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A Review on Pathophysiology, Current Advances in Oral Medication With Respect To Diabetes Mellitus.

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Abstract

Over the last three decades, the status of diabetes has been changed, earlier it was considered as a mild disorder of the elderly people. The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. According to the Diabetes Atlas published by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken. Normal regulation of glucose metabolism is determined by a feedback loop involving the islet βcell and insulin-sensitive tissues in which tissue sensitivity to insulin determines the magnitude of the β-cell response. When insulin resistance is present, the β-cell maintains normal glucose tolerance by increasing insulin output. Now it becomes a major cause of morbidity and mortality affecting the youth and middle aged people. Impaired insulin secretion and increased insulin resistance, the main pathophysiological features of type 2 diabetes, jointly contribute to the development of this disease. Recently, it has become widely recognized that the functional pancreatic cell mass decreases over time and type 2 diabetes is a progressive disease. Impaired insulin secretion is characterized by lowered glucose responsiveness. In particular, the decrease in postprandial-phase secretion is an essential pathophysiological condition. The main force of the epidemic of diabetes is the rapid epidemiological transition associated with changes in dietary patterns and decreased physical activity as evident from the higher prevalence of diabetes in the urban population. A number of new treatment approaches have been developed, but more effective therapies that slow the progressive loss of β-cell function are needed. Modern approaches have also informed regarding the importance of hexoses, amino acids and fatty acids in determining insulin resistance and β-cell dysfunction as well as the potential role of alterations in the microbiome. Therefore, it is necessary to identify the diabetic patients at the earliest and provide appropriate lifestyle intervention in preventing or postponing the onset of diabetes. The goal of diabetes treatment is to secure a quality of life (QOL) and lifespan comparable to those of healthy people. The need of the hour is earlier initiation of proactive intervention must be emphasized, as well as the importance of comprehensive (blood sugar, blood pressure, and lipids) interventional approach is needed for attaining the goal.

Keywords: Type 2 Diabetes, Pathophysiology, oral medication.

Introduction

Diabetes mellitus is not a single disorder, it represents a series of metabolic conditions associated with hyperglycaemia and caused by defects in insulin secretion and/or insulin action. Exposure to chronic hyperglycaemia may result in microvascular complications in the retina, kidney or periphera. DM is a serious, chronic and complex illness characterized by hyperglycemia that resulted from the pancreatic β-cells generate deficient insulin (a hormone that adjusts blood glucose) when the body cannot efficiently custom the insulin or both of them [1, 2, 3] World health organization has categorized DM as the 7th leading cause in USA while it was estimated that 422 million adults present diabetes in 2014. Inhibition of starch digestive enzymes or glucose transporters can reduce glucose release and absorption in the small intestine. This decrement could help to manage DM [4, 5]

Type 2 diabetes mellitus (DM) is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world. 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 healthcare providers, especially in poorly developed countries. Although, DM is one of the highest health crisis of the 21st century the majority of ministries and public health authorities keep being oblivious for the current impact of this disease and its complications.

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 nonsulfonylurea 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 analogoues: dipeptidyl peptidase-IV inhibitors, inhibitors of the sodium-glucose co transporter 2 and 11ß-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.

In a healthy person, the blood glucose level is regulated by several hormones, primarily insulin. Insulin is produced by the pancreas, a small organ between the stomach and liver. The pancreas also makes other important enzymes released directly into the gut that helps digest food. Insulin allows glucose to move out of the blood into cells throughout the body where it is used for fuel. People suffered diabetes either do not produce enough insulin (type 1 diabetes) or cannot use insulin properly (type 2 diabetes), or both (which occurs with several forms of diabetes). In diabetes, glucose in the blood cannot move efficiently into cells, so blood glucose levels remain high. This not only starves all the cells that need the glucose for fuel, but also harms certain organs and tissues exposed to the high glucose levels.

Types of Diabetes

There are two main types of diabetes type 1 and type 2 with their clinical relevance shown in Table 1 and another type of diabetes is gestational diabetes mellitus.

Table 1: Types of Diabetes with clinical relevance

	Type I	Type II
Clinical	Onset <20 years Normal weight Decreased blood insulin Anti-Islet cell antibodies Ketoacidosis common	Onset >30 years Obesity Normal or increased blood insulin No anti-Islet cell antibodies Ketoacidosis rare
pathogenesis	Auto immunity, immunopathologic mechanism Severe insulin deficiency	Insulin resistance Relative insulin deficiency
Genetics	50% concordance in twins HLA-D linked	60-80% concordance in twins No HLA-D association
Islet cells	Insulitis early Marked atrophy and fibrosis Severe β-cell depletion	No insulitis early Focal atrophy and amyloid deposits Mild β-cell depletion

Pathogenesis of Diabetes

Development of the insulin radioimmunoassay led to the identification that individuals with "early maturity onset diabetes" produced insulin and secreted this hormone in response to nutrient ingestion [6]. Subsequently, it was shown that these individuals manifest a defect in the ability of the islet β-cell to respond to intravenous secretagogues including glucose [7]. In these earlier days it was demonstrated that these individuals also did not respond well to insulin [8] and were thus deemed to be "insulin-insensitive". It was subsequently shown that this contributed to increased glucose production by the liver and decreased glucose uptake in muscle and adipose tissue [9]. Today we recognize that a proportion of these abnormalities are explained by adiposity especially that located within the intra-abdominal cavity [10].

