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Review Article

NOVEL AGENTS FOR THE TREATMENT OF HYPERGLYCEMIA IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus (DM) is defined as elevated blood glucose associated with absent or inadequate pancreatic insulin secretion with or without concurrent impairment of insulin. It is a metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipidemia, negative nitrogen balance and sometimes ketone bodies formation. It is the most common endocrine disorder. It is expected that more than 200 million people worldwide will have DM and 300 million will consequently have the disease by 2030. Diabetes mellitus may be categorized into four types but the two major types are type 1 and type 2. Drugs are used primarily to save life and alleviate symptoms. Secondary aims of drug use to prevent long-term diabetic complications and by eliminating various risk factors, to increase durability. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise, and oral medications. No cure has yet been found for the disease, nevertheless, treatment modalities include lifestyle modifications. Oral hypoglycemic agents, and insulin sensitizers like a biguanide that reduces insulin resistance and it is recommended as first-line medication especially for obese patients. The pathophysiology of type 2 DM has led to the introduction of new medications like dopamine agonist, amylin analogues, glucagon-like peptide 1 analogues, dipeptidyl peptidase-IV inhibitors, 11ß-hydroxysteroid dehydrogenase 1, inhibitors of the sodium-glucose cotransporter 2, insulin-releasing glucokinase activators and glucagon receptor antagonists, pancreatic-G-protein-coupled fatty-acid-receptor agonists, metabolic inhibitors of hepatic glucose output and quick-release bromocriptine.

Keywords: *Type 2 diabetes mellitus, Pharmacological agent, Treatment, Novel agent.*

INTRODUCTION

Diabetes mellitus (DM) is defined as elevated blood glucose associated with absent or inadequate pancreatic insulin secretion with or without concurrent impairment of insulin. It is a metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipidemia, negative chronic with disturbances of carbohydrate, fat and protein metabolism [1]. As the disease progresses tissue or vascular damage ensures leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration [2]. Diabetes mellitus may be categorized into four types but the two major types are type1 (IDDM) and type2 (NIDDM). Other specific types of diabetes are gestational diabetes. Sometimes, the term juvenile onset diabetes has been used for IDDM and maturity onset for NIDDM. The two main forms of clinical type 1 diabetes are type 1a (about 90% of type1 diabetes) which is thought to be due to immunological destruction of pancreatic ß cells resulting in insulin deficiency; and type 1b (idiopathic, about 10% of type 1 diabetes), in which there is no evidence of autoimmunity. Type 1a is characterized by the presence of islet cell antibody (ICA), anti-glutamic acid decarboxylates (anti-GAD), IA-2 or insulin antibodies that identify the autoimmune process with ß-cell destruction [3]. There is no known etiological basis for type 1b diabetes mellitus. Some of these patients have permanent insulinemia and are more prone ketone body formation ,but have no evidence of autoimmunity. Type 2 diabetes is the commonest form of diabetes and is characterized by disorders of insulin secretion and insulin resistance [4]. Traditionally, type 2 diabetes is common in individuals over the age of 40. It is often associated with obesity, decreased physical activity and heredity [5]. Recent data from several countries show that type 2 diabetes is increasingly becoming a problem among adolescents and even children [6]. The disease is usually controlled through dietary therapy, exercise and hypoglycemic agents [7]. Gestational Diabetes (GD) Mellitus refers to the onset or initial recognition of glucose intolerance during pregnancy usually in the second or third trimester [8]. Patients with GD have a 30% to 50% chance of developing DM, usually, type 2 DM. Certain drugs like glucocorticoids, pentamidine, niacin, and alpha interferon may also lead to DM, maturity-onset diabetes of the young (MODY) is a familial form of NIDDM with autosomal-dominant inheritance, which usually develops in childhood, adolescence or young adulthood, and presents primarily insulin secretion defects [9].

