REVIEW
OF
LITERATURE
History of diabetes mellitus

Diabetes mellitus was recognized in antiquity. Eber papyrus is the oldest preserved medical document from Egypt which dates back to 1552 BC by the third dynasty physician, Hesy-Ra in which he made a reference of diabetes mellitus like disease. He mentioned this disease as a condition associated with polyuria. Celsus of Greece in 30BC -50 AD also described features of diabetes like disease in great detail. The term diabetes means pass through and was first used by Aretaeus of Cappadocia in the first century AD. Aretaeus who lived in AD 131-201 mentioned diabetes mellitus as a condition characterized by cold melting of flesh and limbs, to urine, and recorded that patients never ceases to make urine with this disease and if anybody develops this condition will ultimately develop marasmus like picture and will not survive. Galen of Rome, (AD164) who was a physician of Pergamum, had the same view of Aretaeus and both of them attributed diabetes to disease of the kidney.

Ancient Indian Medicine considered diabetes as a disease of urinary system under Prameh. Earlier Indian literature described this as an incurable disease, but is amenable to treatment. Old Ayurveda physicians observed the diabetics, and were of the view that a person who was obese, indolent, inactive, and glutton, succumbs to this disease. The true description of polyuria with sweet taste urine was first referred in Sanskrit literature by famous Indian physician Charaka and Susrutha as early as 500-600 AD. They found that the urine from such persons attracted ants. They termed it as Madhumeha. Charaka advised persons with diabetes to decrease body weight and avoid excess food, fresh cereals, cane etc. During the same era, the Chinese and Japanese physicians also described sweetness of urine. Chen Chuan of China particularly provided an early account of diabetes and Li Huan observed that people with diabetes are more prone to boils and other infections. The Arab physician Avicenna (960-1037) described the classical features of diabetes and described gangrene of foot and sexual dysfunction associated with diabetes. Von Hohenheikm who
named himself as Paracelsus, reported that urine of diabetes patients contains white salt after evaporation, and its deposition in kidney caused thirst. Thomas Willis of 17th century (1621-75) made many more observations, and pointed that increase in wine intake may increase numbness and diabetes. He discovered that urine of diabetic patients tastes sweet. Thomas Sydenham (1624-1689) thought diabetes as a systemic disease. It was Mathew Dobson 1735-84, a physician of Liverpool who gave scientific evidence that diabetes patients had sweet tasty substance in urine and blood. Dobson proved that this material was sugar. John Rollo used the word *Mellitus* which means honey. He also described the association of cataract in diabetics and the odour of acetone. Edourard B Languesse and Thomas Cawlin in 1788 observed that diabetes may follow damage to pancreas, through calculus formation. Barton Justus Von Lie Big in 1803-1873 categorized food into protein, carbohydrate and fat, by describing the chemistry of these substances. He demonstrated that proteins are the essential building blocks. Claude Bernard made some observation regarding neuro regulator control of blood sugar and storage of glucose as glycogen. In 1857 Bouchard and his colleagues closely worked on the functions of pancreas and its role in the development of diabetes, and were convinced that pancreas has a major role in the development of diabetes mellitus. Opie first described the pathological changes like hyalinization and sclerosis of islets of Langerhans in diabetes. William Proul (1785- 1859) of Guys hospital first reported coma due to diabetes and described air hunger of ketoacidosis. It was Oskar Minkowski and Josef Von Mering's experiments in the era 1849-1908 which proved that the removal of pancreas will lead to typical features of diabetes mellitus. Geprge Zueker, a Berlin physician experimented with pancreatic extract and was successful in developing the first injectable preparation from pancreatic extract. In 1911 Benedicts published methods of detection of sugar in the urine. During 1920s, easier methods to detect blood sugar was reported by Folin O, Wu H. Allen after three years of study on diabetes published reports on glycosuria and diabetes in 1913, and his book revolutionized the treatment of diabetes mellitus during that period. He established a clinic in Berlin to treat diabetic patients.
The discovery of Insulin was one of the most important milestone in medical history, as insulin was so effective in relieving the symptoms of diabetes and hence got wide recognition immediately following its discovery.

Fredrick Grant Banting and Charles Best discovered insulin. When Banting and Best started injecting pancreatic extract to depancreatized dogs, they noticed reduction in blood sugar level. Banting and Best presented the paper titled "The Beneficial influences of certain pancreatic extract on Pancreatic Diabetes"; summarizing their work in the session of American Physiological society at the Yale university. The paper was not much appreciated during the session and was received with much criticism, but it was subsequently proved to be a landmark event. The first public announcement of Insulin was made in November 14, 1921, at the meeting of Toronto physiological club. The first insulin was prepared from normal ox pancreas and McLeod suggested the name "Insulin" for the pancreatic extract which relieved ketonuria of a patient. On January 11, 1922, Leonard Thompson became the first patient to receive insulin at Toronto general hospital. On 3rd May, 1922 - Toronto group reported their finding to the association of American physiological association in Washington DC in a paper called "The effect produced on diabetes by the extract of pancreas". For this discovery Nobel Prize was awarded to Dr. Banting on October 25th, 1923, which he shared with Best, McLeod and Dr Collip. The Title by Dr Bliss on Discovery of Insulin is a thrilling narration of insulin discovery, the controversies on it and how Banting shared Nobel Prize with his colleagues. The methods for purification of Insulin were attempted as early as in 1923 and by 1926 crystalline Insulin of various concentrations was available. Protamine Zinc insulin was used to prolong the action of insulin. In 1936 Kimmelstiel and Wilson's article on kidney lesion pointed diabetic complications to various organs. Insulin resistance was first reported by Himsworth in 1939 and was a crucial turning point in understanding Non Insulin Dependent Diabetes. The discovery of sulfonyl urea (SU) was a chance discovery by Jan Bon, who noticed the hypoglycemic effect of sulfonamide. Loubatiere found out the insulin secreting property of sulfonyl urea.
The first prevalence study of diabetes was made by Joslin in 1947 which was known as the Oxford Study, and reported a prevalence of 4% in US. Reports of complication like microangiopathy, peripheral vascular disease; myocardial infarction and infections appeared in several journals during 1950's. The noted reports among it were Kessel's paper on cerebral atherosclerosis, Framingham series on non embolic stroke, and Bell's autopsy study of arteriosclerosis. Lente Insulin with short, intermediate, and long duration of action were devised by Hallas Moller et al in 1950. The first sulfonylurea urea compound was introduced by Franke and Fuch's of Germany. In the early period of 1957, Biguanides were introduced and these had different mechanism of action when compared to sulfonylurea. Biguanides are widely used even now with more and more indications, particularly metformin. The effect of sulfonylurea was systematically studied by Augustine, Loubatiere, and Mount Pellier. 

The primary structure of Insulin was first reported by Fredrick Sanger in 1955 while working in Cambridge. Yallow and Berson devised the radioimmunoassay for measuring insulin in body fluids in 1960. In 1965 Thripathy et al. reported that Maturity Onset cases of Diabetes mellitus (MODY) occurs early in India.

An expert committee set up by World Health Organization in 1965 recommended that the type of diabetes to be specified depending on the age of onset. In the year 1966, the first pancreatic transplant was performed at the University of Manitoba. It gained momentum only after 2000, when Edmonton from Canada gave new thrust to pancreatic transplantation with his well known Edmonton Protocol. Danish scientists were successful in isolating mono-component insulin in the early 1970.

The National Diabetic Data Group suggested to classify diabetes into Insulin dependent and Non insulin dependent types. In the early 1970's Indian Council of Medical Research (ICMR) sponsored National collaboration study conducted a nationwide survey among, 16,500 diabetic patients in India, and
this pioneering study was reported in the VIII International Diabetic Federation (IDF) conference in Brussels. This was the first comprehensive Indian study recognized by IDF. A year later another extensive epidemiological data was published from the West which reported high prevalence of diabetes from Trinidad, Pima Indians, UK and USA. More such studies and data were available in the early seventies. The method to synthesis insulin using recombinant DNA technology was also available by this time. Maturity Onset Diabetes Mellitus of Young (MODY), an autosomal dominant variety of NIDDM was described by Robert Tatter Sal in 1974. The development in the understanding of diabetes mellitus and its definition was largely contributed by WHO after the release of its technical series in 1980.

A year later another extensive epidemiological data was published from the West which reported high prevalence of diabetes from Trinidad, Pima Indians, UK and USA. More such studies and data were available in the early seventies. The method to synthesis insulin using recombinant DNA technology was also available by this time. Maturity Onset Diabetes Mellitus of Young (MODY), an autosomal dominant variety of NIDDM was described by Robert Tatter Sal in 1974. The development in the understanding of diabetes mellitus and its definition was largely contributed by WHO after the release of its technical series in 1980.

John Pick up et al, in London introduced portable continuous subcutaneous insulin pump, which can reduce blood sugar nearly to non diabetic level. This paved way for better management of diabetic patients. John in Ireland and his colleagues in Glasgow introduced the pen shaped insulin syringes. By 1970 many second generation sulfonylurea were introduced and Glibenclamide, Glipizid and Glycazide were introduced at short intervals. The popularity of sulfonylurea and Biguanides suffered a beating after suspected link to increased coronary artery disease, as published by University Group Diabetic Programme (UGDP).
In the subsequent study by the American Diabetic Association (ADA) it was proved that UGDP findings on OHA was misleading and there were many flaws in the methodology in UGDP. The WHO expert committee on diabetes mellitus submitted its second report in 1980, and based on this an epidemiological perspective study was conducted 1983, using uniform criteria for case selection. This provided information on diabetes in young adults and children. The Diabetic Retinopathy Study (DRS) provided valuable information regarding the effect of laser in the treatment of retinopathy. Several studies, later indicated that neuropathy is common among patients in India, where there is increased association of diabetes with malnourishment. An eighteen year prospective study from Denmark, the European Diabetic Prospective Complication Study (EURODIAB), studied microalbuminuria and early nephropathy. Studies to prevent diabetes associated hypertension, microalbuminuria, proteinuria or cardiovascular events with ramipril was done in DIABHYCAR study. Trojaborg and Smith et al, found out that pancreatic islet cell transplant is useful in type 2 diabetic patients. The first successful pancreatic transplant was done in 1966, and the availability of newer immunosuppressant agents made transplant cost-effective. Non invasive glucose monitoring was reported by Tameda et al in early 1999. Genetic manipulations and gene therapy in the diabetic management was used by this time to restore the beta cell function. Vaccination with either insulin or a protein called GAD 65 was shown to be useful to protect the beta cells. The discovery of Receptors for Advanced Glycation End Products (RAGE) by Schimidt provided more evidences for the role of glycation end products in the development of diabetic complications. Valsara et al also implicated advanced glycation end products in the development of vascular complications. To have a comprehensive analysis of diabetic epidemiology and to obtain data to initiate preventive care in diabetes, The WHO started collecting data on diabetic complications in the early 90s. In 1999 a diabetic research group to conquer diabetes was established and strategic planning to conquer diabetes by the 21st century was established. This group set priorities for areas of research.
DIABETES MELLITUS: Current scenario

There are approximately 171 to 194 million diabetic patients in the world. Type 2 diabetes mellitus is the most common, affecting 90% of the population. Type 1 and type 2 diabetic patients are on the rise. The Table-1 shows the top ten countries affected in the world. In the year 2000 there were about 151 million type 2 diabetic cases in the world and WHO anticipates an increase to 225 million by 2010. India has the largest diabetic population and it is expected to increase to 174 million in the year 2025. Hogan and Nicolla estimated that the annual cost of diabetic treatment in the United States is $132 billion yearly. In the last twelve years, the number of diabetic patient increased from 11.4% to 14.3% in the United States. The increase in African population was 20% during the same period. Several studies reported a higher prevalence of diabetes in Hispanics than in White, and the number of cases in the Hispanics in United States increased to 61% in the past 10 years and approximately 25 million now stands affected. In China the number of diabetics increased from 3.4% in 1994 by 2.5 times in 8 years. According to Mohan et al, the prevalence among South Indian population was 8.3% in young adults in the year 1989, and it increased to 11.6% by 1995. The prevalence of diabetes in ethnic Asian groups belonging to China, Philipines, Japan, and Korea and in Asian and Pacific Islands are higher and larger compared to other parts of the world. In the next 25 years India alone is expected to see an increase of diabetes to 73 million, and China, the most populous country in the world will have 46 million patients. In the developing countries the majority of peoples with diabetes are in the age group of 45-64 years. The majority of diabetic patients in the developed countries are more than 64 years of age. In the year 2030 the number of people in the world, with diabetes, who are more than 64 years of age will be 82 million of which, about 48 million in developing countries.
Table-1: Top ten countries with diabetes

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence%</th>
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<tbody>
<tr>
<td>India</td>
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</tr>
<tr>
<td>China</td>
<td>16</td>
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<tr>
<td>USA</td>
<td>13.9</td>
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<td>Russia</td>
<td>8.9</td>
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<td>4.3</td>
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<tr>
<td>Mexico</td>
<td>3.8</td>
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<tr>
<td>Ukraine</td>
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LAND MARK STUDIES IN DIABETES MELLITUS

Diabetic Control and Complication Trial (DCCT-1993): The Diabetic Control and Complication Trial (DCCT) is one of the most important studies; often referred and quoted by all in the field of diabetology. The study was developed by National Institute of Diabetes, Digestive and Kidney disease. 1441 volunteers with type 1 diabetes mellitus from 29 centers around USA participated in the study. This is considered as a land mark trial in diabetes. Diabetes Control and Complications Trial concentrated on Type 1 diabetes mellitus, and the aim of the DCCT was to find the impact of lowering blood sugar in preventing the complications in Type 1 diabetes. The well acclaimed and scientifically perfect study by the Diabetes Control and Complication research group, published its finding in 1993. The DCCT study concluded that there was 76% reduction in retinopathy, 54% reduction in nephropathy, and 60% reduction in neuropathy in properly controlled diabetic patients. The further conclusion of the study was that any metabolic control has a favorable outcome. Greater reduction in HbA1c will lead to marked reduction in retinopathy. In the DCCT, intensive control of diabetes made by maintaining
the HbA1c around 7%, found that there was 30-80% reduction in micro and macro vascular complication. The mean follow up for DCCT was 6.5 years.

