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Review Article

DIABETES MELLITUS AND ANTIDIABETICS WITH REFERENCE TO ALPHA GLUCOSIDASE INHIBITORS

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ABSTRACT

Diabetes mellitus is a long term disorder with high blood glucose level associated with other complications. Every year it takes many people in its list to affect. With modern lifestyle and food behavior incidence of diabetes increasing day by day. Proper lifestyle, exercise and proper diet is the mainstay to manage this condition though many drugs are available in the market. Insulin is the first choice of chemical for treatment as insulin control the circulatory blood glucose and its entry to other cells for energy. Other oral antidiabetics like biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides etc are available in the the market for monotherapy as well as combination therapy but they are neither efficient like insulin nor free from adverse effects. The aim of this review is to present in brief about the diabetes burden worldwide with its pathophysiology, diagnosis and proper management. Alpha-glucosidase inhibitors are discussed here as they proved to control the postprandial blood glucose level significantly and some other new targets for glycemic control.

Keywords: diabetes mellitus, glucose, insulin, alpha-glucosidase, obesity, exercise.

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 [1]. Diabetic complications arise due to derangements in the regulatory systems for storage and mobilization of metabolic fuels, including the catabolism and anabolism of carbohydrates, lipids and proteins emanating from defective insulin secretion, insulin action, or both [2,3]. 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.

Experts project that the incidence of diabetes is set to soar by 64% by 2025 [4]. DM caused 4.6 million deaths in 2011 [5]. There are two major types of diabetes mellitus:

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. The incidence of type 1 diabetes is increasing in both rich and poor countries. Furthermore, a shift towards type 1 diabetes occuring in children at earlier ages is imminent [6]. 85 to 95% of all diabetes in high-income countries are of type 2 accounting for an even higher dominance in developing countries. It is intimately associated with improper utilization of insulin by target cells and tissues. It is currently a common and serious health concern globally.

Table 1 showing the characteristic comparison between two types of diabetes mellitus.

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Table 1: Clinical characteristics of patients with Type 1 and Type 2 diabetes mellitus.

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

Source: Guyton and Hall (2006) [7].

Pathophysiology of Diabetes Mellitus:

A regular energy source is a required for every cell to function properly in the human body. Glucose is the body's primary and prime energy source, which circulates in the blood as mobilized fuel source for cells [8, 9, 10]. Insulin is a hormone; secrete from pancreatic β cells 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 [11]. During hyperglycemia, body draws 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. For DM-2 to develop, two defects are necessary: insulin resistance and insulin deficiency relative to the resistance. The dual defect of insulin deficiency and insulin resistance in DM-2 is caused by interplay between genetic and environmental factors like obesity, nutrition and physical activity. Gestational diabetes is caused when there are excessive counter-insulin hormones of pregnancy. This leads to a state of insulin resistance and high blood sugar in the mother. There may be defective insulin receptors.

Diagnosis:

Confirmation of diabetes is not so complicated and based on readily available criterion. The diagnostic criteria and the classification of diabetes was first put forward by the World Health Organization (WHO) in 1965 [12] then by the National Diabetes Data Group (NDDG) in 1979, [13] and this was followed by simplified recommendations by the WHO in 1980 [14]. It is still based on the American Diabetic Association (ADA) guidelines of 1997 or World Health Organization (WHO) National diabetic group criteria of 2006, which is

- Symptoms of diabetes (polyurea, polydipsia, unexplained weight loss, etc) as well as casual plasma glucose concentration = 11.1 mmol/L (200 mg/dL).
- Fasting plasma glucose = 7.0 mmol/L (126 mg/dL), with no caloric intake for at least 8 h [15].

The report of World Health Organization (WHO) in 1999 states that a fasting glucose 126 mg/dl and /or a 2-h glucose 200 mg/dl are necessary. The report indicates that diagnosis should not be based on single determination of blood glucose level but requires confirmatory symptoms or blood/plasma determination. Ideally, therefore, both the 2-h and fasting value should be used. These recommendations contrast with those of American Diabetic Association (ADA) Expert Committee which gives priority to the 'fasting plasma glucose.' In July 2009, the International Expert Committee Oman Medical Specialty Board (IEC) recommended the additional diagnostic criteria of glycated hemoglobin (HbA1c) result ≥6.5% for DM. This committee suggested that the use of the term pre-diabetes may be phased out but identified the range of HbA1c levels ≥6.0% and

<6.5% to identify those at high risk of developing DM [16].

Management:

Insulin replacement therapy is the mainstay of treatment in patient with type 1 diabetes while type 2 diabetes should be regarded as a potentially preventable disease by proper lifestyle and manageable with some medication. Life style is apparently the backbone of management of diabetes mellitus. It is recognized as being an essential part of diabetes and cardiovascular disease prevention. Meta-analyses demonstrate that lifestyle interventions, including diet and physical activity, led to a 63% reduction in diabetes incidence in those at high risk [17]. An important large-scale prospective study in China, examined the effects of diet and exercise upon the rate of progression of IGT to diabetes; both the measures, alone or together reduced the progression of the disease by 40% after 6 years [18].