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EPIDEMIOLOGY

As of 2016, 422 million people have diabetes worldwide, up from an estimated 382 million people in 2013 and from 108 million in 1980 Type 2 makes up about 90% of the cases [10, 11]. Some data indicate rates are roughly equal in women and men [12]. but male excess in diabetes has been found in many populations with higher type 2 incidence, possibly due to sex-related differences in insulin sensitivity, consequences of obesity and regional body fat deposition, and other contributing factors such as high blood pressure, tobacco smoking, and alcohol intake [13]. The World Health Organization (WHO) estimates that diabetes mellitus resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death. using modeling to estimate the total amount of deaths that could be directly or indirectly attributed to diabetes. It is estimated that 439 million people would have type 2 DM by the year 2030. Diabetes mellitus occurs throughout the world but is more common (especially type 2) in more developed countries [14]. The number of people with type 2 Diabetes Mellitus is increasing in every country with 80% of people with DM living in low and middle-income countries. The prevalence of type 2 DM varies significantly from one ecological state to the other as a result of environmental and lifestyle risk factors [15]. It is predicted that the incidence of Diabetes Mellitus in adults of which

type 2 DM is becoming most important will increase in the next two decades and much of the increase will occur in developing countries where the bulk of patients are aged between 45 and 64 years. It is projected that the latter will equal or even exceed the former in developing nations, thus culminating in a double burden as a result of the current trend of transition from communicable to non-communicable diseases [16].

PATHOPHYSIOLOGY

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure [17]. 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. 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 in the case of GLP-1 of glucagon suppression. Although GIP activity is impaired in those with type 2 DM, GLP-1 insulinotropic effects are preserved, and thus GLP-1 represents a potentially beneficial therapeutic option. Study are ongoing on the role of mitochondrial dysfunction in the development of insulin resistance and etiology of type 2 DM. Also very important is adipose tissue, as endocrine organ hypothesis (secretion of various adipocytokines i.e, leptin, TNF-alpha, 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 [18].

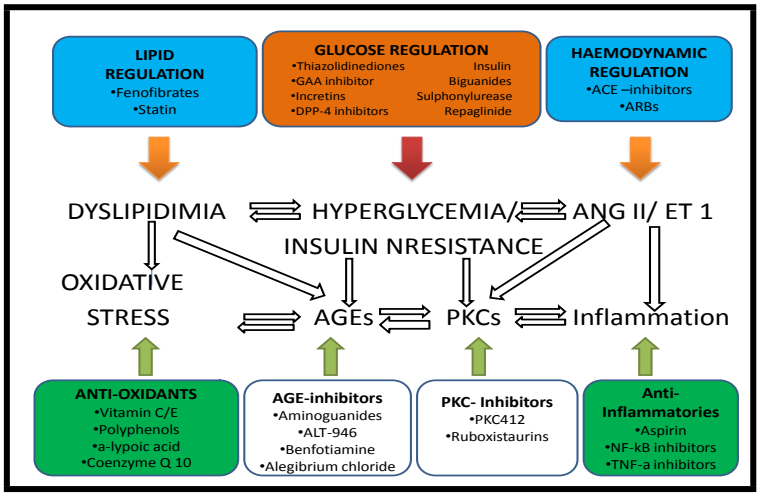

Fig.1: Pathophysiological factors

SYMPTOMS

Symptoms are similar in both types of diabetes but they vary in their intensity. Symptoms develop more rapidly in type 1 diabetes. The symptoms include polyuria, polydipsia, polyphagia, weight loss, fatigue, cramps, constipation, blurred vision [19]. The type 1 DM patients are susceptible to microvascular complications and macrovascular disease (coronary artery, heart, and peripheral vascular diseases). Symptoms in type 2 DM are similar but insidious in onset. Most cases are diagnosed because of complications. Type 2 DM carries a high risk of large vessel atherosclerosis commonly associated with hypertension, hyperlipidemia and obesity [20]. Most patients with type 2 diabetes die from cardiovascular complications and end-stage renal disease [21]. Geographical differences exist in both the magnitude of these problems and their relative contributions to overall morbidity and mortality [22].

