CHAPTER - II

REVIEW

OF

LITERATURE
HISTORICAL BACKGROUND

Diabetes mellitus has been described for more than 2000 years. For the past 2000 years, it has featured in the history of modern medicine yet; our knowledge of the nature of diabetes is still incomplete. This has very important implications for rational approach to basic and clinical research, management and prevention of diabetes mellitus, as it is now expanding as epidemic in many developing and newly industrialized nations. Some of the very important developments in diabetology have emerged through epidemiology and they may not have occurred without these studies. The rising prevalence and incidence of type-2 diabetes has stimulated research on the genetic, environmental, behavioral, socio-economical and cultural factors contributing to the epidemic.

BURDEN OF DIABETES: TREND AND FUTURE PROJECTIONS

The impact of world wide explosion of type-2 diabetes mellitus (which accounts for approximately 85 to 95% of all cases of diabetes) will remain centered in the developing countries, since by the year 2025, 75% of all the people with diabetes will be in the developing countries as compared with 62% in 1995- a majority in the Indian subcontinent (59%) and China (68%). By 2025, there will be a 42% increase from 51-72 million in the developed countries and 170% increase from 84-228 million, in the developing countries. India already faces a grave problem with the largest number of subjects with diabetes (approx 33 million in 2003) and it is expected to escalate further with the number increasing to 57.2 million in the year 2025 and by the year 2030 it may be 80.9 million. The prevalence estimate by
the International Diabetes Federation (IDF) reported the worldwide prevalence to be increasing from 5.1-6.3% (between 2003-2005).\(^{(5)}\)

**RISING PREVALENCE IN INDIAN SUBCONTINENT**

The epidemic of diabetes in India needs to be viewed within the larger demographic and socioeconomic context. India is the second most populous country and has diverse groups of people with respect to caste and religion, habitat, socioeconomic status, education level, lifestyles and food habits etc. Epidemiological studies in India on diabetes were taken up following several reports showing that type-2 diabetes among migrant Asian Indian populations in several countries was high compared with the host population and other migrant ethnic groups.\(^{(6,7)}\) Irrespective of the differences in anthropometry, dietary and socioeconomic factors and migratory patterns- the migrant Indians showed a higher prevalence of type-2 diabetes than Europeans.\(^{(8)}\) Changes in environmental factors are believed to unmask the increase ethnic propensity for diabetes.\(^{(9)}\) Unmasking of ethnic propensity gets highlighted in another epidemiological study from Mauritius, a multiethnic population, with 68% of Asian Indian origin and the remaining comprising of Chinese, African and Creoles population.\(^{(10)}\) The prevalence of type-2 diabetes was found to be 18% in Indian migrants, 17% in Creoles and 11% in Chinese. The rate of prevalence of type-2 diabetes in the migrant Indian population of Mauritius is similar to many of urban rates of prevalence of diabetes in the mainland. In contrast prevalence of diabetes is high among the Chinese migrants, who have low rates of diabetes in mainland China. A similar situation is also evident in the Chinese migrants in Singapore.
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There have been several studies from various parts of India, revealing a rising trend in the prevalence of type-2 diabetes in the urban population.\(^{11}\) A multicentric epidemiological study carried out by Indian Council of Medical research (ICMR) in the early seventies, reported the prevalence of diabetes to be 2.3 % in the urban and 1.5% in the rural areas.\(^{12}\) The World health Organization (WHO) criterion was not available then.

A series of studies from Chennai showed that the percentage of adult urban subjects affected had increased from 5.2% in 1984 to 8.2 % in 1989, 11.6% in 1995 and 13.9% in 2000\(^{13}\) which further increased to 14.3 % in 2004.\(^{14}\) A national Indian survey in 2000 showed that the prevalence of diabetes in urban India was 12.1% in subjects aged\(>\) 20 years. This study revealed that the prevalence of diabetes in southern parts was higher than the eastern and northern parts of India.\(^{15}\)

**RISK FACTORS FOR DIABETES**

**ACQUIRED RISK FACTORS**

1. Age
2. Family history of diabetes

**ENVIRONMENTAL RISK FACTORS**

1. Central obesity
2. Body mass index (BMI)
3. Insulin resistance
4. Physical inactivity and sedentary occupation
5. Urbanization
6. Gestational diabetes
7. Stress
GENETIC FACTORS

Indians have high genetic risk for diabetes. Racial predisposition is evident from the studies in migrant Indians.\(^{6-10}\) Asian migrant living in different countries, have high rates of glucose intolerance compared with inhabitants of other racial origin. Evidence for a genetic component comes from the increased concordance of diabetes in monozygotic twins, a high prevalence in the offsprings of diabetic parents and a high prevalence in certain ethnic groups. Type-2 diabetes is a polygenic disorder, with many candidate genes identified in different populations. Several novel genetic associations have been recently reported with diabetes in Indians. This could at least partly explain the high prevalence of diabetes in Indians.

CLASSIFICATION OF DIABETES MELLITUS

A major requirement for epidemiological and clinical research and for the clinical management of diabetes is an appropriate system of classification that provides a framework within which to identify and differentiate its various forms and stages. While there have been a number of sets of nomenclature and diagnostic criteria proposed for diabetes, no generally accepted systematic categorization existed until the National Diabetes Data Group (NDDG) classification system was published in 1979.\(^{16}\) The World Health Organization (WHO) Expert Committee on Diabetes in 1980, and later, the WHO study group on diabetes mellitus in 1985, endorsed the substantive recommendations of the NDDG.\(^{17}\) These groups divided the diabetes mellitus into five distinct types as follows:
WHO MODIFIED CLASSIFICATIONS (1985) OF DIABETES MELLITUS
AND ALLIED CATEGORIES OF GLUCOSE INTOLERANCE

A. CLINICAL CLASSES

I. DIABETES MELLITUS

(a) Insulin-Dependent Diabetes Mellitus

(b) Non-Insulin Dependent Diabetes Mellitus
   (i) Non-obese
   (ii) Obese

(c) Malnutrition related diabetes mellitus

(d) Gestational Diabetes Mellitus (GDM)

(e) Other types of Diabetes associated with certain conditions and syndrome

II. IMPAIRED GLUCOSE TOLERANCE:

(a) Non-obese

(b) Obese

(c) Associated with certain conditions or syndromes.

B. STATISTICAL RISK CLASSES (Normal glucose tolerance but substantially increased risk of developing diabetes):

I. Previous abnormality of glucose intolerance

II. Potential abnormality of glucose intolerance

The NDDG/WHO classification highlighted the heterogeneity of the diabetic syndrome. Such heterogeneity has had important implications not only for treatment of patients with diabetes but also for biomedical research. When the
classification was prepared, a definitive etiology had not been established for any of the diabetes subclasses, except for some of the "other types". Few susceptibility genes for diabetes had been discovered and an understanding of the immunological basis for most type-1 Diabetes was just beginning. It was subsequently anticipated that as knowledge diabetes continued to develop, the classification would need revision.

The current Expert Committee(18) on the diagnosis and classification of diabetes mellitus has proposed changes to the NDDG/WHO classification scheme after carefully considering the data and rationale accepted in WHO classification and research findings of the last 18 years. According to the Expert Committee, the new classification of diabetes mellitus is given below:

**ETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS**

I. **Type-1 diabetes** (β-cell destruction, usually leading to absolute insulin deficiency)
   a. Immune-mediated
   b. Idiopathic

II. **Type-2 diabetes** (May range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretary defects with insulin resistance)

III. **Other Specific Types of Diabetes**:
   a. Genetic defects of β cell function, characterized by mutations in:
      (i) Hepatocyte Nuclear Transcription Factor (HNF) 4 α (MODY-1)
      (ii) Glucokinase (MODY-2)
      (iii) HNF-1 α (MODY-3)
(iv) Insulin Promoter Factor (IPF) - 1 (MODY-4)
(v) HNF-1ß (MODY-5)
(vi) Mitochondrial DNA
(vii) Pro-insulin or insulin conversion

b. Genetic Defects in Insulin Action:
   (i) Type - A Insulin resistance
   (ii) Leprechaunism, etc.

c. Diseases of the Exocrine Pancreas:
   (i) Pancreatitis
   (ii) Fibrocalculous Pancreatitis, etc.

d. Endocrinopathies
   (i) Acromegaly
   (ii) Cushing’s syndrome, etc.

e. Drug-or chemical induced
   (i) Vacor
   (ii) Pentamidine
   (iii) Glucocorticoids, etc.

f. Infections
   (i) Congenital Rubella
   (ii) Cytomegalovirus
   (iii) Coxsackie virus

(g. Uncommon forms of Immune mediated diabetes
   (i) “Stiff-man” syndrome
(ii) Anti-insulin receptor antibodies etc.

h. Other associated genetic syndromes
(i) Down’s syndrome
(ii) Klinefelter’s syndrome
(iii) Turner’s syndrome etc.

IV. Gestational Diabetes Mellitus (GDM)

I. Type-1 Diabetes Mellitus

(a) Immune-mediated: According to a title\textsuperscript{19} "Implications of the UKPDS" published in diabetes care January, 2001, this form of diabetes, account for only about 10% of total diabetes.

A study demonstrated that type-1 diabetes mellitus results from cell-mediated autoimmune destruction of the β-cells of the pancreas.\textsuperscript{20} Markers of the immune destruction of the β-cells include Islet Cell Auto antibodies (ICAs), Insulin Auto antibodies (IAAs), auto antibodies to Glutamic Acid Decarboxylase (GAD), etc. One and usually more of these auto antibodies are present in 85-90% of individuals when fasting hyperglycemia is initially detected.

Few other studies\textsuperscript{21,22} demonstrated that the disease has strong HLA - associations. Most individuals with type-1 DM have the HLA-DR\textsubscript{3} and/or HLA-DR\textsubscript{4} haplotype. However, the strongest association with type-1A DM has been shown with the DQA1 and DQB1 haplotypes. Although, this form of diabetes is clearly associated with certain predisposing genotypes, most individuals with these haplotypes do not develop diabetes.