Pathophysiology of Diabetes

Type 1 diabetes is the result of a combination of genetic and environmental influences. It most commonly results from autoimmune destruction of insulin-producing β-cells in the pancreas. Eisenbarth proposed that one or more environmental factors, such as enteroviruses, dietary factors or toxins, might trigger the development of T-cell dependent autoimmunity in genetically susceptible individuals [11]. Autoimmunity is manifested by detectable antibodies to ICA512/IA-2, insulin autoantibody (IAA) and glutamic acid decarboxylase (GAD). Insulitis with gradual β-cell destruction leads to pre-diabetes and finally to overt DM. These patients are susceptible to other autoimmune diseases, such as Hashimoto's thyroiditis, celiac disease, Addison's disease, and myasthenia gravis. Forty genetic loci have been associated with type 1 diabetes by a genome-wide association study and meta-analysis [12].

A number of genetic loci in the major histocompatibility (HLA) region are associated with increased susceptibility to developing type 1 diabetes, including the alleles DR3/4, DQ 0201/0302, DR 4/4, and DQ 0300/0302. The risk of type 1 diabetes is approximately 5% if there is an affected first-degree relative and slightly higher if the affected parent is the father rather than the mother. To date, interventional trials have failed to delay the onset or prevent type 1 diabetes in those genetically at risk. Ongoing research by international networks is exploring ways to prevent, delay or reverse the progression of type 1 diabetes (e.g. TrialNet, TRIGR) [13].

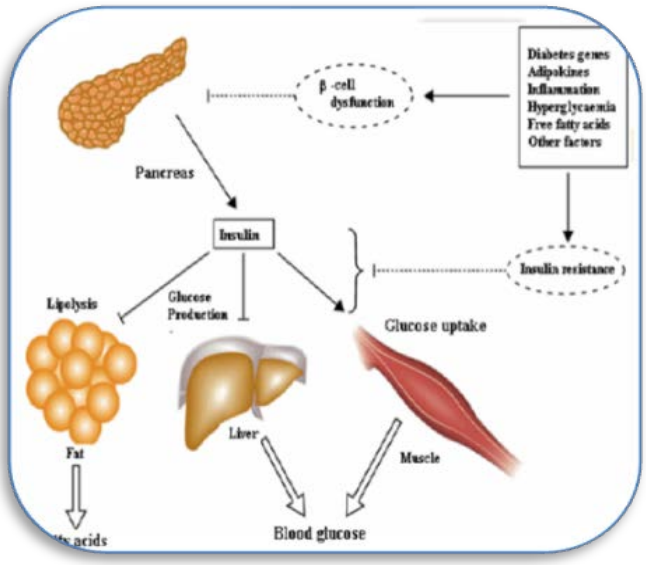

Figure 1: Pathophisiology of type 2 diabetes [14]

Type 2 diabetes is a chronic fuel surfeit is the primary pathogenic and physiological event that drives the development of type 2 diabetes in genetically and epigenetically susceptible people [15,16] (Figure 1). Many chronically over nourished and overweight or obese

individuals, however, do not develop diabetes at all or develop it very late in life. They remain resistant to type 2 diabetes and safely partition excess calories to subcutaneous adipose tissue (SAT) rather than to the heart, skeletal muscle, liver, and islet β cells, owing to the following mechanisms: successful islet β-cell compensation; maintenance of near-normal blood nutrient concentrations; development of minimal insulin resistance; increased expansion of SAT relative to visceral adipose tissue (VAT); and limited increase in liver fat [17, 18].

In this way, key organs of the body avoid nutrient-induced damage. Susceptible over nourished individuals develop type 2 diabetes owing to the failure of these adaptive responses to safely dispose of the fuel surfeit. The following metabolic defects are crucial to the development of type 2 diabetes: inability of islet β -cells to compensate for the fuel surfeit; increased glucagon secretion and reduced incretin response; impaired expansion of SAT, hypoadiponectinaemia, and inflammation of adipose tissue; increased endogenous glucose production; and development of peripheral insulin resistance. Importantly, the fuel surfeit is not safely deposited into SAT, such that it has to be disposed of elsewhere. The “elsewhere” is less healthy VAT and “ectopic” storage in organs, such as the liver, heart, skeletal muscle, and pancreas, which causes widespread tissue damage. Worsening islet β-cell function can lead to the need for insulin therapy [19, 20].

