

Review Article**TYPE2 DIABETES MELLITUS: A REVIEW OF CURRENT TRENDS****Banoo H<sup>1</sup>, Nusrat N<sup>2</sup>, Nasir N<sup>3</sup>**

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**Abstract**

As we learn more about the pathophysiology of Diabetes Mellitus, we find that there is more yet to be learned. This may sound like a trite statement, but in reality it is true. The aim of this paper is to review the information on type 2 diabetes mellitus with emphasis on its etiology, pathogenesis and pathophysiology through literature review. Type 2 diabetes mellitus is caused by genetic and environmental factors. It is a group of genetically heterogenous metabolic disorder that causes glucose intolerance, involving impaired insulin secretion and insulin action. The prevalence of Diabetes is increasing rapidly worldwide and the World Health Organization (2003) has predicted that by 2030 the number of adults with diabetes would have almost doubled worldwide, from 177 million in 2000 to 370 million. A coordinated multidisciplinary approach is needed that involves scientists, public health practitioners, educators, clinicians and diabetics, with support from government authorities and non-governmental organizations to reduce the incidence of diabetes significantly.

**Key words:** Diabetes Mellitus, Pathophysiology, Pathogenesis, Etiology.

**Introduction**

Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago<sup>1</sup>. In 1936 the distinction between type1 and type 2 DM was clearly made<sup>2</sup>. Type 2 DM was first described as a component of metabolic syndrome in 1988<sup>3</sup>. It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million<sup>4</sup>. The prevalence of diabetes is increasing rapidly worldwide and the World Health Organization (2003) has predicted that by 2030 the number of adults

with diabetes would have almost doubled worldwide, from 177 million in 2000 to 370 million<sup>5</sup>. The rise in prevalence is predicted to be much greater in developing than in developed countries (69% versus 20%) . In developing countries, people aged 40 to 60 years (that is, working age) are affected most, compared with those older than 60 years in developed countries<sup>6</sup>.

Diabetes Mellitus (DM) are a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from defects in insulin secretion, insulin action or both. The complications of

diabetes account for most of its morbidity and mortality. 65% of individuals with DM have high BP, heart disease and stroke. Death rates in diabetes are 4 times more than non diabetes. Diabetic retinopathy causes 12000 to 24000 new cases of blindness every year<sup>7</sup>.

Diabetes mellitus is of two types:

**1. Type 1 Diabetes Mellitus, also called Insulin Dependent Diabetes Mellitus (IDDM)**, is caused by lack of insulin secretion by beta cells of the pancreas.

**2. Type 2 Diabetes Mellitus, also called Non-Insulin Dependent Diabetes Mellitus (NIDDM)**, is caused by decreased sensitivity of target tissues to insulin. The reduced sensitivity to insulin is often called insulin resistance.

### **Epidemiology and Etiology Of Type 2 Diabetes Mellitus (NIDDM)**

Type 2 diabetes mellitus (DM) is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world. Type 2 diabetes is the predominant form of diabetes and accounts for at least 90% of all cases of diabetes mellitus<sup>8</sup>. The rise in prevalence is predicted to be much greater in developing than in developed countries (69 versus 20%). This increase in type 2 diabetes is inextricably linked to changes towards a Western lifestyle (high diet with reduced physical activity) and genetics<sup>9</sup>. Obesity is emerging as serious problem throughout the world not only among adults but also children, teenagers and young adults<sup>10</sup>. Obesity has been found to contribute to approximately 55% of cases of

type 2 DM. The increased rate of childhood obesity between the 1960s and 2000s is believed to have led to the increase in type 2 DM in children and adolescents<sup>11</sup>.

Type 2 diabetes is a heterogeneous disorder caused by a combination of:

1. Genetic factors related to impaired insulin secretion, insulin resistance.
2. Environmental factors such as obesity, over eating, lack of exercise, and stress as well as aging<sup>12</sup>.

Genetics are more important in the etiology of T2DM as shown by studies in monozygotic twins where concordance rates for T2DM approach 100%. Genetic contribution is unknown, but several genes are involved. Over 200 susceptible genes have been investigated such as Insulin receptor, GLUT, Glycogen Synthase. Susceptible genes on chromosome 1q,12q and 20q. The GLUT2 gene, expressed in liver and pancreatic beta cells, and GLUT4, expressed in skeletal muscle and adipocytes are strong candidate genes for the genetic susceptibility to type 2 DM<sup>13</sup>.

