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REVIEW ON: DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism. It is the most common endocrine disorder and by the year 2010, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the disease by 2025. As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucoselevels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycaemic agents are also useful in the treatment of type 2 DM. Oral hypoglycaemic agents include *sulphonylureas, biguanides, alpha glucosidase inhibitors,meglitinide analogues, and thiazolidenediones.* The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and inadequate insulin secretion. The main side effects are weight gain and hypoglycaemia with sulfonylureasgastrointestinal (GI) disturbances with metformin, weight gain, GI disturbances and liver injury with thiazolidinediones, GI disturbances, weight gain and hypersensitivity reactions with meglitinides and flatulence, diarrhoea and abdominal bloating with alpha-glucosidase inhibitors.

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from defects in insulin secretion, insulin action or both. Permanent neonatal diabetes is caused by glucokinase deficiency, and is an inborn error of the glucose-insulin signaling pathway.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.[1]

Table 1. Some causes of insulin resistance.[2]

S/No.	Causes
1	Obesity/overweight (especially excess visceral adiposity)
2	Excess glucorticoids (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 γ (PPAR γ)
10	Mutations that cause genetic obesity (e.g., melanocortin receptor mutations)
11	Hemochromatosis (a hereditary disease that causes tissue iron accumulation).

Table 2. Clinical characteristics of patients with Type 1 and Type 2 diabetes mellitus. [3]

Features	**Type 1**	**Type 2**
Age of onset	Usually less than 20 years	Usually greater than 30 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

Symptoms:-

- Symptoms are similar in both types of diabetes but they vary in their intensity.
- Symptoms develop more rapidly in type 1 diabetes and more typical.
- The symptoms include polyurea, polydipsia, polyphagia, weight loss, fatigue,cramps, constipation, blurred vision, and candidiasis.
- Longstanding type 1 DM patients are susceptible to microvascular complications;5-10 and macrovascular disease (coronary artery, heart, and peripheral vascular diseases).
- Symptoms in type 2 DM are similar but insidious in onset.Most cases are diagnosed because of complications or incidentally.
- Type 2 DM caries a high risk of large vessel atherosclerosis commonly associated with hypertension,hyperlipidaemia and obesity.
- Most patients with type2 diabetes die from cardiovascular complications and endstage renal disease.
- Geographical differences exists in both the magnitude of these problems and their relative contributions to overall morb idity and mortality.

Oral hypoglycemic agents: Sulfonylureas[4]

- Sulphonylureas are structurally related to sulphenamides and were discovered accidentally, in 1942 when it was noted that some sulphonamides caused hypoglycaemia in experimental animals. These observations were extended, and 1-butyl-3-sulfonylurea (*carbutamide*) became the first clinically useful sulfonylurea for the treatment of diabetes.
- This compound was later withdrawn because of adverse effects on the bone marrow but led to the discovery of the entire class of sulfonylureas.
- In the 1950s *tolbutamide* was used in type 2 DM and subsequently 20 different agents of this class have been in use worldwide.
- This was followed by the introduction of biguanides, *phenformin,*which was later withdrawn because of an increase in the frequency of lactic acidosis associated with it use.
- Later on *metformin* was introduced and this drug has been used extensively in Europe without the side effects of *phenformin*.
- It was demonstrated that non-sulfonylurea analogues moiety was not necessary for stimulating insulin secretion.
- The first generation of sulfonylureas includes *tolbutamide,acetohexamide, tolazamide, and chlorpropamide*.
- A second generation of sulfonylureas has emerged and includes *glibenclamide,glipizide, gliclazide, andglimepiride.* They are more potent than the earlier agents.

Mechanism of action[4]

1) Sulfonylureas cause hypoglycemia by stimulating insulinrelease from pancreatic ß-cells.
2) They bind to sulfonylurea (SUR) receptors on the ß-cell plasma membrane, causing closure of adenosine triphosphate (ATP)-sensitive potassium channels, leading to depolarization of the cellmembrane.
3) Calcium ions and subsequent secretion of preformed insulin granules.
4) Acute administration of sulfonylureas to type 2DM patients increases insulin release from the pancreas and also may further increase insulin levels by reducing hepatic clearance of

the hormone. Initial studies showed that a functional pancreas was necessary for the hypoglycaemic actions of sulfonylureas.