Insulin resistance and impaired beta cell function, both contribute to Gestational diabetes. Pregnancy is a diabetogenic state characterized by impaired insulin sensitivity. This is particularly noted as the pregnancy enters the 2nd trimester. The major contributors are the placental hormones namely, human placental lactogen, progesterone, cortisol, growth hormone and prolactin. These hormones cause decreased phosphorylation of insulin receptor substrate and thus profound insulin resistance. Cytokines like tissue necrosis factor have also been implicated in pathogenesis of insulin resistance. Logically, the pancreas should compensate for this demand by increasing insulin secretion.

However, in GDM there is deterioration of β cell function, particularly the first phase insulin secretion. In a study on Latino women with GDM, 67% reduction of β cell function was noted as compared to the normal pregnant control. The second phase insulin release is comparable to that in individual with normal glucose tolerance. The defects in β cell have been attributed either to autoimmune process or enzymatic defect like glucokinase. Autoimmunity should be suspected in women who do not have typical characteristics of increased risk of GDM, i.e. who are lean and Caucasians. Thus, the combination of insulin resistance and secretory defect during pregnancy results in GDM [21].

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure [22,23],This leads to a decrease in glucose transport into the liver, muscle cells, and fat cells. There is an increase in the breakdown of fat with hyperglycemia. The involvement of impaired alpha-cell function has recently been recognized in the pathophysiology of type 2 DM [24].

As a result of this dysfunction, glucagon and hepatic glucose levels that rise during fasting are not suppressed with a meal. Given inadequate levels of insulin and increased insulin resistance, hyperglycemia results. The incretins are important gut mediators of insulin release, and in the case of GLP-1, of glucagon suppression.

Although GIP activity is impaired in those with type 2 DM, GLP1 insulinotropic effects are preserved, and thus GLP-1 represents a potentially beneficial therapeutic option. However, like GIP; GLP-1 is rapidly inactivated

by DPP-IV in vivo. Two therapeutic approaches to this problem have been developed: GLP-1 analogues with increased half-lives, and DPPIV inhibitors, which prevent the breakdown of endogenous GLP1 as well as GIP [24].

Both classes of agents have shown promise, with potential not only to normalize fasting and postprandial glucose levels but also to improve beta-cell functioning and mass. Studies are ongoing on the role of mitochondrial dysfunction in the development of insulin resistance and etiology of type 2 DM [25]. Also very important is adipose tissue, as endocrine organ hypothesis (secretion of various adipocytokines, i.e., leptin, TNFalpha, resistin, and adiponectin implicated in insulin resistance and possibly beta-cell dysfunction).

A majority of individuals suffering from type 2 DM are obese, with central visceral adiposity. Therefore, the adipose tissue plays a crucial role in the pathogenesis of type 2 DM. Although the predominant theory used to explain this link is the portal/visceral hypothesis giving a key role in elevated non-esterified fatty acid concentrations, two new emerging theories are the ectopic fat storage syndrome (deposition of triglycerides in muscle, liver and pancreatic cells). These two hypotheses constitute the framework for the study of the interplay between insulin resistance and betacell dysfunction in type 2 DM as well as between our obesogenic environment and DM risk in the next decade.

Therapeutic Treatment

The increasing prevalence of type 2 diabetes has spurred the development of many new approaches to safely treat hyperglycaemia in order to lower and maintain glucose concentrations as close to normal for as long as possible after diagnosis and thereby prevent the development of complications (Figure 2a). While some have already fallen by the wayside because of unwanted adverse effects or minimal therapeutic efficacy, a number are very well accepted and utilized globally. For most of these oral medications, their mode of action of action has been elucidated.

(Figure-3) The organs on which many of them act primarily are depicted in Figure 2b. Individual responses to these medications may be quite different however, likely reflecting the heterogeneous nature of the pathophysiology of type 2 diabetes.