The United Kingdom Prospective Diabetes Study (UKPDS): The United Kingdom Prospective Diabetes Study (UKPDS) is another landmark study in the history of diabetes mellitus and a well-reputed study which is often quoted. This study was initially designed in 1977 to analyze the effect of glycemic control in preventing complications of diabetes mellitus and to determine whether patients with type 2 diabetes can clinically benefit from intensive glycemic control. UKPDS enrolled 5277 patients initially and later 3867 patients from 23 centers in the United Kingdom were included for the final analysis. All the participants were newly diagnosed diabetics, aged 25-65 years. Study was conducted in 15 UK hospitals. The main outcome evaluated in the UKPDS include fasting blood sugar, glycated hemoglobin (HbA1c), plasma lipids and other side effects due to treatments. In the UKPDS, 3867 newly detected type 2 diabetes patients were analyzed for the outcome. 3867 patients were put on intensive treatment policy and compared with conventional treatment protocol. The microvascular complications like retinopathy and nephropathy were studied in detail and the risk reduction in retinopathy was 17%, and need for retinal procoagulation was reduced by 29%. There was 23% reduction in vitreous hemorrhage and 16% reduction in blindness and 30% reduction in microalbuminuria. Regarding cardiovascular mortality, in type 2 diabetes, the intensive group showed 16% reduction of fatal myocardial infarction. The cardiovascular events were significantly reduced and there were no much reduction in mortality due to cardiovascular disease. Incidence of hypoglycemia was 3% per year in the study group. The relationship of control of diabetes and complication was also studied in UKPDS for 14 years with newly detected diabetes. For every 1% reduction in glycated hemoglobin, there was 35% reduction in microvascular complications. This study proved conclusively that adequate control of hyperglycemia with insulin or with sulfonylurea and metformin will decrease the morbidity and mortality due to diabetes. UKPDS is still considered as one of the most important studies on diabetes.
Diab Care Asia Study: This study was a multi centre observational data collection undertaken in the South East Asian countries. Diab Care Asia study evaluated the relation between diabetes control, management and late complications of diabetes and it provided a bench mark to measure quality improvement in diabetic care. Over 22,000 patients over twelve countries were enrolled for the study. The study had a uniform methodology and study protocol. Diab Care Asia Study was done in 26 diabetic care centers in both private and public sectors. The study population consisted of 100 consecutive review patients who were under treatment for diabetes, for more than one year. There were 2,424 patients recruited to this study from 26 centers. Final result was based on 2,269 patients and study revealed that 90.6% had T2DM. Obesity was an important association in the urban centers, with higher BMI in more than 40% cases. The result also showed self monitoring was poor among Indians, and 55% manifests late complications with in a period of 10 years. The result of the study indicated that type 2 diabetes begins earlier in Asians especially in the south Asians and in particular in Indians.

INDIAN SCENARIO AND MAJOR STUDIES FROM INDIA

India is now designated as the world capital of Diabetes mellitus. Several epidemiological studies proved the increasing prevalence of type 2 diabetes. Both urban and rural area is experiencing explosive growth of diabetic patients. Arunachalam and Gunasekharan in their literature review on diabetes noted that most of the genetic epidemiology of T2DM was seen in South India. In the Chennai Urban Population Study (CUPS-7), Deepa et al noticed that insulin resistance and impaired glucose tolerance is increasing in both urban and rural area. Largest increase in diabetes patients is anticipated in India, China and USA over the next 20 years. A striking feature noticed is increasing occurrence of diabetes in young population.

In 1989 Kodali et al reported that 2.2% rural adult population suffered from diabetes mellitus and it is now estimated that it will increase to 12% in the year...
2025. The study of rural diabetic patients by Sadikot et al, titled as PODIS (Prevalence Of Diabetic in India Study), by the Indian task force estimated that prevalence increased from 8.2% to 11.6% over a period of 5 years. Recent study by Gupta et al from several urban centre of the country also noticed a rapid rise in type 2 diabetes mellitus. The prevalence is 5 to 6 times higher in urban area, when compared to rural areas. 64% of the population in India lives in the rural area, but data on the incidence and prevalence of diabetes are rare from India. PODIS showed that 7.06% of the subjects in their study were having type 2 diabetes and 7.8% have impaired glucose tolerance. A similar study from Guwahati in Assam by Shah et al, in 1995 from North Eastern part of the country reported a prevalence of 8.2%. There is a difference in the prevalence of diabetes in the urban and peri urban area, and the incidence is markedly high in the urban area. Even in the urban area the prevalence varies from place to place because all the urban population of a city does not have similar life style or ethnic factors. Insulin resistance is the most important factor noticed among Indians. Truncal obesity is an important risk factor for diabetes than general obesity in Indian population. The risk of diabetes increases in persons who migrate from developing countries to developed countries, and had a fourfold rise in the last decade. Currently there are about 3 crore diabetics in India, and in the year 2025 the number anticipated is 8 crores, more than the predicted value. The recent study from Indian urban centers, the prevalence is thought to be 12.4 percent in Madras. The study at Sri Perumbatur in South India revealed a prevalence of 8.2% in urban and 2.4% in rural area. The National survey of diabetics in India was done by ICMR in the year 1972-1975, and thereafter no large scale nationwide studies were reported. In the ICMR study more males than females were found affected, and those on vegetarian food than non vegetarians are suffering from the disease. No relation was noticed between calorie intake and diabetes in the ICMR study.
Diabetes care in India, Patients Perception, Attitude and Practices Study (DIPPAP-1 STUDY, 1997): This study was conducted with an objective of evaluating the perceptions, attitudes and practice amongst patients with diabetes mellitus in relation to diseases and its management, and to be able to provide comprehensive care including appropriate education and advice. The study was conducted among 475 persons with diabetes in eight urban centers. The study concluded that patients who took insulin felt that they are at greater risk of cardiac problems. Hypertension was noticed in 21%, tiredness in 34% cases, pain-in leg and joints also commonly noticed in 29%, and visual impairment in 25% and 85% patients admitted that they feel better with insulin. This study shows that even in the urban centers in India, persons are fairly ignorant about the implications of the disease.104

Diabetes care in India-Physicians Perceptions Attitudes and Practice Study- (DIPPAP-2 STUDY, 1998): This is the second part of the famous Indian study on current Practices, Attitude and Perceptions among different diabetic care providers regarding diabetes and its management. DIPPAP-2 evaluated the differences on these parameters in different health care providers. The study was conducted among general practitioners, consulting physicians, and diabetologist in the Indian cities. 393 physicians in eight metro cities were participated in the DIAPPAP2 study. The outcome of the study revealed that oral hypoglycemic agents were used in 33% of T2DM, Insulin in 15% cases. Diet and exercise alone were not useful in control of diabetes. 13% had blood sugar below 300mg% and 5% patient were reluctant to use insulin. In 61% cases there is primary drug failure with OHA, 18% remained as uncontrolled diabetes even with insulin. 90% doctors used insulin to treat the patients as and when required. This study focused the importance of metabolic control in prevention of diabetic complications also.

The Bangalore Urban District Diabetes Study: Study by Anil Kapur and Sahoo in 1992 showed that the prevalence of diabetes in rural area was only 2-3%, and a higher prevalence was noticed in urban centres.105
urban district diabetic study was conducted to assess the demographic and cost effectiveness of diabetes mellitus in rural and urban area of Bangalore district. This study was conducted by PH Rayappa, et.al in 1999. The trial design included randomly selected 611 patients from Bangalore urban centre. The study concluded that 28.2% of the diabetes patients visited doctors in the government sector at the time of diagnosis, and 71.8% visited the private doctors. 70% diabetics have one or more complications, and 17.1% were taking insulin. The average cost of therapy in a diabetic patient was around 9,994/- rupees per year and it was concluded that there is an urgent need to find cost effective methods to combat diabetes.\(^{106}\)

**Diabetic Epidemiology Study India group (DESI):** The National Urban Diabetic Survey was conducted in the year 2000AD. The survey was conducted by Diabetic Epidemiology Study India group (DESI). The study was piloted by Madras Diabetic Research Centre at Madras and ORG, an organization of social research, and ORG was entrusted with the work of sample collections in six major cities in India. Samples varied from 1500 to 2500 depending on the population and total number of subjects evaluated in the study were 12,500. Positive family history was noticed in 16.9%. According to this study, diabetes was common among unemployed and retired persons. The maximum number of patients were in the age group of 40 to 59 years and no significant gender difference was observed.\(^{107}\) The table-2 shows various prevalence studies conducted in various regions of the country.
Chennai Urban Population Study 1996 (CUPS): This is another popular study from Tamil Nadu, and was conducted in two residential colonies at Tirumangalam and T.Nagar in Chennai. In the CUPS, adults above 20 years of age were screened in two phases. It was one of the studies which selected different category of persons with urban as well as peri urban back ground belonging two residential colonies. The occupation, diet, physical activity and clinical characteristic of diabetic patients were evaluated. The prevalence of diabetes mellitus in Chennai was found to be 7.2%. CUPS concluded that family history, obesity, low physical activity are risk factors for type 2 diabetes mellitus and those in the urban area had more prevalence of T2DM compared to the peri urban area.108

A national survey of the prevalence of diabetes was done in 1989, and this survey was conducted in rural areas, high altitude areas and in persons of Indian origin staying in Malaysia and Guyana by PV Rao. The study population included subjects from rural population of Delhi, Gujarat and South Aruvikkanam in Kerala. Majority of the subjects studied were individuals above 14 years and agricultural workers from this area. The conclusion of the study was that 2.8% of diabetic patients above the age of 24 years in the rural area were diabetic. The study populations do not include pregnant women and type 1 diabetic. Subjects aged 25-44 years constituted 57.18% and the prevalence was 1.17% in this age group. The mean age of T2DM patients was 52.3 years in the National Rural Diabetic Survey.

Diabetes mellitus in rural population

This is still an area in diabetology where not many studies were conducted in India or abroad. The table 2 enumerated most of the well reputed studies from India. Most of the studies are prevalence studies from urban and rural areas. There is marked increase in the number of diabetics in rural area and their profile is different from that of urban population of India and that of general populations of western countries. The Diab Care Asia study pointed that Asian Indians are at high risk of development of diabetes and coronary artery disease (CAD). They have truncal obesity, hypertension and lipid abnormality compared to Caucasians. Traditionally rural Indians are hard working, and the modern life style have not affected fully in all Indian villages, though there are changes in life style and diet. A proper assessment of life style, diet, BMI, family history and pedigree charting are important in exploring the risk factors of diabetes mellitus. Genetic susceptibility is associated with type 2 diabetes mellitus. Ramachandran et al showed that Indians had more truncal obesity, and there is marked rural and urban difference in the development of diabetes. Impaired glucose tolerance was noticed in 8% rural population.
A glimpse into the geography and life style of Kerala population: Kerala, popularly known as Gods own country and one of the most literally advanced states in India. Many of the health parameters in Kerala are well compared to developed countries. Kerala model development in health sector is widely discussed at national and international forums. Kerala has 14 districts, 63 Taluks, 5 Corporations, and 53 Municipal areas. Majority of the people live in the rural areas and most of the working class is engaged in agriculture related activities. Kannur, Kasargod and Wayanad mainly constitute the North Malabar area. Manual labourers, paddy field workers, workers in coconut plantations, hill produce; rubber and cashew plantations workers are the major work force in the area. Twelve percent of the population are below the poverty line. The major staple food item is rice, and traditionally wheat consumption is less when compared to North Indian population. Fiber rich food consumption is abundant in Kerala especially during some seasons. Fish and other proteins items are regularly used; tinned and refined foods are not regularly consumed by Keralites. Majority of the rural people prefer freshly prepared rice items, plenty of vegetables and fruits. Now in certain urban areas of state, a dietary transformation is taking place, and its implication in the health of the people is yet to be fully ascertained.

Major Studies on Diabetes mellitus from Kerala: A literature search in Medline showed that studies on Diabetes from Kerala are very few in numbers. One major study on diabetes from Kerala was by K.P.Poulose, chief physician of SUT Hospital, Thiruvanathapuram, with a sample size of 8,200. This study gave some epidemiological data regarding the type 2 diabetes in the southern part of Kerala. This was an 11 year study done at SUT hospital. This study concluded that the overall prevalence in the high land was 5.8 % and in the coastal area it is higher at 12.4%. Only 11% of males and 29% of female had BMI more than 25 in his study and the difference between Type 1DM and type 2DM with regard to BMI is very less. Family history was noticed in 58% in first degree relatives. While in Kerala 62% of type 2 patients developed diabetes between 30-50 years. A Population based study by Narendran et al. from
Palakkad in the year 2002 reported that 26% of self reported diabetes patients had retinopathy. Another important study by Raman kitty VR et.al from South Kerala reported much variation in the prevalence and presentation of diabetes among geographic division with in a region. A high prevalence of type 2 diabetes in urban settled population at Thiruvananthapuram was noticed by VR Kutty et. al.\textsuperscript{112}

The Amritha Diabetes and Endocrine Population Study (ADEPS): This study was a community based cross sectional survey done in urban areas of Ernakulam district in Kerala to assess the prevalence of undetected diabetes mellitus and IGT, and probable risk factors for diabetes in Kerala. The study concluded that the overall prevalence of diabetes is 19% higher than other studies from Kerala, and new onset diabetes was 10.5%, and IGT 4.1% and IFG 7.1%. Increase in age, obesity, family history, and acanthosis nigricans are the common risk factor identified in the ADEPS.\textsuperscript{113} Kerala Health Action Plan study by Kutty V.R and Soman C.R of the Health Action Plan Kerala (HAP) is another epidemiological study from Kerala and they noticed a marked variation in the prevalence of diabetes among different geographic groups in Kerala. 518 persons, 227 males and 291 females in the age group above 20 years were studied, this includes both newly detected and known diabetic patients. They found a prevalence rate of 12.4%. A study done in Southern Kerala looked at the variations in the prevalence of type 2 diabetes among different geographic divisions within a region. The prevalence of diabetes was the highest in the urban (12.4%) areas, followed by the midland (8.1%), highland (5.8%) and coastal division (2.5%).\textsuperscript{114} Another study of risk factors of coronary artery disease in Thiruvananthapuram city by Joseph A et.al found increased association of diabetes and coronary artery disease. The prevalence of diabetes in Thiruvananthapuram city was found out to be 16.3 percent, equal in both male and female.\textsuperscript{115} Kerala has a unique place in the diabetic literature, and the first report of Fibrocalcific Pancreatitic Diabetes (FCPD) was made by Prof. Gheevarghese in a major study from Kerala. Prof. K.P Ramamoorthy from Calicut also did an important study from Malabar on fibrocalcific pancreatitis.
and reported more than thousand cases of FCPD. The increased cardiovascular mortality among young Kerala population and marked increase in type 2 diabetes mellitus patients in Kerala is already a matter of concern, and is a hotly debated topic in the scientific forum.

CLASSIFICATION

Classification of diabetes mellitus is becoming more and more complicated with knowledge proliferation in diabetology. Now the classification is based on the etiology rather than the treatment response. The major change in the classification is the discontinuation of the term Insulin Dependent and Non Insulin Dependent Diabetes Mellitus (IDDM and NIDDM). IDDM is now redesignated as Type 1 Diabetes Mellitus (T1DM) and NIDDM as type 2 Diabetes mellitus (T2DM). Now we know that Type 1 DM is due to beta cell destruction and is characterized by the presence of specific antibodies against beta cells. Majority of Type 2 diabetes mellitus with long lasting disease ultimately may need insulin for the control and hence the term Insulin dependent and non dependent is obsolete. Beta cell destruction due to autoimmune process is the main basis of development of type 1 DM. Age is not taken as a criterion in the recent classification and DM can occur at any age. 5 to 10% of persons developing diabetes mellitus after the age of 30 have type 1 diabetes. Similarly type 2 diabetes is also increasingly noticed in obese children. The term Malnutrition Related Diabetes Mellitus (MRDM) is no longer used. Until recently children or young person with diabetes were designated as type 1 DM and was put on insulin, but now it is realized that the entire above category is not having insulin deficiency, and 8-45% of them may have T2DM or MODY (Maturity Onset Diabetes of Young). Maturity onset diabetes mellitus is also common in certain regions, and now six different types of MODY are described. MODY occur at an earlier age, and most of them become diabetics before 25 years.
The differentiation between type 1 and type 2 diabetes mellitus based on clinical or epidemiological basis alone is difficult and most often genetic and immunological studies are required for confirmation. Type 1 A DM is a category of diabetes where autoimmune destruction of beta cell is the predominant mechanism, and type 1 B DM includes the idiopathic variety, and Type 1 B DM is more ketosis prone. A recent inclusion in the classification is the term Impaired Fasting Glucose (IFG), and Impaired Glucose Tolerance (IGT). IFG has been defined as fasting blood sugar more than 110mg%, but less than 126mg%. IGT is defined as 2 hour OGT value more than 140mg% but less than 200mg%. The recent classification and staging provide better scope for research in etiology, prevention, treatment and incorporate recent advances in the knowledge of diabetes.