It was found that most individuals with type-1 DM do not have a first degree
relative with this disorder.\textsuperscript{(23)}

Numerous environmental events like viruses, early exposure to bovine milk proteins and nitrosourea compounds trigger the autoimmune process in genetically susceptible individuals.\textsuperscript{(24)}

Immune mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in 8\textsuperscript{th} and 9\textsuperscript{th} decades of life. Many such individuals with this form eventually become dependent on insulin for survival and are at risk for ketoacidosis.

(b) \textit{Idiopathic diabetes:} Some forms of type-1 diabetes have no known etiologies. They are strongly inherited, lack immunological evidence for \(\beta\)-cell autoimmunity and are not HLA-associated. Individuals with this form suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency in-between episodes.

II Type-2 Diabetes Mellitus

This is the most common form of diabetes, accounting for about 90\% of all cases of diabetes.\textsuperscript{(19)}

This form of diabetes mellitus is characterized by chronic hyperglycemia resulting either form insulin resistance or, relative (rather than absolute) insulin deficiency or, both. At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive.\textsuperscript{(24-28)}

Although the specific etiologies are not known, autoimmune destruction of \(\beta\)-cells does not occur and patients do not have any of the other causes of diabetes listed above.

It was found in a study that most patients were obese and obesity itself causes
some degree of insulin resistance.\textsuperscript{(29)}

Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.\textsuperscript{(30)}

But ketoacidosis seldom occurs spontaneously in this form of diabetes; when seen; it usually arises in association with the stress of another illness such as infections.\textsuperscript{(31, 32)}

This form of diabetes frequently goes unnoticed for many years because the hyperglycemia develops gradually and at earlier stages, is often not severe enough for the patient to notice any of the classic symptoms of diabetes.\textsuperscript{(33-35)}

Nevertheless, such patients are at increased risk of developing micro vascular and macro vascular complications\textsuperscript{(36-39)} whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values, had their \(\beta\)-cell function been normal.\textsuperscript{(40)} Thus, insulin secretion is defective in these patients and insufficient to compensate for the insulin resistance.

However, insulin resistance may improve with weight reduction and/or pharmacological treatment at hyperglycemia, but is seldom restored to normal.\textsuperscript{(41-45)}

The risk of developing this form of diabetes increases with age, obesity and lack of physical activity.\textsuperscript{(34)}

**Genetic Consideration:** Type-2 diabetes mellitus has a strong genetic predisposition and is polygenic and multifactorial. Individuals with a parent with type-2 DM have an increased risk of diabetes; if both parents have type-2 diabetes mellitus, the risk in
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Offspring may reach 40%. Insulin resistance is present in many non-diabetic first degree relatives of type-2 DM.\(^{46,47}\)

**Pathophysiology:** Central to the development of type-2 DM is insulin resistance, impaired insulin secretion and excessive hepatic gluconeogenesis.

The precise molecular mechanism of insulin resistance in type-2 DM has yet to be elucidated. However, polymorphisms in various post receptor molecules, a phosphatidyl-inositol-3 Kinase signaling defect causing reduced translocation of GLUT-4 to the plasma membrane and elevated levels of free fatty acids may be contributed to the pathogenesis of insulin resistance.\(^{48,49}\)

The reasons for the decline in insulin secretory capacity in type-2 DM are not clear. However, Islet amyloid polypeptide or amylin co-secreted with Insulin by β-cells of pancreas likely forms the amyloid fibrillar deposit around β-cells and impairs secretion of insulin. Also, associated glucotoxicity and lipotoxicity worsen islet function.

Increased hepatic gluconeogenesis in type-2 DM results from insulin resistance, giving rise to failure of hyperinsulinemia to suppress gluconeogenesis; which results in fasting hyperglycemia and decreased glucose storage by the liver in the postprandial state.

**DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS**

According to World Health Organization (WHO) study group in 1985, Diabetes mellitus was diagnosed by either fasting plasma glucose (FPG) ≥ 140 mg/dl or, 2-hr. post load plasma glucose (2hPG) ≥ 200 mg/dl during a 75 gm. oral glucose tolerance test (OGTT).\(^{17}\)
In participants in the Second National Health and Nutrition Examination Survey (NHNES-II) only 23% of those with newly diagnosed diabetes by the 1985 WHO criteria had FPG≥ 140 mg/dl, whereas 97% had 2hr. PG ≥ 200 mg/dl.\(^{50}\)

Thus most people being tested for diabetes would not be diagnosed without on OGTT, a procedure not routinely performed in clinical practice unless diabetes is suspected.

In 1997, an International Expert Committee\(^{(18)}\) working under the sponsorship of the American Diabetes Association (ADA) reviewed the scientific literatures on classification and diagnosis of diabetes mellitus and published the criteria for diagnosis of diabetes. They were introduced to facilitate wider recognition of diabetes and to minimize the need for oral glucose tolerance testing to identify people with undiagnosed asymptomatic diabetes.

**CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS AS RECOMMENDED BY ADA**

(I) Symptoms of diabetes (Polyuria, Polydipsia and unexplained weight loss) Plus casual plasma glucose concentration ≥ 200 mg/dl.

Casual plasma glucose is defined as any time of the day without regard to time since last meal.

Or

(II) Fasting plasma glucose (FPG) ≥ 126 mg/dl.

Fasting is defined as no caloric intake for at least 8hrs.

Or
(III) 2hr. post load plasma glucose (2hr. PG) \( \geq 200 \) mg/dl during on OGTT.

The test should be performed as described by WHO\(^{(17)}\), using a glucose load containing the equivalent of 75 gm. anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia with acute metabolic decomposition, these criteria should be confirmed by repeat testing on a different day. The OGTT is not recommended for routine clinical use.

According the report of Expert Committee on diagnosis and classification of diabetes\(^{(20)}\), although the ADA recommendations do allow for diagnosis of type-2 Diabetes mellitus by OGTT (if the 2-h PG\( \geq 200 \) mg/dl) or, by high casual plasma glucose in the presence of symptoms, the ADA recommends using only the fasting level with the FPG criterion of \( \geq 126 \) mg/dl for determining the prevalence or incidence of diabetes.

The prevalence of undiagnosed diabetes by ADA criteria was lower than by the 1985 WHO criteria\(^{(51)}\), but implementation of the ADA recommendations in clinical practice and screening will likely result in a more complete discovery of people with undiagnosed diabetes and detection at an earlier stage.\(^{(18)}\)

A comparison was made of diabetic diagnostic categories in the U.S. population according to 1997 ADA and 1985 WHO diagnostic criteria.\(^{(52-54)}\) Yet there is concern that the diagnosis of diabetes by FPG alone using the ADA criteria will fail to identify people who would be diagnosed by glucose tolerance testing using the 1985 WHO criteria.

In 1999, the WHO made further recommendations regarding criteria for diagnosis of diabetes and other categories of impaired glucose regulation.\(^{(55)}\) They
incorporate the change in FPG diagnostic level to $\geq 126$ mg/dl, but retain the recommendation for OGTT and diagnosis of diabetes, if the 2hr. PG is $\geq 200$ mg/dl.

The Expert Committee recognizes also an intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered altogether normal. According to ADA recommendations 2007, this group is defined as follows:

A. The Categories of FPG values are:

- FPG $< 100$ mg/dl = normal fasting glucose

- FPG $\geq 100$ mg/dl but $< 126$ mg/dl = impaired fasting glucose (IFG)

- FPG $\geq 126$ mg/dl = provisional diagnosis of diabetes.

B. The corresponding categories when the OGTT is used are:

- 2h PG $< 140$ mg/dl = normal glucose tolerance.

- 2h PG $\geq 140$ mg/dl, but $< 200$ mg/dl. = impaired glucose tolerance (IGT)

- 2h PG $\geq 200$ mg/dl = provisional diagnosis of diabetes.

According to a study conducted by third National Health and Nutrition Examination Survey (NHANES-III) in USA population aged 40-74 years, the prevalence of diabetes in those without a medical history of diabetes was 4.35% by 1997 ADA criteria and 6.34% by WHO 1985 criteria. The total prevalence of diabetes (including those with a medical history) was 12.27% by 1997 ADA criteria, but 14.26% by 1985 WHO criteria.
Another study conducted in 5023 Pima Indians asymptomatic individuals aged \( \geq 15 \) yrs. and found that the prevalence of diabetes was 12.5% by 1997 ADA criteria, 14.6% by 1985 WHO criteria and 15.3% by 1999 WHO criteria. The prevalence of impaired glucose tolerance (IGT) was 15%, but that of impaired fasting glucose (IFG) was only 5%. However, the 5 year incidence of diabetes was 37% in IFG individuals, but 24% in IGT individuals.\(^{(56)}\)

The prevalence of impaired glucose tolerance (IGT) was 20.5% and that of NIDDM was 10.2%.\(^{(57)}\)

Only 36% of the subjects with IFG had IGT, whereas 38% of subjects with IGT did not have IFG.\(^{(58)}\)

The prevalence of type-2 diabetes in high risk individuals (most of them were relatives of type-2 diabetic patients) was 15.1%, that of IGT was 26.2% and that of IFG was 27.1%.\(^{(59)}\)

Subjects who had family history of diabetes had a significantly higher prevalence of abnormal glucose tolerance test. In subjects greater than 40 yrs. of age having a family history of diabetes, obesity, higher age (\( \geq 50 \) yrs.), female sex and urban origin have more chance (odds ratio : 4.65, 2.30, 1.87, 1.49 and 1.16 respectively) of developing abnormal glucose tolerance.\(^{(60)}\)

The criteria for diabetes described above are for diagnosis and are not treatment criteria or goals of therapy. No change is made in the American Diabetes Associations recommendations of FPG < 120 mg/dl and HbA\(_{1c}\) < 7% as treatment goals.\(^{(61)}\)

The new diagnostic cutpoint (FPG \( \geq 126 \) mg/dl) is based on the observation
that this degree of hyperglycemia usually reflects a serious metabolic abnormality that has been shown to be associated with serious complications.

Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG) and their clinical relevance

The terms IGT and IFG refer to a metabolic stage intermediate between normal glucose homeostasis and diabetes. A fasting plasma glucose concentration of 109 mg% has been chosen as the upper limit of "normal". Although, it is recognized that this choice is somewhat arbitrary, it is near this level above which acute phase insulin secretion is lost in response to intravenous administration of glucose.\(^{62}\)

‘Whitehall study’ showed that there is increased risk of coronary heart disease in subjects with impaired glucose tolerance.\(^{63}\)

The several folds increase in risk of visual impairment and retinopathy in subjects with IGT, IGT & newly diagnosed type-2 DM.\(^{64}\)

Thus IGT is associated with progressively greater risk of developing microvascular and macrovascular complications.