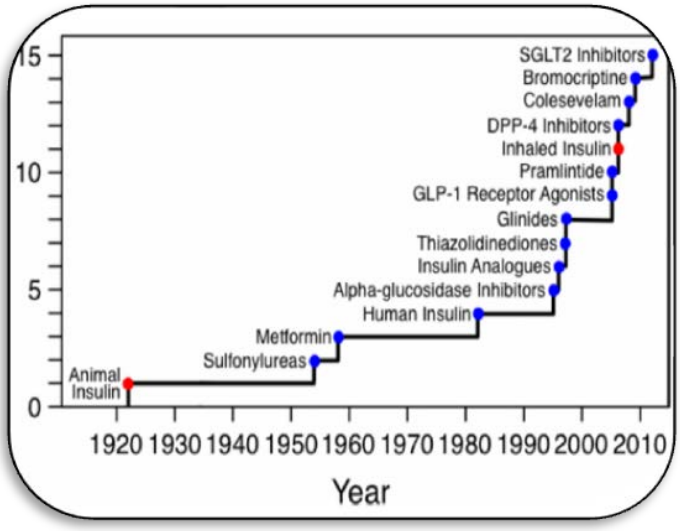

Figure 2a: Class of Glucose lowering Agents over past two decades

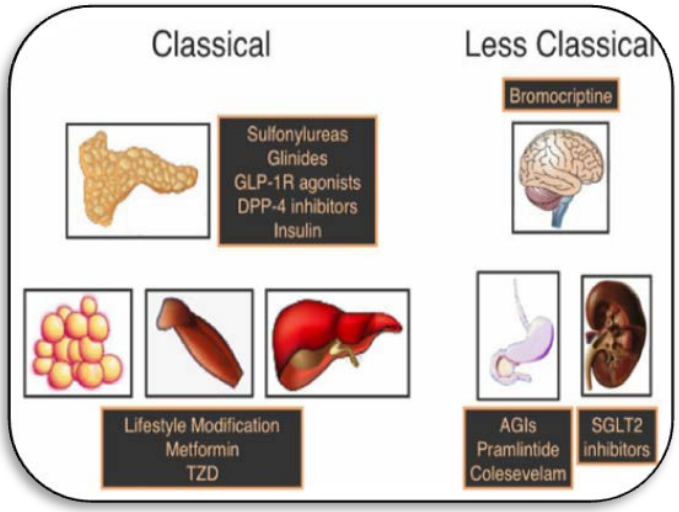

Figure 2b: Organ systems on which the different classes of medications works

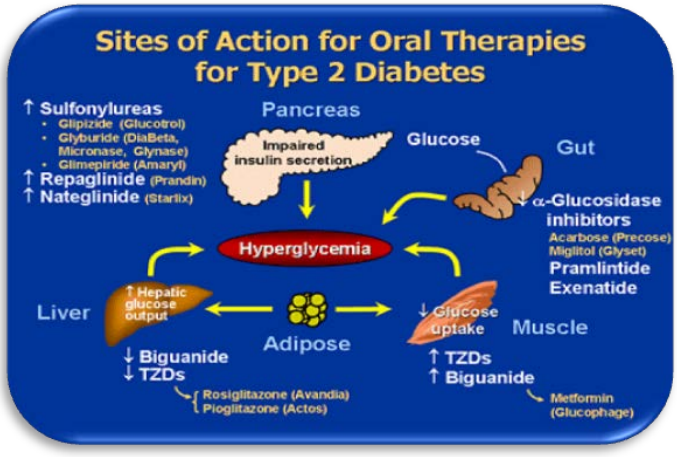

Figure 3: Site of Action for Oral Therapies for Type 2 Diabetes.

A list of the available agents within each class are provided in **Table 2** with further discussion on medications that have been widely available for more than a decade such as sulphonylureas, biguanides, α-glucosidaseinhibitors, and peroxisome proliferator-activated receptor (PPAR) γ agonists are addressed in the supplemental materials.

Table 2: Oral Medications for Type 2 Diabetes

Oral Medications for Diabetes

Type	Brand Name	for	What does it do?	Possible Side Effects
Sitagliptin	Januvia	Type 2	• Increases the level of several hormones, which improves insulin release from pancreas • Decreases post meal glucose spikes	•Upper respiratory symptoms •Abdominal discomfort
Sitagliptin + metformin	Janumet	Type 2	• Increases the body's sensitivity to insulin • Helps the pancreas to release insulin more normally	•Diarrhea •Bloating •Upper respiratory symptoms
Sulfonylureas	Glipizide, Glimerperide, Glyburide	Type 2	• Stimulates the pancreas to make insulin; lowers blood sugars pre and post meals	•Hypoglycemia (low blood sugar)
Metformin	Metformin, Glucophage	Type 2	• Increase the body's (the liver) sensitivity to insulin	•Nausea •Diarrhea
Thiazolidenediones*	ACTOS, Avandia	Type 2	• Increase the body's (muscle) sensitivity to insulin • Improves pre and post meal glucose	•Fluid retention •Weight gain
Alpha-glucosidase inhibitors	Precose, Glycet	Type 2	• Slows absorption of carbohydrates from intestines • Lowers post meal glucose	•Bloating •Gas •Flatus
Colesevelam	Welchol	Type 2	• Generally lowers glucose, mechanism unclear	•Heartburn •Bloating •Constipation
Glinides	Prandin, Starlix	Type 2	• Stimulates pancreas to release insulin after meals • Improves post meal glucose	•Hypoglycemia (low blood sugar)

Future Developments

As the current treatment armamentarium does not readily attain and maintain normal glucose levels as β-cell function progressively declines, new and novel approaches are being developed. **Table 2** lists selected therapeutic targets that represent largely untested mechanisms, some of which may turn out to be successful and others may prove less so.

