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# Diabetes Mellitus: Its Cardiovascular Complications and Mechanism Involved

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**ABSTRACT:**
Diabetes mellitus is a multifactorial disease and currently cardiovascular complications in the diabetes are the leading cause of death in the worldwide. The macro-vascular and micro- vascular complications are observed in both type 1 and type 2 diabetic individuals which is the major cause of morbidity and mortality in all the diabetic population. This review is based on type of diabetes mellitus, causes, pathophysiology involved in the diabetes mellitus and in cardiovascular complications, treatment and prevention strategies involved in diabetes mellitus.
**KEYWORDS: Diabetes mellitus, WHO Classification, Epidemiology, Mechanism of Cardiovascular complications, Treatment.**

## I. INTRODUCTION

***Diabetes mellitus (DM)***

Diabetes mellitus is a chronic metabolic disorder which causes damage to the various organ of the body due to the increase in the blood glucose for the prolong period of time. The high blood glucose level leads to the symptoms like frequent urination, increase thirst and the hunger.[1]Two major pathological factors include in diabetes is when pancreas not produce enough insulin then it leads to the diabetes and when the cell of the body unable to respond the insulin produced in the body properly.[2]Diabetes mellitus is non-communicable disease globally which currently affecting 230 million peoples in the world and by 2025 it is expected to reach 380 million peoples in worldwide.[3] Meanwhile in India currently 60 million individuals diagnose with diabetes and it is predicted that 79.4 million individuals may affect with diabetes up to 2030. [4] Among the type 1 and type 2 diabetes mellitus, type 2 diabetes mellitus is very common affecting more than 90 precent of all cases.[5] In diabetes due to high blood glucose level the symptoms like frequent urination (polyuria), increase thirst (polydipsia) and the hunger (polyphagia).[6] It is the chronic condition characterised by hyperglycaemia[7,8] which is highly associated with the long term micro vascular complications affecting eye, kidney, nerves and increase the risk of various short term and long term cardiovascular complications which includes micro vascular disease like hypertension,hyperlidemia, heart attack, coronary artery disease , strokes[9], cerebral vascular disease and peripheral vascular disease[10] and micro vascular disease like retinopathy, nephropathy and neuropathy.[11-15]

**CLASSIFICATION OF DIABETES**

In 1965 WHO published its 1st classification system for diabetes using four age of diagnosis categories which includes infantile or childhood (with onset between the age of 0-14), young (with onset between the age of 15-25), adult (with onset between the age of 14- 25) and elderly (with onset between the age of 65 years or above). In addition to this WHO also recognised other form of diabetes including juvenile type, insulin resistant, gestational, pancreatic, endocrine and iatrogenic type of diabetes. In 1980 WHO published 1st widely accepted and globally adapted classification of diabetes which further updated in 1985.

There have been recent calls to review and update the classification system of diabetes in 2019. The single classification system for diabetes ideally facilitate three primary purpose including clinical care, aetiopathology and epidemiology and hence with this mind expert consider the best defined classification for diabetes which is internationally acceptable and can check using easy and radially available clinical parameters and resources which are being reliable and equitable and feasible to implement. [16, 17]

| **TYPES** | |
|---|---|
| **Type 1 diabetes** | Destruction of Beta Cells |
| **Type 2 diabetes** | Insulin Resistance |
| **Hybrid forms of diabetes** | A. slowly evolving immune mediated diabetes for adult |
| | B. Ketosis prone type 2 diabetes |
| **Other specific types** | A. Monogenic diabetes |
| | i. monogenic defects of beta cell function |
| | ii. monogenic defect in insulin action |
| | B. disease of exocrine pancreas |
| | C. endocrine disorder |
| | D. Drug- or chemical-induced |
| | E. Infections |
| | F. Uncommon specific forms of immune-mediated diabetes |
| | G. Other genetic syndromes sometimes associated with diabetes |
| **Unclassified diabetes** | This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis of diabetes |
| **Hyperglycaemia first detected during pregnancy** | A.Diabetes mellitus in pregnancy |
| | B. Gestational diabetes mellitus |

***Table 1:*** *Classification of Diabetes Mellitus*

### *A. Type 1 diabetes:*

In type 1 diabetes body fails to produce enough insulin[16] this type of diabetes is also known as insulin dependent diabetes mellitus or juvenile diabetes. [17] The cause of type 1 diabetes is unknown[18]. About 5%- 10 % of people are suffered from type 1 diabetes.[19]

In this type of diabetes the rate of destruction of beta cell is rapid in some individual and slows in other individual. Nearly 70% to 90% of T2DM people at diagnosis have evidence of an immune mediated process with beta cell autoantibodies against glutamic acid decarboxylase (GAD65), islet antigen-2 (IA-2), ZnT8 transporter or insulin and association with the gene controlling immune response.[20]

### *B. Type 2 diabetes*

The type 2 diabetes is result from the resistance of insulin. In type 2 diabetes cell fails to respond the insulin properly and as disease progresses a lack of insulin may develop. Type two diabetes is also called as non-insulin dependent diabetes mellitus or adult onset diabetes. Obesity and lack of exercise, energy dense diet, unhealthy lifestyle and prior gestational diabetes (GDM) is the primary cause of this type of the diabetes mellitus[21]. About 90%- 95% all cases of diabetes is type 2 diabetes worldwide[22, 23] with the highest proportion in low and middle income countries.[24]