LIFESTYLE, GENETICS & MEDICAL CONDITIONS

Type 2 DM is due primarily to lifestyle factors and genetics [23]. A number of lifestyle factors are known to be important to the development of type 2 DM. These are physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol [24]. Obesity has been found to contribute to approximately 55% of cases of type 2 DM [25]. The increased rate of childhood obesity believed to have led to the increase in type 2 DM in children and adolescents [26]. Environmental toxins may contribute to the recent increases in the rate of type 2 DM. A weak positive correlation has been found between the concentration in the urine of bisphenol A, a constituent of some plastics, and the incidence of type 2 DM [27, 28]. Recently, genes discovered to be significantly associated with developing type 2 DM, include TCF7L2, PPARG, FTO,NOTCH2, WFS1, KCNJ11, CDKAL1, IGF2BP2, JAZF1,SLC30A8, HHEX. These genes encode the islet ATP-sensitive potassium channel and TCF7L2 regulates proglucagon gene expression and thus the production of glucagon-like peptide-1 [29]. Moreover, obesity (which is an independent risk factor for type 2 DM) is strongly inherited [30, 31]. There are many medical conditions which can potentially give rise to, or exacerbate type 2 DM. These include obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed metabolic syndrome (it is also known as Syndrome X, Reaven's syndrome) [32]. Other causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer, and drugs [33]. Additional factors found to increase the risk of type 2 DM include aging, high-fat diets and a less active lifestyle [34].

SCREENING & DIAGNOSIS

The test recommended for screening is the same as that for making the diagnosis, with the result that a positive screen is equivalent to a diagnosis of pre-diabetes or DM. Although about 25% of patients with type 2 DM already have microvascular complications at the time of diagnosis suggesting that they have had the disease for more than 5 years at the time of diagnosis. which is for a single raised glucose reading with symptoms (polyuria, polydipsia, polyphagia and weight loss), otherwise raised values on two occasions, of either fasting plasma glucose 126 mg/dL or with an oral glucose tolerance test (OGTT), two hours after the oral dose a plasma glucose 200 mg/dL [35, 36]. The glycelated hemoglobin (HbA1c) and fructosamine are also still useful for determining blood sugar control over time. In July 2009, the International Expert Committee (IEC) recommended the additional diagnostic criteria of an 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 ^{3}6.0% and <6.5% to identify those at high risk of developing DM. Identifying individuals as diabetic against the minimal clinical consequences of delaying the diagnosis in a patient with an HbA1c level <6.5% [37].

TREATMENT

The aim of the treatment is primarily to save life and alleviate symptoms. Secondary aims are to prevent long term diabetic complications by eliminating various risk factors to increase long life [38]. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be

controlled by diet, weight loss, exercise, and oral medications. Oral hypoglycemic agents are also useful in the treatment of type 2 DM. Oral hypoglycemic agents include sulphonylureas, biguanides, alpha-glucosidase inhibitors, and thiazolidinediones. The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and inadequate insulin secretion. They should be prescribed in combination with an appropriate diet and lifestyle changes. Diet and lifestyle strategies are to reduce weight, improve glycemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes. Diabetes is best controlled either by diet alone and exercise (non-pharmacological), or diet with herbal or oral hypoglycaemic agents or insulin (pharmacological) [39].

PHARMACOLOGICAL AGENT

1. GLP-1 Receptor agonist

GLP-1 exerts its effect on postprandial glucose concentrations, including enhancing insulin secretion and suppressing postprandial glucagon secretion in a glucose-dependent manner [40]. GLP-1 also acts as a postprandial satiety signal through neurohormonal networks that signal the brain to suppress appetite and food intake [41]. Furthermore, GLP-1 also has direct effects on the β cells [42]. Liraglutide is a once-daily GLP-1 receptor agonist with an amino acid sequence homologous to endogenous human GLP-1 that was approved by FDA for clinical use in 2010. Currently approved indications are as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Liraglutide at daily subcutaneous monotherapy doses of 1.2 and 1.8 mg as monotherapy decreased HbA1c. It has greater reductions than sulfonylurea therapy [43]. Albiglutide and Dulaglutide also approved by USFDA in 2014 [44, 45]. Lixisenatide approved in Europe in 2013 for the treatment of adults with type 2 diabetes mellitus to achieve glycemic control in combination with oral glucose-lowering agents or basal insulin and these, together with diet and exercise, do not provide adequate glycemic control. It is a once-daily prandial GLP-1 receptor agonist [46]. Oxyntomodulin (OXM) is a peptide activates both GLP-1 receptor (GLP-1R) and glucagon receptor (GCGR) [47]. Hence, the actions of OXM encompass the effects elicited by GLP-1 and glucagon, including reductions in a food intake, gastric emptying, gastric acid secretion, β-cell apoptosis and increases in a hepatic glucose production, insulin secretion, somatostatin secretion [48].