Treatment And Prevention

In 1998, the landmark United Kingdom Prospective Diabetes Study (UKPDS) reported that improving glucose control primarily with sulphonylureas and insulin reduced microvascular complications in recently diagnosed patients with type 2 diabetes [26]. The primary analysis did not show a clear benefit on macrovascular disease, and thus four large intervention studies were designed to examine the effect of more intensive glucose lowering on cardiovascular outcomes. Insulin was a major component of the glucose-lowering interventions in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) [27], VADT (VA Diabetes Trial) [28] and ORIGIN (Outcome Reduction with an Initial Glargine Intervention) [30] trials, while the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study utilized a regimen based on the sulfonylurea gliclazide [31].

In none of these studies did intensive glucose lowering reduce cardiovascular events, and indeed in the vulnerable patient may have been harmful. Analyses from ACCORD suggest that the individual likely to be at greatest risk of an adverse outcome to aggressive glucose lowering had a longer duration of diabetes, poor glucose control at the time of commencing intensive insulin therapy, and did not demonstrate an immediate glucose lowering response [32].

ACCORD, like the UKPDS, demonstrated that improved glucose control reduced microvascular complications [33], but these positive findings must be balanced against the potential deleterious effect of intensified therapy on cardiovascular outcomes. Such a microvascular benefit was also shown in ADVANCE, the magnitude being related to the degree of glucose control and affecting

largely renal outcomes (essentially a reduction in microalbuminuria). Noteworthy from the ORIGIN study was the lack of evidence of an increased risk of cancer with glargine, despite suggestions from pharmacovigilance studies that insulin may promote cancer [34]. This lack of an effect on cancer is in keeping with a recent report that serum from type 2 diabetic patients treated with glargine activates insulin receptors A and B similarly to NPH insulin and does not increase signaling through the IGF-1 receptor [35]. Thus, based on five separate studies, it would seem that current approaches involving intensification of glucose control are valuable for reducing microvascular complications but are not effective in reducing cardiovascular events, possibly even being harmful in those with advanced type 2 diabetes. Similar conclusions were reached by two meta-analyses that included these and other studies [36]. These differences in cardiovascular outcomes underscore the need for individualized glucose control targets as recently highlighted in the ADA/EASD position statement on the treatment of type 2 diabetes [37].

It appears that addressing concomitant cardiovascular risk factors such as LDL-cholesterol and blood pressure may be more effective, and is consistent with the multifactorial approach in the Steno 2 Study that demonstrated a reduction in both cardiovascular and microvascular events which was sustained even after cessation of the initial glucose, blood pressure and lipid lowering regimens [38].

As lifestyle change to reduce body weight has always been a mainstay of type 2 diabetes therapy, the Look AHEAD (Action for Health in Diabetes) trial examined the effect on cardiovascular events of weight reduction achieved by an intensive lifestyle intervention. Despite differential weight loss for over 10 years and improvements in many cardiovascular risk factors, including blood pressure and lipids, lifestyle change did not reduce cardiovascular events compared to diabetes support and education [39]. This may have been because large proportions of subjects in both groups received medical treatment for these risk factors. Interestingly, those in the intensive lifestyle arm with a history of cardiovascular event at baseline demonstrated a tendency for an increased risk of a subsequent cardiovascular event, an observation similar to that in ACCORD. A number of other observations from Look AHEAD are worthy of comment. First, with weight loss a greater proportion of subjects achieved either partial or complete diabetes remission [40] improved glucose control required fewer glucose-lowering agents, including insulin, and a greater proportion of participants achieved a HbA1c.

Oral Hypoglycemic Agents

Metformin (biguanide) Metformin is the only biguanide available. It is currently the recommended first line treatment and the most widely used insulin sensitizer in the elderly because of effectiveness in lowering blood glucose, a low risk of hypoglycemia and relatively low adverse effect profile. It can be used as monotherapy or in combination with other oral hypoglycemic agents such as sulfonylurea, GLP-1 receptor agonists, DPP-4 inhibitors or with insulin. Together with diet, metformin can reduce fasting glucose by 50–70 mg/dL and the HbA1c from 1.3 to 2.0%. It lowers blood glucose levels by sensitizing the liver to the effects of insulin [41].