### *C. Hybrid form of diabetes*

To distinguish T1DM from T2DM amongst the adult have resulted in propose new disease categories and nomenclature which include slowly evolving immune mediated diabetes and ketosis prone T2DM. Slowly evolving immune mediated diabetes most frequently observed in adults who present clinically same symptoms as seen in T2DM, but later shows evidence of pancreatic autoantibodies that can react with non-specific cytoplasmic antigen in islets. This form of diabetes also called as latent autoimmune diabetes in adult (LADA). Ketosis prone type 2 diabetes is a form of diabetes which was initially identified in young African Americans and slowly has emerged as new clinical entry.[17]

*D.* ***Other specific types***

| **MONOGENIC DIABETES** | **OTHER GENETIC SYNDROMES SOMETIMES ASSOCIATED WITH DIABETES** |
|---|---|
| GCK MODY ( maturity-onset diabetes of the young) | Down syndrome |
| HNF1A MODY | Friedreich's ataxia |
| HNF4A MODY | Huntington's chorea |
| HNF1B RCAD( renal cysts and diabetes) | Klinefelter's syndrome |
| mtDNA 3243 MIDD ( maternally inherited diabetes) | Lawrence-Moon-Biedel syndrome |
| KCNJ11 PNDM | Myotonic dystrophy |
| KCNJ11 DEND | Porphyria |
| 6q24 TNDM | Prader-Willi syndrome |
| ABCC8 MODY | Turner's syndrome |
| INS PNDM (permanent neonatal diabetes) | Others |
| WFS1 Wolfram syndrome | Uncommon Form of Immune mdiatd diabetes |
| FOXP3 IPEX syndrome | Insulin autoimmune syndrome (autoantibodies to insulin) |
| EIF2AK3 Wolcott-Rallison syndrome | Anti-insulin receptor antibodies |
| | Stiff man syndrome |
| **DRUG- OR CHEMICAL-INDUCED DIABETES** | **DISEASES OF THE EXOCRINE PANCREAS** |
| Glucocorticoids | Fibrocalculous pancreatopathy |
| Thyroid hormone | Pancreatitis |
| Thiazides | Trauma/pancreatectomy |
| Alpha-adrenergic agonists | Neoplasia |
| Beta-adrenergic agonists | Cystic fibrosis |
| Dilantin | Haemochromatosis |
| Nicotinic acid | Others |
| Pyrinuron | **OTHER CLINICALLY DEFINED SUBGROUPS** |
| Pentamidine | Diabetes associated with massive hypertriglyceridemia |
| **MONOGENIC DEFECTS IN INSULIN ACTION (MUTATED GENE FOLLOWED BY CLINICAL SYNDROME)** | **INFECTIONS** |
| INSR Type A insulin resistance | Congenital rubella |
| INSR Leprechaunism | Cytomegalovirus |
| INSR Rabson-Mendenhall syndrome | Others |
| LMNA FPLD (familialpartial lipodystrophy;) | |
| PPARG FPLD | |
| AGPAT2 CGL( congenital generalized lipodystrophy) | |
| BSCL2 CGL | |

***Table 2:*** *WHO classification of diabetes 2019*

***RISK FACTORS***

Diabetes mellitus is a multifactorial disease involve multiple behaviour, metabolic and genetic factors [25, 26] caused by various patho-mechanism. [27] The risk factors involved in type 1 diabetes mellitus includes family history, viruses, nutrition, Socioeconomic factors.[28,29]