ETIOLOGIC CLASSIFICATION

I. Type I diabetes
   A. Immune mediated
   B. Idiopathic

II. Type II diabetes

III. Other specific types

   A. genetic defects of beta cell function
      A. MODY 1, MODY 2, MODY 3, MODY 4, MODY 5, MODY 6
      B. Mitochondrial DNA
      C. Proinsulin or insulin conversion

   B. Genetic defects in insulin action
      1. Type A Insulin resistance
      2. Leprechaunism
      3. Rabson Mendel hall syndrome
      4. Lipodystrophy syndrome

   C. Diseases of exocrine pancreas
      1. Pancreatitis
      2. Pancreatectomy
      3. Neoplasia
      4. Fibrocalcific pancreatic diabetes
      5. Cystic fibrosis
      6. Hemachromatosis
      7. Wolcott Rallison syndrome
D. Endocrinopathies
- Acromegaly
- Cushing syndrome
- Glucagonoma
- Pheochromocytoma
- Hyperthyroidism
- Somatostatinoma
- Aldosteronoma

E. Drugs and toxins
- Vacor
- Pentamidine
- Nicotinic acid
- Glucocorticoid
- Thyroid hormone
- Diazoxide
- Beta adrenergic agonist
- Thiazide
- Phenytin
- Interferon
- Protease inhibitors
- Clonazipine
- Beta blockers

F. INFECTIONS
- Rubella
- Cytomegalovirus
- Coxsackie
- Echo
- Varicella
- Entero virus

G. IMMUNE MEDIATED
- Stiff man Syndrome
- Anti insulin receptor antibody

H. GENETIC SYNDROMES
- Down’s syndrome
- Klinefelters syndrome
- Turners syndrome
- Wolfram syndrome
- Fredriech’s ataxia
- Huntington chorea
- Laurence Moon Biedles syndrome
- Myotonic dystrophy
- Porphyria
- Prader willi Syndrome
TYPE 1 DIABETES MELLITUS

Type 1 diabetes mellitus was mentioned by the famous Indian physician Charaka as early as 600 BC. This is the most common form of diabetes in children and in the adolescents. The highest number of type 1 DM is reported from the Scandinavian country Finland, and lowest from Japan. The data on the incidence of type 1 diabetes from India is very few, but studies from Chennai pointed out an incidence of 10.5/100000. The type 1 diabetes mellitus results from the interaction of environmental, genetic and immunological factors. The trigger may be an autoimmune process like infections or other factors. The clinical manifestations of diabetes mellitus occur only when the beta cell mass reduction is more than 80%. When there is decreased beta cell mass there is marked decrease in the secretion of C-peptide, the connecting peptide of proinsulin. Hence the measurement of C-peptide is an indicator of insulin activity and this level is markedly decreased before the clinical manifestations noticed. C-peptide level is better correlated with the metabolic derangement, and risk of hypoglycemia. DCCT studies indicated that presence of smaller quantity of C-peptide level is related to improved control of diabetes. The greatest risk factor of type 1 DM is an identical twin with the disorder. Most individuals with type 1 A DM have HLA DR3 and or HLA DR4 haplotype. The haplo type DQA1*0301, DQB1*0302, DQA1*0501, and DQB1*0201 are most strongly associated with type 1 autoimmune diabetes. At least there are 20 regions with some linkage to diabetes. The strongest locus is IDDM 1 locus.

There are around 18 different HLA locus identified varying from IDDM 6p21.3 to IDDM 18 located in 5q.33-q 34. This linkage analysis is a most important tool in identifying type 1 patients. Still there is a need for more homogenous collections of families to study genetic linkage. The HLA associations of North Indians and Caucasians are similar as observed in white Caucasians. The strongest HLA association is found between BW21/DR3 and B7/DR2 is associated with resistance to the development of diabetes. The studies of the HLA DQ alleles conducted in Indians settled in England shown that DR4 associated diabetic susceptibility is determined by DQ allele.
The immunologic markers are different antibodies directed against pancreatic islet cells, and this comprises antibodies such as GAD, IA-2/ICA-512. Islet cell gangliosides serve as marker of the immune process. Islet cell antibodies are present in 3 to 4% first degree relatives. Mapping of epitome recognized by GAD 65 autoantibody indicate that essentially cells are the targets for GAD auto antibodies. The ICA-512 was originally identified as islet cell auto antigen. ICA-512 and IA-2 Beta have homology to tyrosine phosphate like molecule. These cross react with intra cytoplasmic molecule and lead to fusion of secretary granules with in plasma membrane. It was found that 10% patients with Type I DM have ICA 512 antibodies.

Few potential environmental factors are identified in the etiology of Type 1 DM. As mentioned early there is a strong interaction of environmental and immunological factor in the development of diabetes mellitus. The incidence of type 1 diabetes is more in certain geographical areas. Viruses like Coxsackie, ECHO virus, rubella, measles, Varicella and Enteroviral infections, were reported as trigger for diabetes. The probable link between vaccination and diabetes mellitus was disproved by the DAISY study. Bovine milk protein and chemicals like nitro urea is considered as environmental risk factors. Latent Auto Immune Diabetes of adult (LADA) can occur at any age. 5 to 30% of T2DM patients initially diagnosed has immune mediated diabetes and LADA may constitute 50% case of Type 1A DM. In countries like Japan, majority of type 1 diabetes manifest in the adult stage. The Type 1 DM can manifest at any age, but is common before the age of 30 years. Ramachandran et al in 1995 pointed out that T1DM present at a later age in rural area. A seasonal variation in the presentation is also noticed in India as well as in the western country.

Maturity Onset Diabetes Mellitus of Young (MODY)

The term Maturity Onset Diabetes of Young (MODY) was coined by Tatters and Fagan's in 1975 to indicate diabetes that occurs in persons before the age
of 25 and which have an autosomal mode of inheritance, though recently the
genetic factor were given more importance than age of onset. MODY is characterized by early onset, before 25 years, and are not dependent on
insulin for control after 5 years of onset, and presence of significant level of C-
peptide and an autosomal mode of inheritance. MODY phenomenon shows the
progressive reduction of age of onset of diabetes (anticipation). The autosomal
dominant inheritance is a striking feature of MODY which distinguishes from
type 2 diabetes. Both parents are usually affected in early onset type 2 diabetes mellitus. The prevalence of MODY is around 1%. A South African study by
Jialal among Indians, found that 10% type 2 diabetes belongs to MODY. A study from South India by Mohan et.al, reported that 4.8% of type 2 diabetes
had onset before the age of 25 years and 27% had criteria fulfilling MODY.

**Impaired Glucose Tolerance (IGT):** Before clinical or biochemical evidence of
diabetes mellitus manifest, all patients pass through a stage where the serum
blood sugar value is more than the normal. This is called Impaired Glucose Tolerance (IGT), or a pre diabetic state. The blood sugar value in a post
prandial level in the range of 140 to 199 is called impaired glucose tolerance.
Introducing this term the stigma of diabetes mellitus is eliminated from such
patients and all of this may not progress to diabetes mellitus. The fasting blood
sugar value in the range of 110 to 125 is called impaired fasting blood glucose
(IFG). Deo noticed a definite gender difference in IFG and IGT, and found that
IFG is more in male where as IGT more among females. He studied the
occurrence of abnormal glucose level among Indians and came to the
conclusion that 70% affected are female and 50% males. 35% of the patients
were in the age group of 41-50 years. They again noticed that in the Western
India the, age of onset of T2DM decreased among new generation.

**Gestational Diabetes Mellitus (GDM)**
The over all incidence of diabetes in pregnancy is 1-2%. The PGDM is diabetes complicating pregnancy and GDM is gestational diabetes mellitus. Ethnic
differences have been noticed in the development of GDM. Indians have higher predisposition for gestational diabetes mellitus. An elevated blood sugar at any time in pregnancy is associated with a poor out come and may be complicated by miscarriage, still births, eclampsia, increased body weight of fetus and subsequent complications during delivery. Chances of hydramnios, recurrent urinary tract infections are also high in PDGM. The new focus given on diagnosis and management of diabetes during pregnancy has reduced the mortality rate from 45% to 2%. The fetal loss in India is 4-6%. In a study at Madras, prevalence of low birth weight baby in India is estimated to be 14.3% in PGDM, and large sized baby is common in GDM and its incidence is 8.2%. An urban diabetes survey in 1992 indicated a prevalence of 2.6% of diabetes in pregnancy and 9.9% of IGT. Patients with IGT are at a higher chance for developing GDM. Six weeks or more after pregnancy the women should undergo GTT. The diagnosis is made if the blood sugar value after a 75 gm GTT is more than 140mg/dl at the end of 3 hour according to the ADA criteria. Uncontrolled diabetes mellitus during pregnancy can lead to many metabolic and congenital abnormalities in mother and fetus.

Fibro Calcific Pancreatic Diabetes (FCPD): Fibrocalcific pancreatitis (FCPD) is a unique form of diabetes secondary to chronic pancreatitis seen in developing countries. FCDP was formerly known as Tropical calcific pancreatitis, Tropical chronic pancreatitis, or Tropical pancreatic diabetes. The current terminology is fibrocalcific pancreatic diabetes (FCPD). The WHO study group in 1985, identified Malnutrition Related Diabetes Mellitus as a separate entity (MRDM) and subdivided into Fibrocalcific Pancreatic Diabetes (FCPD) and Protein Deficient Diabetes Mellitus (PDDM). It accounts only 1% of total diabetic patients. Even though FCPD is reported from several tropical countries like Uganda, Nigeria, Brazil and several Asian countries, it is the Kerala state in India which tops the list. Gheevarghese one of the pioneers in the studies of FCPD reported over 1,700 cases from Kerala. Few large series studies were conducted in Kerala, Tamil Nadu, Orissa, and Karnataka. The prevalence of FCDP was more at Kottayam district in Kerala during 1960s and constituted
29.3% of total diabetes patients in the area during that period. Balaji made a systematic study of 6079 cases in Quilon district in Kerala and reported prevalence was around 1 in 1000.\textsuperscript{134} KP Ramamoorthy conducted a pioneering study at Calicut medical college for many years and proved that prevalence of FCPD was common in Malabar area of Kerala.\textsuperscript{135} Malnutrition, dietary toxin, genetic factors, and immunological factors were implicated in the genesis of FCPD. The Reg 1A gene encodes a protein associated with regeneration of pancreatic islets and is similar to pancreatic stone protein. Deficiency of Pancreatic Stone Protein (PSP), also known as lithostatine may be one mechanism responsible for chronic pancreatitis. Pain abdomen, pancreatic calculi, and diabetes mellitus are the hallmark of FCPD.

In view of the predominant geographical distribution of FCPD in areas like Kottayam district and other areas where the tapioca consumption was high during that time, lead to the hypothesis that FCPD, is related to tapioca consumption. It is presumed to be due to defective detoxification of cyanide to thiocyanate which will subsequently result in high level of cyanide radicals which will destroy the beta cells leading to diabetes.\textsuperscript{136} Later this Cassava theory was disproved by Balakrishnan and colleagues and in a recent study by Kamalu.\textsuperscript{137}

**Type 2 Diabetes Mellitus (T2DM)**

The term type 2 diabetes mellitus (T2DM) replaces the old name of Non Insulin Dependent Diabetes Mellitus (NIDDM) since 1980. Type 2 diabetes mellitus is the commonest type of diabetes and it accounts for 85 to 90 percent of the diabetes globally. T2DM can be described as a syndrome characterized by insulin deficiency, insulin resistance and increased hepatic glucose output.\textsuperscript{138} In the western countries the peak incidence occurs in persons above 60 to 65 years. The best data on the prevalence of diabetes was obtained from the studies in USA between 1988 and 1994 by the National Health and Nutrition Examination Survey III (NHANES III). The study conducted on 18,885 adults
aged 20 years and older, the overall prevalence was found to be 5.1%. The prevalence of undiagnosed cases during that time was 2.7%. The prevalence in urban and rural area varies. In Kerala, urban population has a prevalence of 16-19% according to studies by Kutty VR. ADEPS reported a prevalence of 16% from Ernakulam district.\textsuperscript{112,113}

**RISK FACTORS OF DIABETES MELLITUS**

**Obesity:** Obesity is an important risk factor in the development of diabetes mellitus.\textsuperscript{18,25,43,83} Obesity as a possible risk factor for diabetes mellitus was pointed out by Elliot Joslin as early as 1920s, and this was subsequently validated by several well documented studies. The most important study was the Nurses' Health Study, were 2,204 cases with type 2 diabetes mellitus were observed. Child hood obesity before 18 years of age and large weight gain during adult hood also increased T2DM. Study of US Male Health Professional over a period of 5 years, comprising 51,529 professionals in the age group of 40 to 75 years proved that, child hood obesity had an important role in the development of diabetes.\textsuperscript{139} The obesity epidemic that started in the middle of last century is continuing unabated. Dowd has recently estimated that twelve million adults in the UK will be obese by 2010.\textsuperscript{140} The risk of development of diabetes increases two to eight times at a BMI of more than 25.\textsuperscript{141} Genome wide scan in Mexican Americans for genetic influence of obesity phenotype demonstrated a genetic reunion chromosome 4p at 42 cm near marker D4S2912.\textsuperscript{142} The concept of nutritional transformation by Drewnowski and Popkin stressed the impact of globalization on the human nutrition. The availability of food, cheap vegetable oils, and increased trans global food movement and imports of meat and vegetables, and variety increased the child hood obesity. Neels thrifty gene hypothesis proposed that the genes selected over previous millennia allow survival in the famine by efficiently storing available energy but lead to obesity at the time of plenty of availability of energy.\textsuperscript{143}
Age and sex factors: Age have profound influence in the development of diabetes. Studies in many populations over years proved this factor. According to Joslin diabetes centre studies the highest increase in diabetes mellitus occurred in the age group of 30 to 59 years. The best data on the occurrence of diabetes mellitus obtained from the population study in Rochester, Minnesota. This population comprising white and all newly diagnosed type 2 diabetes mellitus was identified during period of 1984 and 1989. Males were affected more than women. The prevalence was high in the 60-64 age group in the western countries. Now the diabetes is increasingly noticed in younger population. Deo et al have reported that the age of onset of diabetes did not show much correlation with whether one or both patents were diabetic. Traditionally it was mentioned that T2DM is a disease of middle aged, with typical age of onset after 50 years. In Japan type 2 diabetes mellitus was commonly noticed in children than T1DM. Various epidemiological studies from Asian countries showed that a mean age of onset of diabetes is at 50 years, and among Indians it is 44 years.