Many individuals with IGT are euglycemic in their daily lives and may have normal or near normal glycated hemoglobin levels.\(^{65,66}\) Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized oral glucose tolerance test (OGTT).

In the absence of pregnancy, IFG and IGT are not clinical entities in their own right, but rather risk factors for future diabetes and cardiovascular diseases. So, they can be observed as “Intermediate stages".\(^{63}\)

IFG and IGT are associated with the Insulin Resistance Syndrome (also
known as "Syndrome X" or, the metabolic syndrome) which consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (central or visceral), dyslipidemia of high triglyceride and/or Low-HDL type, hypertension, endothelial dysfunction and accelerated cardiovascular disease.\(^{67}\)

Insulin resistance is directly involved in the pathogenesis of type-2 DM. IFG and IGT appear as risk factors for this type of diabetes at least in part because of their correlation with insulin resistance.\(^{68}\) In contrast, the explanation for why IFG and IGT are also risk factors for cardiovascular disease is less clear. The insulin resistance syndrome includes well-recognised cardiovascular risk factors such as low-HDL levels and hypertension. In addition, it includes hypertriglyceridemia, which is highly correlated with small dense LDL and increased plasminogen activator inhibitor-1 levels. The former is thought to have enhanced atherogeneity and the later is a cardiovascular risk factor probably because it inhibits fibrinolysis. Thus the insulin resistance syndrome contains many features that increase cardiovascular risk. IFG and IGT may not in themselves be directly involved in the pathogenesis of cardiovascular disease, but rather may serve as statistical risk factors by association, because they correlate with those elements of the insulin resistance syndrome that are cardiovascular risk factors.

**DIABETES MELLITUS AND INSULIN RESISTANCE**

Insulin resistance means an impaired biological response to insulin of one or more of its target tissues, with a consequent reduced glucose disposal in response to insulin. This resistance is relative, since supernormal levels of circulating insulin will
normalize the plasma glucose. Insulin resistance is a prominent feature of type-2 diabetes mellitus.\(^{(199)}\)

Insulin dose-response curves exhibit a rightward shift, indicating reduced sensitivity, and a reduced maximal response indicating an overall decrease in maximum glucose utilization. Decreased peripheral glucose usage results in postprandial hyperglycemia.

**Impaired Insulin Secretion**

In type-2 diabetes mellitus, insulin secretion initially increases in response to insulin resistance in order to maintain normal glucose tolerance. Initially the insulin secretory defect is mild and selectively involves glucose-stimulated insulin secretion; eventually progressing to a state of grossly inadequate insulin secretion. This islet dysfunction may be due to:

- Amyloid fibrillar deposit found in islets of individuals with long standing type-2 DM
- Chronic hyperglycemia ("glucose toxicity")
- Elevation of free fatty acid levels ("lipotoxicity")

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<tr>
<th>Fat cells</th>
<th>Resistant to insulin</th>
<th>Antilipolytic effect</th>
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<tr>
<td>LIPO</td>
<td>↑FFA</td>
<td>Produce inflammatory cytokines</td>
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<td>TOXI</td>
<td>Neoglucogenesis</td>
<td>↑hepatic/muscle IR</td>
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<td>CITY</td>
<td>impaired insulin secretion</td>
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Increased Hepatic Glucose Production

In type-2 DM, insulin resistance in the liver arises from the failure of hyperinsulinemia to suppress gluconeogenesis, which results in fasting hyperglycemia and decreased glucose storage by the liver in the post prandial state.

CAUSES OF INSULIN RESISTANCE

- Genetic Defects
- Gender
- Exercise
- Adiposity
- Hyperglycemia
- Immune Mediated

POSTULATED MOLECULAR MECHANISMS OF INSULIN RESISTANCE

(1) After the receptor next event in insulin signaling is tyrosine phosphorylation of the insulin receptor substrates 1 and 2 (IRS-1 and IRS-2). Studies have demonstrated that cytokine TNF-α, can cause a serine phosphorylation of IRS-1 which reduces its signaling capability and also impairs the signaling function (tyrosine phosphorylation) of the insulin receptor \(^{(200-202)}\). TNF-α could be partly responsible for the insulin resistance of obesity. However, immunoneutralisation of TNF-α in humans did not improve insulin sensitivity\(^{(203)}\), so TNF-α seems unlikely to be a major force in obesity-
induced insulin resistance.

(2) Genetic “knockout” of IRS-2\textsuperscript{(204)} causes a syndrome of non-insulin dependent diabetes where there is both insulin resistance and impaired insulin secretion (with reduced β cell mass).

(3) Despite unequivocal evidence of the ability of amylin to cause insulin resistance in muscle, and evidence that an amylin blocker (amylin 8-37) can improve insulin sensitivity in animals in conjunction with changes in fatty acid metabolism\textsuperscript{(205)}, the issue is still unresolved. There has been doubt about whether its circulating levels in the diabetic or prediabetic state are sufficient to contribute significantly to insulin resistance.

(4) A current focus for the pathogenesis of insulin resistance focuses on a PI-3 kinase signalling defect, which causes reduced translocation of GLUT-4 to the plasma membrane, among other abnormalities.
Fig. 1: Insulin signal transduction pathway. The insulin receptor has intrinsic tyrosine kinase activity and interacts with insulin receptor substrates (IRS and Shc) proteins. A number of "docking" proteins bind to these cellular proteins and initiate the metabolic actions of insulin. [GrB-2, SOS, SHP-2, p65, p110, and phosphoinositol phosphate 3-kinase (PI 3-Kinase)]. Insulin increase glucose transport through PI3-kinase, which promotes the translocation of intracellular vesicles containing GLUT4 glucose transporter to the plasma membrane. (47, 49)

(5) Another emerging theory proposes that elevated levels of free fatty acids, a common feature of obesity (206), may contribute to the pathogenesis of type-2 diabetes mellitus in several different ways. (207) The regulation of glucose output from the liver by insulin may be mediated largely by changes in circulating fatty acid levels. (208) In muscle, the defect in insulin action appears to involve glucose transport, glucose oxidation and particularly glycogen synthesis. The reduction in glucose oxidation may be explained by the "Randle cycle" (209) where increased fatty acid supply results in reduced activity of pyruvate dehydrogenase with impaired glycolysis and oxidation of
glucose. However, the impairment of glycogen synthesis and glucose transport are not adequately explained by established biochemical pathways.\(^{(210)}\) There is evidence that fatty acid availability (via diacylglycerols or long chain acyl CoAs) can influence the activation of protein kinase Cs\(^{(211)}\) which, via phosphorylation events, could modulate the activity of IRS-1 or other signaling molecules. Long chain acyl CoA may also modulate gene transcription\(^{(212)}\) or directly affect glycogen synthase.

**Measurement of Insulin Resistance**

Considering all the facts about insulin resistance, it is important to evaluate insulin resistance for the prevention and treatment of type-2 diabetes. Recently, the oral insulin-sensitizing agents, like rosiglitazone, pioglitazone etc. have been used clinically for glycemic control in diabetic patients. We thus need a simple, precise and easily repeatable index of insulin resistance.

Through euglycemic hyperglycemic clamp (clamp - IR) is the gold standard\(^{(77,78)}\) for evaluation of insulin resistance, it is time-consuming costly and complex to be utilized in epidemiological studies.

In vivo measurement of insulin sensitivity in humans severed methods for evaluating insulin resistance: Fasting plasma insulin level, Homeostasis model assessment (HOMA), insulin tolerance test, insulin suppression test, steady state plasma glucose method and minimal model technique. Among these indexes, fasting plasma insulin level and the insulin resistance by HOMA are likely to be the most simple and repeatable indexes in epidemiological studies.\(^{(77)}\)
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There were no reports on the validity of substituting HOMA_{IR} for clamp IR in a large series of type-2 diabetes patients, although HOMA_{IR} has been adopted as an index of insulin resistance in recent clinical studies.\(^{(79)}\)

HOMA_{IR} did not show a significant strength or consistency of association with clamp-IR in type-2 diabetic subjects.\(^{(81)}\)

However another study reported that HOMA_{IR} is highly correlated with the insulin resistance index assessed by euglycemic-hyperinsulinemic clamp (clamp IR) in type-2 diabetic patients (RS=0.69, \(P<0.0001\)) and also with the fasting insulin level (RS=0.81, \(P<0.0001\)) and also with the fasting insulin levels (RS=0.81, \(P<0.0001\)).\(^{(80)}\)

A strong correlation between HOMA_{IR} and clamp IR in type-2 diabetic subjects was reported in another study. In this study, the HOMA_{IR} showed a hyperbolic relationship with clamp IR. The log-transformed HOMA_{IR} (all subjects, \(r = -0.725, \ P<0.0001\)) correlated more strongly with clamp IR than did HOMA_{IR} (all subjects, \(r = -0.594, \ P < 0.0001\)).\(^{(79)}\)

In population studies, only the fasting insulin level should be used as a marker of insulin resistance, particularly in subjects with abnormal glucose tolerance. Correlation of insulin resistance by clamp IR with fasting or, postload insulin levels were remarkably consistent, ranging from -0.58 to -0.74 (\(P<0.01\)) in subjects with normoglycemia. In contrast, only the fasting insulin level correlated significantly with insulin resistance (-0.47, \(P<0.05\) and -0.48, \(P<0.01\) respectively) in subjects with impaired glucose tolerance and type-2 diabetes subjects.\(^{(82)}\)

HOMA provides a useful model to assess insulin resistance and \(\beta\) cell function.
in epidemiological studies in which only fasting samples were available., HOMA insulin resistance (HOMAI_\text{IR}) was very strongly correlated with fasting insulin (r=0.98). In Mexican-Americans, HOMAI_\text{IR} in NIDDM subjects was 9.5 compared to 2.7 in normal glucose tolerance (NGT) subjects. And also, HOMAI_\text{IR} in subjects with impaired glucose tolerance (IGT) was higher in comparison to NGT subjects.\(^{(83)}\)