2. Dipeptidyl Peptidase-IV (DPP-IV) Inhibitors

Dipeptidyl peptidase IV inhibitors are compounds that increase an endogenous concentration of incretins, including GLP-1, by limiting the proteolytic cleavage by DPP-IV [49]. inhibition of DPP-IV has been suggested as a viable alternative to promote circulating GLP-1 levels and overcome the limitations of GLP-1 administration [50]. Sitagliptin is a selective DPP-IV inhibitor and approved in 2006 in the US [51]. Studied that sitagliptin monotherapy decreases HbA1c [52]. Adding on one another agent decreases HbA1c from 0.45% to 1.0% [53]. In monotherapy, the incidence of hypoglycemia was reported [54]. Saxagliptin, Linagliptin, Alogliptin also is a selective DPP-IV inhibitor and Approved in the US in 2009, 2011 and 2013 respectively [55, 56].

3. Sodium-glucose transport protein (SGLT2) inhibitor:

Canagliflozin was approved in 2014 by USFDA in a fixed dose combination with metformin is an SGLT2 inhibitor. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [57]. The most common side effects of canagliflozin are the vaginal yeast infection and urinary tract infection because it has a diuretic effect. it can cause a reduction in intravascular volume leading to orthostatic or postural hypotension [58]. Dapagliflozin also approved in October 2014 by US FDA in a fixed dose combination with metformin [59]. Empagliflozin most recently USFDA approved drugs of SGLT2 inhibitor class of anti-diabetic medications [60].

4. Delayed Release Metformin:

Metformin is one of the prescribed oral antidiabetic agent in the US and worldwide, yet its mechanism of action remains poorly understood. Bioavailability of metformin is ~ 40–60%, and the biguanide is mainly absorbed in the upper small intestine. In diabetic rats, metformin acutely lowers blood glucose levels, when given orally or intraportal ly but not intravenously [61]. Plasma metformin levels compare poorly with the drug's glucose lowering effect. Metformin is concentrated in the cells of the distal small intestine and has been shown to increase GLP-1. cooperatively these observations suggest that the glucose-lowering effect of metformin, at least in part, results from a pre-systemic effect on the enteroendocrine L cells in the small intestine to release gut hormones. When using a delayed-release formulation that escapes absorption in the upper small bowel in comparison normal metformin [62].

5. Insulin sensitizer:

Thiazolidinedione is an insulin sensitizer, selective ligands transcription factor peroxisomes proliferator-activated gamma [63]. Pioglitazone use is not associated with hypoglycemia and can be used in cases of renal impairment and it is 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 elder adults with type2 DM. Pioglitazone should be avoided in aged patients with congestive heart failure and is contraindicated in patients with class III-IV heart failure [64]. Pioglitazone and rosiglitazone have glucose- and lipid-lowering activity [65]. These compounds decrease insulin resistance and thereby enhance the biological response to endogenously produced insulin, as well as insulin administered by injection.This drug use as monotherapy, therapy that results in a significant reduction in fasting plasma glucose by 60-80 mg/dl and in HbA1c by 1.4-2.6% [66]. In addition, pioglitazone is approved for use in combination with insulin, metformin, or a sulfonylurea, and rosiglitazone is approved for use in combination with metformin or a sulfonylurea [67]. Thiazolidinediones, highly effective at increasing insulin sensitivity and lowering HbA1c continue to be troubled by safety concerns [68]. The Lobeglitazone is a dual PPARα / PPARγ (peroxisome proliferator-activated receptor) thiazolidinedione agonist that was approved for glycemic control in Korea in 2013. There are a number of published studies reporting the pharmacokinetics, safety, tolerability, and clinical efficacy of this novel compound [69]. Aleglitazar is classified as a pan-PPAR agonist, ie affinity to PPARα, PPARγ, and PPARδ. The aleglitazar is a non-thiazolidinedione structure with a selective transcriptional activation profile distinct from other first-generation PPARγ agonists [70].

6. Bile Acid Sequestrant:

It is poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide. Colesevelam hydrochloride is a non-absorbed Polymeric glucose-lowering and lipid-lowering agent intended for oral administration. It is excreted primarily in the feces. Colesevelam hydrochloride is a high-capacity bile acid-binding molecule. colesevelam have glucose-lowering efficacy when added to insulin, metformin, or sulfonylurea-based therapy, in patients with inadequately controlled type 2 diabetes [71]. Anti-diabetes therapy result in a reduction of HbA1c [72].