5) With chronic administration,circulating insulin levels decline to those that existed before treatment.
6) But, despite this reduction in insulin levels,reduced plasma glucose levels are maintained.

Table 3: Classification of oral antidiabetic agents[5]

Sulfonylureas	*Thiazolidinediones*
Acetohexamide	Pioglitazone
Carbutamide	Rosiglitazone
Chlorpropamide	Troglitazone
Glibenclamide	
Glibornuride	*Meglitinides*
Gliclazide	Nateglinide
Glimepiride	Repaglinide
Glipizide	
Gliquidone	Aldose Reductase
Inhibitors	
Glisentide	Epalrestat
Glisolamide	Sorbinil
Glisoxepide	
Glyclopyramide	*Alpha Glucosidase*
Inhibitors	
Glycyclamide	Acarbose
TolazamideMiglitol	
Tolbutamide	Voglibose
Biguanides	*Miscellaneous*
Buformin	Glybuzole
Metformin	Glymidine
Phenformin	Guar Gum
Midaglizole	

Pharmacokinetics:-[6]

- Though the rates of absorption are different for differentsulfonylureas, all are effectively absorbed from the gastrointestinal tract. However, food and hyperglycaemia retards absorption.
- In general sulfonylureas with short halflives may be more effective when given 30 min before eating due to the time required to reach optimal concentration in the plasma.
- The first-generation sulfonylureas vary considerably in their half-lives and extents of metabolism. The half-life of acetohexamide is short, but the drug is reduced to an active compound with a half-life that is similar to those of tolbutamide and tolazamide (4-7 h).
- Therefore it is necessary to take these drugs in divided daily doses.
- The short-acting sulfonylureas include glipizide, which has the shortest half-life (1-5 h) and
- no active metabolites; other sulfonylureas with short halflives are glibornuride (5-12 h), gliclazide (6-15 h), glimepiride (5-9 h), tolazamide (4-7 h), and tolbutamide (6-12 h), and these have metabolites with little or no activity.
- Chlorpropamide has the longest elimination half-life (24 to 48 h, or longer in subjects with renal impairment) of allsulfonylureas currently in use, and is very long-acting.
- Gliquidone has the next longest elimination half-life (24 h),but little is known of its clinical duration of action and therisk of long-lasting hypoglycaemia, mainly because the use of this sulfonylurea has so far been very limited.
- The second-generation agents are approximately 100 times more potent than those in the first group.
- Although they have shorter half-lives (3 to 5 h) they are generally given twice daily but it is often possible to give them once daily.
- Glibenclamide was reported in some studies to have a short elimination half-life of (2-10 h), a recent study has showed that the elimination half-life is rather long (15-20 h).
- This appears to be the case since the drug has a long duration of action, more widely used, and is implicated in more cases of long-lasting hypoglycaemic episodes than other sulfonylureas.

- All of the sulfonylureas are metabolized in the liver, and the metabolites are excreted in urine. Chlorpropamide is not completely metabolized, 20% of the drug is excreted unchanged.
- Thus, sulfonylureas should be administered with caution in patients with either renal or hepatic insufficiency. All sulfonylureas have a low clearance.
- Some, but not all, sulfonylureas have active metabolites thatmay depend upon renal function for their elimination.