It was concluded that there was significantly higher fasting serum insulin (FSI) (P<0.05) in the African American first degree relatives (16±3.0 mU/L) when compared with healthy control subjects (6.3±1.4 mU/L). It was also reported that obesity had been implicated in 90% of African-American type-2 diabetic populations and also been associated with hyperinsulinemia and insulin resistance in first degree relative of African-American type-2 diabetic subjects.\(^{(84)}\)

Glucose tolerant first degree relatives of type-2 diabetic patients were having both fasting hyperinsulinemia and insulin resistance as compared to healthy control subjects, so also the fasting glucose and post stimulation glucose level.\(^{(85, 86)}\)

The prevalence of insulin resistance was increased two fold in subjects with IFG/IGT (2.83±1.69) and three fold in patients with type-2 diabetes (6.58±1.87) compared with subjects with normal glucose tolerance (1.8±1.13).\(^{(87)}\)

Insulin sensitivity was lower in first degree relatives of type-2 DM as compared to healthy controls (36.3% vs. 51.8%, p = 0.0001). Relatives with lower insulin sensitivity have higher BMI (29.2 vs. 25.6 Kg/m\(^2\)), hyperglycemia (5.7 vs. 5.1 mmol/L), hyperinsulinemia (116 vs 59 pmol/L) and hypertriglyceridemia (1.4 vs. 1.0 mmol/L) as compared to healthy controls.\(^{(88)}\)
Average insulin sensitivity was higher in controls (8±0.32 vs 7.1±0.2, P< 0.05) than in first degree relatives of type-2 diabetic patients. The prevalence of insulin resistance in first degree relatives of type-2 diabetes mellitus was 40%. In obese insulin resistant first degree relatives of type-2 diabetic patients, absolute hyperinsulinemia was combined with reduced and delayed relative early insulin release.\(^\text{(89)}\)

Insulin sensitivity and basal insulin levels were higher in NGT first degree relatives of type-2 DM patients than controls without having family history of type-2 DM (3.6±0.4% vs. 3.9±0.4%, p= 0.000).\(^\text{(57)}\)

To clarify the problem that whether IFG and IGT differ with respect to insulin secretion or sensitivity, it was stated in a study that compared with subjects with NGT, subjects with IFG were more insulin resistant (HOMA\(_{IR}\) values 2.64±0.08 vs. 1.73±0.03, p<0.0005) had higher waist-Hip ratio (p<0.005), had higher triglyceride and total cholesterol concentrations (p<0.0005) and lower HDL-cholesterol concentrations (p=0.0001). Compared with subjects with IFG, subjects with IGT had impaired insulin secretion in relation to glucose concentration. A progressive decline in insulin sensitivity was observed when moving from NGT to IGT and to subjects with type-2 DM (p < 0.05).\(^\text{(58)}\)

Subjects with impaired fasting glucose (IFG) had shown higher insulin resistance and a weaker association to hypertriglyceridemia when compared to IGT subjects.\(^\text{(90)}\)

Comparing fasting insulin, HOMA, Insulin-to-glucose ratio, Bennett index and a score based on weighted combinations of fasting insulin, BMI
and fasting triglycerides with the euglycemic insulin clamp to determine the most appropriate method for assessing insulin resistance in epidemiological studies, it was concluded that the variables best predicted insulin sensitivity were fasting insulin and fasting triglycerides. The use of a score based on \( \frac{MFFm}{I=\exp [2.63-0.28\ln (\text{Insulin})-0.31\ln (\text{TG})]} \) rather than the use of fasting insulin alone resulted in a higher sensitivity and a maintained specificity when predicting insulin sensitivity.\(^{(91)}\)

However in few other studies fasting insulin alone was as accurate at predicting insulin resistance in the normoglycemic subjects as HOMA, insulinogenic index and Bennett index.\(^{(82,91)}\)

In another study, various measures of obesity were assessed, i.e., Body Mass Index (BMI), waist circumference and waist-hip ratio (WHR) as predictors of insulin resistance measured by a euglycemic insulin clamp and finally stated that BMI would not have been as important in predicting insulin resistance, as insulin resistance would be over estimated in over weight individuals. The correlation between insulin sensitivity index (ISI) and waist circumference was better as compared to that between ISI and BMI after the correction for fat-free mass.\(^{(91)}\)

Obesity defined by a high WHR was clearly more common than obesity defined by BMI > 30 Kg/m\(^2\). The relative risk of developing insulin resistance was higher in obese with high WHR than in obese with high BMI. The prevalence of insulin resistance was 59% in IFG/IGT and 88% in Type-2 diabetic subjects.\(^{(87)}\)

Bruneck study showed that the prevalence of insulin resistance was 66% in subjects with IGT and 84% in subjects with type-2 diabetes.\(^{(92)}\)
Physiological maneuvers, such as caloric restriction in overweight subjects and regular physical exercise can improve tissue sensitivity to insulin.\(^{(78)}\)

**DIABETES MELLITUS & DYSLIPIDEMIA**

Individuals with DM may have several forms of dyslipidemia. Because of the additive cardiovascular risk of hyperglycemia and hyperlipidemia, lipid abnormalities should be aggressively detected and treated as part of comprehensive diabetes care. The most common pattern of dyslipidemia is hypertriglyceridemia and reduced HDL cholesterol levels. Diabetes mellitus itself does not increase level of LDL, but the small dense LDL particles found in type-2 DM are more atherogenic because they are more easily glycated and susceptible to oxidation.

**Category of risk based on lipoprotein levels in adults with diabetes**

<table>
<thead>
<tr>
<th>Risk</th>
<th>LDL Chl. (mg/dl)</th>
<th>HDL Chl. (mg/dl)</th>
<th>TG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>$\geq 130$</td>
<td>$&lt; 35$</td>
<td>$\geq 400$</td>
</tr>
<tr>
<td>Border line</td>
<td>$100 - 129$</td>
<td>$35 - 40$</td>
<td>$150 - 399$</td>
</tr>
<tr>
<td>Low</td>
<td>$&lt; 100$</td>
<td>$&gt; 40$</td>
<td>$&lt; 150$</td>
</tr>
</tbody>
</table>

For women, the HDL cholesterol values should be increased by 10 mg/dl.

According to ADA and American Heart Association, the lipid profile in diabetic individuals without cardiovascular disease (Primary Prevention) should be: LDL $< 100$ mg/dl, HDL $> 40$mg/dl in men and $> 50$ mg/dl in women and triglyceride $< 150$ mg/dl. In diabetic individuals with cardiovascular disease, the LDL goal should be $< 100$ mg/dl.
DIABETES MELLITUS & METABOLIC SYNDROME

In 1998, WHO proposed a unifying definition for the previously called "syndrome X" or "insulin resistance syndrome" and chose it to call the "Metabolic Syndrome".\(^{93}\) The IR / metabolic syndrome is characterized by the variable coexistence of hyperinsulinemia, obesity, dyslipidemia and hypertension.\(^{69,70}\) Other features include proinflammatory states, microalbuminuria and hypercoagulability.\(^{71-74}\) The pathogenesis of the syndrome has multiple origins. Obesity and sedentary lifestyle coupled with diet as well as largely still unknown genetic factors clearly interact to produce the syndrome.\(^{74}\) The term syndrome –X was originally introduced by Reaven and IR was the common denominator.\(^{75}\) Other terms used for the metabolic syndrome are deadly quartet; DROP syndrome (dyslipidemia, insulin resistance, obesity and high blood pressure), Multiple metabolic syndrome and IRS.\(^{76}\) The definitions to Aid clinical application of Met-S (Metabolic Syndrome) have been laid down by WHO and NCEP –ATP III expert panel:

<table>
<thead>
<tr>
<th>WHO(^{93})</th>
<th>ATP III(^{198})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One of the following</strong></td>
<td><strong>At least three of the following</strong></td>
</tr>
<tr>
<td>a. insulin resistance HOMA –IR ≥ 2.5</td>
<td>waist circumference Men &gt; 102 cm women &gt; 88 cm</td>
</tr>
<tr>
<td>b. Impaired glucose tolerance 2 hour OGTT 8-11 mmol/l</td>
<td></td>
</tr>
<tr>
<td>c. Type-2 diabetes mellitus fasting glucose ≥ 7 mmol/l; 2 hour OGTT ≥ 11 mmol/l</td>
<td>fasting triglycerides ≥ 1.7 mmol/l</td>
</tr>
<tr>
<td><strong>Plus at least two of the following</strong></td>
<td>HDL cholesterol Men &lt; 1 mmol/l Women &lt;1.3 mmol/l</td>
</tr>
<tr>
<td>- blood pressure ≥140/90 mm Hg</td>
<td>blood pressure ≥ 130/85 mm Hg</td>
</tr>
<tr>
<td>- BMI=30 KG/ m(^2) or Waist to hip ratio Men &gt; 0.90 Women &gt; 0.85</td>
<td></td>
</tr>
<tr>
<td>- Fasting triglycerides ≥ 1.7 mmol/l and/or</td>
<td>Fasting glucose ≥ 6.1 mmol/l</td>
</tr>
<tr>
<td>- Low serum HDL concentration Men &lt; 0.9 mmol/l Women &lt; 1 mmol/l</td>
<td></td>
</tr>
</tbody>
</table>
- Albumin creatinine ratio
  Men > 2.5 mg/mmol
  Women > 3.5 mg/ mmol

A person with type-2 diabetes or, IFG/IGT has the metabolic syndrome if two of the criteria listed above are fulfilled.

A person with normal glucose tolerance (NGT) has the metabolic syndrome if he/she fulfills two of the criteria in addition to being insulin resistant. Insulin resistance is defined as the highest quartile of the HOMA_{IR} index.

