people who are aware of the problem suffer fewer complications than those who are not aware.

While the average annual direct cost for out-patient care for all people with diabetes was 4724 INR (82.7 EUR), the cost of care for those without complications was 18% lower, but 48% higher for those with three or more complications. As with ambulatory care, the cost of hospitalization increased with the number of complications.

ECONOMICS

Despite such an alarming prediction that the prevalence of diabetes in India is expected to increase by 195% by 2025, there have been few studies of the status and economic burden of diabetes in India. Health resources in India and other developing countries are very limited with only 5% of Gross Domestic Product (GDP), (USD. 23 per capita) being spent on healthcare. Currently, only 10% of patients in India receive appropriate treatment. The reasons for this could
include the variability of healthcare available in different areas or the reluctance of the general public to attend government clinics. Lack of education and awareness may also contribute.

**COST OF TREATING DIABETES IN INDIA**

In India, the annual cost of diabetes care (direct cost) was at US $310/patient in a secondary care facility for type 1 diabetes; US $100/patient for type 2 diabetes in the same set-up. The costs was at US $343/patient/annually for those with foot and other complications. Patients in the low socioeconomic group spent nearly 24.5% of their annual income for diabetes care while in the high income group the expenditure was at 3.5% of their total income.

The Cost of Diabetes in India (CODI) study, was a large community-based survey of diabetes costs, designed to provide cost estimates of diabetes care at the national level.

**Table 51** Total overall mean direct and indirect costs (57 INR = ~1 EUR)

<table>
<thead>
<tr>
<th>Item</th>
<th>Costs(INR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor visit</td>
<td>853</td>
</tr>
<tr>
<td>Monitoring and lab</td>
<td>1,609</td>
</tr>
<tr>
<td>Treatment</td>
<td>2,262</td>
</tr>
<tr>
<td>Hospitalisation(annualized)</td>
<td>2,434</td>
</tr>
<tr>
<td>Mean total direct cost</td>
<td>7,158</td>
</tr>
<tr>
<td>Mean indirect cost</td>
<td>12,756</td>
</tr>
<tr>
<td>Total estimated annual cost</td>
<td>19,914</td>
</tr>
</tbody>
</table>

Table 51 gives the total overall mean direct and indirect costs of diabetes in India. Ambulatory care constitutes 65% of cost while the hospitalization cost is 35%. Cost of medications is 31% – of which specific diabetes drug costs are only 17%. Ambulatory care including monitoring and doctor visits constitute 34% of costs.
**DRUG TREATMENT**

Treatment with insulin was more expensive. As all type 1 diabetes patients used insulin, the overall mean direct costs of type 1 diabetes was higher compared with type 2 diabetes (Rs. 3804/ USD. 80 ± 1892/ USD. 40 and Rs. 2180/ USD. 46 ± 1823 / USD. 38 per annum, respectively). Also more patients with type 2 diabetes used OHAs, which are relatively cheap in India. However, with increasing duration of the disease, a lower proportion of patients take OHAs and more patients use insulin.

**DISEASE MONITORING**

The next most significant component of direct costs for diabetes patients in India was disease monitoring. This includes costs for routine blood and urine tests as well as more specialised tests, such as kidney function and lipid analysis. The fact that 85% of patients preferred to visit pathology laboratories for all their tests rather than self-monitoring at home had a major impact on direct costs. Relying on pathology laboratories resulted in additional costs, such as transport, loss of income due to days lost from work and laboratory fees.

On average, patients spent Rs. 1609/ USD. 35 per annum on pathology tests, although this cost was higher in type 1 patients (Rs. 3169/ USD. 67 per annum) due to more frequent testing. The mean total expenditure per visit was Rs. 177/ USD. 4, the greatest proportion of which consisted of blood tests (28%) and urine tests (17%). Although carried out in very few patients, other tests, such as
lipid analysis, kidney function tests, eye examinations or ECG were generally only conducted once per year or even less often.

Self-monitoring at home was carried out by less than 12% of patients and only 2% exclusively monitored their diabetes at home. Actual expenditure on home testing includes the one-off cost of a glucometer (Rs. 4771/USD. 100) plus Rs. 577/USD. 12 on urine test strips and Rs. 1589/ USD. 33 on blood test strips. Averaged over the typical 8-year duration of diabetes in this survey, the average annual cost for home testing was Rs. 2762/ USD. 58. This was higher than the total average cost of laboratory testing but lower than the average costs for type 1 patients. However, among the patients who self-monitored at home in this survey, only 13% owned a glucometer. It was common practice for patients to share the glucometer with relatives, neighbours or at a doctor's clinic.

While monitoring was intermittent (on average, type 2 patients only monitored their diabetes 10 times per year), a surprisingly high percentage of patients (95%) attended routine check-ups with a doctor. Average one-off doctor's fees for check-ups were Rs. 63–77/ USD. 1–2 resulting in a total mean expenditure on check-ups, including transportation, of Rs. 853/ USD. 18. Patients attended check-ups, on average, nine times per year.

Transportation costs to clinics or pathology laboratories were less important among mainly urban participants, but were still almost equivalent to doctor's fees and accounted for, on average, 24% of the whole cost of laboratory-based disease monitoring.
HOSPITALISATION

Of the 44% of patients who had been hospitalised, 72% were hospitalised due to known complications of diabetes. However, hospitalisation costs were difficult to assess annually as patients were hospitalised, on average, twice over a period of 8 years after diagnosis. Although costs increased with the number of complications, this was mostly as a result of higher costs of treatment and longer stays rather than more frequent hospitalisations. Mean expenditure per hospitalisation was higher in type 2 patients (Rs. 13200/ USD. 271), than type 1 patients (Rs. 7668/USD. 160) with an overall average of Rs. 12781/ USD. 267. A higher investment in treatment and monitoring did not appear to reduce hospitalisation expenditure. Hospitalisation costs were the largest component of direct costs in type 2 diabetic patients accounting for 30–36% of total direct costs. In type 1 patients, hospitalisation costs accounted for 17% of total direct costs.

Overall, 33% of all respondents had no diabetes-related complications at the time of this study. In total, 44% of patients had been hospitalised for various reasons. Hospitalisation was more common amongst type 1 patients (63%) than type 2 patients (43%).

SOURCE OF FUNDING

The majority of patients (89%) used their household income to fund the monitoring and treatment of their diabetes. Household savings were used in 22% of retired patients and in 19% of those in the lowest income bracket. However, the percentage of patients using household savings increased to 34% to pay hospitalisation fees because of
increased costs compared with routine treatment. A small proportion of patients (9% and 10% respectively) received loans from their employers or relatives and only 1% claimed the costs of treatment on insurance. While there is some government subsidy available, the vast majority of patients (90%) visited private institutions for disease monitoring.

**COMPLICATION**

The impact of complications on costs was clear: expenditure on pathology tests, insulin and other medicines increased with the number of complications. Patients with complications also spent more time in hospital; mean expenditure for each hospital admission thus increased with the number of complications. Complications resulting in disability or premature death also had an effect on productivity, income and savings.