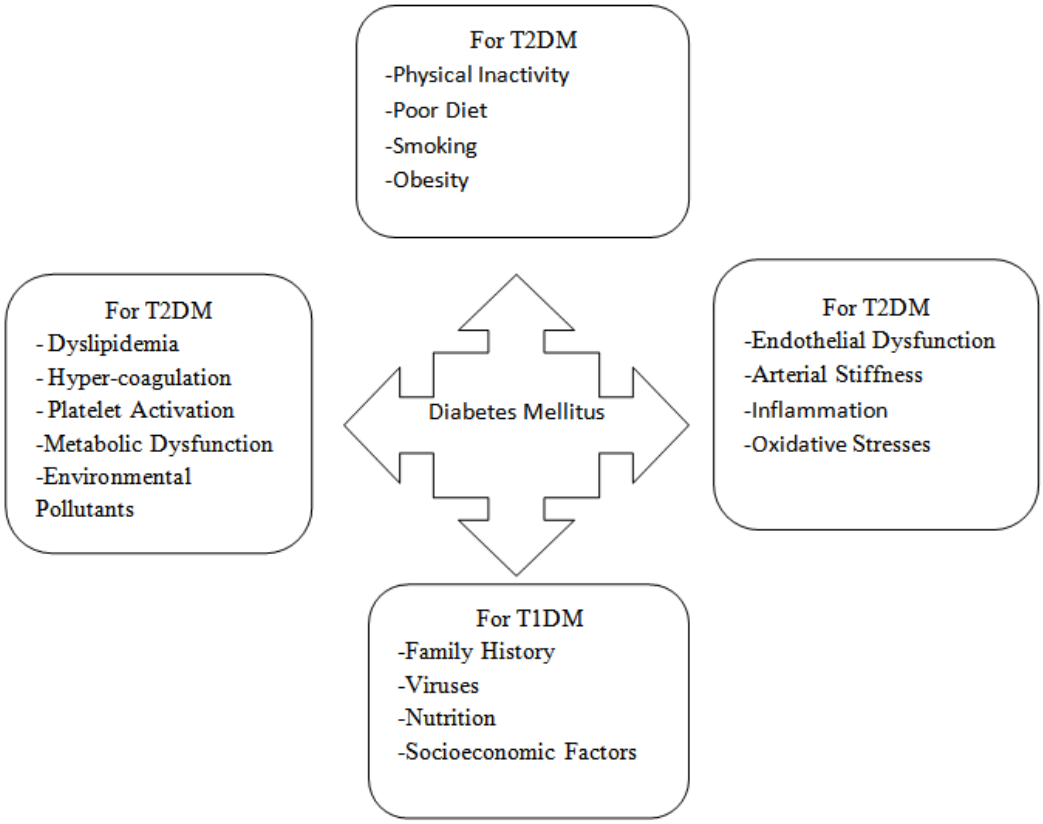


***Figure 1:*** *Risk factors involved in type 1 and type 2 diabetes mellitus*

The risk factors involved in type 2 diabetes are more diverse;[30]some risk factors can be easily modified and some are non-modified. Modified risk factors includes diet rich in saturated fat, simple carbohydrates, impaired glucose tolerance, metabolic syndrome, high blood pressure, elevated plasma triglyceride and the non-modified risk factors includes age (≥ 45), family history, ethnicity, gestational diabetes. [31]

| RISK FACTORS | |
|---|---|
| Modifiable | Non-Modifiable |
| -Diet rich in saturated fat<br>-Simple Carbohydrates<br>-Impaired Glucose Tolerance<br>-Metabolic Syndrome<br>-High blood pressure<br>-Elevated Plasma Triglyceride<br>-Physically Inactive | -Age (≥ 45)<br>-Family history<br>-Ethnicity<br>-Gestational Diabetes |

***Table 3:*** *Modifiable and Non-Modifiable risk factors.*

## II. EPIDEMIOLOGY

***Burden of diabetes worldwide***

The burden of diabetes is high in every country and still rising. In 2013 global prevalence of disease was 382 million [32] which rises to 422 million in 2016 particularly in low and middle income countries and 1.6 million death happens per year due to diabetes globally.[33] Approximately 463 million adult in between the age of 20 – 79 years were living with diabetes in 2019 and 79% adult were living in low to middle income countries were affected by diabetes [34] which is estimated to rise to 592 million by the 2035. From type 1 and type2 diabetes, type 2 diabetes accounts for majority (> 85 %).[35] The International Diabetes Federation gives the prediction of diabetes prevalence for top 10 countries. From the prediction it is found that China and India have a highest number of diabetes prevalence.[36]

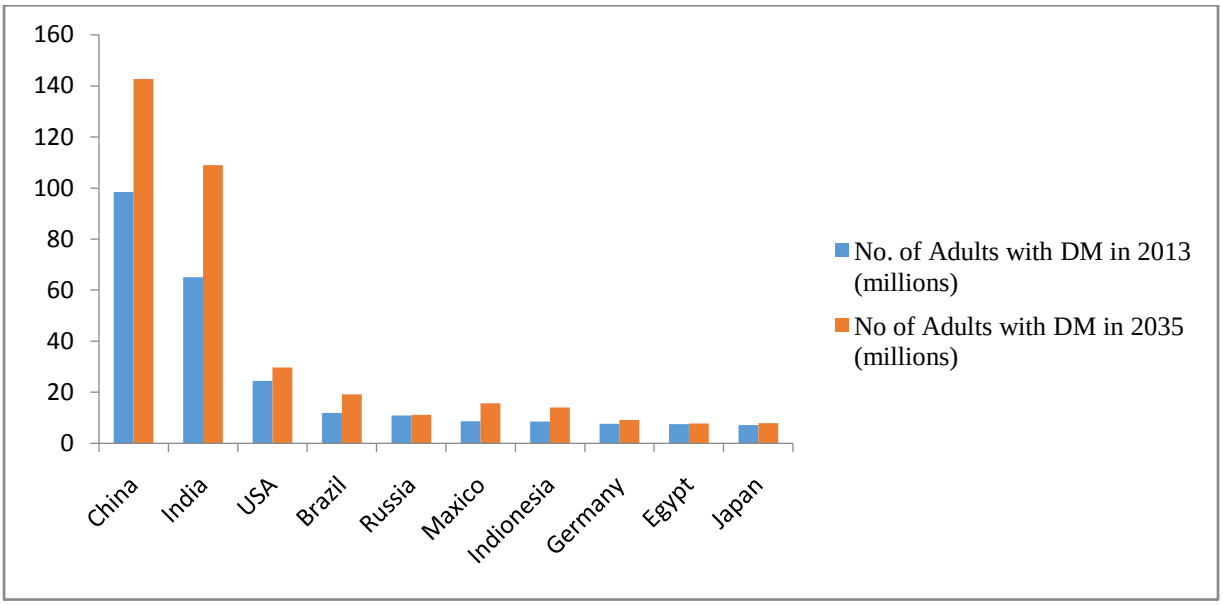


*Figure 2: Top 10 countries in number of people in diabetes*

***Burden of Diabetes in India***

After the China in the global diabetes epidemic, India rank second in prevalence of diabetes in both the rural and urban areas. In India type 2 diabetes is most important driver in diabetes epidemic. [37] The prevalence of type 1 diabetes mellitus and type 2 diabetes mellitus rise in India but since 2000 type 2 diabetes much more rapidly risen in India.[38, 39]