The combination of obesity and dyslipidemia or combination of obesity and hypertension was the most common risk factor combination for metabolic syndrome in subjects with IFG/IGT and diabetes. The metabolic syndrome was present in approximately 10% of subjects with NGT, about 50% subjects with IFG/IGT and about 80% of subjects with type-2 diabetes. It was more common in males than in females among subjects with NGT (15% vs. 10%), and IFG/IGT (64% vs. 4%) but not in patients with type-2 diabetes mellitus (84% vs. 78%).\(^{(87)}\)

The first degree relatives of type-2 diabetes mellitus having low metabolic glucose clearance rate were significantly correlated with the endothelial dysfunction thus with insulin resistance independent of the classic cardiovascular risk factors.\(^{(84)}\)

The metabolic syndrome was present in 23% cases (relatives risk =8.7, 95% confidence interval 2.4 - 31.6) of first degree relatives of type-2 diabetic patients.\(^{(88)}\)

The first degree relatives of type-2 diabetic patients with IGT and NIDDM displayed more features of the metabolic syndrome than when compared to relatives with NGT.\(^{(57)}\)
Dyslipidemia in the Metabolic Syndrome

Dyslipidemia, the hallmark of the met-S, is summarized as\(^{(95)}\)

1. Increased flux of free fatty acids
2. Raised TG values
3. Low high density lipoprotein (HDL) cholesterol values
4. Increased small, dense low density lipoprotein (LDL) values, and
5. Raised apolipoprotein (apo) B values

Dyslipidemia is widely established as an independent risk factor for cardiovascular disease. Low HDL cholesterol and hypertriglyceridemia have been found to be independently and significantly related to myocardial infarction / stroke in patients with Met-S. Additionally, a combination of high fasting glucose and low HDL cholesterol were shown to have primary predictive ability for coronary heart disease.\(^{(96)}\)

The clinical relevance of the metabolic syndrome is related to its role in the development of cardiovascular disease. Management of the metabolic syndrome involves patient-education and intervention at various levels. Soon, metabolic syndrome will overtake cigarette smoking as the number one risk factor for heart disease.\(^{(97)}\)

It is rare to see type-2diabetes, dyslipidemia, obesity or hypertension in isolation. Insulin resistance and resulting hyperinsulinemia have been implicated in the development of glucose intolerance (and progression to type-2 diabetes); hypertriglyceridemia, hypertension, polycystic ovary syndrome, hypercoaguability and vascular inflammation, as well as the eventual development of atherosclerotic cardiovascular disease, treatment and consequent improvement of insulin resistance.
have been shown to result in better outcomes in virtually all of these conditions.

**DIABETES MELLITUS & OBESITY**

Obesity is a degree of overweight that is associated with increases in morbidity and mortality. In 1998, the National Heart Lung and Blood institute (NHLBI) of the National Institutes of Health published guidelines on the diagnosis and treatment of overweight and obesity. The expert panel advocated using specific body mass index (BMI) cut-off points to diagnose both conditions. The BMI is calculated by dividing a person's weight in kilograms by height in meters squared. A BMI (kg/m²) of 25 or less is normal; 25-29.9, overweight; 30-34.9, mild obesity; 35-39.9, moderately obese; and >40, severe or morbid obesity.

Accumulation of excessive adipose tissue in a central-or upper-body distribution (android or male pattern) is associated with a greater risk of adverse health consequences than lower-body obesity (gynoid or female pattern). It appears that it is the absolute amount of central fat that confers adverse health risks.

For this reason, the waist circumference is now the favored measure for risk stratification based on fat distribution. High risk is conferred in men by a waist circumference greater than 40 in. (>102 cm) and in women by a waist circumference greater than 35 in. (>88cm). Waist circumference is most useful for risk stratification of people whose BMI is between 25 and 30 kg/m². In this intermediate-risk area, those with an increased waist circumference should undertake greater efforts directed at preventing further weight gain, while those with a smaller waist circumference can be reassured that their weight does not pose major health hazards.

Waist circumference should be measured with a tape measure at midway
between the iliac crest and the subcostal margin parallel to the floor at the end of a relaxed expiration. The hip circumferences measured at the maximum buttock circumference.

Obesity has clearly been associated with diabetes, hypertension, hyperlipidemia, coronary artery disease, degenerative arthritis, gallbladder disease, and cancer of the endometrium, breast, prostate, and colon. The incidence of these conditions rises steadily as body weight increases. It is surprising how risks increase with even modest gains in weight. Health risks are magnified with advancing age and a positive family history of obesity-related diseases.

An NIH publication from 2003 estimated the direct and indirect health care costs due to obesity and $122.9 billion for the year 2001. In addition, NIH estimated that Americans pay $33 billion for weight loss products and services, many of which provide little or no benefit. These costs suggest that obesity accounts for 5.5-7% of national health expenditures.
Chapter 2: Review of Literature

Obesity has reached epidemic proportions in the United States. The national Health and Nutrition Examination survey (NHANES) conducted by the federal government uses direct measures of height and weight in a representative sample of Americans to estimate the prevalence of obesity.

The prevalence of obesity has risen over such a short period; it seems that the primary culprit is a changing environment that promotes increased food intake and reduced physical activity. This statement should not be taken to mean, however, that body weight is not subject to physiologic regulation. The control of body weight is complex with multiple interrelated systems controlling caloric intake, macronutrient content of the diet, energy expenditure, and fuel metabolism.

Professionals are increasingly viewing obesity as a chronic metabolic disease much like diabetes or hypertension. This model requires a conceptual shift from the previous widely held belief that obesity is simply a cosmetic or behavioral problem. Development of obesity requires a period of positive energy balance; that is energy intake must exceed energy expenditure. Maintaining energy balance is one of the most important jobs of any organism. Between age 20 and 60 years, the average human eats over 32 tons of food. A sustained negative imbalance between energy intake and expenditure is potentially life threatening within a relatively short time. To maintain energy balance, the organism must assess energy stores within the body; assess the nutrient content of the diet; determine whether the body is in negative energy or nutrient balance; and adjust hormone levels, energy expenditure, nutrient movement, and consumptive behavior in response to these assessments.

Obesity is clearly more common in people who have family history of obesity.
The problem of human obesity involves an interaction between genetic susceptibility and environmental triggers. The genes that we possess to regulate body weight evolved somewhere between 200,000 and 1 million years ago. The environmental factors controlling nutrient acquisition and habitual physical activity were dramatically different then. While a few cases of human obesity caused by single gene mutations have been found, most human obesity appears to be polygenic involving probably 10-30 genes in any individual. Genetics appears to be responsible for 20-40% of the variance in weight in most populations.

**OBESITY IN THE INDIAN CONTEXT**

Obesity amongst Indians may have a different face. Recent studies have shown that Indians, even if non-obese, metabolize lipids like their obese Caucasian counterparts. This is a disquieting observation and it implies that an Indian need not be obese to have a higher risk of type-2 diabetes mellitus and coronary heart disease. Even non-obese Indians have a risk of development of these disorders just like obese Caucasians.

As defined by the WHO, the cut off point of $BM_\text{i} \geq 23 \text{ kg/m}^2$ is used to define obesity amongst Indians. This is in contrast to the Caucasians where the cut off of 25 is used.

Abdominal obesity is defined if the waist circumference or WHR are greater than 80 cm. or 0.80 respectively.

Various studies have been carried out as regards obesity amongst Indians high prevalence of diabetes, obesity and dyslipidemia was found in urban slum population in northern India. Appreciable prevalence of obesity, dyslipidemia, diabetes mellitus,
substantial increase in body fat, generalized and regional obesity in middle age, particularly in females, need immediate attention in terms of prevention and health education in such economically deprived populations.\textsuperscript{98}

In sensitivity to insulin was significantly associated with risks of cardiovascular disease and diabetes, despite there being a low prevalence of obesity (9.0\%) among urban subjects. Hypertension, diabetes, hypertriglyceridemia, intolerance of glucose and central obesity were significantly associated with insensitivity to insulin and coronary disease for urban but not for rural people.\textsuperscript{99}

A comparative study was carried out between different ethnic groups which included Asian Indians, Mexican Africans and Whites. Age and BMI were predictive factors of NIDDM in all while waist to hip ratio (WHR) was significant only in Asian Indians and Mexican Africans, although Whites had high WHR. This may be an indicator of differences in genetic susceptibility. This study also highlights the similarity in risk factors between Asian Indians and Mexican Africans living in urban environment and the significance of distribution of adiposity in the comparatively lean Asian Indians.\textsuperscript{100}

High prevalence of NIDDM and IGT was found in an elderly south Indian population. This study highlights the high prevalence of glucose intolerance in elderly south Indians having low mean BMI (mean $\pm$ SD; urban 21.7 $\pm$4.6, rural 17.9 $\pm$ 3.3 kg/m$^2$). Although there was a twofold higher prevalence of diabetes in the urban area, the occurrence of IGT was similar in urban and rural populations.\textsuperscript{101}

The relationship between obesity, plasma immunoreactive insulin concentration and blood pressure in newly diagnosed Indian type-2 diabetic patients
was found. Multivariate analysis revealed that systolic blood pressure in diabetic patients was related to BMI (p<0.01) and fasting immunoreactive insulin (p<0.05) while diastolic blood pressure was related to BMI [P < 0.001] and waist-hip ratio (p<0.01). Thus, blood pressure is associated with obesity even in our relatively non-obese population and it is also associated with plasma immunoreactive insulin concentrations. The mechanism of these associations remains to be established.

LEPTIN

In 1993, Kennedy introduced the lipostatic theory of body weight control, according to which adipose tissue produced a hormone responsible for regulating body size. 5 years later, Harvey demonstrated the presence of a hormone that regulated body weight through an interaction with the hypothalamus. Coleman by conducting parabiosis experiments concluded that the ob/ob mice lacked some kind of signalling factor associated with fat. In 1994, Jefferey Friedman successfully cloned the ob/ob obese gene and in 1995 discovered leptin. Leptin (leptos means thin) is a protein hormone encoded by the obesity (ob) gene.

The mouse ob gene codes for a protein of 167 amino acids, called leptin. The human analogue is secreted mainly from adipose tissue and is 84% homologous to the mouse protein.

Leptin consists of a four-helix bundle similar to the long chain helical cytokine family (G-CSF, Leukemia inhibitory factor, ciliary neutrotrrophic factor, human growth factor). It is believed that leptin will undergo a conformational change upon receptor binding from a coil to a helix. Recessive mutations in the genes encoding leptin and its receptor have been identified and linked with the pathological conditions
of morbid obesity, diabetes and infertility.

