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NEWER THERAPEUTIC APPROACHES IN DIABETES-MELLITUS

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Abstract:

Diabetes mellitus is a heterogeneous group of disorders characterized by hyperglycaemia due to an absolute or relative deficit in insulin production or action. There are mainly two types of diabetes mellitus, Type 1 diabetes mellitus (insulin dependent diabetes mellitus -IDDM), Type 2 diabetes mellitus (non-insulin dependent diabetes mellitus). Controlling blood sugar through diet, oral medication for insulin is the main treatment. Regular screening for complications is also required. Oral hypogylcemic drugs are used for the treatment of diabetes mellitus and insulin is also used for its treatment in case of high glucose level. Nano formulations not only improve solubility of the drug but also provide several other benefits such as reduced dose, rapid onset of action, sustained drug release, fewer side effects, targeted drug delivery, enhanced half-life of the drug, reduced patient variability along with improved bioavailability and may thus overcome many of the limitations of the current anti-diabetics. Here in this review, we summarise diabetes mellitus and newer therapeutic approach in diabetes mellitus.

Keyword: *Diabetes mellitus, Insulin,*

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INTRODUCTION:

Diabetes mellitus is a heterogeneous group of disorders characterized by hyperglycaemia due to an absolute or relative deficit in insulin production or action. The chronic hyperglycaemia of diabetes mellitus is associated with end organ damage, dysfunction, and failure, including the retina, kidney, nervous system, heart, and blood vessels.[1,2]

Diabetes mellitus:

Diabetes mellitus (DM) is commonest endocrine disorder that affects more than 100 million people worldwide (6% population). It is caused by deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood. It is found to damage many of body systems particularly blood vessels, eyes, kidney, heart and nerves. [2]

The presence of DM shows increased risk of many complications such as cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure, retinopathy, blindness, amputations etc [4,5]

Drugs are used primarily to save life and alleviate symptoms. Secondary aims are to prevent long-term diabetic complications and, by eliminating various risk factors, to increase longevity. 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 [6]

Types:

- Type 1 diabetes mellitus (insulin dependent diabetes mellitus -IDDM)
- Type 2 diabetes mellitus (non-insulin dependent diabetes mellitus)

Type 1 Diabetes Mellitus:

Type I diabetes is an autoimmune disease characterized by a local inflammatory reaction in and around islets that is followed by selective destruction of insulin secreting cells. This type of diabetes is additionally known as reaction diabetes and also referred to as juvenile-onset or ketosisprone polygenic disease. [7]

This form of diabetes, which accounts for only 5–10% of those with diabetes. Type I diabetes, or juvenile-onset diabetes(T1DM) is a chronic disease characterized by hyperglycaemia secondary to inadequate production of insulin by the pancreas. The classic clinical presentation of T1DM is an acute onset of symptoms caused by β-cell failure. The typical symptom triad is weight loss, polyuria and polydipsia.

Type 2 Diabetes Mellitus:

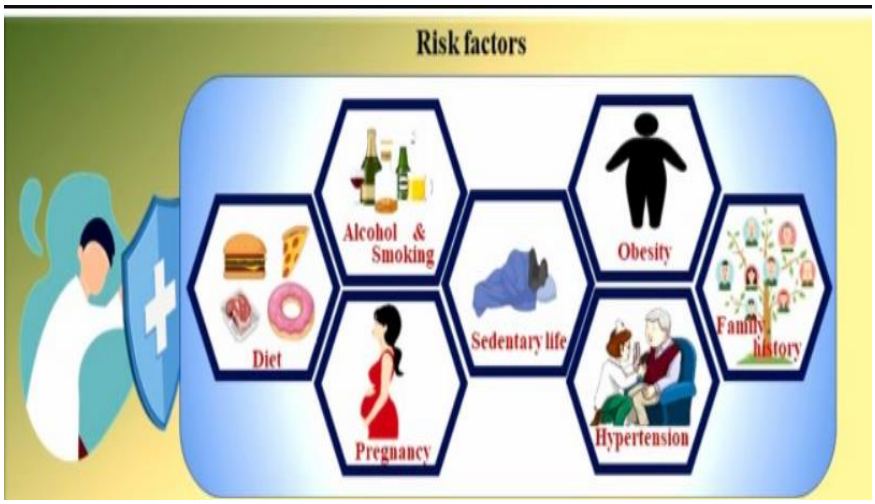
Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycaemia, insulin resistance, and relative insulin deficiency. (3)