The genes that predispose to type 2 DM are incompletely identified, but recent genome-wide association studies have identified a large number of genes that convey a relatively small risk for type 2 DM (>20 genes, each with a relative risk of 1.06–1.5). Most prominent is a variant of the transcription factor 7-like 2 gene that has been associated with type 2 diabetes in several populations and with impaired glucose tolerance in one population at high risk for diabetes. Genetic polymorphisms associated with type 2 diabetes have also

been found in the genes encoding the peroxisome proliferators-activated receptor- $\gamma$ , inward rectifying potassium channel, zinc transporter, IRS, and calpain 10. The mechanisms by which these genetic loci increase the susceptibility to type 2 diabetes are not clear, but most are predicted to alter islet function or development or insulin secretion. While the genetic susceptibility to type 2 diabetes is under active investigation (estimation that <10% of genetic risk is determined by loci identified thus far), it is currently not possible to use a combination of known genetic loci to predict type 2 diabetes<sup>14</sup>.

Type 2 diabetes mellitus has a greater genetic association than Type 1 DM, A population based twin study in Finland has shown a concordance rate of 40%, for Type 2 diabetes mellitus than for Type 1 diabetes mellitus. Type 2 diabetes mellitus affects 1 to 2% of Caucasians<sup>15</sup> but it is much higher in some ethnic groups such as Pima Indians<sup>16</sup> and Arabs and approaches 50% in South India. This indicates that genetic factors are more important than environmental factors determining the molecular genetic etiology can help to define the prognosis.

**Environmental factors:** Increase in type 2 diabetes is inextricably linked to changes towards a Western lifestyle, high diet with reduced physical activity. Obesity has been found to contribute to approximately 55% of cases of type 2 DM. During last 40 years investigators have noted that many overweight individuals with diabetes were hyperinsulinemic or normoinsulinemic. That cellular insulin receptor numbers were down

regulated by hyper insulinemia and that coincidentally insulin-responsive tissues became resistant to the metabolic effects of both endogenous and exogenous insulin<sup>17</sup>. The increased rate of childhood obesity between the 1960s and 2000s is believed to have led to the increase in type 2 DM in children and adolescents<sup>18</sup>. The incidence of diabetes increases with age, with most cases being diagnosed after the age of 40 years. This equates to a lifetime risk of developing diabetes of 1 in 10<sup>19</sup>.

It is typically a multifactorial disease involving multiple genes and environmental factors to varying extents. It is not an autoimmune disorder, and the susceptible genes that predispose to NIDDM have not been identified in most patients. This could be due to the heterogeneity of the genes responsible for the susceptibility to NIDDM<sup>20</sup>. As a result of this trend, it is fast becoming an epidemic in some countries of the world with the number of people affected expected to double in the next decade due to increase in ageing population, thereby adding to the already existing burden for health care providers, especially in poorly developed countries.

### **Pathogenesis of Type 2 Diabetes Mellitus**

Under normal physiological conditions, plasma glucose concentrations are maintained within a narrow range, despite wide fluctuations in supply and demand, through a tightly regulated and dynamic interaction between tissue sensitivity to insulin (especially in liver) and insulin secretion<sup>21</sup>. In type 2 diabetes these mechanisms break down with the

consequence of two main pathological defects.

**A. Impaired insulin secretion through a dysfunction of the pancreatic  $\beta$ -cells<sup>22</sup>.**

That is pancreatic  $\beta$  cell failure, this can be due to:

1. Moderate reduction in total mass of pancreatic islet tissue, so fall in insulin concentration.
2. Deposition of amyloid accompanied by atrophy of normal tissue [islet epithelial cells] this is not the cause but rather reflects a pathological process.
3.  $\beta$  cell number is reduced to 20 to 30 % in T2DM, glucagon secretion is increased thus hyperglycemia. Insulin resistance tends to raise blood glucose which stimulates insulin secretion, but when maximum insulin secreting capacity has been exceeded it causes decline in insulin generation. So possible B cell decompensation which gives rise to:-

- x Glucotoxicity.
- x An intrinsic failure of insulin production.
- x A switch to abnormal processing of pathways producing inactive products and chronic degranulation of B cells.

- x In addition, elevation of free fatty acid levels ("lipotoxicity") and dietary fat may also worsen islet function.

**B. Impaired insulin action through insulin resistance<sup>23</sup>.**

Type 2 diabetes is caused by decreased sensitivity of target tissues to insulin. The reduced sensitivity to insulin is often called insulin resistance and this resistance can be due to any of these general causes:

1. Abnormal insulin molecule
2. An excessive circulating antagonist
3. Target tissue defects, this is the most common cause of insulin resistance in T2DM.

**Table 1. Some causes of insulin resistance**

S.No.	Cause
1.	Obesity/overweight (especially excess visceral adiposity)
2.	Excess glucocorticoids (cushing's syndrome or steroid therapy)
3.	Excess growth hormone (acromegaly)
4.	Pregnancy, gestational diabetes
5.	Polycystic ovary disease
6.	Lipodystrophy (acquired or genetic, associated with lipid accumulation in liver)
7.	Autoantibodies to the insulin receptor
8.	Mutations of insulin receptor

9. Mutations of the peroxisome proliferators' activator receptor  $\gamma$  (PPAR $\gamma$ )
10. Mutations that cause genetic obesity (e.g., melanocortin receptor mutations)
11. Hemochromatosis (a hereditary disease that causes tissue iron accumulation)

A characteristic feature of T2DM is that it is often associated with other medical disorders. Some features of insulin resistance [metabolic syndrome] are:

- x Hyper insulinemia
- x Hypertension.
- x Genetic obesity
- x Low HDLcholesterol, elevated triglycerides
- x Microalbuminuria
- x Increase fibrinogen
- x High plasma uric acid
- x High plasminogen activator inhibitor.

