Chapter 1

Introduction
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Diabetes Mellitus (DM) is one of the oldest diseases to be mentioned in medical texts across the ancient civilizations. It is also mentioned as one of the eight dangerous diseases in Ayurveda, which identifies 20 types of the disease. However, diabetes became a recognized clinical entity under allopathic system in 1812 when the New England Journal of Medicine and Surgery was founded. Prior to the discovery of insulin and its extraction, diabetes was a major fatal disease at least in the western world. However, towards the end of 19th century medical breakthroughs gave a hope for the diabetics.

In 1889, Joseph von Mering and Oskar Minkowski found that removing the pancreas from dogs resulted in fatal diabetes, providing the first clue that pancreas plays a key role in regulating glucose concentrations. In 1910, Sir Edward Albert Sharpey-Schafer hypothesized that diabetes was due to the deficiency of a single chemical produced by the pancreas which he called insulin. In 1921, Frederick Banting and Charles Best actually discovered insulin when they reversed diabetes that had been induced in dogs with an extract from the pancreatic islet cells of healthy dogs. Together with James Collip and John Macleod, they purified the hormone insulin from bovine pancreases and were the first to use it to treat a patient with diabetes. The production of insulin and its therapeutic use quickly spread around the world. However, by 1933 a new form of diabetes was discovered which didn’t respond to insulin treatment. This spurred further research in diabetes pathology, and diagnosis.

DM is now known to be a group of metabolic diseases caused by a deficiency of the pancreatic hormone insulin, which results in a failure to metabolize sugars and starch. It is a progressive and chronic endocrine disorder that often leads to a serious micro- and macrovascular complications, including cardiovascular diseases (1). Generally insulin is either insufficient or ineffective in individuals with DM (2).

1.1 Classified types of Diabetes Mellitus

The classified types of diabetes mellitus are:

1. Type 1 diabetes mellitus (T1DM) is caused by autoimmunological destruction of the insulin-producing cells of the pancreas and accounts for 5–10% of all cases of diabetes, with the key susceptibility gene mapping to the human leukocyte antigen (HLA) region of chromosome 6 (3).

2. Type 2 diabetes mellitus (T2DM), the most common form of diabetes, accounts for approximately 90% of cases, affecting 10–20% of those over 45 years of age in many developed countries (3). An individual suffering from T2DM has a physiological resistance to the effects of insulin within the peripheral tissues. Essentially, the insulin, which the body is still capable of producing, is not physiologically effective due to either insufficiency in volume or quality (4).
3. Other specific types (5) include:

- genetic defects of beta-cell function; genetic defects in insulin action;
- diseases of the exocrine pancreas (such as Pancreatitis; Trauma/pancreatectomy; Neoplasia; Cystic fibrosis; Hemochromatosis; and Others);
- Endocrinopathies (such as Acromegaly; Cushing's syndrome; Glucagonoma; Pheochromocytoma; Hyperthyroidism; Somatostatinoma; Aldosteronoma; and Others);
- Drug- or chemical-induced (Vacor*; Pentamidine; Nicotinic acid; Glucocorticoids; Thyroid hormone; Diazoxide; Beta-adrenergic agonists; Thiazides; Phenytoin; Alfa-interferon; and Others);
- Infections (such as Congenital rubella; Cytomegalovirus; and Others);
- Uncommon forms of immune-mediated diabetes;
- Other genetic syndromes sometimes associated with diabetes (Down syndrome; Klinefelter's syndrome; Turner's syndrome; Wolfram syndrome; Friedreich's ataxia; Huntington's chorea; Lawrence-Moon Beidell syndrome; Myotonic dystrophy; Porphyria; Prader-Willi syndrome; and Others); and
- Gestational diabetes mellitus.

*Vacor is an acute rodenticide that was released in 1975 but withdrawn as a general-use pesticide in 1979 because of severe toxicity. Exposure produces destruction of the beta cells of the pancreas, causing diabetes mellitus in survivors.

1.2 Etiology of Type 2 Diabetes Mellitus

The etiology of T2DM appears to involve complex interactions between environmental and genetic factors. Presumably, the disease develops when a diabetogenic lifestyle (i.e., excessive caloric intake, inadequate caloric expenditure, obesity) is superimposed on a susceptible genotype.

The body mass index (BMI) at which excess weight increases risk for diabetes varies with different racial groups. For example, compared with persons of European ancestry, persons of Asian ancestry are at increased risk for diabetes at lower levels of overweight. Hypertension and prehypertension are associated with a greater risk of developing diabetes in whites than in African Americans. So, T2DM is a complex disorder that is strongly familial, but clearly arises from the interactions of many genetic and non-genetic factors with some forms of the disease resulting from mutations in a single gene, while others are multifactorial in origin (3,5,6).
1.2.1 Risk factors of Type 2 Diabetes Mellitus

The risk factors for T2DM include environmental effects such as obesity (particularly abdominal obesity), aging, ethnicity, family history of diabetes, history of gestational diabetes, sedentary lifestyle, low birth weight, and polycystic ovary syndrome (7). Generally, 80% or more of the people with T2DM are obese with the remaining above ideal weight indicating obesity as a predominant link to the development of T2DM (8). These risk factors are classified into non-modifiable, and modifiable.