Sulfonylureas: Sulfonylureas stimulate insulin release by binding to a specific site on the sulfonylurea receptor on cells (KATP channel complex) and inhibiting its activity which causes cell membrane depolarization and the cascade of events leading to insulin secretion. It remains an effective means of achieving blood glucose control after failure of diet alone in older patients. Hypoglycemia is the major concern with sulfonylureas especially with long acting ones in elderly patients with reduced renal

function and liver dysfunction and in patients with poor nutritional status and alcohol abuse. Weight gain (up to 1–3 kg) and overeating to counteract or prevent hypoglycemia are major limitations to achieving optimal glycemic control [42].

Meglitinides – (repaglinide and nateglinide): Meglitinides are insulin secretagogues with rapid onset and relatively short duration of action that control postprandial hyperglycemia. Hypoglycemia risk is less than with sulfonylureas, which makes this class of medication a more suitable alternative in elderly patients with CKD or those that are intolerant to metformin or sulfonylureas. Nateglinide is mainly metabolized by the liver and excreted by the kidneys unchanged. Therefore, it does not require dose adjustment in renal failure. Repaglinide is metabolized primarily (90%) by the liver and the remaining 10% is metabolized by the kidneys, requiring dosage adjustment in renal failure. Repaglinide should be used cautiously in patients with hepatic insufficiency and CKD. However, several studies reported the safety and efficacy of repaglinide with a lower risk of hypoglycemia in elderly patients with DM .The need for multiple daily doses may reduce compliance with this medication class [43.].

Thiazolidinediones (rosiglitazone and pioglitazone): Thiazolidinediones (TZDs) are insulin sensitizers that reduce insulin resistance in peripheral tissue especially in muscle and also decrease hepatic gluconeogenesis by activating the peroxisome proliferator-

activated receptor gamma [44].

α-Glucosidase inhibitors Acarbose, miglitol, voglibose (only in Europe) are the available glucosidase inhibitors. They are extensively studied and widely used in Europe and Japan. They slow the rate of carbohydrate absorption by inhibiting the upper gastrointestinal enzymes (α-glucosidases) that convert complex polysaccharide carbohydrates into monosaccharides in a dose-dependent fashion. In addition, they stimulate secretion of glucagon like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)[45]. They are much more effective in lowering blood sugar in patients on high starch diets. They show modest HbA1c reduction (0.5–0.8%) and can be used in combination therapy. They can be quite useful in the elderly because of absent hypoglycemia risk and their effect on postprandial hyperglycemia. In addition, αglucosidase inhibitors can increase insulin sensitivity in elderly diabetics [46].

Incretins: Incretins, GLP-1 and GIP, are short-lived gut hormones. They enhance the synthesis and release of insulin from pancreatic β- cells and decrease glucagon release from pancreatic-β -cells. These incretin hormones are released in response to oral glucose and other nutrients and increase insulin secretion, attenuate postprandial glucagon secretion and hepatic gluconeogenesis with resulting improvement in postprandial glycemia. Both GIP and GLP-1 are rapidly metabolized by the enzyme dipeptidyl peptidase-4 (DDP-4) resulting in short plasma half-lives [47]. Incretin based therapy is a good choice for elderly diabetics because of its low risk of hypoglycemia, a fairly benign side effect profile, and its glucose dependent mechanism of action which limits hypoglycaemia [48] .

New oral agents Bile acid sequestrates: Colesevelam is a bile acid binding resin approved for treatment of hypercholesterolemia. It can also lower blood glucose and can be used in DM treatment (Figure 4). It lowers HbA1c 0.5% when added to metformin, sulfonylurea or insulin. The major side effect of colesevelam is constipation; thus, it should be avoided in patients with gastroparesis or other gastrointestinal motility disorders, in patients after major gastrointestinal surgical procedures, and in others at risk for bowel obstruction. Other adverse effects include:

elevated serum triglycerides and possible malabsorption of fat-soluble vitamins. There are no data in the elderly [49].

Bromocriptine Bromocriptine (Cycloset), a sympatholytic dopamine D2 receptor-agonist, was FDA-approved for DM treatment. The dose range is 1.6–4.8 mg, taken with food in the morning within two hours of awakening. It is used as mono therapy or in combination therapy with insulin and oral agents and has a favourable safety profile and tolerability. Its effect on blood glucose may be due to action in the central nervous system. The mechanism of action of bromocriptine in diabetes has not been clearly elucidated. Side effects include nausea, fatigue, dizziness, orthostatic hypotension, vomiting, and headache. Its efficacy in glycemic control is modest (HbA1c reduction of 0.1–0.4%). There are no data in the elderly [50].

Insulin: Insulin is the most effective antidiabetic medication when dosed appropriately. The progressive decline of β-cell function with advancing age means that the majority of elderly diabetics will require insulin eventually [51]. However, insulin has been underutilized in elderly diabetics due to concern about hypoglycemia and complexity of administration. Nevertheless, insulin should not be perceived as the last resort in the elderly. At the same time, laboratory values e.g. blood glucose and HbA1c, should not be the only guides to starting insulin. Before initiating insulin, assessment of psychosocial condition, functional, and cognitive status of patients is essential for the safe and effective use of insulin [52]. Major limitations include inability to self-administer due to poor vision, impaired manual dexterity, poor functioning or impaired cognition and potential for hypoglycaemia [53].