Ethnicity and Regional factors: Geographical and ethnic differences in the occurrence of Type 2 diabetes can be used to evaluate genetic and environmental factors. The highest prevalence of type 2 diabetes was reported in Pima Indians and among Papago Indians in Arizona. By the age of 50 years, 50% of the population in this region is affected. This is attributed to high incidence of obesity and genetic factors. The next highest incidence is reported in Mexican Americans. The prevalence is very low in Chinese in mainland China, and intermediate among Chinese in Singapore and high in Chinese living in islands of Mauritius. The prevalence is less in rural India and varies from 5% in rural areas and 12-16% in urban areas. The prevalence is still higher among Indians residing in other parts of the world. These variations are accounted by different frequencies of environmental factors, physical activity, obesity, genetic susceptibility and yet there are many other factors to be identified.
Genetic factors: The type 2 diabetes mellitus get clustered in the family. The role of a definite genetic factor in the development of diabetes was noticed for many years. The widely used measure of familial aggregation is the sibling recurrence ratio. It is the ratio of risk of disease in sibling when compared to the general population. A ratio above one suggests a familial aggregation. Various studies have shown that if one parent was affected 17.8% of siblings were affected, and if both parents were affected 25.2% were affected. Karter Aj et.al, who studied more than 25,659 siblings, found that nearly 18% of siblings were affected in USA. Study from South India- by Mohan et.al, showed a higher incidence of diabetes if both parents were diabetic, and the occurrence was high in his study and was nearly 55%. Chandak GR et al., showed recently that a common variant in the TCF7L2 gene is strongly associated with risk of type 2 diabetes among Indian population. The risk of transmission of diabetes is more through affected than an unaffected parent. According to the Wisconian Epidemiologic Study of Diabetic Retinopathy (WESDR), in 31% of cases, a definite family history of diabetes was available. Whereas James H and Warren noticed much higher percentage and put it as more than 50%. Diabetes mellitus with retinopathy is more commonly noticed in families. This proves that diabetes mellitus has a strong clustering in families. The single gene defect causes diabetes in less than 5% cases. The wide linkage mapping of multiple populations to identify susceptibility gene or related traits revealed the loci for Type 2 DM at chromosome 1q21, 3, 5,11q, 12q and 20q. Horinkawa in 2000 demonstrated rising linkage disequilibrium localized at the gene Calpain 10 (CAPIN 10). There are more than 50 such linkage studies shown, and in many populations such linkage studies were conducted, but only few regions were replicated Horinkawa and hence he could not apply for a universal validity. The University of Pittsburgh USA and Guru Nanak DEV University, India in Katri under took a population study in North India for a genome wide search to map Asian Indian diabetic. The mutation in Neuro D1 noticed in patients with MODY pedigree and another mutation in the same gene in a family with type 2 diabetes was noticed by Malecki, Jhala et al.
It was noticed that non-coding variants of sulfonylurea receptor gene ABCC8 were associated with altered insulin secretion and T2DM. A subunit type 1 protein phosphates (PPPIR3) is related to insulin sensitivity. Jackson et al. studied the role of Ala45 Thr polymorphism of neurogenic differentiation-1 (NEUROD1), Ser 199 Phe Polymorphism on Neurogenin-3 (NEUROG3) and Ala98 Val polymorphism of Hepatic Nuclear Factor alpha TCF1 or HNF-1α in Type 2 DM and he found that all three genes were linked with higher plasma blood glucose. A polymorphism near P2 promoter of HNF4α is reported to have an association with T2DM and excess insulin resistance among Asians by Abate and Colleagues. Dixit and Bhattacharya also proved the monogenic association among Indians, but due to poor study design the outcome was inadequate for any conclusion.

**Physical inactivity and sedentary life style:** The change in life style and disease pattern is closely related. Recently, traditional life style has altered in the developing nations. The pattern of life of indigenous population is changing due to the influence of western civilization. Better communication and travel facility helped in interchange of culture. The change in occupation and income had its effect on the physical and recreational activities. And the life style change affected the food intake in quantity, quality and its availability, daily living and behavioral pattern, and this was proved by studies in Australia and the Pacific. The coca colonization as suggested by Arthur Koestler is an apt term to show the impact of western culture in developing country. The physical inactivity and life style change is considered as a major factor in the development of diabetes. Several prospective controlled studies now give direct evidence that physical activity has protective effect on the development of diabetes. The Surgeons Generals report on physical Activity and Health emphasized beneficial effect of exercise. The Physician Health Study involving 21,271 health professionals and later the Finnish Men Study, showed the protective effect of exercise in type 2 DM. The Iowa Women’s Health study cohort involving 34,257 women aged 55 to 69 years for 12 years was yet another large study which reinforced this fact. All this study proved that all
those who exercised moderately have less incidence of type 2 diabetes when compared to those who lead a sedentary life style. Exercise is moving out of our daily lives due to the changing work culture and time factors and this is a major contributory factor for the development of diabetes mellitus.

**Environmental factors:** Diabetes mellitus is viewed as a complex disorder, and Williams et. al noticed a close interaction with environmental and genetic factors.\(^{159}\) The traditional work force (blue collar jobs) subsisting on agriculture was replaced by sedentary workers (white collar jobs) and the life style is undergoing dramatic changes even in the remote rural areas. The Information Technology and Computerization warrants prolonged sitting and sedentary life style. Change in the socio cultural factors also influences the development of diabetes. The undercurrent illness, viral infections, and certain drugs are also diabetogenic. The incidence of type 2 diabetes was rare in the Pima Indians when they led a frugal existence in desert conditions. The incidence of diabetes markedly increased in the Pima Indian in Mexico after rapid urbanization and change in their life style. Over nutrition and inactivity consequent to urbanization lead to obesity and now the prevalence is over 50% in Pima Indians as reported by Gareth Williams.\(^{160}\)

**Stress:** Environmental factors like stress may contribute to the development of T2DM. Stress may be environmental, professional, or psychosocial. Environmental stress can also lead to diabetes and can lead to early onset diabetes. Recent research by Surwit and colleagues noted increased evidence of altered sympathetic activity in T2DM. Mooy et al also showed that stressful events increases diabetes.\(^{30}\) It is not clear whether such neuroendocrine activity is responsible for hyperglycemia or simply a chance finding in patient with diabetes mellitus. It is an important area of future research. Stress influences the metabolic activity to varying extend and can alter the glucose metabolism. Geringer in his study on relation between affective disorder and diabetes mellitus pointed out that stress and depression can lead to alteration in hypothalamic pituitary axis which results in increased rate of cortisol production.
and subsequent hyperglycemia. Social and family environment is another important factor in the development of chronic illness. Only limited studies have looked into the effect of environmental stress in the development of diabetes. A recent report by Ramachandran in the tsunami hit area of coastal Tamil Nadu, reported an increase in type 2 diabetes due to stress.

**Hypertension and diabetes:** Hypertension (HTN) and diabetes mellitus are closely related conditions and this was noticed sixty years ago by several authors. Hypertension, as defined by blood pressure level of more than 140/90mmHg, increases the risk of developing diabetes by two times. Studies by Ferrannini et al. proved that hypertension is a key factor in inducing insulin resistance and there are many studies pointing that hypertension can lead to glucose intolerance.\(^{161}\) The European group for the study of Insulin resistance examined the relationship between a specific measure of insulin resistance and blood pressure in 333 normotensive persons studied in 20 different clinical research centres, and the result indicated that, the blood pressure was directly related to both insulin resistance and insulin concentration.\(^{162}\) The pathogenesis of diabetes in hypertension is not fully understood, and is considered as multifactorial in origin. The prevalence varies from type 1 and type 2 diabetic patients.

**Lipid disorders in type 2 diabetes**

The population based studies demonstrated that type 2 diabetes is associated with various lipid abnormalities. Plasma VLDL is markedly elevated. Increased production of triglyceride and Apo B, decreased clearance of triglyceride and delayed clearance of chylomicron and subsequent accumulation fat are noticed in diabetes mellitus.\(^{163}\) Diabetes may occur in presence of familial syndromes of triglyceridemia. Three large scale studies, the Scandinavian Simvastatin Survival Study (SSSS), Cholesterol And Recurrent Events Trial (CARE), and Long Term Intervention with Pravastatin in Ischemic Disease(LIPID) trial had shown that, use of statin is useful in the primary prevention of diabetes.\(^{164}\) The CARE study included a large number of patients.\(^{165}\) Lopez and Virella
studied the effect of pravastatin and found that it induced more glycation and oxidation of LDL and render them more immunogenic, and leads to increased risk of atherosclerosis. Fielding and Reavens through Immunoadsorption of lipoprotein studies showed that HDL is decreased in diabetes mellitus and this also causes an increased risk. Atherosclerosis is a leading cause of mortality in type 2 diabetes, and predispose to myocardial infarction, stroke, and peripheral vascular disease. 50% of the diabetic will have coronary artery disease at the time of initial diagnosis. This studies clearly indicate dyslipidemia as an increased risk factor in the development of type 2 diabetes and adequate control is effective for primary prevention.

**Pathogenesis of type 2 diabetes**

Type 2 diabetes mellitus is the most common metabolic disorder of human and it is characterized by chronic and sustained hyperglycemia. According to Khan, the two main mechanism of development of type 2 DM is the failure of beta cells to secrete adequate insulin and impairment in the ability of muscle and fat to respond to insulin with increased glucose uptake. This decreased glucose uptake may be due to insulin resistance. Insulin secretion occurs in waves of rapid spurts at an interval of 5 to 15 minutes. The simultaneous measurement of calcium ions and secretion of single mouse islets have shown that oscillations are synchronous in all regions of beta cells and each oscillations are associated with secretion of insulin. Pancreatic beta cells sense glucose level and other nutrient molecules and respond to this signal by synthesizing insulin. It is essential to maintain these natural pulses of secretion to maintain the glucose level of plasma and tissue normally. Glucose is supplied to brain during fasting state through glycogenolysis and hepatic gluconeogenesis. The extraction of this glucose to tissue is mediated by availability of insulin. The action of insulin is initiated by its binding to specific receptors in the plasma membrane and later it gets transferred to the beta subunit and later mediates the phosphorylation and release of tyrosine kinase. The high capacity Na+ independent carrier, GLUT-2 transport glucose into the cells which gets
phosphorylated by glucokinase enzyme and metabolized in the Krebs cycle.\textsuperscript{171} The resulting depolarization opens voltage sensitive Ca\textsuperscript{++} channels which leads to increase in the intracellular calcium.\textsuperscript{172} The presence of calcium ion stimulates insulin secretion. The insulin secretion and its regulation are influenced by strong genetic factors. The gene involved in GLUT 2 and glucokinase gene action was investigated by Frougel et al and found that certain types of MODY were due to mutation in this gene.\textsuperscript{173} The major step in insulin action is the activation of insulin receptor substance and phosphatidylinositol 3 kinase (PI3K). PI3K has a role in the mobilization of Glucose transporter 4 (GLUT-4) from the central cytoplasmic pool to cell surface. The glucose transporters are essential for transport of glucose to muscle and adipose tissue. 20\% to 80\% of the insulin secreted by the beta cells enters to the portal system. Hence measurement of insulin in the portal venous system is a good indicator of insulin secretion by pancreas. C-Peptide factor of proinsulin does not enter the portal system. Insulin secretory defect and consequent defective action of the insulin at different levels contribute to the pathogenesis of diabetes mellitus. There is a strong genetic factor in the development of diabetes as evidenced by clustering of cases in families and high prevalence in certain ethnic group as described earlier.\textsuperscript{174}

Steiner and colleagues reported rare gene mutation in the insulin gene 11p15. These occurred in A or B chain in the primary sequence. Insulin Chicago (B Phe 25 Leu) and insulin Wakayama (A Val 3 Leu) and insulin Los Angeles (B Phe 24 Ser) are examples. These mutations impair the binding of insulin to the receptor which leads to hyperglycemia.\textsuperscript{175} Recent studies point to the possibility of impairment in insulin secretion in Type 2 diabetes due to genetic alterations in extra pancreatic hormonal system regulating beta cell function. The Glucagon like peptide GLP-1 and GIP Glucagon dependent insulino trophic polypeptide are gut hormones that act as Incretins and activate receptors in beta cells and aid in the release of insulin. Nauck and Heimsal noticed that the level of GIP is generally decreased in Type 2 diabetes.\textsuperscript{176} Leptin and Leptin receptors are closely associated with obesity and also have role in the genesis of Type 2 DM.
The β3 adrenergic receptor (β3AR) stimulates lipolysis and thermogenesis in adipocytes. The role of this extra pancreatic hormonal system is currently under evaluation for its role in obesity and diabetes mellitus.\(^{177}\) There is an interrelationship between glucose and free fatty acid metabolism in beta cells and this was noticed by Randal and co-workers.\(^{178}\) The chromosome 2q37 and Calpain 10 was the first locus of gene, significantly related to type 2 diabetes mellitus.\(^{179}\) An association is noticed with fetal malnutrition and diabetes mellitus. The unequivocal reports of long term beta cell dysfunction in Marasmic Kwashiorkor and MMDM (Malnutrition Modulated Diabetes Mellitus) point to the relation of malnutrition with diabetes.\(^{180}\) An elevated blood sugar level has much metabolic effect on the tissues. The non-enzymatic glycosylation of hemoglobin A leads to HbA1c formation and it accounts for about 4% of hemoglobin.\(^{181}\) In sustained hyperglycemia this glycation increases substantially.\(^{182}\) Even though HbA1c is the most investigated glycosylated protein, there are several other Glycosylated proteins called Advanced Glycosylation End product (AGE). The most prevalent AGE is N-Epsilon Carboxymethyl lysine.\(^{183}\) As the life span of RBC is 120 days, this non-enzymatic glycosylation takes continuously during this period and it provides a good index of average blood glucose level of the preceding 3 months. The amount of HbA1c correlates well with the fasting and postprandial blood glucose levels. The HbA1c measurement can be done using immunological methods as well as affinity chromatography. This is presently the most widely used test in treatment and risk analysis of diabetic patient.

**Metabolic syndrome:** Metabolic syndrome is otherwise called Insulin Resistance Syndrome (IRS), or Syndrome X. It was first described by Vagu et al. In 1988, Reaven described the entity clearly and named it as syndrome X. The possibility of diabetes mellitus due to insulin resistance in which ketosis does not develop was considered by Reaven way back in 1967.\(^{184,185}\) The syndrome X described by him includes insulin resistance (IR), hyperinsulinemia, visceral obesity, impaired glucose tolerance, dyslipidemia and atherosclerosis. Subsequently microalbuminuria, hyperuricemia and hyperhomocysteinaemia and hyperleptinaemia, and other metabolic and cardiovascular risks were also
described. The recent definition of metabolic syndrome was established by National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) in 2001. In the United States as per the NCEP ATP III criteria, the prevalence of metabolic syndrome (MS) is 20% in young and 40% in above 50 years of age. The overall prevalence of metabolic syndrome is 7% in young and 60% in people above 60 years. There is a genetic predisposition in the development of insulin resistance, and studies by Ford et al showed that there is 40% chance to inherit this metabolic abnormalities. Kereiakes et al of the view that metabolic syndrome-attained a epidemic proposition and systemic thrombosis, oxidative stress and systemic inflammation are associated features of this epidemic.

Insulin resistance can be associated with many clinical features. A number of rare form of severe insulin resistance include features like Acanthosis nigricans, hirsutism, acne, and oligomenorrhea. The two different types of insulin resistance noticed in adults are the type A and type B. Type A is the severe form of insulin resistance. The type A affects young women and lead to hyperinsulinemia and obesity and excess androgens. Type B insulin resistance has auto antibodies directed against insulin receptors. The glucose insulin sensitivity test introduced by Himsworth is used to assess the insulin sensitivity. High levels of insulin in fasting state and response to insulin secretagogue indicates the presence of insulin resistance. Studies by Warren et al. proved that skeletal muscle is the most common site of glucose metabolism and in insulin resistance, entry of glucose in skeletal muscles are markedly impaired. Obesity is a trigger factor in IR, and it reduces insulin action. Free fatty acid interferes with the insulin action by interfering in the GLUT-4 pathway. Endothelial dysfunction and tumor necrosis factor (TNF) also plays a role in the development of insulin resistance.