Leptin is produced by adipose tissue and acts as a satiety signal to the ventromedial hypothalamus. It suppresses expression of hypothalamic neuropeptide Y, a potent appetite stimulatory peptide.\(^{(107)}\)

Fig. 2: Figure shows the feedback regulation of adipose tissue in the obese ob/ob (left) and fa/fa (right) rodents. LRs, brain leptin receptor; NPY, neuropeptide Y; HPA, hypothalamic-pituitary adrenal axis. Thick lines represent augmented processes; dotted line represents an absent process; double slash through LRs represents mutated LRs.\(^{(107)}\)

In parallel, leptin increases the expression of α-MSH, which decreases appetite by acting on the MC4R melanocortin receptor. Thus leptin activates a series of downstream neural pathways that alter food-seeking behaviour and metabolism.\(^{(108)}\)

However, leptin deficiency, which occurs in conjunction with the low adipose tissue stimulates appetite and induces other adaptive responses including inhibition of hypothalamic Thyrotropin Releasing Hormone (TRH) and Gonadotropin Releasing Hormone (GnRH).
**Chapter-2: Review of Literature**

*Known mutations in man*

**Fig.3:** A central pathway through which leptin acts to regulate appetite and body weight. Leptin signals through proopiомelanocortin (POMC) neurons in the hypothalamus to induce increased production of a melanocyte stimulating hormone (α-MSH), requiring the processing enzyme PC-1 (pro-enzyme convertase 1), α-MSH acts as an agonist on melanocortin-4 receptors to inhibit appetite, and the neuropeptide AgRP (Agouti-related peptide) acts as an antagonist of this receptor. Mutations that cause obesity in humans are indicated by *.

Leptin has two general types of receptors:

- the long form (ObRb), primarily expressed in the hypothalamus, and

- the short forms (OB-Ra, -Rc, -Rd and -Rf), which are expressed throughout the body.

Interestingly, the signaling pathway that leptin activates in the periphery and centrally is the same pathway activated by insulin *i.e.* the PI3K pathway (through IRS-1 and IRS-2). In addition, leptin receptors are located in the pancreas directly on β and δ cells. A complicated feedback loop between insulin and leptin may exist to coordinate energy status.
Leptin has been described as a “pliotropic” hormone.\textsuperscript{(105)} It functions as a

- Satiety factor inhibiting food intake
- Stimulator of energy expenditure
- Signal to the reproductive system

Some reported effects of leptin on different organs and tissues\textsuperscript{(109)}

<table>
<thead>
<tr>
<th>Organ/tissue</th>
<th>Effect</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>↓ food intake</td>
<td>↓ NPY, ↓ AGRP, ↑ POMC</td>
</tr>
<tr>
<td></td>
<td>↑ energy expenditure</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>↑ SNS activity</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>↓ HPA activity</td>
<td>↓ CRH release</td>
</tr>
<tr>
<td>Liver</td>
<td>↑ GNG</td>
<td>central and/or ↑ PEPCK</td>
</tr>
<tr>
<td></td>
<td>↑ HGP</td>
<td>↑ GNG</td>
</tr>
<tr>
<td>Pancreas</td>
<td>↓ insulin</td>
<td>+ PDE3</td>
</tr>
<tr>
<td>Muscles</td>
<td>counteracts diet-induced insulin resistance</td>
<td>↑ Glut 4</td>
</tr>
<tr>
<td></td>
<td>↑ glucose uptake</td>
<td>↑ Glut 4</td>
</tr>
<tr>
<td></td>
<td>↑ fat Metabolism</td>
<td>?</td>
</tr>
<tr>
<td>Adipocytes</td>
<td>↓ fatty and acid synthesis</td>
<td>?</td>
</tr>
</tbody>
</table>

NPY-neuropeptide Y; AGRP-Agouti-Related-Protein; POMC- Pro Oplo Melanocortin; SNS-; GNG-Gluconeogenesis, HGP- Hepatic Glucose Production

Thus our understanding of its physiological role has evolved from that of a satiety signal to that of an integrative hormone that responds to and regulates different endocrine pathways with direct metabolic effects on peripheral tissues.

Other than adipose tissue, leptin is also secreted by stomach, placenta, intestine and testes. In the circulation, it can be measured using either immunoprecipitation or radioimmunoassay.\textsuperscript{(110,111)} The proportion of free leptin in the
circulation increases with increasing adiposity\textsuperscript{[112]} and women have 2-3 fold higher values than men at any given BMI.\textsuperscript{[113,114]} It is conceivable, therefore, that the higher serum leptin levels in women may reflect gender variation in regional body fat distribution and leptin expression.

LEPTIN AND DIABETES MELLITUS

Over 75\% of type-2 diabetic patients are overweight or obese and there is strong relationship between obesity and type-2 diabetes. Obesity is a well established risk factor for cardiovascular disease and type-2 diabetes mellitus.\textsuperscript{[115]} As human obesity is frequently associated with hyperleptinemia\textsuperscript{[116,117]}, a state of decreased leptin sensitivity similar to that described in fa/fa rats could occur in human obesity syndromes as well. Leptin delivered to the CSF is the most potent weight-reducing peptide known. Leptin-induced weight loss is completely specific for adipose tissue, whereas food restriction results in loss of both adipose tissue and lean body mass.\textsuperscript{[118]}

Leptin also seems to correlate with other markers of the metabolic syndrome, such as plasma TG and Apo B levels and with systolic blood pressure independent of the BMI and glucose disposal rate which suggests that leptin may be in the causal pathway between obesity and diabetes.\textsuperscript{[119]} The recent finding of a hypersensitive limbic-hypothalamus-pituitary-adrenal (LHPA) axis in the metabolic syndrome may provide an explanation to both the cardinal symptoms of this syndrome viz. insulin resistance and visceral fat accumulation.\textsuperscript{[120,121]} Therefore, it is possible that insulin resistance and leptin resistance act together in the onset of obesity and diabetes.\textsuperscript{[122,123]}

Plasma leptin and insulin levels correlate with each other possibly because insulin stimulates leptin synthesis and release. A study was conducted to
assess the relationship between leptin and fasting plasma insulin concentrations in a large cohort of well-defined diabetic patients participating in the United Kingdom Prospective Diabetes Study. The results showed a strong positive relationship between basal plasma insulin levels and plasma leptin concentration in a large cohort of diabetic patients, even after adjustment for any confounding factors such as BMI and sex.\(^{(123)}\)

The Hoorn study, conducted in The Netherlands established a relationship between insulin and leptin and in addition suggests a relationship between triglyceride concentration and leptin independent of sex, BMI, waist circumference and insulin.\(^{(124)}\)

Interestingly, several studies have reported that type-2 diabetic patients have significantly lower leptin levels compared to non-diabetic subjects after controlling for age and percentage body fat.\(^{(125)}\) Progression from obesity to type-2 diabetes mellitus may reduce leptin hypersecretion. Patients with chronic type-2 diabetes mellitus (disease duration of >20 years) have a 50% reduced leptin response to dexamethasone injection as compared to recently diagnosed diabetics and non-diabetic controls. In addition, a negative correlation has been found between the percentage of HbA\(_{1C}\) and leptin levels in type-2 diabetes mellitus patients.\(^{(126)}\) Thus, chronic hyperglycemia with increased duration of type-2 diabetes could reduce leptin levels at rest and in response to physiologic stimuli.

The increased leptin levels resultant on obesity interfere with insulin signaling contributing to insulin resistance.\(^{(127)}\) In fact, leptin has been found to inhibit insulin receptor autophosphorylation.\(^{(128)}\) It has been has hypothesized that leptin has an
influence on insulin resistance. (129)

Clear evidence demonstrating a strong relationship between insulin sensitivity and leptin, in both men and women, with or without diabetes mellitus was shown in a Miami community health study. It found that the rate of insulin-mediated glucose uptake (M) was negatively associated with leptin concentrations in both men ($r = -0.83$, $p<0.001$) and women ($r = -0.59$, $p<0.001$). After adjustment for the covariates sex, percentage body fat and AUC (the 2-hour insulin area under the curve), leptin was still significantly correlated with M ($p=0.04$). Thus leptin was significantly associated with insulin resistance. (130)

In patients with gestational diabetes mellitus (GDM) leptin concentrations were lower than normal pregnant women. (131) In another study, higher plasma leptin concentrations were observed in noticeably insulin resistant women with gestational diabetes and make hyperleptinemia a marker of latent metabolic syndrome. (132)

ADIPONECTIN

Obesity is closely associated with type-2 diabetes mellitus. Central to this link is the adipose tissue. Recent observations bring to light the fact that adipose tissue is not just a passive store house of fat rather, an important metabolic tissue giving rise to a number of hormones. Hormones secreted by adipocytes are knows as adipokines these are leptin, adiponectin, visfatin and resistin.

Whereas, all the adipokines are increased in diabetes mellitus and obesity, one adipokine is seen to be reduced; this marker, adiponectin, termed ACRP 30 (Adipocyte Complement Related Protein of 30 KDa) (151), adipo $Q$ (152) is produced as
a result of adiponectin, gene expressed exclusively in both WAT (white adipose tissue) and brown adipose tissue. Hypoadiponectinemia is associated with obesity, insulin resistance, type-2 diabetes mellitus, dyslipidemia, cardiovascular disorders, hypertension, increased sex hormones (androgen and testosterone), increased oxidative stress and carbohydrate rich diet.\textsuperscript{(133-148)}

Adiponectin is a member of a gamut of markers that deal with diabetes. Increased adiponectin levels are observed with administration of thiazolidinediones, angiotensin receptor blocker, ACE inhibitor therapy, weight loss and dietary factors like soya protein\textsuperscript{(163-165)}.

Adiponectin is a fairly young molecule for research on diabetes. It is a hormone that is produced by the adipocytes and secreted into the circulation and can be measured by sensitive assays.

It was reported that reduced blood concentrations of adiponectin appear to indicate a significant risk of cardiovascular disease in one of the first studies to focus on risk of the disorder among patients with diabetes mellitus. Studies suggest that adiponectin, a protein specific to fat tissues, is involved in obesity, diabetes and heart disease. Adiponectin levels in individuals might be predictive of future cardiac events. Adiponectin has been closely linked with insulin resistance, a known risk factor for heart disease. Adiponectin is one of the most abundant circulating proteins in human plasma, and it also seems to act as an anti-inflammatory molecule.