In 2000 about 32.7 million [40] people were affected which rises in to 35.5 million in 2003.[41] 40.9 million in 2007 [42, 43], 50.8 million in 2010[44,] 61.3 in 2011 million [45], 65.1 million in 2013,[46] 69.2 million in 2015. [47] and 72 million in 2017[48] which expected to rise almost double in 2025and 80 million by 2030.[49]

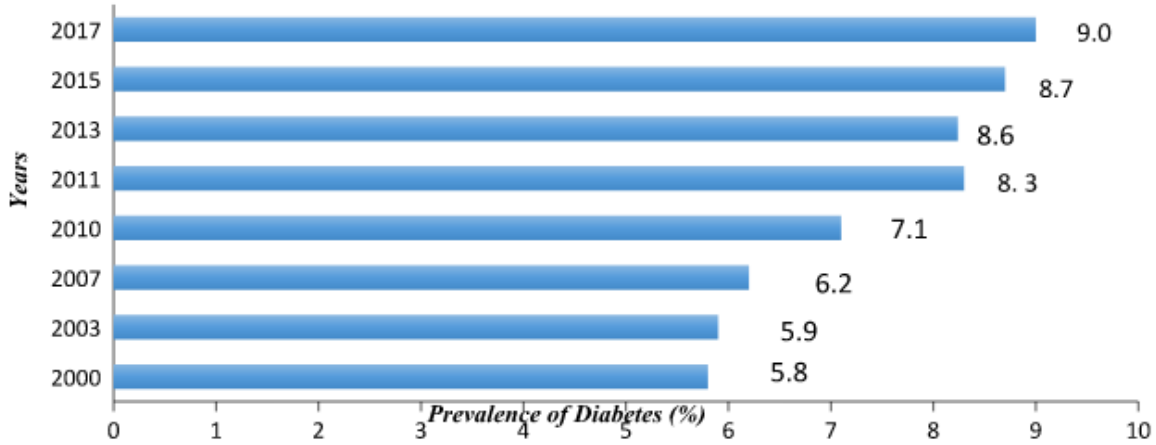


***Figure 3:*** *History of prevalence of diabetes in India*

***PATHOPHYSIOLOGY***

Two major pathological factors include in diabetes the first one is when pancreas not produce enough insulin then it leads to the diabetes and the second one is when the cell of the body unable to respond the insulin produced in the body properly.[50]

***Type 1 diabetes mellitus***

Type 1 DM is autoimmune disease in which destruction of insulin producing pancreatic beta cells take place, the characteristics of type 1 diabetes mellitus is an autoimmune diseases includes the immune competent and accessary cell in filtered pancreatic islets are present, islet cell specific antibodies are present, the monokinase and TH1 cells producing interleukin are present in the disease process, organ specific autoimmune disease occurs frequently in affected individual, the T cell mediated immune regulation is altered in CD 4+T cells compartment.[51, 52, 53]