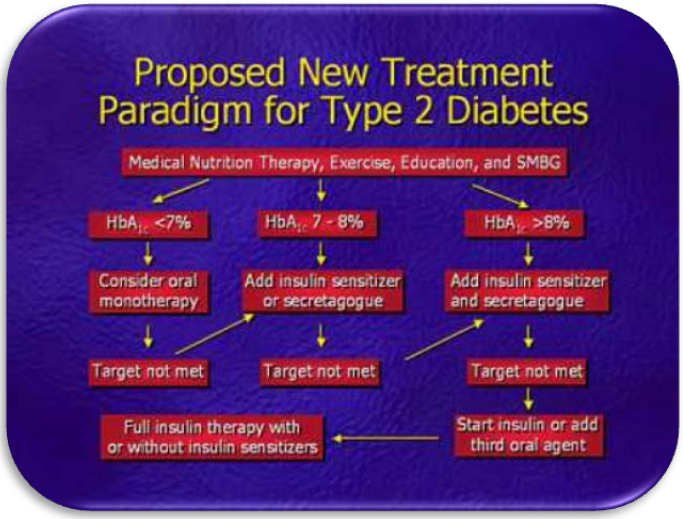

Figure 4: New Proposed treatment for Type 2 Diabetes

Diabetes Management

Management of diabetes is through lifestyle and diet modification. Studies have shown that there was significant reduction in the incidence of type 2 DM with a combination of maintenance of body mass index of 25 kg/m2, eating high fibre and unsaturated fat and diet low in saturated and trans-fats and glycemic index, regular exercise, abstinence from smoking and moderate consumption of alcohol [54, 55]. Suggesting that majority of type 2 DM can be prevented by lifestyle modification. Patients with type 2 DM should receive a medical nutrition evaluation; lifestyle recommendations should be tailored according to physical and functional ability [56].

Pharmacological Agents like Biguanides Biguanides, of which metformin is the most commonly used in overweight and obese patients, suppresses hepatic glucose production, increases insulin sensitivity, enhances glucose uptake by phosphorylating GLUT-enhancer factor, increases fatty acid oxidation, and decreases the absorption of glucose from the gastrointestinal tract [57]. Researcher showed further mechanism of action of metformin as activation of AMP-activated protein kinase, an enzyme that plays a role in the expression of hepatic gluconeogenic genes [58]. Due to the concern of

development of lactic acidosis, metformin should be used with caution in elderly diabetic individuals with renal impairment. It has a low incidence of hypoglycemia compared to sulfonylureas. Sulfonylureas These generally well tolerated but because they stimulate endogenous insulin secretion, they carry a risk of hypoglycemia.

Elderly patients, with DM who are treated with sulfonylureas have a 36% increased risk of hypoglycemia compared to younger patients [59]. Glyburide is associated with higher rates of hypoglycemia compared to glipizide [60]. Some of the risk factors for hypoglycemia are age-related impaired renal function, simultaneous use of insulin or insulin sensitizers, age greater than 60 years, recent hospital discharge, alcohol abuse, caloric restriction, multiple medications or medications that potentiate sulfonylurea actions [61]. Use of long acting sulfonylurea such as glyburide should be avoided in elderly patients with DM and use of short-acting glipizide should be preferred.

Meglitinides Repaglinide and nateglinide are non-sulfonylurea secretagogues which act on the ATP-dependent K-channel in the pancreatic beta cells thereby stimulating the release of insulin from the beta cells, similar to sulfonylurea, though the binding site is different [62]. Meglitinides have a rapid onset and a short duration of action (4-6 hrs) and thus lower risk of hypoglycemia. Meglitinides are given before meals for postprandial blood glucose control. Preprandial administration allows flexibility in case a meal is missed without increased risk of hypoglycemia [63]. Repaglinide is mainly metabolized in the liver with very minimal amounts excreted via the kidneys and thus dose adjustment is not necessary in patients with renal insufficiency except those with end-stage renal disease.

Thiazolidinediones Thiazolidinedione is an insulin sensitizer, selective ligands transcription factor peroxisomes proliferator-activated gamma. They are the first drugs to address the basic problem of insulin resistance in type 2 DM patients, [64]whose class now includes mainly pioglitazone after the restricted use of rosiglitazone recommended by Food and Drug Administration (FDA) recently due to increased cardiovascular events reported with rosiglitazone. Pioglitazone use is not associated with hypoglycemia and can be used in cases of renal impairment and thus well tolerated in older adults. On the other hand, due to concerns regarding peripheral edema, fluid retention and fracture risk in women, its use can be limited in older adults with DM. Pioglitazone should be avoided in elderly patients with congestive heart failure and is contraindicated in patients with class III-IV heart failure [65].