Pharmacological agents:

The aim of the treatment is 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 [19]. In patients with type 2 diabetes, diet and physical activity are essential first line therapies. In spite of the underscored importance of lifestyle measures in diabetes therapy, most diabetics cannot escape the value of pharmacotherapy to achieve target glucose concentrations. Some class of agents is

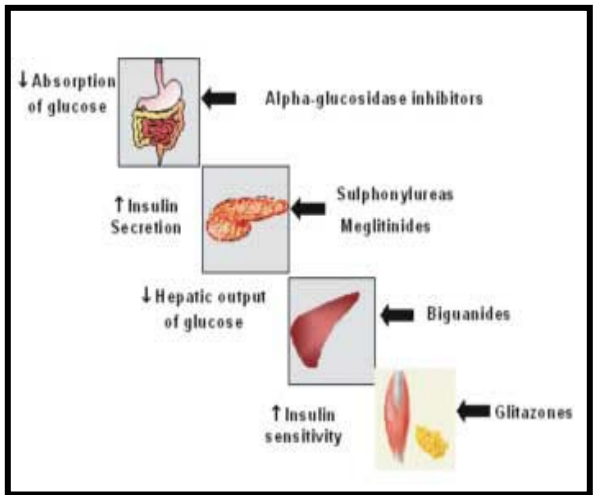

Figure 1: Primary site of action of oral antidiabetics

1. Biguanides:

These class of agents containing biguanide group in their structure and they are Metformin, Phenformine and Buformine. The latter two were withdrawn in many countries in the 1970s because of an association with fatal lactic acidosis [20]. Metformin is recommended as first-line therapy in the obese and overweight, and is recommended as first-line therapy in non-obese patients in some countries. Metformin works by decreasing hepatic gluconeogenesis while at times also increasing peripheral glucose mobilization and disposal [21]. It can be used in combination with sulphonylurea and other oral hypoglycemic agents as well as insulin. Metformin does not cause hypoglycaemia or weight gain, but often leads to troublesome gastrointestinal side effects, which are frequently dose dependent. Metformin should stopped or withdrawn 3 days before major surgery of any patient.

2. Sulfonylureas:

Sulphonylureas are structurally related to sulphonamides and were discovered accidentally, in 1942 when it was noted that some sulphonamides caused hypoglycaemia. Carbutamide was 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 [22]. The first generation of sulfonylureas includes tolbutamide, acetohexamide, tolazamide, and chlorpropamide. A second generation of sulfonylureas has emerged and includes glibenclamide (glyburide in USA), glipizide, gliclazide, and glimepiride. First generation sulphonylureas are rarely used now days, second generation sulphonylureas remain the mainstay of treatment of type 2 DM. Sulfonylureas cause hypoglycemia by stimulating insulin release from pancreatic ß-cells. They bind to sulfonylurea receptors (SUR) on the ß-cell plasma membrane and so on causes stimulation and release of Insulin. However, they usually lead to weight gain, and can cause hypoglycaemia (particularly with chlorpropamide and glibenclamide), [23] especially in the elderly, and in those with renal or liver disease. Thus, sulphonylureas should usually be used as second- or third-line agents.

3. Thiazolidinediones:

The thiazolidinediones improve insulin sensitivity in adipose tissue and skeletal muscles, by improving cellular response to insulin action; however they, such as rosiglitazone and pioglitazone, do not enhance insulin production. They do not cause hypoglycaemia and.decrease HbA1c by approximately 1–2%. Insulin sensitivity is brought about by binding to nuclear peroxisome proliferator-activated receptor-gamma (PPARɣ) leading to increased glucose transporter expression. This action on adipocytes reduces plasma free fatty acids (FFA) and also inhibits hepatic glucose output. The main adverse effects are weight gain though it usually results from increased subcutaneous fat, rather than an accumulation of visceral fat. Fluid retention may occur, and in those with pre-existing heart disease, cardiac failure may be precipitated. Pioglitazone should be avoided in elderly patients with congestive heart failure and is contraindicated in patients with class III-IV heart failure [24].

4. Meglitinides:

These medications also lower serum glucose by increasing insulin secretion. Repaglinide and nateglinide are meglitinides which act on the ATP-dependent K-channel in the pancreatic beta cells to stimulate the release of insulin from the beta cells. They are often used in the place of sulfonylureas in sulfonylurea -allergic patients or when their shorter half-life is required. 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 [25]. Metformin used in combination with different doses of nateglinide produced significantly lower glycaemic values than metformin monotherapy. Effects on weight and hypoglycemia risk are comparable to sulfonylureas.

