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Review Article

Diabetes Mellitus and Diverse Approaches to Its Management in Practical Application

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Diabetes is a lifelong (chronic) disease and is a group of metabolic disorders characterized by high levels of sugar in blood (hyperglycemia). More than 230 million people worldwide are affected, and it is expected to reach 350 million by 2025. Globally the affected people are unaware of the disease and only half receive adequate treatment. It is caused due to deficiency of insulin or resistance to insulin or both. Insulin is secreted by β-cells of pancreas to control blood sugar levels. Advancing age, obesity and history of diabetes in the family have been identified as a major risk factors for diabetes in a study conducted by National Institute of Diabetes and Digestive and Kidney Diseases. Although not highly correlated, gender and lack of sufficient exercise were also found to be risk factors for diabetes. A life style intervention with weight loss, exercise regimen and diet control is often the first step in treatment of patients with newly diagnosed with diabetes and recommended by the ADA. The main goal of diabetes management is, as far as possible, to restore carbohydrate metabolism to a normal state. To achieve this goal, individuals with an absolute deficiency of insulin require insulin replacement therapy, which is given through injections or tablets. Insulin resistance, in contrast, can be corrected by dietary modifications and exercise.

Keywords: Diabetes Mellitus, insulin, hyperglycemia, oral hypoglycemic.

Introduction

Diabetes mellitus refers to a set of physiological dysfunctions marked by hyperglycemia, a result of factors such as insulin resistance, insufficient insulin secretion, or excessive glucagon secretion [1-3]. This condition is a lifelong (chronic) disease, encompassing metabolic disorders characterized by elevated blood sugar levels. The global impact is substantial, with over 230 million affected individuals, and projections indicate an increase to 350 million by 2025. Unfortunately, a significant portion of those affected globally remains unaware of their condition, and only half receive adequate treatment [3-7]. The root causes involve insulin deficiency, insulin resistance, or a combination of both, with insulin, produced by the pancreas's β-cells, playing a crucial role in blood sugar regulation. Metabolic abnormalities arise from insufficient insulin levels for an appropriate response and/or insulin resistance in target tissues, primarily skeletal muscles, adipose tissue, and, to a lesser extent, the liver, at the insulin receptors, signal transduction system, and/or effector enzymes or genes.

The severity of symptoms varies based on diabetes type and duration. Some individuals, particularly those with type 2 diabetes in the early stages, may be asymptomatic. Conversely, those with marked hyperglycemia, especially children with absolute insulin deficiency, may experience symptoms like polyuria, polydipsia, polyphagia, weight loss, and blurred vision. If left uncontrolled, diabetes can progress to serious complications such as stupor, coma, and, if untreated, may lead to death, primarily from ketoacidosis or, rarely, nonketotic hyperosmolar syndrome [7-9].

Persistent hyperglycemia associated with diabetes mellitus results in long-term damage, dysfunction, and failure of various organs, particularly 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. Defective insulin secretion and defective insulin action frequently coexist in the same patient. It is still obscure which abnormality is the primary cause of the hyperglycemia [9-15]. Hyperglycemia is characterized by polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Stunted growth and susceptibility to opportunistic infections may also be associated with chronic hyperglycemia. Uncontrolled diabetes mellitus leads to hyperglycemia with ketoacidosis as well as the nonketotic hyperosmolar syndrome. Long-term metabolic complications of diabetes mellitus include retinopathy, nephropathy, peripheral neuropathy, amputations, and Charcot joints as well as autonomic neuropathy causing gastrointestinal, genitourinary, cardiovascular symptoms and sexual dysfunction. Diabetics are also at a greater risk atherosclerotic, cardiovascular, peripheral arterial and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism also accompany uncontrolled diabetes mellitus [15-17].