Pathological changes in diabetes mellitus: The pathological changes seen in pancreas in diabetes mellitus depend on the duration, adequacy of metabolic control and genetic factors. The gross examination of pancreas in Type 2 DM is
usually normal. The patients with uncontrolled DM for more than 10 to 15 years can have microvascular complications like retinal microangiopathy, nephropathy, neuropathy and atherosclerosis in blood vessels. Pathological analysis of tissue shows thickening of basement membrane, and these changes are most marked in skin, skeletal muscle, retina, renal glomeruli and adrenal medulla. The connective tissue stroma may be replaced by type IV collagen and diabetic capillary leak leads to more plasma protein in the interstitial space than normal. Gepts and Co workers noticed reduction in pancreatic size and beta cell degranulation and depletion of stored insulin. Doniach and Morgan also noticed similar changes. Hyalinization was noticed in the pancreas by many, including Bell and Melato. Amyloidal replacement of the islets is the commonest finding, and appears as pink, amorphous material beginning in and around capillaries and in between cells. The hyalinization noticed earlier in the pancreas by Bell et al was thought to be due to deposits of amyloid material. Deposits of amyloid in more than 25% of islets were noticed during post mortem examination of diabetes patients. Nagolotimath and co workers noticed marked fibrosis, especially in the Fibrocalcific pancreatitis. Thickening of duct was absent, but pigment deposit was common in pancreas.

**DIAGNOSIS**

The diagnosis of diabetes once made, requires life time care and management. It involves a lot of physical, social, economic and psychological burdens on patient and poses multiple challenges to the health providers. Declaring a person as diabetic should be done with utmost care and after definitive clinical and biochemical examinations. Polyuria as an early symptom of diabetes was recorded by ancient physicians like Susrutha and Charaka. Normally small amount of sugar is passed in the urine i.e. up to 30 to 150 mg. It was Benedict who discovered the method of detection of glucose in the urine. Urine sugar estimation is semi quantitative and is widely used. Fluid intake and renal concentration may influence the urine glucose and hence is not a sensitive method. The urine glucose detecting strips (clinitest) now being used are more specific for reducing sugars. The glucose oxidase impregnated test strips are
simpler, specific and sensitive in the detection of urine sugar and ketone bodies (clinistix, diastix). Uristix are available to detect albumin. The test is usually positive if more than 300mg/dl sugar is present in the urine. False positive test is obtained with vitamin C, glucoronic acids, uric acid, PAS, galactose and fructose. Presence of glucose in the urine with normal fasting blood sugar should suggest the possibility of renal glycosuria. The disadvantage of using urine sugar testing for diagnosing diabetes is that there is individual variation in the renal threshold levels. Though there are limitations, urine sugar test is still useful in the mass screening and detection of diabetes. Uristix are used to detect albumin in urine which may indicate early nephropathy.

The blood sugar estimation was described by Epstein AA. The oral GTT was first described by Hofmeisen in 1889. Later Folin and Wu procedure was adopted by Somogyi Nelson. O-Toludine and ferric cyanide methods were also very commonly used, till the glucose oxidase and hexokinase method was available. The difference in the capillary and venous blood was appreciated by Hagedorn and later by Gold Berg and Lift. Arterial blood sugar may be 25-40mg% higher when compared to the venous sample and 8 to 15mg after 2 hours post prandial samples. Plasma blood sugar is more useful than the whole blood sugar. Lipid profile analysis is also important in the management of type 2 DM. Test for microalbuminuria is an independent risk factor for cardiovascular events. Hence urine protein analysis should be done to detect early nephropathy. GAD (Glutamic Acid Decarboxylase) antibodies detection is helpful in identifying Latent Autoimmune Diabetes of Adults (LADA). The term LADA may be used in patients whom the GAD antibody titer is more than 5RU and less in case the antibody titer is less. Antibody testing was found useful for prediction of insulin requirement in person with onset less than 45 years. Routine assay of C-peptide is not done, but in selected cases the measurement of C-peptide will help for determining appropriate therapy. Chest X-ray, ultrasonographic studies, and Doppler and nerve conduction studies, electrocardiogram etc, also form part of diagnostic evaluation in selected group of patients.
Diagnostic criteria of Diabetes mellitus: To accommodate the rapidly accumulating clinical and biochemical knowledge of diabetes mellitus, the diagnostic criteria was modified several times. The newer diagnostic methods and epidemiological data were considered in the modification of diabetic diagnostic methods and interpretation of values. In 1997 and in 1999, the American diabetic association (ADA) changed the diagnostic criteria for diabetes mellitus and recommended the use of Arabic numerals 1 and 2 for major form of diabetes. The earlier classification of Insulin Dependent and Non Insulin Dependent Diabetes-Mellitus (IDDM and NIDDM) was changed to Type 1 and Type 2 diabetes mellitus accordingly. Type 1 diabetes mellitus can occur without any autoimmune antibodies, and these individuals who require insulin for control of diabetes is included in Type 1 B, and where presence of autoimmune antibodies like GAD noticed is designated as Type 1 A. The previous ADA criteria of fasting plasma glucose of more than 140 for diagnosis of diabetes mellitus was changed, and the fasting blood glucose of 126mg/dl was accepted as the criteria for diagnosis. This in turn helped to identify many diabetes mellitus patients in the early stage. WHO also recommended same blood glucose level of 126mg/dl for the diagnosis of diabetes. Normal and abnormal blood glucose value was adopted by Fajan and Conn, based on standard deviation, from mean value, as the cutting line between the two. Later the criteria put forwarded by National Diabetic Data Group (NDDG) and WHO also were used.

Table-3: Diagnostic Criteria of Diabetes*

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<table>
<thead>
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<tbody>
<tr>
<td>Fasting Blood Sugar</td>
<td>&gt;7.0mmol/L (&gt;126mg/dl) or</td>
</tr>
<tr>
<td>Random Blood Sugar</td>
<td>11.1mmol/L (&gt;200mg/dl) or</td>
</tr>
<tr>
<td>Post prandial Blood Sugar</td>
<td>11.1mmol/L (&gt;200mg/dl)</td>
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</table>

*American Diabetic Association criteria modified in 2003

Fasting blood sugar means no calorie intake for last eight hours and random means with no regard to the time of meal intake. Postprandial blood sugar estimation is performed using a glucose load containing the equivalent of 75gm
glucose dissolved in water. In the absence of unequivocal hyperglycemia the test should be repeated on a different day. The OGTT should be done in the morning after the patient had days of unrestricted diet containing about 150 mg carbohydrates daily and normal physical activity. The patient should not smoke during the test. Medications and concurrent infection should be considered when interpreting the result. Take a fasting blood sample and administer 75g glucose or partially hydrolyzed starch with equivalent carbohydrate content in 150 to 300 ml of water, over a 5 minutes period. In children the glucose should be 1.75g/kg of body wt. upto 75g. The blood sample is collected before meals and after 2 hours. A venous sample should be collected for interpretation.

The fasting plasma glucose (FPG) less than 5.6mmol (100mg/dl) is considered normal and FPG >5.6mmol/l (100mg/dl) but less than 7.0mmol/l (126mg/dl) is defined as Impaired Fasting glucose or IFG. A blood sugar value between 7.8 and 11.1mmol/l (140 to 200mg/dl) is considered impaired glucose tolerance or IGT. Individuals with IFG or IGT are at higher risk for developing diabetes. Survey in Japan revealed that IGT was associated with a higher death rate due to cardiovascular causes when compared to IFG. The prevalence of diabetes will be lower when FPG value according to ADA criteria is used, compared to that of WHO criteria, by a rate of 6.32. The WHO committee recommended the use of OGTT whenever the fasting glucose values are in between 100-125mg/dl. The American Diabetic Association recommended screening for diabetes in individuals aged more than 45 years every 3 years, and frequent screening in patients with additional risk factors at an earlier age. In 1997 the ADA and in 1999 WHO recommended a fasting blood glucose value of less than 110 mg/dl (6.2 mmol/l as normal and 110-125 mg/dl[6.1 to 6.9 mmol/l) as impaired glucose tolerance. In 2003 the ADA expert committee recommended, 100mg/dl as normal and 100-125 mg/dl as impaired glucose tolerance and more than 126mg/dl as diabetic range.

American diabetic association clinical practice recommendations in 2003, and WHO in 1999 and many national diabetic organizations have contributed
immensely in modifying the diagnostic criteria periodically and formulating treatment guidelines of diabetes mellitus. Glycosylated Hemoglobin (HbA1c) is also used in the diagnosis and assessing the severity of hyperglycemia and in the risk stratification. The non enzymatic glycosylation of hemoglobin leads to HbA1c formation and it is about 4% of hemoglobin red cells. In sustained hyperglycemia this glycation increases substantially. The clinical relevance of glycosylated hemoglobin was established in 1989 itself. In the DCCT study the intensive control of diabetes maintained an average HbA1c level at 7% and in the normal group at 9%. Few studies regarding the diabetic control in relation to glycated Hb pointed out that a good control is indicated by a value of <7%, and fair control when the value is between 7-8% and poor control when the value is >8%.

**Diabetes in the elderly:** The number of elderly diabetes patients, both men and women aged more than 65 years are increasing rapidly. It is estimated that the number of elderly diabetics will increase by 20% by the year 2040. Diabetes was considered as disease of the aged in the past and 10% of people aged more than 65-74 years is diabetic. Currently in India there are 60 million people aged more than 60 years. The glucose intolerance is primarily manifested as an increase in post prandial blood glucose in elderly and this may increase by 15mg/dl per decade after 30 years. The WHO criteria or the diagnostic criteria issued by the expert committee on diagnosis and classification of diabetes mellitus does not adjust the glycemic criteria for the elderly. Data on serum fructosamines is limited in the elderly and initial reports suggest that it may be more useful for the diagnosis of diabetes. Incidence of cardiovascular diseases are equal among diabetic men and women of same age. Effects on platelets, increased glycation of vascular tissue, and lipoprotein alteration are associated with more complications in elderly diabetics. The American geriatric society and the California health care foundation panel are in the process of developing an evidence based protocol for management of elderly diabetic patients.
**Diagnosis of diabetes in pregnancy:** There is a lack of international consensus on the screening, diagnosis and follow up of gestational diabetes mellitus. Universal screening programme based on blood glucose is done in all pregnant women. The early screening will help to identify undiagnosed pregestational diabetes. The American Diabetic Association (ADA) and American College of Obstetrician (ACOG) recommended 50 gm OGTT at 24 to 28 weeks of gestation. The American Diabetes association recommends 3 hour 100gm OGTT and GDM is diagnosed if any 2 values equals or exceeds FPG>95mg/dl, 1hr PG>180mg/dl - 2hr PG 155mg/dl and 3 hr PG 140mg/dl. Carpenter and Couston who recommended this earlier now advise 75gm of glucose. Now the WHO recommendation is widely accepted in diagnosing gestational diabetes mellitus. WHO proposes a 2hr 75gm OGTT. Fasting glucose <6.0 and 2 hour venous plasma glucose <9.0mmol% is considered normal during gestation. Fasting glucose >8.0mmol% is diabetes and a 2 hour plasma glucose >11.0mmol% is considered to be diabetic. This will correspond to a fasting more than 95mg% and 2 hour 155mg%. There is a criticism that both ADA and WHO have not projected the influence of glycemic level on the fetal outcome. The screening is recommended between 24 and 28 weeks of pregnancy. All pregnant women should undergo screening. The recent trend is to screen for diabetes in the first trimester itself as the fetal beta cell recognizes and responds to maternal glycemic level as early as 16th week of gestation.

**CLINICAL EVALUATION OF DIABETIC PATIENT**

A detailed history taking and clinical examination is the corner stone of identifying diabetes and planning a management system, and this forms the foundation of diabetic care. The family history, age of presentation, and presence of specific antibodies will help to identify whether the patient will have type 1 or 2 diabetes mellitus. Body weight, family history, and duration of symptoms, will help to identify type 1 and 2 diabetes. It may not be always possible to identify type 1 and 2 based on this factor and some time detection of antibodies like glutamic acid decarboxylase (GAD) are needed to identify...
them. The classical symptoms of polyuria, polydipsia and polyphagia may be common presenting feature in Type 2 DM. Weight loss is usually noticed. The weight loss may not be much obvious in obese patients. Trunkal obesity is noticed more among Asians. Increased waist-hip ratio or waist circumference is associated with type 2 diabetes in Asians. Body mass index (BMI) and vascular status assessment should be done in all newly detected diabetics. Many a times other than biochemical evidence of diabetes, no clinical finding is noticed. The patient may have dry mouth and tongue due to dehydration secondary to polyuria. Carotid bruit may be audible due to vascular occlusion and indicate atherosclerosis. Hypertension is a co morbid condition of diabetes in 40% of the patients. There is 2.5 times chance to develop diabetes mellitus in hypertensive when compared to normal population. Ferranni et al pointed out that essential hypertension is an insulin resistant condition. 78.3% men and 82.8% women with diabetes had elevated blood pressure above 140/90mmHg according to the Health Survey of England. Absent peripheral pulses may be an indication of peripheral vascular disease. Hepatomegaly due to fatty liver is a common finding in a clinical examination. Examination of the hand will show limited joint mobiity. This is some time called cheiroarthropathy. Cheiroarthropathy is associated with difficulty in extending metacarpophalangeal of at least one joint bilaterally. Dupytrens contracture is common in diabetes and may include nodules or thickening of the skin and knuckle pads. Hallux valgus, bunions, callouses, nodules and hammertoe and other joint deformities should be carefully looked for. In a recent study 31% were found to have Acanthosis nigricans at the time of presentation of diabetes. ADEPS from Kerala also noticed that acanthosis nigricans is risk factor for type 2 diabetes in their study. Carpel tunnel syndrome is common and may present as wrist pain radiation. The examination of feet will show callus formation at the weight bearing area. Claw hand may be seen due to ulnar nerve neuropathy. Discoloration of skin, local infection and deformities of the feet may be associated with Charcot neuropathy. Light touch using 10 mm monofilament, vibration test using 128Hz turning fork over big toe or malleoli, proprioception and pain sensation should be tested appropriately. Study by Thivolet et al it is
noticed that 51% diabetic have features of neuropathy. Superficial pain assessment and vibration testing will detect early cases of diabetic neuropathy.