In both types of diabetes mellitus, metabolism of all the main food stuffs is altered. The basic effect of insulin lack or insulin resistance on glucose metabolism is to prevent the efficient uptake and utilization of glucose by most cells of the body, except those of the brain<sup>24</sup>. As a result of this, blood glucose concentration increases, cell utilization of glucose falls increasingly lower and utilization of fats and proteins increases. The clinical characteristics of patients with type 2 diabetes mellitus are shown in Table 2.

**Table 2. Clinical characteristics of patients with Type 2 diabetes mellitus.**

<b>Age of onset</b>	Usually greater than 30 years
<b>Body mass</b>	Obese
<b>Plasma insulin</b>	Normal to high initially
<b>Plasma glucagon</b>	High, resistant to suppression
<b>Plasma glucose</b>	Increased
<b>Insulin sensitivity</b>	Reduced
<b>Therapy</b>	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

### **Pathophysiology of Type 2 Diabetes Mellitus (NIDDM)**

Individuals with NIDDM have detectable levels of circulating insulin, unlike patients with IDDM. On the basis of oral glucose tolerance testing the essential elements of NIDDM can be divided into four distinct groups:

- i) Those with normal glucose tolerance.
- ii) Chemical diabetes (called impaired glucose tolerance).
- iii) Diabetes with minimal fasting hyperglycemia (fasting plasma glucose less than 140 mg/dl).
- iv) Diabetes mellitus in association with overt fasting hyperglycemia (fasting plasma glucose greater than 140 mg/dl).

The individuals with impaired glucose tolerance have hyperglycemia in spite of having highest levels of plasma insulin,

indicating that they are resistant to the action of insulin. In the progression from impaired glucose tolerance to diabetes mellitus, the level of insulin declines indicating that patients with NIDDM have decreased insulin secretion. Insulin resistance and insulin deficiency are common in the average NIDDM patients. Insulin resistance is the primary cause of NIDDM, however some researcher contend that insulin deficiency is the primary cause because a moderate degree of insulin resistance is not sufficient to cause NIDDM. Most patients with the common form of NIDDM have both defects. Recent evidence has demonstrated a role for a member of the nuclear hormone receptor super family of proteins in the etiology of type 2 diabetes. Relatively new classes of drugs used to increase the sensitivity of the body to insulin are the thiazolidinedione drugs. These compounds bind to and alter the function of the peroxisome proliferators-activated receptor  $\gamma$  (PPAR- $\gamma$ ). PPAR- $\gamma$  is also a transcription factor and when activated, binds to another transcription factor known as the retinoid x receptor (RXR). When these two proteins are complexed a specific set of genes becomes activated. PPAR- $\gamma$  is a key regulator of adipocyte differentiation; it can induce the differentiation of fibroblasts or other undifferentiated cells into mature fat cells. PPAR- $\gamma$  is also involved in the synthesis of biologically active compounds from vascular endothelial cells and immune cells<sup>25</sup>.

No cure has yet been found for the disease; however, treatment modalities include lifestyle modifications, treatment of obesity,

oral hypoglycemic agents and insulin sensitizers like metformin, a biguanide that reduces insulin resistance, is still the recommended first line medication especially for obese patients. Other effective medications include non-sulfonylurea secretagogues, thiazolidinediones, alpha glucosidase inhibitors, and insulin. Recent research into the pathophysiology of type 2 DM has led to the introduction of new medications like glucagon-like peptide 1 analogues: dipeptidyl peptidase-IV inhibitors, inhibitors of the sodium-glucose co-transporter 2 and 11 $\beta$ -hydroxysteroid dehydrogenase 1, insulin-releasing glucokinase activators and pancreatic-G-protein-coupled fatty-acid-receptor agonists, glucagon-receptor antagonists, metabolic inhibitors of hepatic glucose output and quick-release bromocriptine. Inhaled insulin was licensed for use in 2006 but has been withdrawn from the market because of low patronage<sup>26</sup>.

## Conclusion

The global burden of diabetes is increasing worldwide as it is a costly disease for developing economies of the world. To reduce the pandemic of type 2 diabetes and its effects on lives and economies worldwide, it is necessary to have an improved understanding of its etiology, pathogenesis and pathophysiology to focus therapeutic and research efforts appropriately. A coordinated multidisciplinary approach is needed that involves scientists, public health practitioners, educators, clinicians and diabetics, with support from government

authorities and nongovernmental organizations to reduce the incidence of diabetes significantly.

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