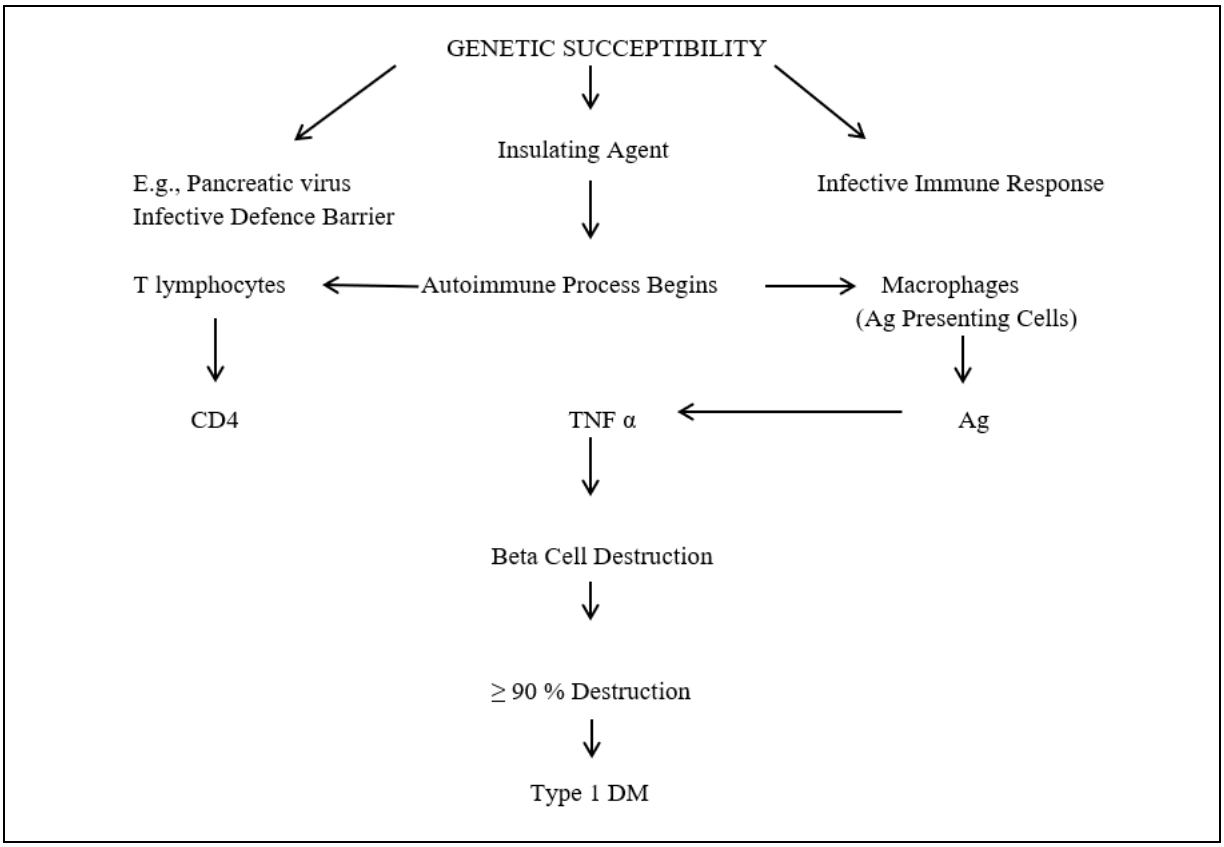


***Figure 4**: Pathophysiology of type 1 diabetes mellitus*

***Type 2 Diabetes Mellitus***

Impaired insulin secretion due to dysfunction of pancreatic beta cell and impaired insulin action due to insulin resistance which means insulin in the body does not exert sufficient action proportional to its concentration in blood. This is major pathophysiology involved in type 2 diabetes. Molecular mechanism of insulin resistance is related to the genetic factor[54] and environmental factor (hyperglycaemia, free fatty acids, and inflammatory mechanism). The genetic factors involves for insulin resistance are the genetic polymorphism of insulin receptor, insulin receptor substrate (IRS)-1, $\beta_3$ adrenergic receptor gene and uncoupling protein (UCP) gene which are associated with visceral obesity and promote insulin resistance.[55]