Investigators found that for people with diabetes, decreased concentrations of adiponectin was associated with coronary artery disease. Interestingly, this effect was independent of conventional risk factors such as smoking, cholesterol
levels or body weight. Remarkably, it also was a better predictor than our markers for inflammation and insulin resistance, as well as other factors. Adiponectin concentration may prove not only a useful marker of cardiovascular risk, but also a potential therapeutic agent for prevention, particularly among high-risk individual.

A hypothetical model for the secretion and action of adiponectin

The synthesis and secretion of adiponectin is increased by activation of the nuclear receptor PPAR-γ, and reduced by caloric excess, presumably associated with leptin deficiency or resistance. Once released, adiponectin can directly increase fatty-acid transport, oxidation and dissipation in skeletal muscle, reducing the levels of intramyocellular lipids, thus improving insulin signaling. The protein can also increase the sensitivity of the hepatocyte to insulin, either through a direct action, or indirectly by lowering circulating lipids due to its action on muscle. Thus, administration of adiponectin can result in improved insulin sensitivity and glucose tolerance, and can correct hyperglycemia associated with obesity.

Of the adipokines, adiponectin has recently attracted much attention because of its antidiabetic and antiatherogenic effects and is expected to be a novel therapeutic tool for diabetes and the metabolic syndrome\(^{69}\). Indeed, a decrease in the circulating levels of adiponectin by genetic and environmental factors has been shown to contribute to the development of diabetes and the metabolic syndrome. The thiazolidinedione (TZD) class of antidiabetic drugs, which also have pleiotropic effects on cardiovascular diseases and lipid metabolism, is known to exert its effects partly through increasing the levels of the active form of adiponectin, as described below.
Association of hypoadiponectinemia with insulin resistance, diabetes, and the metabolic syndrome

Adiponectin, also termed Acrp 30\(^{(151)}\), AdipoQ\(^{(152)}\), apM1\(^{(153)}\) or GBP28\(^{(154)}\), was originally identified independently by 4 groups using different approaches. The Adiponectin gene encodes a secreted protein expressed exclusively in both WAT (white adipose tissue) and brown adipose tissue. Adiponectin has a carboxyl-terminal globular domain and an amino-terminal collagen domain and is structurally similar to complement 1q\(^{(155,156)}\), which belong to a family of proteins that form characteristic multimers.\(^{(157,158)}\) Adiponectin exists in a wide range of multimer complexes in plasma and combines via its collagen domain to create 3 major oligomeric forms: low-molecular weight (LMW) trimer, a middle-molecular weight (MMW) hexamer, and high-molecular weight (HMW) 12-to 18-mer adiponectin.\(^{(159,160)}\) In contrast to the expression of adipokines such as TNF-\(\alpha\) and resistin, which cause insulin resistance, adiponectin expression is reduced in obese, insulin-resistant rodent models.\(^{(161)}\)

Importantly, a decrease in plasma adiponectin levels preceded the onset of diabetes in animals studies, in parallel with the observation of decreased insulin sensitivity\(^{(161)}\), plasma adiponectin levels have also been reported to be reduced in obese humans, particularly those with visceral obesity, and to correlate inversely with insulin resistance.\(^{(133-136)}\) Prospective and longitudinal studies\(^{(136-141)}\) have shown that lower adiponectin levels are associated with a higher incidence of diabetes. Adiponectin, but not inflammatory markers such as C-reactive protein and IL-6, has been shown to be significantly related to the development of type-2 diabetes in Pima Indians.\(^{(136)}\) Hypoadiponectinemia has also been demonstrated to be independently
associated with the metabolic syndrome—indeed, more strongly than are any other inflammatory markers. Reduced plasma adiponectin levels are also commonly observed in a variety of states frequently associated with insulin resistance, such as cardiovascular disease and hypertension.

There is a sexual dimorphism in the circulating levels of adiponectin. Indeed, female humans and rodents have higher plasma adiponectin levels than males, suggesting that sexual hormones regulate the production of adiponectin, although it is controversial how these hormones, such as estrogen and testosterone, are involved in the regulation of plasma adiponectin level. Nevertheless, this may partly account for the fact that females are more sensitive to insulin than males. Some dietary factors, such as soy protein, fish oils & linoleic acid, are also suggested to increase plasma adiponectin levels, which is consistent with the fact that intake of these factors is thought to have a protective effect on the development of diabetes. On the other hand, a carbohydrate-rich diet appears to decrease plasma adiponectin level. Oxidative stress has also been suggested to inhibit the expression of adiponectin. Although the mechanism underlying this regulation is unclear, this may contribute to the decrease in plasma adiponectin in obesity, which is associated with increased oxidative stress in adipose tissue.

Thus, the plasma adiponectin level is affected by multiple factors including gender, aging, and lifestyle.
Discovery of the insulin-sensitizing action of adiponectin

The insulin-sensitizing effect of adiponectin was first identified by 3 independent groups in 2001 in KKA γ mice (KK mice overexpressing the agouti protein), as a model of the metabolic syndrome and type-2 diabetes linked to obesity. Plasma adiponectin levels were decreased in KKA γ mice fed a high-fat diet. Replenishment of adiponectin significantly ameliorated high-fat diet-induced insulin resistance and hypertrigly-ceridemia, which showed that adiponectin, is an insulin-sensitizing adipokine. These data also strongly suggested that the high fat diet induced obesity linked insulin resistance and the metabolic syndrome. An acute increase in the level of circulating adiponectin triggers a transient decrease in basal glucose level by inhibiting both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production in both wild-type and type-2 diabetic mice, and they proposed that adiponectin sensitizes the body to insulin.\(^{(151)}\)

Subsequently, the chronic effects of adiponectin on insulin resistance in vivo were investigated by generation of adiponectin transgenic mice \(^{(166, 167)}\) or adiponectin-deficient mice.\(^{(168, 169)}\) Globular adiponectin transgenic ob/ob mice showed partial ameliorator of insulin resistance and diabetes.\(^{(166)}\) Full-length adiponectin transgenic mice showed suppression of insulin-mediated endogenous glucose production.

With respect to the molecular mechanisms underlying the insulin-sensitizing action of adiponectin, full-length adiponectin stimulated AMP-activated protein kinase (AMPK) phosphorylation and activation in the liver, while globular adiponectin did so in both skeletal muscle and the liver.
Adiponectin gene {SNPs} in human insulin resistance and type-2 diabetes

The adiponectin gene is located on chromosome 3q27, which has been reported to be linked to type-2 diabetes and the metabolic syndrome.\textsuperscript{(97,101,102)} Therefore, the Adiponectin gene appears to be a promising candidate susceptibility gene for type-2 diabetes. Among the SNPs in the Adiponectin gene, 1 SNP located 276 bp downstream of the translational start site (SNP 276) was concomitantly associated with decreased plasma adiponectin level, greater insulin resistance, and an increased risk of type-2 diabetes.\textsuperscript{(170)} The subjects having both alleles G (G/G genotype) of SNP 276, had an approximately doubled risk for developing type-2 diabetes as compared with those with the T/T genotype.\textsuperscript{(170)} It is noteworthy that more than 40% of Japanese individuals have the “at-risk” G/G genotype, which makes subjects prone to genetically decreased adiponectin levels and thus susceptible to type-2 diabetes.\textsuperscript{(170)}

Role of High Molecular Weight adiponectin in insulin resistance and type-2 diabetes

Several observations support the hypothesis that high molecular weight adiponectin is the more active form of the protein and has a more relevant role in insulin sensitivity and in protecting against diabetes. First, rare mutations – G84R and G90S in the collagen domain are closely associated with type-2 diabetes.\textsuperscript{(151,170)} Subjects with increased ratio of plasma HMW adiponectin levels to total adiponectin levels correlate with improvement in insulin sensitivity during treatment with an insulin-sensitizing drug, TZD, in both mice and human diabetic patients, whereas increases in total serum adiponectin levels do not show good correlations with improvement in insulin sensitivity during treatment with TZD at the individual level.
Cloning, function, and regulation of adiponectin receptors

Adipo R1 and Adipo R2 appear to be integral membrane proteins; the N-terminus is internal and the C-terminus is external. T-cadherin may be one of the adiponectin-binding proteins. The expression levels of both Adipo R1 and Adipo R2 were significantly decreased in muscle and adipose tissue of insulin-resistant ob/ob mice, probably in part because of obesity-linked hyperinsulinemia.

Adiponectin and adiponectin receptors as therapeutic targets

A therapeutic strategy for the treatment of insulin resistance, type-2 diabetes, the metabolic syndrome, and cardiovascular disease may include the up-regulation of plasma adiponectin levels, the up regulation of adiponectin receptors, or the development of adiponectin receptor agonists.

TZD mediated up-regulation of plasma adiponectin level. TZDs are known to improve systemic insulin sensitivity in animal models of obesity-linked insulin resistance and diabetes, by enhancing glucose disposal in skeletal muscle and suppressing gluconeogenesis in the liver. TZDs have been widely used as therapeutic agents for the treatment of type-2 diabetes. TZDs have been proposed to ameliorate insulin resistance by binding to and activating PPAR-γ in adipose tissue, thereby promoting adipocyte differentiation and increasing the number of small adipocytes that are more sensitive to insulin. Plasma adiponectin levels have been shown to be up regulated by TZDs. TZDs may up regulate adiponectin by generating small adipocytes that abundantly express and secrete adiponectin and/ or directly activating Adiponectin gene transcription. TZDs may also directly facilitate the generation of HMW adiponectin.
Up regulation of adiponectin receptors and development of adiponectin receptor agonists

Since Adipo R1 and Adipo R2 are down regulated in obesity-linked insulin resistance and diabetes, both up-regulation of AdipoR1 and AdipoR2 expression and agonism of AdipoR1 and Adipo R2 may be logical approach to providing a novel treatment modality for insulin resistance and type-2 diabetes.