7. Dopamine Agonist:

Bromocriptine mesylate used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Bromocriptine is a centrally-acting dopamine D2 receptor agonist that has been approved for the treatment of hyperprolactinemia associated dysfunctions, acromegaly, and Parkinson's disease. Some Study demonstrated that a modest improvement in fasting glucose and HbA1c levels. The most common adverse events are nausea, fatigue, dizziness, vomiting and headache. This drug is contraindicated in patients with known hypersensitivity to bromocriptine or ergot-related drugs or patients with syncopal migraine. It is also contraindicated in nursing women because it may inhibit lactation [73].

8. Amylin analogues:

The pramlintide is a soluble synthetic analog of human amylin. The hormone amylin is co-secreted with insulin by the pancreatic β cells in response to nutrient stimuli [74]. Patients with type 1 diabetes may develop an absolute deficiency of both insulin and amylin [75], and those with type 2 diabetes have impaired beta-cell secretion amylin in response to a meal [76]. Amylin suppresses post-prandial arginine and stimulated glucagon secretion [77], and slows gastric emptying time [78]. When added to pre-prandial insulin, pramlintide improves post-prandial sugar control and promotes weight loss in patients with both type of diabetes [79], Effects on HbA1c reduction are humble [80].

9. Insulin Receptor Activators:

Recently, reported a monoclonal antibody Mab (human monoclonal antibody that is an allosteric activator of the insulin

receptor. This Mab monoclonal antibody binds to the insulin receptor with high affinity and mimics the glucoregulatory actions of insulin, but not the mitogenic actions of insulin [81].

10. Fibroblast growth factor 21 Analog:

Fibroblast growth factor 21 (FGF21) is a metabolic hormone predominantly produced by the li,er but is also expressed in adipocytes and pancreas. It regulates glucose and lipid metabolism through Pleiotropic actions in these tissues and also in the brain [82]. A recently published study evaluating the effects of an analog of FGF21 (LY2405319). In obese individuals with type 2 diabetes has found that this intervention exhibited clinically meaningful effects on several co-morbidities associated with type 2 diabetes [83].

11. Antagonism of Glucocorticoid Receptor:

Glucagon is a hormone that counters many of the actions of insulin in the context of insulin resistance and types 2 diabetes. Glucagon drives hepatic glucose production in poorly controlled individuals with type 2 diabetes and uncontrolled glucagon action can play a pivotal role increasing blood glucose levels. IONIA-GCGRRx is an anti-sense drug designed to reduce the amount of glucagon receptor [84]. Glucocorticoid excess results in pro-diabetic consequences due to a variety of glucocorticoid-mediated actions on key target organs in metabolism along with effects in opposing insulin action [85].

12. 11β-hydroxysteroid Dehydrogenase Type 1 (11β -HSD1) Inhibitors:

Inhibition of the enzyme 11β -HSD1 has been novel approach for treatment of type 2 diabetes. The 11β -HSD enzymes fall into two categories i.e type 1 and type 2. The 11β -HSD1 isoform is predominantly expressed in liver and adipose tissues along with the CNS. where it catalyzes the conversion of cortisone (inactive) into cortisol (active). The 11β-HSD2 isoform is predominantly expressed in the kidneys, where it catalyzes the reverse reaction cortisol, thereby reducing glucocorticoid action. The 11β -HSD1 inhibitors have been well tolerated and have improved glycemic control, lipid profiles, blood pressure, and even induced reticent weight loss [86].

13. Receptor Modulators:

Leptin released from fat cells indicates their substrate congestion and induces insulin resistance. Leptin deficiency in the hypothalamus induced by leptinopenia or restriction of leptin transport across the blood-brain barrier may initiate antecedent pathophysiological sequelae of both type 1 and type 2 diabetes [87]. Leptin suppresses hyperglucagonemia, normalizes HbA1c, lowers (in contrast to insulin monotherapy) both lipogenic and cholesterolemic transcription factors and enzymes reduces lipid either in plasma tissue lipids [88]. Pyridinyl and piperazinyl carbamate compounds have been identified as therapeutic leptin receptor modulators [89]. The leptin effects are only a few patients who are obese (with leptin defect) would respond [90].