Alpha-Glucosidase Inhibitors Acarbose, Voglibose and Miglitol have not widely been used to treat type 2 DM individuals but are likely to be safe and effective. These agents are most effective for postprandial hyperglycemia and should be avoided in patients with significant renal impairment. Their use is usually limited due to high rates of side-effects such as diarrhoea and flatulence. Voglibose, which is the newest of the drugs, has been shown in a study to significantly improve glucose tolerance, in terms of delayed disease progression and in the number of patients who achieved normoglycemia [66].

Incretin-Based Therapies Glucagon-like peptide 1 (GLP-1) analogues are the foundation of incretin-based therapies which are to target this previously unrecognized feature of DM pathophysiology resulting in sustained improvements in glycemic control and improved body weight control. They are available for use as monotherapy, as an adjunct to diet and exercise or in combination with oral hypoglycemic agents in adults with type 2 DM. Examples are Exenatide, an incretin mimetic, and

Liraglutide. There is no risk of hypoglycemia with the use of GLP1 therapies (unless combined with insulin secretagogues). In addition, emerging evidence suggests incretin-based therapies.

Dipeptidyl-Peptidase IV Inhibitors: Dipeptidyl-peptidase (DPP) IV inhibitors inhibit dipeptidyl peptidase-4 (DPP-4), a ubiquitous enzyme that rapidly inactivates both GLP-1 and GIP, increase active levels of these hormones and, in doing so, improves islet function and glycemic control in type 2 DM. DPP-4 inhibitors are a new class of anti-diabetogenic drugs that provide comparable efficacy to current treatments. They are effective as monotherapy in patients inadequately controlled with diet and exercise and as add-on therapy in combination with metformin, thiazolidinediones, and insulin. The DPP-4 inhibitors are well tolerated, carry a low risk of producing hypoglycemia and are weight neutral. However, they are relatively expensive [67]. The long-term durability of effect on glycemic control and beta-cell morphology and function remain to be established [68].

Insulin Insulin is used alone or in combination with oral hypoglycemic agents. Augmentation therapy with basal insulin is useful if some beta cell function remains. Replacement of basal-bolus insulin is necessary if beta cell exhaustion occurs. Rescue therapy using replacement is necessary in cases of glucose toxicity which should mimic the normal release of insulin by the beta cells of the pancreas [69].

Insulin comes in injectable forms - rapid acting, short acting, intermediate acting and long acting. The long acting forms are less likely to cause hypoglycemia compared to the short acting forms. Insulin analogues Insulin therapy was limited in its ability to mimic normal physiologic insulin secretion. Traditional intermediate- and longacting insulins (NPH insulin, lente insulin, and ultralente insulin) are limited by inconsistent absorption and peaks of action that may result in hypoglycemia. [70]

The pharmacokinetic profiles of the new insulin analogues are distinct from those of the regular insulins, and their onset and durations of action range from rapid to prolonged. Currently, two rapid-acting insulin analogues, insulin lispro and insulin as part, and one long-acting insulin analogue, insulin glargine, are available.

Upcoming in Drug Therapy- Inhaled Insulin: The inhaled form of rapidly acting insulin which became available, [71] after it was approved by both the European Medicines Evaluation Agency and FDA for treatment of type 1 and type 2 DM in adults. [72] It is a rapid acting form of insulin that was indicated for use in adults with type 1 and type 2 DM and has the advantage of delivery directly into the lungs. Studies have however shown that inhaled insulin is as effective as, but not better than short acting insulin. It was withdrawn from the market by the manufacturer due to poor sales.

Conclusion

Diabetes mellitus a metabolic disease and its management have aware the clinicians in all over the countries. In current status, a high number of populations have this disease which is related with the modern life style, unhealthy diet and sedentary life. The management of Diabetes Mellitus for Type I, is usually injectable insulin delivery in contrast to Type II which the majority of drugs are orally administered. Currently, the management of Type II diabetes focuses on glucose control via lowering of fasting and postprandial blood glucose and hemoglobin A(1c). In the foreseeable future, researchers believe that the replacement of subcutaneous injections of insulin with nanocarriers could improve the quality of diabetic patients. One can only hope that the next 30 years will provide us with the knowledge and approaches that will allow us to limit the global harm of type 2 diabetes by not

only managing the condition more effectively with a combination of non-pharmacological and pharmacological approaches, but also by preventing the disease and identifying new strategies to directly target its complications. Furthermore, reducing of blood sugar levels with active ingredients of plants either as primary treatment or as adjunct therapy to conventional medications is a hopeful therapy.

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