COMPPLICATIONS OF DIABETES MELLITUS

Diabetic retinopathy: Diabetes mellitus is a multisystem disease and it can affect the eye. Blindness is twenty five times more common in diabetes patients. Diabetic retinopathy is a common complication of both Type 1 and Type 2 DM. Nearly almost all Type 1 patients will ultimately develop retinopathy changes over a period of 15 to 20 years. Risk factors like pregnancy, chronic hyperglycemia, hypertension, renal disease and hyperlipidemia lead to eye complications in diabetes. Retina is most vulnerable in diabetes because of its high metabolic rate, and oxygen demand. UKPDS and DCCT studies have clearly indicated that retinopathy is a common complication of diabetes and more than 35% of type 2 subjects have features of retinopathy at the time of diagnosis of which 60% have retinopathy in advanced stage. According to the Wisconsin Epidemiologic Study of Diabetic retinopathy (WESDR), 3.6% of young patients with Type 1 diabetes and 1.6% of type 2 diabetes were legally blind. Prevalence of retinopathy is less in Indian populations than the west. The reported prevalence of diabetes varies from 19.9% to 47.8% in diabetic population at specific geographical locations. Madras diabetic retinopathy study shows a prevalence of retinopathy among 26% of patients referred from various diabetology centres and 47% among the patients in the Madras Diabetic Research Centre. Hypertension can accelerate retinopathy in diabetic patients. Narendran et al from Palakkad showed that the prevalence of retinopathy among self reported diabetic patients was 26%. Long duration of diabetes is another risk factor. HLA-DR phenotype is a major risk factor in the development of proliferative retinopathy. Oxidative stress. Advance glycosylated end products is another risk factor. Intraretinal microvascular abnormalities (IRMA) and advanced changes can lead to hemorrhage, retinal detachment and glaucoma. Glaucoma due to PDR should be treated early as recommended by the ETDRS study (The Early Treatment of Diabetic

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The diagnosis of diabetic retinopathy is essentially based on clinical examination. The loss of retinal pericytes, micro aneurysms and venous dilation are early clinical sign of diabetic retinopathy. A combination of binocular indirect ophthalmoscopy and slit lamp biomicroscopy of the posterior segment using contact lens or non contact lens is essential for proper diagnosis and identifying the stage of retinopathy. Roger noticed that there is decreased corneal sensitivity and elevated tactile corneal threshold. Incidence of cataract is 1.6 times higher in diabetics. Lenticular opacities have been related to poor metabolic control of the disease. Duration of diabetes, associated retinopathy, use of diuretics, and decreased intraocular pressure and smoking are the risk factor in the development of cataract in diabetics. Reduced corneal sensitivity in diabetics have been noticed as a major sign of disease. Other less common complication include keratitis, microcystic edema, bleb formation, and thinning of epithelium. Brown et al in their study concluded that diabetes is the second leading cause of neovascular glaucoma accounting for 32.2% of cases. 40 to 60% of cases with advanced proliferative retinopathy will have associated glaucoma.

Diabetic nephropathy (DN): Diabetic nephropathy occurs in 30% of type I and 50% of type 2 diabetic patients. The Pima Indians and African Americans have high incidence of diabetic nephropathy. Caramour and Firotto in their study on the risk factors of diabetic nephropathy were of the view that albumin excretion rate can predict onset of diabetic nephropathy. Now there is a rapid increase in diabetic kidney disease and it is the most common cause of End Stage Renal Disease (ESRD). Hypertension is one of the important factors which determine renal dysfunction in diabetes. A blood pressure level of more than 130/80 strongly predicts the development of proteinuria. Genetic factors are also equally important, and there is more than 80% concordance for normal urinary excretion of protein. The most extensively studied gene is Angiotensin converting enzyme gene (ACE gene) for its role in the renal function. Elevated blood sugars stimulate angiotensinogen, Angiotensin II and angiotensin 2 receptors (AT2). This AT2 receptors influence the
hemodynamics of renal system and leads to trophic and profibrotic effects. A strong association between diabetic nephropathy and polymorphism in the Aldose reductase gene has been recently confirmed. Recent evidence suggest that high glucose induced traffic in mitochondrial electron transport generates reactive oxygen species (ROS), which are involved in the development of DN. Microalbuminuria is the hall mark of DN, and it is defined as urinary excretion of more than 30-300mg/24hr or equivalent to 20-30mg/hr in a timed specimen. Microalbuminuria is noticed in 30 to 40% of diabetic patients. The prevention of diabetic nephropathy mainly aimed at controlling blood sugar to optimum, and the HOPE and LIFE trial showed that renin angiotensin system blockage prevents the onset of diabetic nephropathy and ACE inhibitors are useful for this purpose. Renal replacement therapy is required for End Stage Renal Disease (ESRD).

**Neurological complications of diabetes mellitus:** The prevalence of diabetic neuropathy is 50% in both type 1 and type 2 diabetes. 30% of the patients will have evidence of diabetic neuropathy and only 10% will be symptomatic. Micro infarcts and fibrinoid changes are noticed in the peripheral nerves. The role of AGE and AGE receptor nuclear factor NF-kB, cell adhesion molecules (CAM), nitric oxide and eicosanoids are strongly associated in the pathogenesis. Tuck et al in their experiments in rats demonstrated a 50% reduction in the blood flow to the nerves in diabetic patients. The diabetic nerves are extra sensitive to alpha adrenergic agonist and endothelin. A reduction in nitrous oxide and nitric oxidase synthetase are important. The polyol inisitol pathway is another factor which have major role in the development of peripheral neuropathy. Due to the over activity of polyol inisitol pathway there is production of sorbitol as action of aldose reductase and this is also implicated in diabetic neuropathy. The myoinositol abnormality leads to Na+ K+-ATPase dysfunction in peripheral nerves. Deficiency of gamalinoleic acid and increase protein kinase C is also considered in the pathogenesis. Increased lipid peroxidation and alteration in the pattern of glutathione is noticed even in the young patients with diabetic neuropathy. Recent studies
showed alterations in the myelin sheath after six months in uncontrolled diabetic patients. Schwanns cells are said to be the targets of oxidative stress.

The biopsies of sural nerve in diabetic patients have shown many changes suggestive of vascular abnormality like endothelial cell proliferation and vessel occlusion. Genetic and immunologic mechanisms are also considered in the pathogenesis of diabetic neuropathy. It was noticed that 12% of patients with peripheral neuropathy had positive GM ganglioside antibodies and these antibodies are more often seen in distal symmetric polyneuropathy. Antiphospholipid antibodies are also seen in high titre. Autonomic neuropathies are common in diabetes. It is very disabling. Sweating, postural hypotension, gastroparesis, diarrhea and bladder dysfunction are common manifestation of autonomic neuropathy. Tachycardia or fixed heart rate, colonic atony, impotence, retrograde ejaculation and pupillary abnormality were also noticed in diabetic autonomic neuropathy. Clinical assessment of diabetic neuropathy is tedious and sometimes immunohistochemical methods may be needed to establish the diagnosis. Biopsy and quantitative sensory testing are done now for the diagnosis of autonomic neuropathy. The major intervention tried in the treatment of diabetic neuropathies are drugs like aldose reductase inhibitors, clonidine, nerve blocking with anesthetics, blockage of NMDA receptors through dextromethorphan, mexilitine antidepressants, alpha lipoic acids which inhibit the reuptake of serotonin and nor epinephrine. The gamma linoleic acid, amino guanidine, and human intravenous immunoglobulin, topical capsaicin, and carbamezepine, gabapentin, pregabalin, calcitonin and variety of analgesic are tried. Transcutaneous nerve stimulations and recombinant human growth factor are under trial and are used in the treatment of diabetic peripheral neuropathy with varying success.

**Diabetes and heart diseases:** Cardiovascular mortality is twice in diabetics when compared to the general population. There is 50% chance for myocardial infarction in a diabetic. The multinational study of vascular disease by WHO showed that cardiovascular disease is the most common cause of mortality in...
Atherosclerosis was noticed in 65 to 80% of all persons with diabetes. There is a fourfold rise in mortality due to coronary artery disease. Male gender, black race, and long duration of illness was found to be associated with increased cardiovascular mortality. As already discussed, metabolic syndrome is a collection of risk factors associated with diabetes. Serum glucose level is an important indicator for risk factor of cardiac diseases and the San Antonio Heart Study which looked into the all cause mortality due to diabetes proved that higher blood glucose level increase mortality due to cardiac diseases. A similar finding was reported in the Atherosclerosis Risk in Communities (ARIC) STUDY. The important factor which lead to the development of atherosclerosis in diabetes is dyslipidemia. Increased oxidative stress in diabetes is another factor which will contribute in the development of cardiovascular disease. The Heart Outcome Prevention Evaluation (HOPE) study have shown that treatment with antioxidant is not much used full in prevention of oxidative stress. Diabetic are more prone for thrombosis and fibrinolysis. Acute coronary syndrome and sudden death and stroke are common in diabetes patients. There is increased platelet activity and decreased antithrombotic activity in diabetics. Activity of protein C and thrombin are also high in diabetes and it may lead to hypercoagulable state. Endothelial dysfunction is another important factor in the pathogenesis of cardiovascular disease in diabetes. There is increased vascular resistance. Endothelial derived relaxing factor, later known as nitric oxide is important in the control of peripheral vascular resistance.

Silent or unrecognized myocardial infarction is common in diabetic patients. Diabetic with myocardial infarction have greater mortality when compared to normal persons. In the Thrombolysis and angioplasty in myocardial infarction (TAMI) trials the mortality is twice in diabetic. This was also observed in the GUSTO trial (Global Utilization of Streptokinase and tissue plasminogen activator for occluded coronary Arteries). Congestive cardiac failure is frequent in diabetic patients. Framingham study showed a two fold rise in cardiac failure in diabetic patients. 15 to 25% of patients with cardiac failure have associated...
diabetes mellitus. The long term prognosis in diabetic with cardiac failure is poor. Cardiomyopathy in diabetic was first noticed by Rubier. The recent dilated cardiomyopathy study (DCS) also considered association of cardiomyopathy with diabetes. Both cellular and molecular factors contribute in the development of cardiomyopathy. Decreased intracellular concentration is also noticed in patients with cardiomyopathy. Various forms of arrhythmias are common in diabetic patients. Ventricular dysfunction and sudden death is noticed in myocardial infarction. Associated autonomic neuropathy also causes arrhythmias. The Honolulu Heart Programme also demonstrated that those with diabetes mellitus are more prone for sudden death without other complications.

Peripheral vascular disease in diabetes: Peripheral vascular disease is a common cause of amputation in diabetes mellitus patients. The socio economic implications of diabetic foot are enormous. More than 40% of lower extremity amputations are done for diabetes mellitus. The main contributory factors in the development of peripheral vascular disease are ischemia, neuropathy, infections and trauma. Autonomic denervation and consequent cracking of dry skin predispose to diabetes foot. Changes in the vessel can occur due to injury of the axon and nociceptive C fibers. Endothelial dysfunction is seen in diabetes mellitus and abnormal endothelium dependent vasodilatation are noticed more common in diabetics. Threefold rise in intermittent claudication is noticed in diabetes patients. Arterial insufficiencies can lead to non healing ulcers. Measurement of venous return and return of rubor and pallor on elevation are other simple measure to assess vascular status of patient. Simmens-Weinstein monofilament wire is an effective tool to detect whether a patient is prone for diabetic foot ulcers. Inability to perceive a gently bend filament implies lack of protective sensation. Doppler evaluation and measurement of ankle-brachial index is also useful. Frequent neurological tests, prevention of trauma and frictions, use of correct shoes and control of blood glucose are useful methods to prevent diabetic foot ulcers and amputations. The non healing diabetic foot ulcer is a challenging problem for surgeon and diabetologist. Damage to the motor nerves, neuroarthropathy and rocker bottom
deformity with weight bearing in distal tarsal row can precipitate ulcer in the distal part. Neuropathic feet abnormality in distribution of pressure resulted in 20% ulceration over 2.5 years.\textsuperscript{306} Patients have two fold risk of developing atherosclerosis in lower limb when compared with upper limb.\textsuperscript{307} The combination of increased plasma viscosity and increased platelet adhesion and other thrombogenic factor can lead to further ischemia and peripheral vascular disease.\textsuperscript{308}

**Erectile Dysfunction in diabetes (ED):** Impotence is the most common form of sexual dysfunction. It is estimated that 1 in 10 males have impotence, and the prevalence among men aged 40 to 70 year is 50%. 2.3 million Americans suffers from impotence according to current data. In diabetics, impotence starts 15 years earlier than non diabetics and prevalence among diabetic is 35% to 70%.\textsuperscript{309} Men with diabetes have decreased REM associated erection.\textsuperscript{310} Autonomic neuropathy, vasculopathy and venous occlusive dysfunction can lead to ED. Vascular disease of medium and small size is an important contributor of ED and this leads to altered blood flow.\textsuperscript{311} Arteriosclerosis is another important factor in the pathogenesis of diabetes.\textsuperscript{312} In clinically significant peripheral vascular disease, 50% are having impotence. Cigarette smoking, hypertension and hyperlipidemia are the contributing factors in ED. Validated sexual questionnaire such as International Index of Erectile Function (IIEF) may be a helpful tool in the evaluation of erectile dysfunction.\textsuperscript{313} The specialized test like nocturnal tumescence, biothesiometry, and penile vascular studies using duplex Doppler ultrasound, dynamic infusion cavernosometry, and cavernosography are useful. Oral erectogenic drugs like sildenafil citrate, yohimbine hydrochloride, phentolamine which is an alfa 1 and 2 adrenergic antagonist that decrease adrenergic tone will increase the erectile function. Apomorphine and vardanafil, is in clinical trial. Cialis is a new potent phosphodiesterase inhibitor which shows statically significant improvement in ED\textsuperscript{314} Protein C inhibitors are currently under trial. Topical application of topiglan 1% which contain 1% Alprostadil in a formulation with 5% soft enhancer for percutaneous absorption is useful. Vacuum constrictive devices,
intracavernosal self injections, surgical prosthesis,\(^{315}\) and venous surgeries are used in the management of erectile dysfunction.\(^{316}\)

**Infections in diabetes mellitus:** Diabetes mellitus is a condition with primary immunodeficiency. In type I diabetes there is alteration of some lymphocytes subpopulation and reduction in the CD4/CD8 ratio. The most frequent site of infections is skin, urinary tract and respiratory tract.\(^{317}\) The macrophagic action and ability to kill staphylococci is impaired if blood sugar is more than 200mg%.\(^{318}\) Infection due to Klebsiella, Pseudomonas, Citrobacter, E.coli, Proteus are common. Emphysematous pyelonephritis, perinephric abscess, fungal infections like Candida may be a presenting feature. Fungal infections like Candida are very common and genital candidiasis may be the presenting manifestation of diabetes. Other fungal infections like histoplasmosis, dermatophytes, mucormycosis, aspergillosis pneumonia and coccidiomycosis, are seen more often in diabetic ketoacidosis. Patients with diabetes have more morbidity and prolonged hospital stay when compared to non diabetic.\(^{319}\) Paronychia, scalp infection, seborrheic dermatitis, dental infections like peridentitis, cellulitis, occur in varying dimensions. Malignant external otitis media occurs in uncontrolled diabetes and this is due to pseudomonas. Tuberculosis is common in diabetic and diabetic have 11 times higher chance for developing tuberculosis.

**Dermatological manifestations:** Wide varieties of cutaneous manifestations are noticed in diabetic patients. The frequency of cutaneous manifestations ranges from 30% to 70%.\(^{320}\) Candidial infection of mucosal membrane and genitalia are more in diabetic. 9.6% patients have evidence of candidial paronychia. Dish washing, and other occupations which lead to constant contact with water predispose paronychia.\(^{321}\) Candidial vulvovaginitis is increasingly noticed, and is characterized by itching, erythema of vulva, pustules and fissures. Severity of pruritis is related to glycosuria and hyperglycemia.\(^{322}\) In many patients who present with candidial balanitis, it may the early indication of diabetes.\(^{323}\) Phycomyces infections due to rhizopus, and

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Mucor can occur. Onychomycosis, Paronychia, and Tinea pedis also commonly noticed. Erythrasma is common in obese diabetic patients.