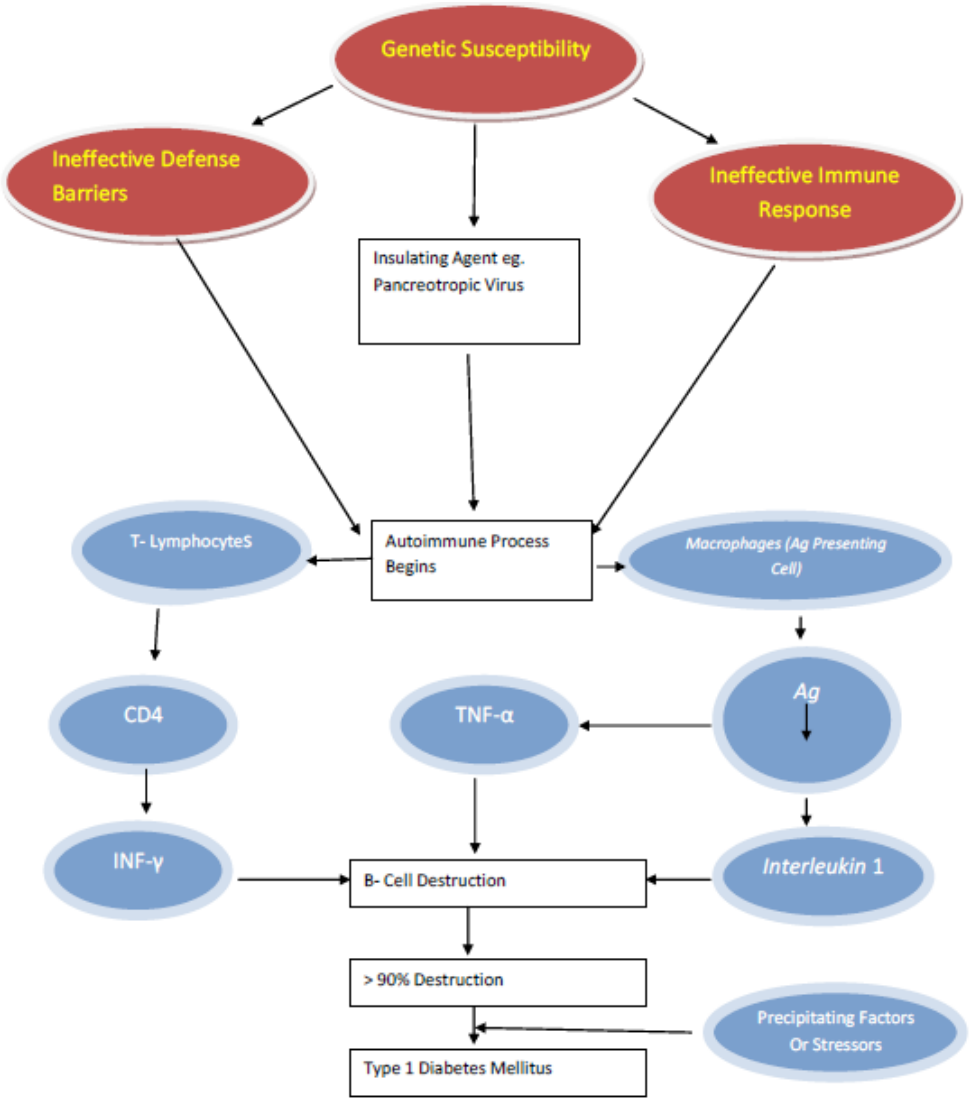
There are two main types of diabetes mellitus:[7]

i. Type 1 diabetes, also called insulin dependent diabetes mellitus (IDDM), is caused by lack of insulin secretion by beta cells of the pancreas.

ii. Type 2 diabetes, also called non-insulin dependent diabetes mellitus (NIDDM), is caused by decreased sensitivity of target tissues to insulin.

Pathogenesis of type 1 diabetes:-

1. Presence of immuno-competent and accessory cells in infiltrated pancreatic islets;
2. Association of susceptibility to disease with the class II (immune response) genes of the major histocompatibility complex (MHC; human leucocyte antigens HLA);
3. Presence of islet cell specific autoantibodies;
4. Alterations of T cell mediated immunoregulation, in particular in CD4+ T cell compartment;
5. The involvement of monokines and TH1 cells producing interleukins in the disease process;
6. Response to immunotherapy and;
7. Frequent occurrence of other organ specific auto-immune diseases in affected individuals or in their family members.



Pathogenesis of type 2 diabetes

In type 2 diabetes these mechanisms break down, with the consequence that the two main pathological defects in type 2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance.