Type 2 diabetics is an hetrogeneous condition caused by both genetic and environmental factors The management of the disease usually requires a step wise adjustment of pharmacological therapies in combination with lifestyle modifications. It is a common disease whose prevalence marketly increases with age. (>10% above 65 years)

Insulin resistance often associated with obesity, and insulin secretion defects are major risk factors of type 2 DM. A progressive decrease of β cell functions leads to glucose intolerance, which is followed by type2 diabetics. [8]

ETIOLOGY:

Diabetes mellitus has a number of reasons that are still unknown. It is now largely understood that DM is complex in nature, with hereditary and environmental factors both playing a role. [9]



EPIDIOMOLOGY:

Diabetes mellitus is a complex metabolic disorder with distinct subtypes related to differing underlying causes for the hyperglycemia which is the hallmark of the disease. Type 1 diabetes is caused by an autoimmune-mediated destruction of pancreatic beta cells resulting in the absence of insulin, a key hormone regulating blood glucose. Other types of diabetes may feature resistance to the action of insulin and/or insulin deficiency. Approximately 5% of all diabetes is type 1, 90% type 2, and 5% other subtypes. The incidence and prevalence of diabetes has been increasing across the world over the past 30 years. The World Health Organization has estimated that in 1980, there were 108 million adults living with diabetes in the world; by 2014 there were 422 million persons with diabetes. The prevalence of adults with diabetes rose from 4.7% to 8.5%; increasing prevalence was noted in all regions. Perhaps most striking was the increase in diabetes in poorer and middle-income countries observed during this epoch. Estimates of diabetes prevalence across Africa was 3.1% in 1980 and 7.1% in 2014.21 The largest numbers of people with diabetes are found in China (114.4 million), India (72.9 million), the United States (30.2 million), Brazil (12.4 million), Mexico (12.0 million), and Indonesia (10.3 million).

PATHOPHYSIOLOGY:

	TYPE 1 DIABETES	TYPE 2 DIABETES
Trigger	Antigen presentation	Metabolic stress
Process	Autoimmune response	Islet –derived and /or circulating cytokines
	Islet infiltration and focal cytokines release	Increased numbers of macrophages in islets
Result	Beta –cell destruction	Islet dysfunction Beta-cell death

Signs And Symptoms:

- Blurry vision
- Feeling hungry
- Numbness in hands or feet
- Feeling tired
- Unplanned weight loss
- Frequent urination

TREATMENT:

Controlling blood sugar through diet, oral medication for insulin is the main treatment. Regular screening for complications is also required. Drugs used for the treatment of diabetes mellitus include,

CLASSIFICATION:

Enhance Insulin Secretion

1.Sulfonylureas

First generation: Tolbutamide

Second generation: Glibenclamide, Glipizide

2.Meglitinide analogues

Repaglinide, Nateglinides

3.Glucagon-like peptide (GLP-1) receptor agonist

Exenatide, Liraglutide

4.Dipeptidyl peptidase-4 (DPP-4) inhibitors

Sitagliptin, Vildagliptin

Sulfonylureas:

Mechanism of action:

Sulfonylureas act by activating beta cell sulfonylurea receptor 1(SUR1) leading to closure of ATP dependent potassium channels. Thus, the potassium flow across plasma membrane is stopped leading to depolarisation, which opens voltage sensitive calcium channels. Consequently, there is an uptake of extra cellular calcium, activating a cyto skeletal system, which causes translocation of secretory granules to the cell surface and extrusion of insulin through exocytosis. Exocytosis results in the fusion of the secretory granules with the plasma membrane leading to the release of insulin into the extracellular space to reach the capillary blood flow. Hence, sulfonylureas administration must be carefully monitor since it can lead to hypoglycemia, weight gain and hyperinsulinemia.