Necrobiosis lipoidica diabeticorum is rare disease most commonly associated with diabetes mellitus and this was described as early as 1929 by Utz et al. These are ovoid plaque with a violaceous indurated periphery and yellow central atrophic area, and there may be telangiectasia and scattered hyperkeratotic plugs over the skin. Granuloma annulare are common in diabetes and in 50%-only a single lesion noticed. Diabetic patients may have other dermatological manifestations like scleroderma diabeticorum. Ichthyosis is another skin disease noticed among diabetic patients and the prevalence is 48%. 10% of diabetics have yellow skin. Xanthelasma is common in middle aged diabetic woman. This usually does not disappear when diabetes is controlled. Vitiligo, generalized pruritis and perforating skin disease are common in diabetics.

Rheumatologic disorders in diabetes: Various musculoskeletal complaints are noticed in diabetes mellitus and some of them may be very debilitating. Adhesive capsulitis of shoulder is a common problem in diabetes and this is noticed in 11% with diabetes mellitus. Adhesive capsulitis has a familial predisposition and characterized by severe pain disproportionate to physical finding. Holt et. al noticed higher prevalence of Rheumatological manifestations in diabetes. Diabetic hand syndrome, also termed as stiff man syndrome was first described by Gregic. The overall prevalence of diabetic hand syndrome (DHS) is 35%. This disease is a newly described entity characterized by stiffness of small joints of hand and other sites, and is an indication for diabetic microvascular disease.

Dupytrens contracture is seen in 25% of long standing diabetic patients, and this mainly affects the middle and little finger in contrast to non diabetes patients. There is increase in muscle mass and tendon nodules. Trigger finger is associated with nodular swelling within the flexor sheath, and is
associated with stenosing flexor tenosynovitis. Sudek's dystrophy occurs in
around 7% diabetic patient. It is associated with causalgia, segmental pain, or
hypersensitivity in one or more joints. Carpel tunnel syndrome is commonly
seen in diabetic patients. There is a close association with HLA A1, DR3 and
DR4 in rheumatoid arthritis and diabetes mellitus. Scleroderma,
dermatomyositis, poliomyelitis, amyloid arthropathy and septic arthritis are more
common in diabetes. Gout and hyperuricaemia are other common conditions
noticed in diabetics.

Gastrointestinal complications
The gastrointestinal complications may result due to hormonal abnormality or
due to diabetic neuropathy. Acute abdominal pain and vomiting are the
earliest manifestation of diabetic ketoacidosis. Pharyngeal and esophageal
dysmotility is common in diabetes. Reflux oesophagitis and candidial infection
of oesophagus are common. Diabetic gastroparesis is found in 50% patient with
type 1 diabetes and in 30% of patient with type 2 diabetes. Colonic motility is
also decreased in severe diabetes mellitus. The delayed whole gut transit is
decreased by 26% in diabetics. Hepatic steatosis is accumulation of fat in the
liver and is common in diabetes. Though the incidence of fatty liver is less in
type 1 diabetes the incidence is common in type T2DM.

Diabetic Keto Acidosis (DKA): Diabetic ketoacidosis is diagnosed when the
blood sugar more than 200mg/dl, ketosis and academia (PH less than 7.3) are
present. Insulin resistance is a contributing factor in the development of
ketosis in T2DM. Hyperglycemia occurs due to gluconeogenesis or
glycogenolysis and decreased peripheral utilization of glucose. When the
glucose level is high it can lead to osmotic diuresis, dehydration, and ultimately
hypotension. DKA may be the presenting feature in 20% of the newly
diagnosed cases. The most important precipitating factor is infection. Urinary
tract and lung infections are most common infections which precipitate ketosis.
Cerebrovascular accidents, myocardial infarction, pancreatitis, alcohol abuse
and pregnancy can also precipitate DKA. On examination patients are usually
dehydrated and there is evidence of Kussmanal's respiration. There is decreased skin turgor. Increased pulse and blood pressure changes also occur. 25% patients complaint of vomiting at the time of presentation. Diffused pain abdomen may be an early presentation. Treatment mainly aims fluid replacement and maintanace of normal osmolality. IV fluids and insulin is mainstay of treatment. Most patients with DKA will develop hypokalemia during treatment and this has to be corrected. The benefit of bicarbonate therapy in DKA is not yet proved.345

HHS (Hyperosmolar hyperglycemic syndrome): This condition represents the other spectrum of metabolic derangements. HHS is characterized by severe hyperglycemia and hyperosmolality. HHS also leads to osmotic diuresis and dehydration. In the management of Hyperosmolar non ketotic diabetic coma, the fluid therapy is the mainstay of treatment.

Hypoglycemia: Hypoglycemia is a common complication noticed in diabetes patient. Glucose concentration in the venous plasma obtained after overnight fasting below 60mg /dl is considered hypoglycemia. The diagnosis of hypoglycemia based on Wippines triad is most convincing. It includes symptoms of hypoglycemia, decreased blood glucose level, and relief of symptoms when exogenous glucose is given.346 Insulin over dose commonly causes hypoglycemia in diabetes. The major symptoms and sign result from neuronal deprivation of glucose. Hypoglycemia may be fasting or reactive. Reactive hypoglycemia occurs in a post prandial state and not during fasting and may not imply a serious disorder. Blood glucose level may be normal in reactive hypoglycemia.347 Hypoglyceminc unawareness can occur in those who take drugs like can betablockers, dysopiramide and albuterol and Pentamidine, Biguanides.348 Early detection and treatment is required in hypoglycemia. Beta blockers may induce hypoglyceminc unawareness in diabetic patients, and a direct hypoglycemic effect of beta blocker is not proved.349 Sweating is an important early symptom of hypoglycemia and is mediated by cholinergic routes and should be watched in all diabetic patients.350 Hypoglycemia should be
corrected immediately, using intravenous glucose at a dose needed to normalize blood sugar level. At times it may need high dose of glucose.

MANAGEMENT OF DIABETES MELLITUS

All the major studies of diabetes mellitus like the UKPDS, Kumamoto trials DCCT and recent follow up of these studies concluded that tight glycemic control is most important in the prevention of diabetic complications. The changes in life style and obesity contribute very much in the development of diabetes. The prevalence of diabetes in a community will also influence the management option of diabetes. Socio economic status, availability of insurance coverage, regional, religious and cultural back ground should be considered before setting a management goal in such patient. The treatment should be individualized, and treatments of geriatric patients need special consideration. Recent follow up of Kumamoto trial showed glycosylated hemoglobin level of less than 6.5%, and fasting glucose level of 110 mg% and post prandial blood sugar of less than 180 mg/dl as the optimal levels to prevent complications. A good glycemic control in the prevention of diabetic complications was supported by studies like Scandinavian Simvastatin Survival Study (4S) and Cholesterol And Recurrent Events trial. The HOT study i.e. Hypertension Optimal Treatment HOPE. Studies also stressed the importance of tight glycemic control. The minimum laboratory tests required in a diabetic patient are complete urine analysis, determination of blood glucose level, and HbA1c. It is beneficial to include measurement of lipid profile, liver and kidney function, and electrolyte level and complete blood count. Lipid profile analysis is important to assess the cardiovascular risk. The physician, dietician, diabetic educator, exercise physiologist, social worker and psychologist should be part of the diabetic management team. This integrated team approach will be the most useful in the management of diabetes mellitus.
Primary prevention of Type 2 Diabetes and economics of diabetic treatment: DM is the most important metabolic cause of disability in the world. With an anticipated diabetic population of 366 million by 2030, it is imperative to meticulously plan the treatment strategies for diabetes mellitus.\textsuperscript{360} Primary prevention with the use of life style modification and metformin intervention was studied in the Diabetes Prevention Programe.\textsuperscript{361} The cost of treatment of diabetes is very high, and according to Cost of Diabetes in India study (CODI), the mean cost is estimated at Rupees 16,831.\textsuperscript{362} The primary prevention involves early screening of diabetes and Indian Diabetic Risk Score (IDRS) help in selective screening of patients.\textsuperscript{363} Age, abdominal obesity and family history of diabetes and leisure time physical activity were used in primary screening. Exercise was studied in the Da Qing IGT and Diabetic study, and there is an overall 38% reduction when both are combined.\textsuperscript{364} In the Finnish study after 3.2 year follow up of diabetes patients showed that lifestyle modification reduced type 2 diabetes by 50%. In the Indian diabetic prevention programme, life style changes and metformin were combined and overall reduction of 28.2% was observed.\textsuperscript{365}

Education in the management of diabetes: The world Health Organization declared in 1980 that education is the corner stone of diabetic management, and vital to the integration of diabetic society.\textsuperscript{366} Now several organized programmes impart diabetic education. The American Diabetic Association, the American Association of Diabetic Educators, and National Certification Board on Diabetic Education are major participants in this area of education among diabetes.\textsuperscript{367} National and regional diabetic associations also have a major role to play. A study at USA showed that 60% of diabetic patient did not receive any diabetic education.\textsuperscript{368} Lack of education is the frequent cause of treatment relapse.\textsuperscript{369}

Patient compliance is the most important aspect of success in diabetic management. Miller and Goldstein had shown better out come in the diabetic management if patients are well educated.\textsuperscript{370} There should be a good rapport
with patient and the treating physician. WHO recommended the Therapeutic
Patient Education (TPE), in first place in the management of diabetes mellitus
patients. TPE is a systematic patient oriented learning process and involves
understanding the patient, communication with patient on all aspect, but care
has to be taken not to overwhelm patient with surfeit information, Dietary
instructions have the most important effect on diabetes. Self management of
insulin helps in preventing complications in diabetes. Diabetic education will
also decrease the cost of treatment. Scott et al from New Zealand pointed out
that hospital admission was less in-those who got education regarding diabetes
self care and management. The diabetic education programme should focus
on their understanding of the disease, attitudes, and practice related to
wellbeing of diabetes and this should help them to have a better self
management. Eliot Joslin's remark that patient is his own nurse, doctor's
assistant and chemist is most appropriate when considering the issue of
diabetic management. In the American Diabetic Association's guideline, the
National standard for diabetes self management education is very useful tool in
planning a diabetic education. Several meta analysis showed that diabetic
education improve metabolic and psychological out come. Factors like
patients' family, social and cultural environment, socioeconomic status, and
other health problems and overall physiological and emotional wellbeing should
be considered when planning a proper diabetic education.

Special issues in the management of elderly patients: Nearly 10 to 25% of
erly patients are diabetic. In the Caucasian population nearly 6 to 8%
diabetics are over 60 years of age. 13.4% elderly above the age group of 60
years in India are diabetic according to studies by Ramachandran et. al from
diabetes research centre and MV hospital. The increased life expectancy leads
to increase in the number of older diabetic patients. Co morbidity like
hypertension, other cardiovascular diseases, multiple chronic diseases, other
geriatric syndromes like cognitive impairment, depression, urinary incontinence
in elderly need special focus and consideration. Older diabetics are more
susceptible to micro and macro vascular complication. The incidence of stroke

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is more among elderly diabetics due to poor glycemic control. Study from Birmingham UK reported a 22% admission with DKA aged more than 60 years. Long hospital stay, high mortality, psychological problems risks of dementia and hypoglycemia are reported more often in the elderly. Cognitive impairment, also add to the problems in elderly diabetic. The drug treatment of elderly should also need frequent monitoring, since hypoglycemia, and adverse effect due to drugs are common in the elderly.

**Medical nutrition therapy:** In 1900 Dr Fredric M Allen in US developed a starvation diet to control diabetes and he prolonged the life of many patients before the discovery of insulin. The term diabesity is often used to stress the importance of obesity in diabetes. Lipid containing diet and weight gain will lead to insulin resistance. Weight reduction will help in the control of diabetes. Paisey B et al, in a five year long follow up study concluded that calorie restriction and intense physical activity is beneficial in the control of diabetes and is independent of the effects of weight loss. Modest weight loss of 5 to 10% will improve glycemic control. The need for individualization of diabetic diet was accepted after the US dietary guidelines in 2000. The importance of diet and exercise was emphasized by UKPDS and DCCT team. The more recent randomized clinical trial, the Diabetes Prevention Programme (DPP) also focused on diet and exercise and this study started in 1996. 3,234 people were recruited, and it concluded that lifestyle modification reduced the risk of getting diabetes in 58%. The concept of Glycemic index suggested by Jenkin is important in the calculation of diabetic diet. Glycemic index is the post prandial response to a particular food in comparison to a standard amount of glucose. A low glycemic index food like vegetables, fruits, and legume and a moderate amount of protein and unsaturated fatty and fewer refined carbohydrate foods are preferred in diabetics.

Ideally 30% to the total calorie intake should be from protein. Fish, tuna, sardine chicken, and other poultry are preferred over red meat. 30% calorie may be obtained from fat, and poly unsaturated fat is preferred. The diabetic diet should
contain adequate fiber and 20 to 35 gm/day is recommended. Current recommendations of the American Diabetes Association include a trial of diet and exercise as first-line therapy for the treatment of patients with type 2 diabetes. Exercise: As early as 600BC Susrtutha advocated exercise for the control of diabetes mellitus. Charaka in his Charaksamhitha also gave importance to exercise in the treatment of diabetes. Now it is confirmed that exercise have a major role in the control of hyperglycemia and hyperlipidemia. Exercise improves insulin sensitivity and help to reduce hyperglycemia and decrease body weight in obese patient. Exercise also help in utilizing oxygen and help in fluid balance. Skeletal muscle takes up glucose through GLUT 4 glucose transport proteins. Highly trained athletes have better beta cell activity in pancreas. Those above the age of 35 should be given an exercise testing before prescribing any exercise regimen and underlying coronary heart disease to be excluded. When used in combination with dietary changes, it helps to preserve the lean body mass and may promote beneficial redistribution of body fat. Regular exercise also improves the lipid abnormality, and help in the weight management. Exercise increases the insulin sensitivity and is most beneficial in type 2 diabetic and IGT. As pointed out earlier, the blood glucose level is maintained by the production of glucose in the liver and uptake of glucose by body tissue. Carbohydrate metabolism increase significantly with onset of exercise and glycogen break down increases. Multiple studies confirmed that exercise has protective effect against development of diabetes. The benefits of exercise in diabetic disappear within days of stopping exercise. Aerobic exercises are preferred and should be continuous for 30 minutes. The beneficial effect is more, if exercise is done at least 3 days per week. Walking, swimming, cycling, and jogging are better exercises than isometric exercises.

Yoga and meditation: Previously confined to some Yogis and traditional health providers, the subject and technique of Yoga is now subject to extensive
scientific evaluation. Its beneficial effect is being accepted by the modern medical profession and is incorporating in the health management. It is a time tested way of prevention of many diseases. Yoga is the great contribution of Indian culture to the world. Many psychosomatic disorders and metabolic diseases benefited by programmed Yogic exercise. The best way of preventing Type 2 diabetes is proper maintainance of weight. Present day yoga is made simpler by practioners when compared to the yoga advocated by Patanjali Maharshi. Limited studies documented the efficacy of Yoga in the control of diabetes, and found that regular yoga practice will lead to better glycemic control. Yogasana involve complete coordination of body, mind, and intellect. It reduces the requirement of OHA and Insulin. Certain Asana like Soorya Namaskara is found to be useful in the control of diabetes. Yoga decrease body mass index and increase insulin receptors. An integrated yoga practice will uplift a person physically, mentally, socially and spiritually. Raju et.al, noticed that normal healthy volunteers showed a significant decrease in the oxygen consumption and blood lactate level after 90 days of pranayama and yoga training. When compared to physical training exercise, the Yoga improved physical tolerance without increasing oxygen demand. To conclude, Yoga is more commonly accepted by patients and physician for its beneficial effect on the control of diabetes Mellitus.