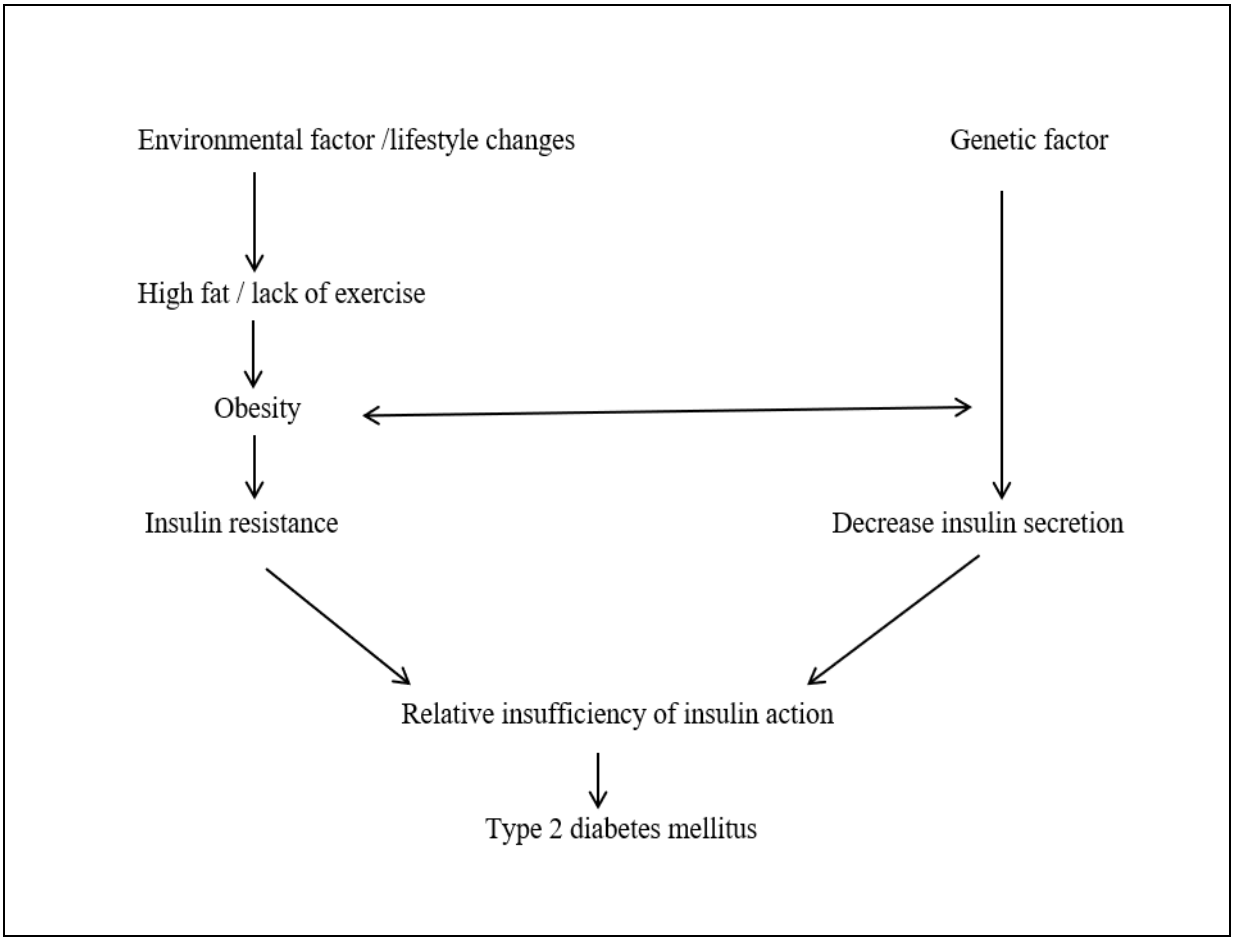


***Figure 5:*** *Pathophysiology of type 2 diabetes mellitus*

***CARDIOVASCULAR COMPLICATIONS ASSOCIATED WITH DIABETES MELLITUS***

The primary cause of the morbidity and mortality in pre-diabetics and type 2 diabetes mellitus is cardiovascular diseases.[56,57] The activation of protein kinase, rennin angiotensin system, advance glycation end product occurs when blood glucose level increases. The AGE-RAGE activation are due to metabolic syndrome and insulin resistance mechanism precipitate obesity, physical inactivity and genetic susceptibility.[58] In type 1 and type 2 diabetes mellitus, there is significantly increases risk of developing atherosclerotic cardiovascular disease. The macro-vascular and micro-vascular diseases are major independent risk factor for CVD. At the age of 50, about 67% life time risk for CVD in females are there.[59] 4,47,064 people were included in meta-analysis of 37 prospective cohort study of fatal coronary heart disease, the preliminary result found that 3.5 fold higher rate of fatal coronary heart disease in diabetic patient than that of non-diabetic patients.[60] In another study about 6, 98,782 individuals were included in meta-analysis which was recently carried out, the results shown that in diabetic patients the coronary heart disease and ischemic stroke independently double the risk in diabetic than conventional risk factor and it is also found that the risk of cardiovascular complications is higher in women than men. [61]

***Mechanism involved in cardiovascular complications*** [62- 67]

There are different molecular mechanism associated with cardiovascular complications in diabetes includes-

***Polyol pathway***

In the polyol pathway aldose reductase (AR) and sorbitol dehydrogenase (SDH) is the rate limiting enzyme. Normally AR reduces toxic aldehyde to inactive alcohol which is responsible for the protection of the cell. AR does not metabolize the significant amount of glucose as it has low affinity for the glucose but in hyperglycaemic state AR act as catalyst of glucose which results production of sorbitol further which get converted to fructose by metabolism of sorbitol dehydrogenase and intracellular accumulation of the sorbitol causes to increase the osmotic pressure. NADPH needed for regeneration of the glutathione but due consumption of the NADPH oxidative stresses increase which ultimately responsible for various short term and long term complication in diabetes mellitus.

***Formation of advance glycation end product***

Intracellular accumulation of the glucose leads to the generation of reactive dicarbonyls, like glyoxal, methyl glyoxal and 3-deoxyglucosone which form AGE by reacting amino group of protein. Due to the hyperglycaemia the formation of AGE leads to development of atherosclerotic lesion and causes various chronic complications in diabetes mellitus. Fructose increases the formation of advance glycation end product (AGE)