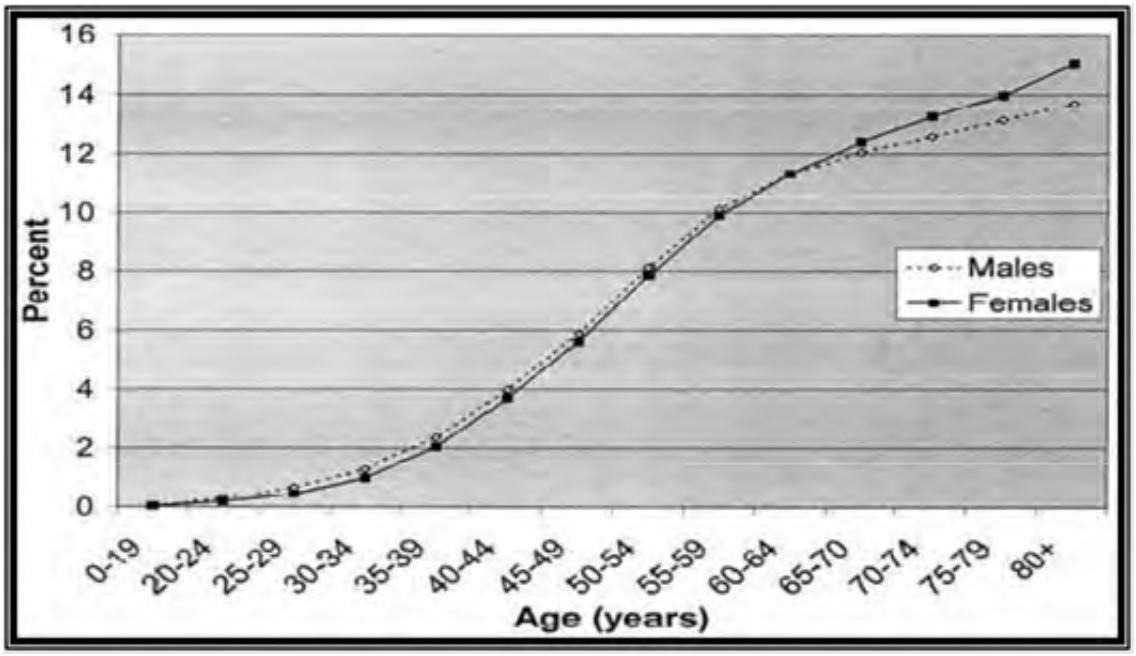

Figure 1. ***Epidemiology of diabetes: A global view [8-17]***

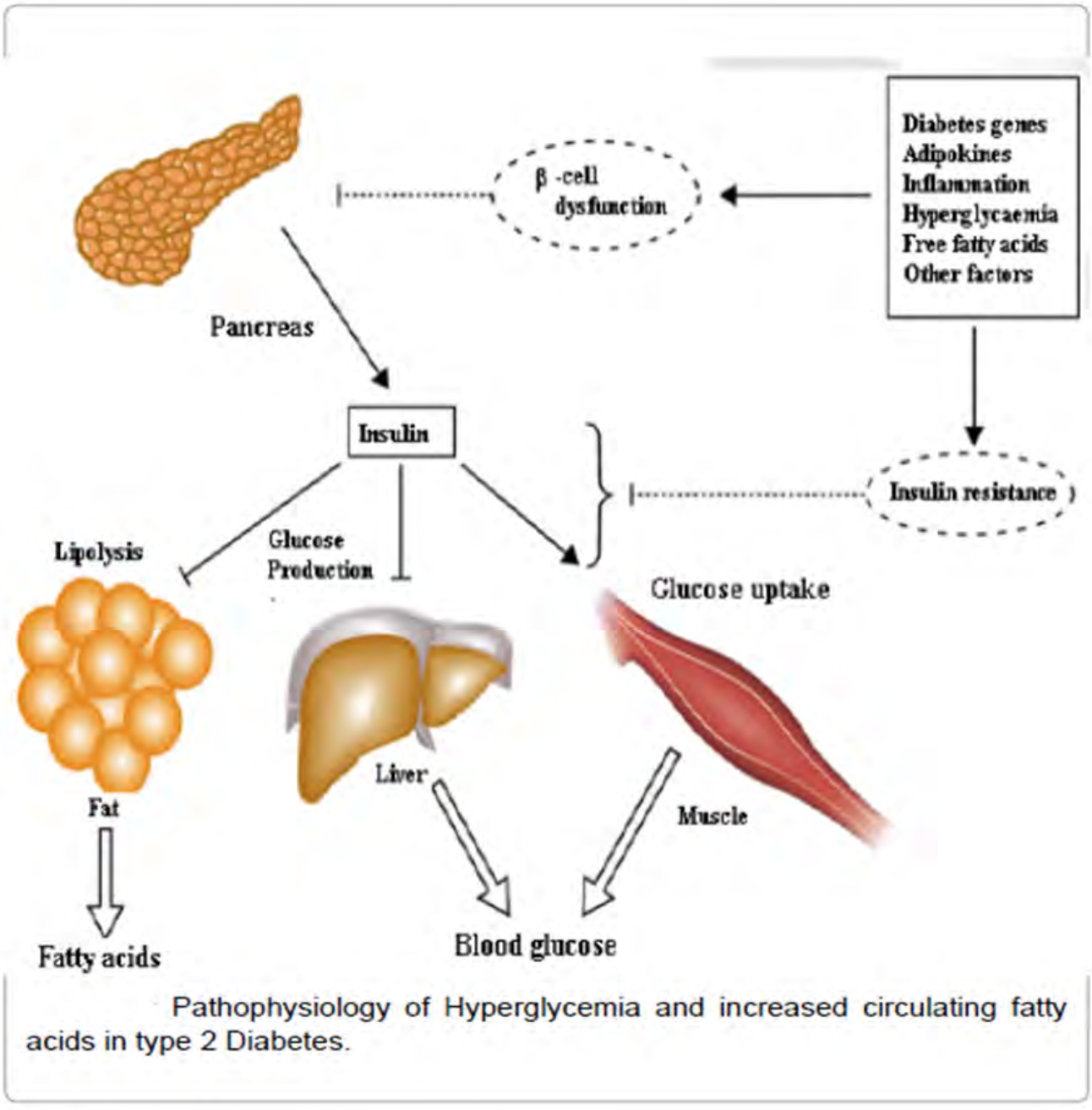

Figure 2. ***Pathophysiology of hyperglycemia [17-19]***

Etiologic classification of Diabetes Mellitus

New DM classification was redefined in an ADA's publication in 1997 and of WHO in 2006. Updated national and international directions recommend DM's classification in four categories: type 1 DM (DM1), type 2 (DM2), other types and gestational diabetes[19-22].

Etiologic classification of diabetes mellitus

I. Type 1 diabetes
A. Immunologically mediated
B. Idiopathic
II. Type 2 diabetes
III. Other specific types
Genetic disorder of β-cell function (MODY, mitochondrial DNA)
Genetic disorders in insulin action (lipoatrophic diabetes)
Exocrine pancreas diseases (pancreatitis, hemochromatosis)
Endocrinopathies (acromegaly, Cushing's syndrom)
Drug-induced (*glucocorticoids*, tiazidics)
Infections (cytomegalovirus, congenital rubeola)
Uncommon immunological forms (insulin receptor antibodies)
Other genetic syndrome (Down, Turner, Prader-Willi syndrom)
IV. Gestational diabetes

Source: adapted from American Diabetes Association[8].

Figure 3.

Type 1 Diabetes Mellitus: Type 1 diabetes mellitus, often referred to as juvenile diabetes, is characterized by the autoimmune destruction of beta cells, typically resulting in absolute insulin deficiency [13]. Diagnosis of Type 1 diabetes is often confirmed by the presence of anti–glutamic acid decarboxylase, islet cell, or insulin antibodies, indicating the autoimmune processes responsible for beta cell destruction. Ultimately, individuals with Type 1 diabetes will require insulin therapy to maintain normal blood glucose levels [22-26].

Type 2 Diabetes Mellitus: The ongoing debate revolves around the relative significance of defects in insulin secretion versus peripheral hormone action in the development of Type 2 diabetes mellitus (DM2). DM2 accounts for 80% to 90% of all diabetes cases, and most individuals with this type exhibit intra-abdominal (visceral) obesity, closely linked to insulin resistance. Additionally, hypertension and dyslipidemia, characterized by high triglyceride and low HDL-cholesterol levels along with postprandial hyperlipidemia, are common in Type 2 diabetes. This prevalent form of diabetes is strongly associated with a family history of diabetes, older age, obesity, and a sedentary lifestyle. It is more prevalent in women, especially those with a history of gestational diabetes, as well as in Black, Hispanic, and Native American populations [26-29].

Gestational Diabetes Mellitus (GDM): Gestational diabetes mellitus is a classification used to identify women who develop diabetes during pregnancy, regardless of the pathophysiological condition. Women who develop Type 1 diabetes during pregnancy or those with undiagnosed asymptomatic Type 2 diabetes discovered during pregnancy are categorized under Gestational Diabetes Mellitus (GDM). In most cases, GDM manifests in the third trimester of pregnancy [29-31].