Meglitinide analogues:

Mechanism of action:

Meglitinides are insulin secretagogues with a similar mechanism of action to sulfonylureas, acting on ATP-dependent potassium channels. Therefore, they fail to have any effect in patients who have already been treated with maximal therapeutic dosage of sulfonylureas.

Glucagon-like peptide (GLP-1) receptor agonist:

Mechanism of action:

GLP-1 exerts direct effects in several organs, due to interaction with its receptor located in organs such as pancreas, brain, heart, lung, stomach, intestine, and kidney. On pancreatic-cells, this interaction leads to activation of adenylate cyclase and production of cAMP, that mediates its stimulatory effect on insulin secretion via protein kinase A. However, GLP-1 stimulates insulin secretion via several other mechanisms, including a direct inhibition of ATP-dependent potassium channels. As sulfonylureas, this leads to an increase in intracellular levels of calcium and a rise in mitochondrial ATP synthesis which leads to a further membrane depolarization. Finally, it causes insulin granule exocytosis from pancreatic-cell.

Dipeptidyl peptidase-4(DPP-4) inhibitors:

Mechanism of action:

DPP-4 inhibitors competitively and reversibly inhibit DPP-4 providing up to 90% inhibition of its activity during a 24-hour period. Therefore, DPP-4 inhibitors promote insulin secretion and inhibit glucagon secretion, being these actions dependent on the presence of glucose. [6]

Newer therapeutic approaches in diabetes mellitus:

Emergence of nanoparticulate drug delivery systems in diabetes has facilitated improved delivery of small molecule drugs which could dramatically improve the quality of life for diabetics. Conventional dosage forms of the anti-diabetic drugs exhibit variable/less bioavailability and short half-life, demanding frequent dosing and causing increased side-effects resulting in ineffectiveness of therapy and non-compliance with the patients. Considering the chronic nature of diabetes, nanotechnology-based approaches are more promising in terms of providing site-specific delivery of drugs with higher bioavailability and reduced dosage regimen. Nanomedicines act at the cellular and molecular levels to enhance the uptake of the drug into the cells or block the efflux mechanisms thus retaining the drug inside the cell for a longer duration of time. Many studies have hinted at the possibility of administering peptide drugs like glucagon like peptides orally by encapsulation into nanoparticles. Nanoparticles also allow further modifications including their encapsulation into microparticles, polyethylene glycol (PEG)-PEGylation- or functionalization with ligands for active targeting.

Limitations of conventional oral anti-diabetic formulations:

Solubility and permeability problems are quite common among the commercially available anti-diabetic drugs (as enlisted in Table 1) particularly sulfonylureas leading to less bioavailability. This results in a frequent dosage regime, causing non-compliance of the patients and increased probability of skipping a dose [19]. On the other hand, metformin often prescribed as a first line medication for T2DM belongs to Biopharmaceutics Classification System (BCS) class III and is thus highly soluble

Nanomedicines for diabetes: significance and status:

Nano formulations not only improve solubility of the drug but also provide several other benefits such as reduced dose, rapid onset of action, sustained drug release, fewer side effects, targeted drug delivery, enhanced half-life of the drug, reduced patient variability along with improved bioavailability and may thus overcome many of the limitations of the current anti-diabetics.

Latest advancements in diabetes therapy:

Apart from the traditional small molecule therapeutics, a number of novel strategies have also been developed for the treatment of diabetes. Among them the most popular is the treatment via short interfering ribonucleic acid (siRNA) and clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein (Cas) system. Si RNA unlike a traditional RNA molecule is double stranded and is used for knocking down the expression of a particular gene by binding to the complementary.

CONCLUSION:

Diabetes mellitus (DM) is commonest endocrine disorder that affects more than 100 million people worldwide (6% population). It is caused by deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood.

Nanotechnology holds a great deal of promise for the world of medicine and it is very likely that some of the first truly revolutionary changes noticeable in our everyday lives will be brought about by nanomedicine. Years of extensive research and experiments in nano formulations has led to significant growth in the development of nanoparticulate delivery systems for anti-diabetic drugs.

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