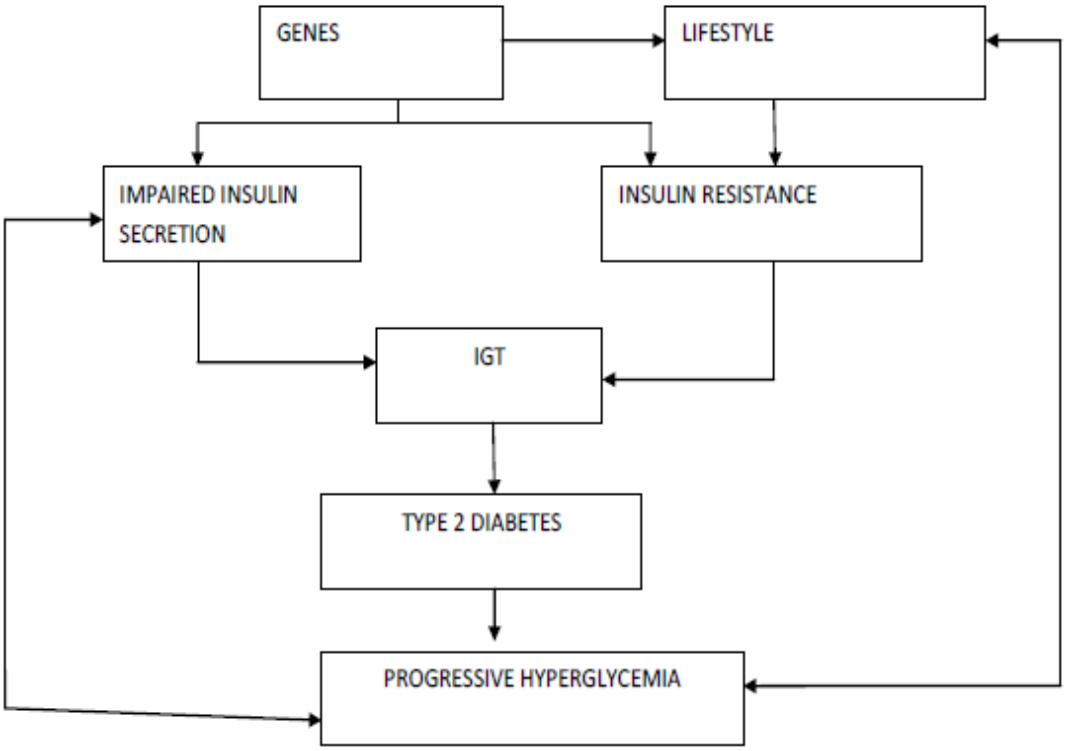


Figure 2. Pathogenesis of type 2 diabetes characterized by impaired insulin secretion and insulin resistance

NEWER APPROACHES-:[8]

A. Peroxisome Proliferator Activated Receptors(PPARs)
B. PPAR dual agonist
C. Glucagon like peptide-1 (GLP-1) Hormone:
D. Beta 3 adrenoreceptor Agonist
E. Alpha- lipoic Acid
F. Liver selection Glucorticod antagonists
G. Dipeptidyl peptidase IV inhibitors
H. Alpha-lipoic acid
I. Protein tyrosine phosphate-1b
J. PTP-1B Inhibitors
K. Glycogen synthesis kinase
L. Estrogn receptors

BIOCHEMICAL BACKGROUND OF DIABETES MELLITUS[9,10,11]

- ✓ A combination of ketosis and acidosis lead to a condition called ketoacidosis. If left untreated, ketoacidosis leads to coma and death. A regular energy source is a prerequisite for every cell to function in the human body.
- ✓ Glucose is the body's primary energy source, which circulates in the blood as a mobilizable fuel source for cells.
- ✓ Insulin is a pancreatic hormone responsible for blood glucose level regulation.
- ✓ The hormone binds to its receptor sites on peripheral side of the cell membranes.
- ✓ It affords entry of glucose into respiring cells and tissues via requisite channels. Insulin stimulates catabolism on glucose into pyruvate through glycolysis.
- ✓ It also upregulates glycogenesis from excessive cytosolic glucose and lipogenesis from excessive cytosolic acetyl-COA.
- ✓ These metabolic events are antagonistic to metabolic events triggered by the hormone glucagon. When glucose levels are at or below threshold, glucose stays in the blood instead of entering the cells .
- ✓ The body attempts to arrest hyperglycemia, by drawing water out of the cells and into the bloodstream.
- ✓ The excess sugar is excreted in the urine. This is why diabetics present with constant thirst, drinking large amounts of water, and polyuria as the cells try to get rid of the extra glucose. This subsequently leads to glucosuria.
- ✓ As hyperglycemia prolongs, the body cells are devoid of glucose due to the lack of insulin. This forces the cells to seek alternative mobilizable energy sources.
- ✓ In this regard, the cells turn to fatty acids stored in adipose tissue. The fats are not fuel sources for the red blood cells, kidney cortex and the brain.
- ✓ The red blood cells lack mitochondria in which beta-oxidation pathway rests. The fatty acids cannot pass the blood-brain barrier.
- ✓ To avail energy to such cells and tissues, the acetyl-CoA arising from catabolism of fatty acids is diverted to ketogenesis to generate ketone bodies, which can serve as alternative fuel sources for such cells and tissues.
- ✓ These ketone bodies are also passed in the urine, thereby leading to ketonuria, which characterizes diabetes mellitus.