Other Specific Types (Monogenic Diabetes): Various types of diabetes mellitus with known etiologies are grouped under "Other Specific Types." This category includes individuals with genetic defects in beta-cell function (formerly known as MODY or maturity-onset diabetes in youth), defects in insulin action, diseases of the exocrine pancreas (e.g., pancreatitis or cystic fibrosis), dysfunction associated with other endocrinopathies (e.g., acromegaly), and pancreatic dysfunction caused by drugs, chemicals, or infections. These specific types comprise less than 10% of diabetes

cases [32].

Diagnosis

As per the American Diabetes Association (ADA), routine screening for diabetes involves using fasting glucose concentration, although postprandial blood sugar, random blood sugar, and glucose tolerance tests are also employed for blood sugar assessment. The ADA specifies that for a diabetes diagnosis, at least one of the following criteria must be met: the presence of diabetes symptoms (such as polyuria, polydipsia, unexplained weight loss, etc.) along with a casual plasma glucose concentration of ≥11.1 mmol/L (200 mg/dL).

Regarding fasting plasma glucose, its normal range is 70-110 mg/dL after a minimum of 8 hours without caloric intake. The World Health Organization (WHO) classification aligns with the ADA in terms of clinical stages (normoglycemia, impaired glucose tolerance/impaired fasting glucose -IGT/IFG, diabetes) and etiological types of diabetes mellitus. However, the WHO classification includes additional categories such as gestational impaired glucose tolerance (GIGT) and gestational diabetes mellitus (GDM). The criteria for GDM include fasting glucose levels of ≥7.0 mmol/L (126 mg/dL) and/or 2-hour glucose levels of ≥7.8 mmol/L (140 mg/dL) after a 75-g oral glucose tolerance test (OGTT) [33-39].

Management of Diabetes Mellitus

Lifestyle mLifestyleodifications

Advancing age, obesity and history of diabetes in the family have been identified as a major risk factors for diabetes in a study conducted by National Institute of Diabetes and Digestive and Kidney Diseases. Although not highly correlated, gender and lack of sufficient exercise were also found to be risk factors for diabetes [40]. Surgical interventions such as gastric bypass surgery in highly obese people have demonstrated that it helps in maintaining weight and glucose levels close to normal in patients with diabetes [41]. Weight loss also helps in improving hypertriglyceridemia, and hyperuricemia and maintaining these benefits over time. A weight loss of more than 20kgs over time had almost a curative effect on the subjects [41-45]. Intensive lifestyle along with metformin therapy is found to reduce the need for drug therapy for management of comorbidities like hypertension and hyperlipidemia in patients with diabetes when compared to treatment with metformin and placebo. Intensive dietary control has also shown that it is an effective treatment in patients recently diagnosed with diabetes and can be used in the initial stages instead of oral medications or insulin. These studies emphasize the important role of weight loss in reducing the risk associated with diabetes mellitus. A life style intervention with weight loss, exercise regimen and diet control is often the first step in treatment of patients with newly diagnosed with diabetes and recommended by the ADA. Pharmacological therapy is often started immediately with lifestyle interventions if the glycosylated hemoglobin is high [45-50].

Drugs used in diabetes

Failure to maintain weight loss and progressive loss of beta cell functions requires the use of anti-diabetic agents in most patients for sustained maintenance of glycemic goals. The choice of an anti-diabetic drug and its dose depends on drug-related factors such as its effectiveness in lowering glucose levels, its side effects, safety profile, cost and patient related factors such as baseline severity of hyperglycemia, other associated comorbidities, allergies, contraindications and tolerability [50-55]. Since it dependent on several patient factors, the drug and dose needs to be individually titrated to achieve stable levels at initiation and during the course of the treatment .The most commonly accepted strategy is to use a drug with rapid action and higher glucose lowering property when HbA1c > 8.5% and a drug with slower onset and lower glucose reducing property when HbA1c < 7.5% . The following sections describe the hypoglycemic agents that are used in treatment of diabetes mellitus [55-60].

Biguanides

Galega officinalis was used in the early twentieth century in Europe due to its ability to lower glucose levels attributed to a compound guanidine. However toxicity associated with use of guanidine led to clinical investigation of related biguanide derivatives phenformin, buformin and metformin. Phenformin and buformin were withdrawn from many countries including U.S. owing to lactic acidosis as a major adverse event. Metformin is not only an inexpensive drug but also has several other beneficial pharmacologic effects which include weight stabilization/reduction, improvement in lipid profile, reduced chances of hypoglycemia and otherbeneficial vascular effects. Metformin has several pharmacological pathways that make it favorable as first line therapy. It requires the presence of insulin and primarily acts by reducing gluconeogenesis i.e. the production of glucose from non carbohydrate sources as well as glycogenolysis i.e. glucose production from glycogen and oxidation of fatty acids in the liver. It decreases HbA1c levels by 1%-2% [60-65].