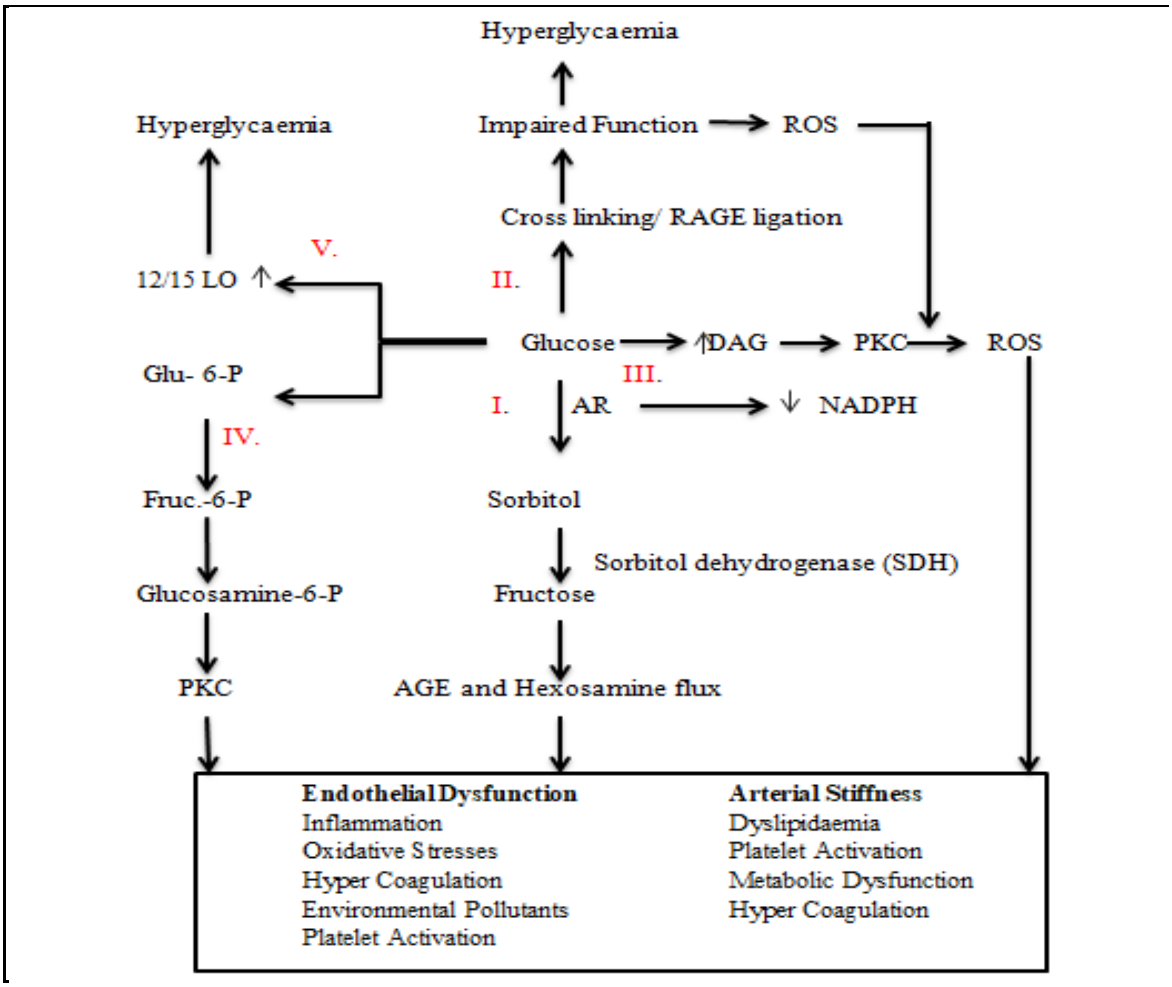


***Figure 6:*** *Mechanism involved in cardiovascular complications in diabetes mellitus*

I. Polyol pathway II. AGE formation III.PKC activation
IV. Hexosamine pathway V. 12/15 LO pathway

***Protein kinase c pathway***

Intracellular hyperglycaemia activates the protein kinase c through the diacylglycol (DAG) which promote the atherogenesis. Indirectly activation of PKC takes place due to activation of polyol pathway or 12/15-LO pathway activation.

***Hexosamine pathway***

The fructose –6 –phosphate is converted to the glucosamine-6-phosphate through the glucosamine fructose -6-phosphate aminotransferase (GFAT) activity in hexosamine pathway which provides the substrate for the synthesis of glycoprotein and prosteoglycans, glucosamine activate the protein kinase which is responsible for the atherohenesis. The role of hexosamine in diabetic complications is not yet clear but there are some studies which shows that there is relationship between macro vascular complications and the diabetes.

***12/15 Lipooxygenase (12/15-LO) pathway***

The 12 and 15 lipooxygenase is the enzyme which is involved in the formation of 12(S) and 15(S)-hydroxyeicosatetraeonic acid by inserting the oxygen at 12 and 15 carbon positions into the arachidonic acid. This enzyme is expressed on the endothelial cell, smooth muscle cells, monocytes and macrophages. The activity of this enzyme is directly related to the hyperglycaemia.

***DIAGNOSIS OF DIABETES***

The requirements for diagnostic confirmation for a person presenting with severe symptoms and gross hyperglycaemia differ from those for the asymptomatic person with blood glucose values found to be just above the diagnostic cut–off value. The diagnosis of diabetes in an asymptomatic subject should never be made on the basis of a single abnormal blood glucose value. For the asymptomatic person, at least one additional plasma/blood glucose test result with a value in the diabetic range is essential, either fasting, from a random (casual) sample, or from the oral glucose tolerance test (OGTT). Glycated haemoglobin, reflecting average glycaemia over a period of weeks, was thought to provide such a test. [52] The WHO Consultation concluded that HbA1c can be used as a diagnostic test for diabetes, provided that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement. [68]

***Diagnostic criteria of Diabetes***

Type 2 diabetes mellitus (NIDDM) normally diagnosed after the occurrence of classical symptoms like thirst, tiredness, glycosuria and hyperglycaemia. [69]

The major change recommended by WHO in the diagnostic criteria for diabetes mellitus is the lowering of the diagnostic value of the fasting plasma glucose concentration to 7.0 mmol/l (126 mg/dl) and above, from the former level of 7.8 mmol/l (140 mg/dl) and above. For whole blood the proposed new level is 6.1 mmol/l (110 mg/dl) and above, from the former 6.7 mmol/l (120 mg/dl). Furthermore, several studies have shown increased risk of micro vascular disease in persons with fasting plasma glucose concentrations of 7.0 mmol/l (126 mg/dl) and over, and of macro vascular disease in persons with such fasting concentrations, even in those with 2–h values of less than7.8 mmol/l (140 mg/dl). [4] Glycated Haemoglobin (HbA1c) of 6.5% is recommended as the cut point for diagnosing diabetes. A value less than 6.5% does not exclude diabetes diagnosed using glucose tests. The expert group concluded that there is currently insufficient evidence to make any formal recommendation on the interpretation of HbA1c levels below 6.5%. [70]