- ✓ Build up of ketone bodies in the blood produces ketosis.
- ✓ Ketone bodies are acidic in nature and therefore, their build up in blood lowers blood pH, leading to acidosis.

ROLE OF INSULIN IN DIABETES MELLITUS[12,13]

- Insulin is a polypeptide hormone synthesized in humans and other mammals within the beta cells of the islets of Langerhans in the pancreas.
- The islets of Langerhans form the endocrine part of pancreas, accounting for 2% of the total mass of the pancreas,with beta cells constituting 60-80% of all the cells of islets of Langerhans.
- Insulin exhibits a multitude of effects in many tissues, with liver, muscle, and adipose tissue being the most important target organs for insulin action.
- The basic physiological function of insulin is promoting the synthesis of carbohydrates, proteins, lipids, and nucleic acids.
- The effects of insulin on carbohydrate metabolism include stimulation of glucose transport across muscle and adipocyte cell membranes, regulation of hepatic glycogen synthesis, and inhibition of glycogenolysis and gluconeogenesis.
- The end result of these actions is a reduction in blood glucose concentration. With regard to protein metabolism, insulin promotes transfer of amino acids across membranes, stimulates protein synthesis, and inhibits proteolysis.
- Incorporation of fatty acids from circulating triglyceride into adipose triglyceride and lipid synthesis are stimulated by insulin; lipolysis is inhibited. Insulin contributes to nucleic acid synthesis by stimulating the formation of ATP, DNA, and RNA.
- The ability of insulin to mediate tissue glucose uptake is a critical step in maintaining glucose homeostasis and in clearing the postprandial glucose.
- The insulin production is directly proportional to the amount of sugar (carbohydrate) consumed. The more sugar one consumes, the more insulin the body will have to produce, but, the tiny pancreatic beta cells were never designed to produce this level of insulin.
- With a limited capacity to produce insulin, a capacity that is more than sufficient to last a lifetime under normal dietary conditions, the forced over-production of insulin will eventually exhaust that capacity and the cells will cease to operate.

- However, insulin production does not always depend on blood glucose levels; insulin is stored in cells prior to its release.
- Insulin deficiency plays a central role in all forms of diabetes because it is the major hormone that enables cells (primarily muscle and fat cells) to uptake glucose from the bloodstream.
- Insulin makes it possible for most body tissues to remove glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage.
- Furthermore, insulin is also the major regulatory signal for glycogenesis in the hepatocytes and myocytes.
- Higher insulin levels upregulate various anabolic processes including cell growth, cellular protein synthesis, and fat storage. Insulin is more of an anabolic hormone rather than catabolic.
- Insufficient amounts of insulin or poor cellular response to insulin as well as defective insulin leads to improper handling of glucose by body cells or appropriate glucose storage in the liver and muscles.
- This ultimately leads to persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements (WHO, 1999).
- As a consequence of the widespread prevalence of diabetes and the severity of its complications, extensive research and treatment development efforts must be undertaken to identify and develop more effective remedies to improve the quality of life of those affected by the disease.
- The chronic hyperglycemia arising from diabetes mellitus accompanies long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.
- Pathogenesis of diabetes mellitus underlies autoimmune destruction of the pancreatic beta cells leading to insulin deficiency and biosignalling derangements that are consequent to insulin resistance or insensitivity.

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