Pharmacokinetics and Contraindications: Metformin has a bioavailability of 50%-60% and reaches peak plasma concentrations in 2 hours. It is absorbed from the small intestine and has a half-life of 2-5 hours. Since most of the drug is eliminated unchanged in the urine it is typically not prescribed in patients with more than mild renal impairment. Although the relationship between metformin as a cause of lactic acidosis has not been established, it is can precipitate the risk of lactic acidosis in the presence of other conditions. Metformin increases the conversion of glucose to lactate and this action is potentiated in presence of liver dysfunction. Hence it is contraindicated in patients with impaired liver function. It is also given in combination with drugs from other classes. Renal excretion is competitively inhibited when administered simultaneously with cimetidine, resulting in increased levels of metformin in the blood. Hence it should be used carefully in patients on cimetidine. It is also contraindicated in patients with cardiac insufficiency, alcohol abuse or presence of metabolic acidosis. Metformin can decrease the absorption of cyanocobalamin when used over a long period of time. Although it does not have a potential to cause anemia, annual examination of hemoglobin levels is recommended along with measurement of creatinine clearance [65-70].

Sulphonylureas

Sulphonylureas (SU) belong to insulin secretagogues class of drugs and acts by stimulating the release of insulin from β cells of Islets of Langerhans in the pancreas. It binds to sulphonylurea receptor on β cells of the pancreas which results in depolarization and opening of the calcium channels. The influx of calcium causes insulin to be released due to its action on calcium dependent proteins. Since the release of insulin by sulphonylureas is not regulated by levels of blood glucose, hypoglycemia is a common side effect associated with this class of drugs especially in patients with irregular eating habits and tightly controlled blood glucose. It is used in patients who are not responsive to increased glucose levels but have retained their ability to secret insulin. It is effective in reducing the HbA1c levels by 1%-2% [70-75].

The first generation SU include tolbutamide, chlorpropamide, tolazamide and acetohexamide while second generation SU include glyburide, glipizide and glimepiride. The second generations SU differ from the first generation SU essentially in their potency, dose, duration of action and the extent to which they cause hypoglycemia. The SU currently in use in the U.S. are chlorpropamide, glyburide, glipizide and glimepiride [75-78]. Sulphonylureas are commonly used first-line oral anti-diabetic therapy. The dose needs to be titrated individually after careful monitoring of blood glucose levels on initiation of therapy. Since the duration of action of different sulphonylureas ranges from 12 to >24 hours therapy often involves combination of different sulphonylureas or combination with drugs from other classes to obtain optimal and stable HbA1C levels. SU treatment is effective as long as β cell function is intact. Progression of β cell impairment requires the need to switch to another class of drug or insulin treatment [78-80].

Pharmacokinetics and Contraindications: SU has a high volume of distribution as it is bound to

plasma protein albumin. They are metabolized in the liver and eliminated by the kidneys on conversion to active or inactive metabolites. SU are contraindicated in patients suffering from type 1 diabetes due to their inability to produce insulin and in type 2 diabetes patients scheduled for surgery as insulin is generally used to maintain glucose levels. Although not contraindicated, it is not recommended in obese patients as it leads to weight gain. Allergic reactions are rare. Alcohol-induced facial flushing reaction maybe observed in patients on chlorpropamide [80-85] .Several drugs are known to have the capability to induce hypoglycemia when co-administered with SU necessitating dose adjustment. Warfarin, monoamine oxidase inhibitors (MOI), chloramphenicol, phenylbutazone decrease the metabolism of SU, while salicylates, probenecid, allopurinol reduces the renal excretion. Some drugs also cause displacement of SU from plasma proteins and hence the dose needs to be titrated individually in patients [86].