| Diagnose/measurement | WHO 2006 /WHO 2011 | ADA |
|---|---|---|
| Diabetes | Can be used | Recommended |
| HbA1c | If measured ≥6.5%<br>(48 mmol/mol) | ≥6.5%<br>(48 mmol/mol) |
| • FPG | ≥7.0 mmol/mol<br>(≥ 126 mg/dl) | ≥7.0 mmol/mol<br>(≥ 126 mg/dl) |
| • 2h PG | ≥11.1 mmol/l<br>(≥200mg/dl) | ≥11.1 mmol/l<br>(≥200mg/dl) |
| IGT | | |
| • FPG | <7.0 mmol/l<br>(126mg/dl) | <7.0 mmol/l<br>(126mg/dl) not required |
| • 2hPG | ≥ 7.8- <11.1mmol/l<br>(≥140- < 200 mg/dl) | If measured 7.8-11.0 mmol/l<br>(140- 198 mg/dl) |
| • | | |
| IFG | | |
| • FPG | 6.1- 6.8 mmol/l<br>(110- 125 mg/dl) | 5.6- 6.9 mmol/l<br>(100- 125mg/dl) |
| • 2hPG | <7.8 mmol/l<br><140 mg/dl | - |

***Table 4****: Diagnostic criteria of Diabetes*

***PRIMARY PREVENTION OF CVD EVENTS IN PATIENTS WITH DIABETES MELLITUS***

For the prevention of cardiovascular complications in diabetes the lifestyle management, Exercise, Nutrition, Smoking cessation, Weight management, BP control, Control of blood cholesterol. Glucose-lowering agent selection for CV, risk reduction is the predominant factors.[71- 75]

| Risk Intervention | Goal | Recommendations |
|---|---|---|
| • Smoking | Complete Cessation | Provide counselling, nicotine replacement, encourage to attain formal cessation programs |
| • Blood Pressure Control | 130/85 mmHg | Regular blood pressure monitoring<br>Life style modifications: weight control, physical activity, moderation in alcohol, sodium restriction |
| • Cholesterol Management | Primary : < 130 mg/dL<br>Secondary :<br>HDL : > 35 mg/dL<br>TG : <200 mg/dL | Measure total and HDL cholesterol and TG; estimate LDL<br>Diet containing ≤30 % saturated fat, <200 mg/dL cholesterol, suggested drug therapy (statins resin fibrate). |
| • Glucose control | Near normal fasting glucose<br>HbA1c ≤ 1% above normal | Weight reduction and exercise<br>Oral hypoglycaemic agents<br>Insulin therapy |
| • Antiplatelet agent | Aspirin 80-325 mg/d | If not contraindicated for prevention of high risk diabetic patients |
| • Physical Activity | Regular Exercise 3-4 times per week for 30 min. | 30 minutes of moderate- intensity exercise<br>Increase physical activity |
| • Weight management | Maintain desirable BMI and waist circumference | Desired BMI range – 21-25kg/$m^2$<br>Desired waist circumference < 102 cm for men and < 88cm for women |
| • ACE inhibitors in post MI patients | To manage blood pressure | Start early post MI in stable high risk patents |
| • Beta blockers | Manage angina, rhythm, or blood pressure | Start early post MI in stable high risk patents |
| • Estrogen | Observational studies suggest benefits. | For postmenopausal women,especialy for those having multiple CHD risk factors |

***Table 5**: Primary Prevention of CVD Events in Patients with Diabetes mellitus*

***DRUGS IN DIABETES***

***Insulin***

• Human insulin is made by recombinant DNA technology. For routine use, it is given subcutaneously (by intravenous infusion in emergencies).

***Insulin Formulations***

Different formulations of insulin differ in their duration of action:

- Fast and short acting soluble insulin: peak action after subcutaneous administration is 2-4 hours and duration 6-8 hours; it is the only formulation that can be given intravenously.
- Intermediate-acting insulin (isophane insulin).
- Long acting forms (insulin zinc suspension). [76,77]

***Oral hypoglycaemic drugs***

- Biguanides : Metformin
- Sulfonylureas And Other Drugs That Stimulate Insulin Secretion: Tolbutamide, Glibenclamide, Glimepiride, Glipizide, Cliclazide
- Thiazolidinedione's : Rosiglitazone, Pioglitazone
- Alpha – Glycosidase Inhibitors : Voglibose, Acarbose
- Dipeptidyl-Peptidase 4 –Inhibitors : Saxagliptin, Sitagliptin, Vildagliptin
- SGLT 2 Cotransport Inhibitors : Dapagliflozine, Canagliflozin [78,79,80]

## III. CONCLUSION

Diabetes mellitus is chronic metabolic disorder and cardiovascular complications are the major cause of mortality and morbidity in diabetes mellitus especially in type 2. Currently 79% young adults having age between 20- 79 are affected by diabetes in lower income countries. Injectable is the only option for the type 1 diabetes mellitus and glucose control via lowering of fasting and postprandial blood glucose and haemoglobin A (1c) is the only option for the type 2 diabetes mellitus. The pathophysiology of both types of diabetes mellitus is complicated. There are various treatments are available now a days still there is no cure available for DM. Life style management is also the responsible factor for prevention of diabetes mellitus.

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