Osmotin is a member of the pathogenesis related-5 (PR-5) family of plant defense proteins (24 members in Arabidopsis thaliana) that induce apoptosis in yeast. It is ubiquitous in fruits and vegetables, etc., and the genes encoding the PR-5 protein sequenced from many different species are about 50-95% identical. PR-5 family proteins are also extremely stable and may remain active even when in contact with the human digestive or respiratory system. Studies revealed that both globular adiponectin and osmotin consist of antiparallel β- strands arranged in the shape of a β-barrel. Domain 1 (lectin like domain) of osmotin showed similarity to globular adiponectin in 3D structure, suggesting that these 2 proteins share the lectin-like domain. Interestingly, osmotin activates AMPK via adiponectin receptors in mammalian C2C12 myocytes. These data raise the possibility that further research examining similarities in adiponectin and osmotin may facilitate the development of potential adiponectin receptor agonists. The enhancement or mimicking of adiponectin action through modulation of expression and/or function of AdipoR1 and AdipoR2 can be a novel therapeutic strategy for the treatment of insulin resistance, the metabolic syndrome, and type-2 diabetes.
PREVENTION OF DIABETES MELLITUS

India is going to face a big challenge posed by the rising prevalence of diabetes and its complications unless steps are taken to implement the primary and secondary prevention in diabetes. For this purpose it is essential to identify the risk factors for diabetes and also for the vascular complications.

UK Prospective Diabetes Study in type-2 diabetes and DCCT study in type-1 diabetes have shown that tight control of hyperglycemia and hypertension could reduce the risk of vascular complications to a great extent.\textsuperscript{(171,172)} Early diagnosis of diabetes and control of hyperglycemia and hypertension will help in secondary prevention in diabetes.

Prevention of type-2 diabetes is possible with changes in lifestyle. While the genetic component for the development of diabetes can not be corrected, the environmental factors can be modified. Obesity, diet and physical activity are the modifiable factors. The interaction of diet and exercise influences the body fat pattern, which has a significant role in determining insulin sensitivity. Traditional lifestyle characterized by a diet including less saturated fat and complex carbohydrates, and greater physical activity may protect against the development of cardiovascular risk factors and diabetes, even in the presence of potential genetic predisposition. Primary Prevention of diabetes is possible by modifying the environmental risk factors influencing diabetogenesis such as obesity, diet and physical activity. Long term studies have shown the beneficial effects of lifestyle modifications on reducing the risk of diabetes.\textsuperscript{(173,174)}

Diabetes which is a complex disorder results from a strong genetic
environmental interaction. Evidences showing high probability of preventing diabetes in subjects with IGT by lifestyle modification up to an extent 58% suggested the role of environmental factors which are modifiable. It is likely that environmental susceptibility is also governed by particular genotypes. Genetic studies are now focusing attention on these aspects.

A prospective study has been conducted in Chennai to study the possibility of prevention of diabetes in the relatively non-obese, insulin resistant Indian population using lifestyle modification and or insulin sensitizers. The need of this hour is early screening for glucose intolerance in population and institution of preventive measures at an early age.

With the incidence of diabetes rising globally, the management has put a large burden not only over the patients and families, but also over the governments. So, in the current period, most studies in the diabetology are being planned to prevent future developments of diabetes.

Primary Prevention of type-2 diabetes mellitus is possible, strategies for controlling type-2 diabetes mellitus pandemic remain under development. This primary prevention can be implemented:

a. **Through a population strategy:** By changing the life style and environmental determinants that are known to be risk factors for the future development of type-2 diabetes mellitus.

b. **Through high risk strategy:** By targeting preventive measures only at those specific individuals or groups that are at high risk for the future development of type-2 Diabetes Mellitus.
The later is the strategy of Diabetes Prevention Program (DPP)\(^{(177)}\), a clinical study sponsored by National Institute of Diabetes, Digestive and Kidney Disease in USA.

For identification of high risk subjects for a clinical trial of prevention of NIDDM a two-step strategy was followed.\(^{(178)}\) Such a strategy also offers the advantage of reducing the necessary sample size.

**Screening for Type-2 Diabetes Mellitus**

*Purpose of screening:* To identify asymptomatic individuals who are likely to have diabetes or pre-diabetic states. For diabetes mellitus, most of the conditions employed for screening are met.

Randomized clinical trials would be the best means to evaluate the benefits and risks of diabetes screening and early treatment. However, rigorous studies that apply currently available treatments to a screened group, but not to a control group have not been done and are unlikely to be performed soon because of feasibility, ethical concerns and costs.

A large clinical trial, the Diabetes Prevention Program (DPP), is underway in USA.\(^{(177)}\) It is designed to answer the question of whether treatment with life style interventions or, with metformin for patients with IFG or IGT detected through a screening program will reduce the incidence of type-2 diabetes mellitus. If the DPP demonstrates in the incidence of type-2 diabetes as a result of one or more of the interventions, then more widespread screening for these conditions, which would incidentally detect many cases of asymptomatic diabetes, may be justified.

Sufficient data suggests that life style modifications or pharmacotherapy
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directed at improving insulin sensitivity or insulin secretion in subjects with impaired glucose tolerance may reduce progression to diabetes.\(^{(179)}\)

To increase the cost effectiveness of testing undiagnosed, otherwise healthy individuals testing should be considered in high risk populations. On the basis of expert opinion, evaluation of high risk individuals should be considered by their health care providers at 3 years intervals beginning at age 45. Testing should be considered at a younger age or, be carried out more frequently in individuals with one or more of the risk factors shown in the following table.

**Major Risk factors for type-2 diabetes mellitus\(^{(180,181)}\)**

1. Having a first degree relative with diabetes.
2. Obesity (i.e. \( \geq 20\% \) over desired body weight or, \( \text{BMI} \geq 27 \text{ Kg/m}^2 \))
3. Habitual physical inactivity.
4. Race/ethnicity (e.g. African-Americans, Hispanic-American, Asian-Americans)
5. Previously identified IFG or, IGT
6. Hypertension (\( \geq 140/90 \text{ mm Hg in Adults} \))
7. HDL cholesterol level \( \leq 35 \text{ mg/dl and/or triglyceride level} \geq 250 \text{ mg/dl.} \)
8. History of Gestational diabetes mellitus or, delivery of a baby weighing \( > 9 \text{ lbs.} \)

Diabetes is the single most important metabolic disease and is, widely recognized as one of the leading causes of death and disability worldwide.\(^{(6,182)}\) The rapid increase in prevalence of diabetes related to lifestyle and rapid socioeconomic
changes. Diabetes causes profound alterations in both the micro- and macrovascular system affecting nearly every organ in the body. It magnifies the risk for vascular disease several fold and is thus one of the major causes of morbidity and mortality worldwide.

Presently over 170 million individuals are affected by diabetes and these numbers are predicted to increases further in the future and the most dramatic increase is excepted to occur in India. According to world health organization (WHO), by the year 2030, India would have about 80 million diabetic subjects and would contribute to more than 20% of the world's diabetic population. Various migrant studies have shown that south Asians are more prone to diabetes compared to the indigenous population. Recent studies within the Indian subcontinent show that in urban India, prevalence rates of diabetes are fast approaching those seen in more affluent migrant Indians.

PRIMARY PREVENTION IN TYPE-2 DIABETES MELLITUS

Prevention of the emergence or development of risk factors in population groups in which they not yet appeared by taking action prior to the onset of disease, which removes the possibilities that a disease will ever occur. This may be achieved by modifying environmental and behavioral risk factors through mass education in susceptible individuals or populations. There are two main primary prevention strategies include high-risk and population approaches. Burden of disease in the community will be reduced by primary prevention programs which are aimed at lifestyle modifications in delaying or preventing diabetes successfully. However it has been acknowledged that very few diabetes primary prevention intervention trials have
been conducted, demonstrated positive results.

**High Risk Group**

A high risk strategy primarily aims to bring preventive care to individuals with a family history of diabetes who carry a genetic susceptibility, individuals with impaired glucose tolerance or pre-diabetes, ageing individuals, sedentary individuals and the large obese proportion of the population, certain ethnic groups who usually require a screening tool or clinical method to identify the risk. This approach has the advantage of directing appropriate interventions as well as providing potential motivations for individuals to make the necessary changes to reduce the impact of disease. A number of prospective studies conducted in impaired glucose tolerance subjects have shown a reduced progression to diabetes by controlling weight, die and increasing exercise. Disadvantage of high risk approach is that individual or group interventions are costly, need to be sustained for long periods and that it does not alter the underlying cause of the disease in the whole population as prevention and control measures are limited to those at risk.\(^\text{195}\)

**Population at Study**

The aim of this approach is to lower the mean level of risk for the entire population and influence favorably as a whole irrespective of individual risk levels by increasing physical activity, improving diet and reducing obesity. This not only increases the chance of preventing high risk individuals from developing diabetes, but also reduces the chance of individuals with low-risk becoming high-risk.\(^\text{196}\)
Strategies for primary prevention

Preventive measures for diabetes must be initiated in south Asian countries at least during the pre-diabetic stage in order to decrease the spiraling epidemic of diabetes in south Asia. Intervention studies in the West have provided hope that both lifestyle and pharmacological intervention can successfully prevent diabetes. Though pharmacological measures have shown favorable results, they should be considered only when intensive lifestyle interventions are unsuccessful or at least in combination with lifestyle modification. Prevention strategies must be implemented at the community level, by mass education camps and awareness programs emphasizing the importance of lifestyle intervention.

SECONDARY PREVENTION

Secondary prevention refers to action which halts the progress of a disease at its incipient stage and prevents complication. The specific interventions are early diagnosis and adequate treatment which may reverse the disease or reduce its progression and the development of complications.

TERTIARY PREVENTION

Defines all the measures available to reduce or limit impairments, diabetic complications and disabilities, thereby minimizing and controlling suffering caused by diabetes and to rehabilitate the patients.

Though our country is having enormous number of patients of diabetes and as this number is going to increase in the coming time, the information about the prevalence of diabetes and incidence of it’s complications and associated
characteristics of metabolic syndrome is not very well defined in this country. Time has come where all this information about potential diabetics should be handy so that the treatment and preventive program can be initiated to scrap off the disease morbidity and economic burden. There is an urgent need to identify potential diabetics which are likely to be prevalent amongst FDRs of type-2 DM patients. This is important to evaluate the state of abnormal glucose tolerance, insulin resistance, obesity and other correlating factors which have been the basic idea and core concept of the present study. With this goal and aim, accomplished strategies to prevent the development of diabetes in these “at risk” individuals can be chalked out and put into action considering that prevention of development of diabetes is the only answer to this metabolic epidemic first around the corner.