Thiazolidinediones

Thiazolidinedine (TZD) class of drugs includes troglitazone, rosiglitazone and pioglitazone. Troglitazone was withdrawn almost immediately upon introduction (1997) in the UK and in 2000 in the US due to hepatotoxicity. Since then rosiglitazone and pioglitazone have been used in treatment of diabetes since no hepatotoxicity was observed in the newer drugs [24, 31]. Increasing evidence on adverse events led to the FDA recently placing restriction on the use of rosiglitazone and complete withdrawal from the European market [87]. TZD’s require the presence of insulin and its main mechanism of action is to increase glucose uptake by stimulating peroxisome proliferator-gamma receptors in adipose tissue and increasing insulin sensitivity. It also reduces gluconeogenesis and increases lipogenesis which further increases glucose utilization. TZD’s can be used as monotherapy or in combination with metformin, SU or insulin [24, 33]. They are effective in reducing HbA1c levels by 0.5%-1.5% [88].

Pharmacokinetics and Contraindications: Rosiglitazone and pioglitazone are rapidly metabolized in the liver and reach peak plasma concentration in 1-2 hours. Rosiglitazone is eliminated in the urine while pioglitazone is eliminated in bile. They are highly protein bound however the low concentrations do not result in displacement or interaction with any other drugs. They are metabolized by cytochromes that do not interfere significantly with metabolism of other drugs. In Europe, they are used as primary therapy in patients who have a contraindication for metformin. Glitazones have been known to cause fluid retention resulting in increased plasma volume and subsequent reduction in hemoglobin levels. Hence they are contraindicated in patients suffering from congestive heart failure and regular evaluations of hemoglobin levels are suggested [89-90]. Since they are metabolized extensively by the liver and troglitazone was associated with fatal hepatotoxicity, periodic liver function tests are highly recommended. Some studies demonstrated a higher risk for edema in patients receiving TZD’s in combination with insulin. Although not contraindicated caution should be exercised when administering a combination therapy of TZD and insulin. It is also not recommended during pregnancy unless the benefits outweigh the risks. TZD’s may resume ovulation in women suffering from polycystic ovary syndrome and result in preganacy [91].

α Glucosidase inhibitors

Alpha-glucosidase inhibitors such as acarbose and miglitol act by delaying the process of digestion and thereby absorption of carbohydrates from the intestinal lumen. α-Glucosidase inhibitors act by inhibiting the α-glucosidase enzymes from breaking complex carbohydrates into monosaccharide and hence temporarily interrupt the digestion and absorption process thereby preventing post-prandial hyperglycemia. It is taken before meals with a diet rich in complex carbohydrates [21, 36, 24]. It reduces the HbA1c levels by 0.4%-0.8%. These drugs have a fairly high rate of discontinuation (25%-45%) owing to flatulence as a common side effect [92].

Pharmacokinetics and Contraindications: These drugs are not systematically absorbed into the bloodstream as they are only responsible in delaying the absorption of carbohydrates from the

intestine. It is degraded by the enzymes in the small intestine and the metabolites absorbed into the bloodstream are eliminated in the urine. It is contraindicated in patients with significant renal impairment, inflammatory bowel disease and ulcers in the colon [93].

Glinides

Repaglinide and nateglinide are commonly used to control post-prandial hyperglycemia. It is a rapid acting insulin releaser with insulin released within 15-20 minutes of administration and having pharmacological effect lasting for about 3 hours. Hence these are taken about 15-20 minutes before meals and commonly used in patients who are otherwise on non-pharmacological methods for insulin control. It is also administered with drugs from other classes of oral antidiabetics; however not with SU since both classes of drugs use the same biological pathway as calcium channel opening agents whilst binding to different receptors. There is no impact on weight change and lesser chances of drug induced hypoglycemia due to shorter duration of action. However it requires more frequent administration when administered as monotherapy. It is a viable option when used with metformin [94].

Pharmacokinetics and Contraindications: Glinides have rapid onset of action with plasma peak concentrations being achieved in 60 minutes and 20 minutes with repaglinide and nateglinide respectively. The drugs are metabolized by the liver and excreted in bile. The reduction in HbA1c levels is comparable to that achieved by SU (1%-2%) without inducing any hypoglycemia [95].

Glucagon like peptide 1 (GLP-1) agonists

Exenatide injection is administered in patients who are not sufficiently stable on metformin or sulphonylurea. GLP-1 is an incretin hormone secreted by endocrine L cells in the small intestine. GLP-1 is released when there an increase in the plasma glucose levels. It stimulates the release of insulin, inhibits the release of glucagon and retards gastric emptying [26, 27] .However it is very short acting (t ½ = 90 seconds) and the release stops when glucose serum levels are restored. Moreover it is actively degraded by dipeptidyl peptidase IV enzyme resulting in the short halflife. Exenatide is homologous to human GLP-1 and mimics its actions while having a longer duration of action. It is administered twice a day and results in 0.5%-1.0% reduction in HbA1c levels. It is typically used in conjunction with SU, metformin and/or TZD [39-41].