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

These drugs act differently than others. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are hormones that stimulate insulin secretion and suppress glucagon. These incretin hormones are rapidly degraded by dipeptidyl peptidase-4 (DPP-4). DPP-4 inhibitors enhance the effect of these incretin hormones by inhibiting DPP-4. There are three DPP-4 inhibitors currently available: sitagliptin, vildagliptin and saxagliptin and they are not associated with weight gain.

6. Alpha-Glucosidase Inhibitors (AGI):

α-Glucosidase, is involved in carbohydrate synthesis and breakdown, plays crucial role in diabetes, viral infection and cancer. α-glucosidase has been considered to be a preferred drug target in the pharmaceutical area and a number of α-glucosidase inhibitors have been discovered and studied for various purpose [26]. These agents are most effective for postprandial hyperglycemia. Novel research presented some agents from natural as well as synthetic sources in clinical trials and lots of attention of researchers still arrowing this class of agents.

Mechanism:

Although the gastrointestinal tract does not play a significant role in the pathogenesis of either type 1 or type 2 diabetes, modification of its physiological activities can be used to improve glycemic and lipid control in these disorders. They acts by competively inhibiting alpha glucosidase, the enzyme in the small intestine brush border, which breaks down oligosaccharides and disaccharides into monosaccharides to free glucose in blood stream [27, 28]. Thus the absorption of glucose is delayed. They have a lowering effect on postprandial blood glucose and insulin levels. Commercially available a-glucosidase inhibitors are acarbose, miglitol and voglibose.

Use and Dosage:

Alpha-Glucosidase inhibitors may be used as monotherapy and in combination with other class of agents and/or insulin for glycemic control. Specially used for elderly patients or in patients with predominately postprandial hyperglycaemia. In patients with type 2 diabetes, alpha -glucosidase inhibitors when added to a high carbohydrate diet treatment lower fasting plasma glucose by a mean of 24 mg/dl, postprandial plasma glucose by a mean of 54 mg/dl, and HbA(1c) by a mean of 0.90%. When added to the treatment of type 2 diabetic patients on insulin, metformin, or sulfonylureas, there is an additional decrease in HbA(1c), of 0.54, 0.73, and 0.85%, respectively [29]. They should be given at the start of a meal.

The starting dosage is 25-50 mg once daily, and then increased to 50 mg twice or thrice a day. Hypoglycemia rarely seen with monotherapy and if occurs from combination therapy then treatment should be with oral glucose rather than sucrose.

Pharmacokinetics:

Acarbose is poorly absorbed (less than 2%) being orally administered and 35% of an oral dose appears as metabolites in the urine [29]. Miglitol is not metabolized and is excreted quantitatively by the kidney. However, because of its close resemblance to the glucose molecule, miglitol is significantly absorbed through a jejunal transport mechanism identical to that of glucose.

Adverse effects:

The adverse events associated with alpha-glucosidase inhibitor treatment are flatulence, abdominal discomfort, and bloating. These major effects are the consequences of undigested carbohydrate reaching the colon, where it is fermented by the bacteria.

Contraindications:

Inflammatory bowel disease, cirrhosis of liver and malabsorption syndromes (30) are reported till now as the contraindications of acarbose treatment.

7. Other approaches:

Some newer approaches for the treatment of diabetes also developing and some these findings proved significant in clinical results. They are

i. PPAR α/ϰ dual agonist likes KRP-297, tesaglitazar, ragaglitazar etc and somehow they acts like glitazones [31].

ii. Sodium-glucose cotransporter 2 (SGLT2) Inhibitors. This class works for glucose excretion and increasing the urinary glucose clearance. This effect causes a light osmotic diuresis effect and net excretion of calories through the glucose urination. Canagliflozin, dapagliflozin are available drugs of this class.

iii. Inhibition of phosphodiesterase (PDE) activity in islet ß-cells offers a potentially therapeutic approach to raise intracellular cAMP and thereby increase insulin biosynthesis and secretion.

iv. Vanadium salts exert insulin-like effects on glucose metabolism in vitro and lower blood glucose levels in animal models of hyperinsulinaemic and hypoinsulinaemic animal models of diabetes [32].

v. Alpha and beta adrenergic receptors also proving their value for blood glucose and insulin control process.

vi. Vitamins such as niacin, thiamine also counters their effect by facilitating glucose metabolism [15].

Conclusion:

Diabetes mellitus still known as devastating metabolic disorder and silent killer. A wide number of drugs and target have been developed to treat diabetes mellitus but treatment is addressed as manageable not curable. As prevention is better than cure so proper lifestyle and exercise is prior aim to minimize the risk of diabetes mellitus. Education of the populace regarding diet control, and control of overweight and obesity are still key to the control of this emerging epidemic. In this review there are various classes of agents are provided for treatment with their safety profile and adverse effects. Alpha-glucosidase inhibitors are now the hot topic and target for postprandial blood glucose management and extensive studies shows that there is minimum adverse effect with no result of mortality and morbidity. With lots of hope we are looking for a future where we can say that diabetes mellitus is no longer a fear to us and we are not in the list of diabetes burden.

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