Oral Hypoglycemic Agents (OHA)

Modification of diet and life style is the mainstay of diabetic management but it alone will not produce adequate control of diabetes. Four to twelve weeks trial with diet and life style is to be attempted in control of the blood sugar before initiating pharmacological treatment. The major categories of oral anti hyperglycemic agents include drugs which increase the insulin secretion called secretagogue, and those which reduce the insulin resistance, and those modify the insulin entry in to the cell by impairing absorption.
Sufonyl urea (SU): Sufonyl ureas are the major group of antidiabetic agents used in the treatment of T2DM. This compound was introduced in 1930 and commonly used hypoglycemic agents since 1950s. The older first generation agents like Chlorpropamide and Tolbutamide are superseded by the second generation agents like glipizid, glimipiride and still newer agents are being introduced. The outcome of University Group Diabetes Programme study (UGDP) initially questioned the efficacy of Sulfonyl Urea. Oral hypoglycemic agents like sulfonyl urea are the most commonly used drugs for the treatment of type 2 diabetes. Drugs like Glibenclamide, Glipizid, and glimipiride are the common agents used in the treatment. Sufonyl ureas usually act by activating the K⁺-ATP channels. Sufonyl Urea (SU) is having an insulinomimetic action. Sufonyl urea does not synthesis insulin and infact higher doses of sulfonylurea are less effective than modest doses. In the skeletal muscle it stimulates glucose uptake. SU stabilizes the GLUT-1 protein in the plasma membrane and leads to increased glycogen synthesis. The site of action of the SU may be related to GLUT-4. It was found that Glycazid inhibits increased adhesiveness of monocytes to endothelial cells and reduces the production of TNFα by endothelium in diabetics. It also reduces the oxidative stress and Glycazide has a free radical scavenging property due to the amino azabicyclo octane ring. SU can retard atherosclerosis in diabetics and it also improve the acetyl choline induced endothelium dependent relaxation of blood vessel dysfunction. Glibenclamide (glyburide) is commonly used in the treatment of type 2 diabetes, but its side effect profile is high and its effectiveness wears off after one or two year on starting the treatment. Glimipiride produces rapid and short duration of insulin secretion than Glibenclamide. It is administered as a once daily dose of 1-8mg. It is absorbed rapidly and maximum blood glucose lowering action is noticed in 2 to 3 hours. Hypoglycemia is less than Glibenclamide. Repaglinide: is a non sulfonyl urea insulin secretagogue belonging to Meglitinide family. It binds the SUR-1 subunit that is distinct from the sulfonyl urea binding site but causes closure of K⁺ATP channel. It is rapidly absorbed and insulin releasing actions occur in 30 mts. 0.4 to 4mg per day is the usual recommended dose. Nateglinide: Is a
derivative of phenyl alanine. It does not contain sulfa moiety and binds to SUR-1 subunit. It binds the same binding site on SUR1 subunit as Glibenclamide.\textsuperscript{421} Nateglinide has the highest efficiency in improving the timing of early meal mediated insulin secretion.\textsuperscript{422} The maximum recommended dose of Nateglinide is 60-120mgm given 10 mts before meal. Hypoglycemia, allergic manifestations, oral ulcers, Stevens Johnson syndrome, Leucopenia, agranulocytosis, thrombocytopenia, hemolytic anemia and aplastic anemia are also reported with SU.\textsuperscript{423} Glibenclamide may block the opening KATP channels and may prevent the ischemic preconditioning.\textsuperscript{424}

**Insulin sensitizers**

Type 2 diabetic patient have insulin resistance in addition to decreased insulin secretion. Hence overcoming the insulin resistance will improve the hyperglycemia. Now biguanides and Thiozolindinediones are two classes of drugs useful in the treatment of diabetes. Biguanides: Metformin, Phenformin and Buformin, are the common Biguanides. Biguanides, Phenormin and Buformin are not used now days due to increased incidence of lactic acidosis and are only of historical importance. Phenformin is not currently used, and was withdrawn due to lactic acidosis.\textsuperscript{425}

**Metformin:** Guanidine was the active ingredient of French lilac (gallega officianalis) which was used in Europe for several centuries as a hypoglycemic agent. Metformin is the commonly used Biguanide. In conjunction with diet, metformin reduces fasting glucose concentration by 2.78 to 3.90 mmol/L (50 to 70 mg/dl), which corresponds to a, 1.3% to 2.0% reduction in HbA\textsubscript{1c} values.\textsuperscript{426} The efficacy of metformin monotherapy has been shown to be independent of age, body weight, ethnicity, duration of diabetes, and insulin and C-peptide levels.\textsuperscript{427} They increase the peripheral glucose utilization and enhance aerobic glycolysis and these two mechanisms cause reduction in blood sugar level and increase insulin-stimulated glucose uptake in skeletal muscle and adipocytes.\textsuperscript{428} The Biguanides competitively and specifically bind to a divalent cation sites on proteins and may interfere with calcium efflux in mitochondria.\textsuperscript{429} In the skeletal
muscles. Metformin facilitates glucose transport by increasing tyrosine kinase activity in insulin receptors\(^4\) and also activates tyrosine kinase activity in insulin-like growth factor-1 receptor of vascular smooth muscles.\(^5\) Increased fatty acid oxidation inhibits key enzymes of the glycolysis pathway by accumulation of acetyl coenzyme A, citrate, and lactic acidosis.\(^6\) Metformin also improves hyperglycemia by decreasing intestinal absorption of glucose. This may cause decreased postprandial blood sugar.\(^7\) Repaglinide plus metformin is superior and this will avoid the need to switch to insulin therapy.\(^8\) Metformin given in a dose of 500 to 2000 mg as twice or thrice a day along with food to minimize the gastrointestinal side effect. The side effects are bitter metallic taste, anorexia, nausea, and abdominal discomfort and lactic acidosis and allergic reaction.

**Thiazolidinediones (TZD):** Glitazones are a class of oral insulin sensitizers. These were discovered in early 1970s and were introduced in 1997. The common drugs now used are Rosiglitazone and Pioglitazone. Other members of the group are Ciglitazone and Englitazone. Thiazolidinediones are orally active drugs, and they activate the nuclear Peroxosome Proliferators Activated Receptors-\(\gamma\) which modify the insulin dependent glucose transporter.\(^9\) TZD increases fatty acid uptake, thus lowering triglyceride and fatty acid levels and leading to adipocytes differentiation. It also increases the peripheral glucose utilization.\(^10\) The major side effects are anemia, weight gain, and may precipitate cardiac failure. The usual dose of Rosiglitazone is 2-4 mgm twice a day or once a day and Pioglitazones given in the dose of 15-45 mgm once a day. Safety in children and in pregnancy is not fully assessed.

Pioglitazone belongs to the group of Thiazolidinediones. It has several biological actions. It is involved in fat redistribution through PPAR-\(\gamma\) receptors. Several studies indicated the efficiency of Pioglitazones in combination with other OHA.\(^11\) Pioglitazones alone or in combination with other drugs reduce the FBS\(^12\) Pioglitazone has anti-atherosclerotic properties.\(^13\) The usual dose is 15-30 mg daily. Peripheral edema and hepatotoxicity are common side effects.
Alpha glucosidase inhibitors

The drugs under this group delays postprandial carbohydrate absorption and lowers postprandial plasma glucose level. The three common alpha glucosidase inhibitors available are Acarbose, Voglibose and Miglitol. These drugs are given with each meal in a dose of 25mg for Acarbose and Miglitol and for Voglibose 0.2 to 0.3 mg twice daily is given. The major side effects are gastrointestinal symptoms like abdominal discomfort, flatus, and diarrhea.

Glitazars: Glitazars are novel agents used in the treatment of type 2 diabetes mellitus and stimulate insulin secretion. Glucagon like Peptides (GLP-1) is a gastrointestinal hormone which increase insulin secretion and prevent beta cell failure. GLP-1 analogue and replacement of GLP-1 have number of positive attributes in increasing insulin secretion and modulation of insulin sensitivity in peripheral tissues. Muraglitazar (MURA) is a novel PPAR-A agonist belonging to glitazars group. In a double blinded controlled study it is demonstrated that Muraglitazar 5mg daily was found to be effective in diabetic control. Tesaglitazar - another dual PPAR alpha and gamma agonist is in phase III trials. Naveglitazar is a partial agonist of PPAR gamma and alpha that is under trial. Pan PPAR agonist have both alpha and delta activity. This molecule titled as GSK 677954 is in phase II trial. Another molecule PLX 204 has completed several preclinical trials and is potent Pan PPAR agonists. The reduction in HbA1c level with this agent is more than 50% when compared to placebo.

Incretins

Incretins are hormones produced in the gastrointestinal tract in response to food which stimulate secretion of insulin. Glucagon like peptide-1 also have similar property like that of incretin. These also enhance the glucose dependent insulin secretion and several other glucoregulatory actions of incretin. Exenatide, Vildagliptin, Sildagliptin, Liraglutide Dipetidyl peptidase-
Amylin analogue, Pramlintide, are other drugs available now for the treatment of type 2 diabetes mellitus.

**Insulin**

Discovery of Insulin by Banting and Best in 1921 was a landmark event in the history of medicine. The first person to receive Insulin injection was Leonard Thompson at Toronto general hospital. Pancreatic islet cells stores 200 units of insulin, and releases 50 unit (2mg) per day. The maximum release of insulin occurs when the blood sugar is around 300-350. This is more so with intravenous administration of glucose. The failure of this early response of insulin release is the important physiological abnormality in diabetes mellitus. Insulin action is influenced by various conditions like cellular integrity, which lead to insulin resistance (IR). The causes of insulin resistance may have genetic predisposition due to a mutation in the insulin receptor. Different type of insulin based on their action are now available. Most commonly used one is the short acting or regular Insulin. The peak effect is noticed around 2 to 4 hours after injection. This should be administered 30 to 45 mts before meals. NPH with zinc have a longer duration of action around 13 to 16 hours. Human insulin made by recombinant technology was available now. The DNA recombinant technology made it possible to produce synthetic human insulin from E coli, and the first human insulin was tested in 1980. Rapid acting meal time insulin like Lispro or Aspartate are now available. Lispro acts within 15min and reaches peak action in one hour. Incidence of hypoglycemia is less with Lispro. Lispro is the preferred insulin before each meal and also used in pump therapy. Insulin Aspartate is similar to Lispro and is rapidly absorbed, and frequency of hypoglycemia is less. This is preferred when multiple injections are needed. Insulin glargine (Lantus) is long acting biosynthetic human insulin. Insulin glargine has high isoelectric point and hence has a longer action when compared to human insulin. Insulin glargine should not be mixed with other insulin. Insulin detemir is long acting insulin, and an intensive insulin therapy showed 64% reduction in the development of neuropathy. Insulin in type 2 diabetic patient is indicated when adequate
hypoglycemia is not achieved with initial diet, exercise and OHA therapy. UKPDS data showed 12% reduction in diabetes related endpoints and 25% risk reduction in microvascular complications. The DIGAMI (The Diabetes mellitus Insulin Glucose infusion in Acute Myocardial Infarction) trial showed that intensive insulin therapy following MI decrease mortality. Continuous Subcutaneous Insulin Infusion (CSII) is also preferred for the management of T2DM. Addition of metformin and insulin will have better control of diabetes than increasing the dose of insulin. Insulin sensitzers like TZD can be combined with insulin and found to have better result in glycemic control.

**Newer delivery systems**

In addition to the traditional delivery system, pen devices are available now. Other method of delivery is subcutaneous insulin infusion. This was available since 1980s. A pre programmed basal insulin delivery is possible in CSII. Cost of equipment is the limiting factor for its wide use. Storage, mixing of insulin, injection techniques and monitoring of blood glucose are important in optimizing the effect of insulin therapy. Hypoglycemia, weight gain, atherosclerosis, lipoatrophy or hypertrophies are common side effects of insulin therapy. Oral Insulin is not available now, and technique for prevention of degradation of insulin in the intestine are being developed. Rectal insulin administration is investigated but poor bioavailability is major hindrance. Insulin spray (oralin spray), AERx®IDMS system, and other devices like Techosphere and Inhale employ dry powder inhaler system, and the onset and duration of action is well comparable to other route administration. Inhaler insulin produced more respiratory complication and this limit its use as of now. Insulin pump is usually implanted under skin in the abdomen. Insulin delivery can be controlled with special communicators. The advantage of implantable pump is that it resembles the physiological delivery system. So it causes less hypoglycemia. Now sensor augmented pump systems are also available (Paradigm 522/722). These pumps will display real time glucose value. It will give retrospective values of previous 3 hour and 24 hour glucose data.
Pancreatic transplantation

As early as 1983, the concept of pancreatic replacement was being attempted by transplanting sheep pancreas in a 15 year old child in Bristol. But the procedure was more widely applied in the mid 1980. Sirolimus introduced to prevent rejection improved the survival of pancreatic transplants. Restoration of insulin secretion in diabetic by auto grafting of engineered cells offer good therapeutic response. In an experiment by Fujimoto and Takashi established new insulin secreting cells, that are retro virally transformed by recombinant human pro insulin cDNA (Ins/fur) whose processing site were designed as to be cleaved by prohormone convertase. This finding will pave way for genetic engineering technique to produce cells from stem cells which will provide sufficient insulin.

Stem cell research in diabetes mellitus

Stem cells have wider capacity for differentiation into different cells. Recently, there is much optimism that stem cell can be modified to develop new insulin secreting cells. This facultative or functional stem cells are capable of producing new cell line, and this can be properly stimulated to produce pancreatic duct cells or acinar cells. Another method is to create beta cell equivalent by adding gene or inhibiting the expression of existing gene.

THE FUTURE OF DIABETOLOGY

Medicine is the fastest changing branch of science. The diabetic research will be a thrust area for academicians and health providers. Advances in molecular cell biology made it theoretically possible to manipulate cell lines by genetic engineering to use for transplants or to produce unlimited supply of insulin. By adding gene, or inhibiting gene, and manipulating gene expression, human cell can be converted to beta cell equivalent. Converting normal cell line to produce and store insulin by this genetic manipulation is a well perceived concept. The possibility of making insulin directly from intermediate lobe of pituitary is other possibility in thought. Newer Immunosuppressant and
immunomodulators will facilitate more pancreatic transplantations. Gene transfer techniques will gain momentum in diabetology and pharmacology in the years to come. The information pouring from the human genome project and consequent revolution in the biotechnology and bioinformatics will boost our understanding and this will markedly influences management of diabetes. Some of our present thinking and technology will become obsolete. Newer input will throw new light in the etiology and pathogenesis of this common metabolic disease. Newer diagnostic techniques, introduction of newer drugs and delivery system, organ transplant, stem cell transplant, artificial components and the integration of information technology in the development of intergrated medical systems will change the face of modern medicine. So there will be better understanding, and intervention in the management of Diabetes mellitus and this will immensely help the outcome in the treatment and care of both type 1 and type 2 diabetes.