Dipeptidyl peptidase 4 inhibitors (DPP-4 Inhibitors)

As mentioned in the previous section DPP-4 is responsible for rapid degradation and inactivation of GLP-1. Sitagliptin and saxagliptin are inhibitors of DPP-4 and help in prolonging the action of GLP-1. Sitagliptin is an oral DPP-4 inhibitor that was approved by the FDA in October 2006. It is recommended for use as monotherapy or in combination with metformin or TZD’s [26, 27] .Several clinical trials were conduction to compare the efficacy of Sitagliptin as monotherapy. It was found that the drug was well tolerated and did not lead to any adverse hypoglycemic events or significant weight gain. The overall reduction in HbA1c levels was consistent in the trials and typically ranged from 0.4%-0.9% [42-45]. Many randomized clinical trials have assessed the effect of adding sitagliptin to existing metformin, TZD or SU therapy. All trials found a statistically and clinically significant reduction in HbA1c levels when compared to existing therapy without sitagliptin. Saxaglitin is currently in the investigational phase as a supplemental drug, however clinical trials have demonstrated it to be promising future drug with 0.7%-0.8% decrease in HbA1c levels [95].

Amylin agonists

Amylin is an amino acid peptide that is secreted along with insulin during ingestion of meals. It is found that patients with type 2 diabetes secrete insufficient quantities of this peptide which retards the rate of gastric emptying and reduces the quantity of glucagon released by the liver thereby alleviating hyperglycemic conditions. Pramlitide injection is an analogue of amylin that is approved

for use with insulin or its analogues. It has shown to reduce HbA1c levels by 0.50.7% with nausea being the only reported side effects which improves with the course of the therapy [21, 26, 27, 46, 47,96].

Pharmacokinetics and contraindications: Pramlitide reaches peak levels in about 20 minutes with a half-life of 29 minutes and is eliminated by the kidneys. Owing to its rapid onset of action and short duration of action, it is administered just before meals. It has not demonstrated any contraindications till date [21, 26, 48,97].

Insulin and its analogues

Human insulin and its analogues is the standard treatment used in type 1 patients. Failure of oral hypoglycemic agents to maintain HbA1c levels and progressive loss of β cell function requires the use of insulin in type 2 diabetes patients. Structurally insulin is composed of two amino acid chains A and B connected by two disulphide bonds. Human insulin is synthesized by inserting the genes responsible for formation of the amino acids into Escherichia coli and subsequent fermentation [26, 49]. Analogues of insulin chiefly differ in their duration of action. Faster acting analogues show peak pharmacological effect in 2-4 hours of administration and have duration of action of 6-8 hours. Longer acting analogues comparatively have duration of action for up to 24 hours. They are formulated injectable suspensions to release the drug uniformly over extended period of time thereby reducing the possibility of hypoglycemic events compared to faster acting analogues [26, 27,98].

Pharmacokinetics and contraindications: Insulin is primarily metabolized in the liver and eliminated by the kidneys. Although not contraindicated, hypoglycemia is the most common adverse event associated with its use [21, 26, 50, 51]. Severe hypoglycemia can lead to significant permanent brain damage. Ingestion of alcohol by patients on insulin can trigger hypoglycemic events as alcohol inhibits gluconeogenesis. Patients are advised to follow regular eating habits and avoid sudden strenuous exercise [26, 27,99-105].

Conclusion

Diabetes mellitus comprises a set of metabolic disorders characterized by persistent hyperglycemia arising from deficiencies in insulin secretion, insulin action, or both. The metabolic disruptions extend to carbohydrates, lipids, and proteins due to insulin's crucial role as an anabolic hormone. The primary objective in managing diabetes is to restore carbohydrate metabolism to a state of normalcy. For individuals with a complete lack of insulin, insulin replacement therapy becomes necessary, administered through injections or tablets. Conversely, insulin resistance can be addressed through dietary adjustments and exercise. Additionally, the broader goals of diabetes management include preventing or treating the various complications that may arise from the disease itself and its therapeutic interventions.

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