1.2.1.1 Non-modifiable risk factors

Nonmodifiable risk factors include a first-degree relative with DM, a genetic predisposition to insulin resistance, race and ethnicity, and, in women, history of polycystic ovarian syndrome, gestational diabetes, or giving birth to a baby weighing more than 9 pounds (9-15). The risk of developing DM also increases with advancing age (9, 16).

1.2.1.2 Modifiable risk factors

Modifiable risk factors for DM include obesity or a high percentage of visceral (abdominal) fat, physical inactivity, smoking, and consumption of a diet high in saturated fat. DM is also frequently associated with other health conditions, such as hyperlipidemia, hypertension, and metabolic syndrome (9,10,13,17,18).

1.2.2 Type 2 Diabetes Mellitus and genetics

Though insulin resistance and progressive pancreatic β-cell dysfunction have been recognized as the two fundamental features in the pathogenesis of T2DM, the specific molecular defects affecting insulin sensitivity and/or β-cell function remain largely undefined.

Significant scientific evidence exists for the role of genetic factors in the pathogenesis of T2DM. For instance, T2DM clusters in families, its concordance rate in monozygotic twins is higher than in dizygotic ones, and there are ethnic groups with a very high prevalence of this disease (19).

While the genomewide-scans have recognized numerous potential chromosomal susceptibility regions across different human populations, finding a causative gene for T2DM has remained vague. Hanis et al. (1996) reported linkage to a region on chromosome 2q37.3 among Mexican Americans and identified the foremost susceptibility locus, located in the interval that spans markers D2S125–D2S140 (20). Following a combined strategy of positional cloning and a newly developed statistical method of partitioning linkage, these investigators identified a novel gene, Calpain 10 (CAPN10, as a putative T2DM susceptibility gene in this region (Horikawa et al. 2000).
Polymorphisms in this gene (SNP-43, SNP-44, del/ins-19, and SNP-63), all located in intronic sequences, were found to be involved in increased risk of the disease. Though the common G allele at SNP-43 was initially found to be significantly associated with the phenotype in families that showed linkage to non-insulin-dependent diabetes mellitus-1 (NIDDM1) region on chromosome 2. Variation in CAPN10 has been associated with a threefold increased risk of T2DM in Mexican-Americans and an increased risk of diabetes in Northern European populations (21,22).

Understanding the genetic basis of T2DM could assist in the development of screening tests to identify subjects at risk of developing T2DM at an early stage so that prevention strategies, lifestyle advice, and medical treatment can be initiated at the earliest possible stage. In addition, an understanding of the genetic basis of T2DM can lead to discovering new approaches for the prevention and more effective treatment of this condition.

1.2.3 Type 2 Diabetes Mellitus and epigenetics

Epigenetics is defined as the study of heritable changes in genome function that occur without a change in DNA sequence. The epigenetics of T2DM is the interaction between gene activation and epidemiology, where gene activation can be in the form of DNA methylation, histone modification or RNA activation. This could be affected by different epidemiological factors, namely age, obesity, nutrition, physical activity and intrauterine environment. Environmental factors that contribute to the development of T2DM can lead to a disease phenotype by affecting gene expression through epigenetic modifications. Epigenetic modifications of the genome provide a mechanism that allows the stable propagation of gene expression from one generation of cell to the next.

Many studies have linked T2DM with low birth weight, as shown by Hales et al. who found that men with a birth weight of less than 2.5 kg were seven times more likely to have glucose intolerance or T2DM than those who were heavier in their body weight (24). The environmental role in regulating epigenetic phenomena may be explained by methylation, and it has been suggested that DNA methyl transferase might act on chromatin, which is methylated at H3K9Ac. Epigenetic modifications might be reversible, which provide a therapeutic tool that can be used to prevent common diseases like T2DM.

1.3 Landmarks in Diabetes Management

The discovery of insulin in 1921 and the availability of home blood glucose monitoring in 1981 perhaps represent the greatest advances thus far in the world of diabetes. But in the past few years, numerous incremental developments have also remarkably improved the prognosis and quality of life for patients with T1DM and T2DM.
Continuous glucose monitoring (CGM) has revolutionized the care of T1DM, and it has also allowed for better troubleshooting in some patients with T2DM.

1.4 Overall aim of the study

Although, a) Parashar and associates (25) studied prevalence of diabetes mellitus among bank employees of Meerut district in India; b) ASSOCHAM did a survey on the prevalence of diabetes among private employees in India; c) and, Cassell and associates researched on haplo type combinations of Calpain 10 gene polymorphisms association with increased risk of impaired glucose tolerance and T2DM in South Indians – no one has studied the prevalence of T2DM exclusively among ITeS employees in Hyderabad and much less the association of Calpain 10 gene among them. The present study aimed to fill this gap.

The overall aim of the present study is to assess calpain-10 gene polymorphisms in T2DM patients working in Information Technology Enabled Service (ITeS) sector in Hyderabad, Telengana. Hereafter this population is referred to as Hyderabad-ITeS (HiTeS)

The specific Objectives are:

1. To evaluate the impact of environmental factors such as sleep, alcohol/caffeine consumption on Type 2 Diabetes Mellitus patients working with BPO, and KPO companies in Hyderabad.
2. To study the prevalence of common variants in Calpain 10 gene, SNPs -43, -44, -63 and del/ins-19 in T2DM as compared to control subjects
3. To evaluate the relation of these variants in the development of Type 2 Diabetes Mellitus in HiTeS