14. Mitochondrial target of TZDs:

Emerging evidence suggests that the insulin-sensitizing, glucose-lowering action of TZDs can be separated from their effect to serve as a ligand for peroxisome proliferator–activated receptor (PPAR)-γ [91]. The Metabolic Solutions Development company have been shown to improve insulin resistance in multiple tissues, suppress hepatic gluconeogenesis and also lipogenesis, to reduce plasma glucose and levels of insulin, and increase plasma adiponectin concentration in wild-type and PPAR-γ knockout mice. The Ongoing studies indicate that Metabolic solution development company targets a previously uncharacterized mitochondrial complex (mitochondrial target of TZDs [mTOT]), which contains two well preserved mitochondrial proteins (Mpc1 and Mpc2) that appear to modulate pyruvate entry into the mitochondria and regulate pyruvate oxidation [92]. In a 12-week phase 2b trial with 258 patients with type 2 diabetes, doses of 100 and 150 mg/day of MSDC-0160 were as effective as pioglitazone (45 mg/day) in reducing A1C and were associated with less fluid retention and weight gain. Developers of a second mTOT-modulating compound recently have completed a phase 2a trial in patients with type 2 diabetes with similar results [93].

15. Pyruvate dehydrogenase kinase inhibitors:

The pyruvate dehydrogenase is a key enzyme controlling the rate of oxidative glycolysis. The pyruvate dehydrogenase complex catalyzes the irreversible oxidation of pyruvate generating acetyl-CoA and carbon dioxide. Its dephosphorylated form, PDC is active [94]. There are four pyruvate dehydrogenase kinase isoenzymes with tissue-specific distribution. The Inhibition of PDHK-4 in muscle increases pyruvate oxidation in muscle and decreases the supply of gluconeogenic precursors (lactate and alanine amino acid) to the liver, whereas inhibition of PDHK-2 in the liver decreases gluconeogenesis and the excessive rate of HGP that is characteristic of type 2 diabetes. Two PDHK inhibitors, AZD 2545 and lee lamina, have proven effective in lowering blood glucose levels in diabetic rodent models [95] and JTT-251 shows promise in preclinical trials as a PDHK inhibitor for the treatment of type 2 diabetes.

16. Diacylglycerolacyl Transferase-1 inhibitors:

There are two isoenzymes of diacylglycerol acyltransferase (DGAT). DGAT-1 catalyzes the formation of triglycerides from diacylglycerol (DAG) and acyl-CoA, the terminal and committed step in triglyceride synthesis. By inhibiting DGAT-1 in the GI tract, postprandial hyperlipidemia can be reduced and has been shown to be associated with insulin sensitization, reduction in liver triglycerides, and weight loss in preclinical studies [96]. In a 1-week, randomized, placebo-controlled study in 62 obese male subjects, AZD 7687 produced a consistent dose-dependent reduction in postprandial plasma triglyceride excursion, indicating inhibition of gut DGAT-1 activity in subject [97]. However, noticeable GI side effects, mainly diarrhea, occurred at drug doses that inhibited triglyceride excursions by ≥ 250%. The further concern about this approach is the observation that DGAT-1 inhibition increases muscle levels of DAG and ceramide, two fatty acid derivatives shown to cause insulin resistance. Moreover, DGAT overexpresses in skeletal muscle lowered levels of lipotoxic fatty acid derivatives and inhibited triglyceride synthesis, enhanced fatty acid oxidation, and improved insulin-mediated muscle glucose disposal [98].

17. Glucokinase Activators:

Glucokinase is the enzyme that facilitates the phosphorylation of free glucose after entry into the cell. Because of its have high Km value, the enzyme can rapidly respond to an increase in plasma glucose concentration. In the β-cell, a specific glucokinase is the rate-limiting step for glucose metabolism and thus for insulin secretion, whereas in the liver, a different glucokinase responds to an increase in ambient glucose levels by preventing glycogen synthesis and inhibiting HGP. The clinical importance of glucokinase is highlighted by inactivating mutations, which are responsible for maturity-onset diabetes of the young type 2 diabetes. The unique features of glucokinase and its central role in the regulation of insulin secretion and HGP have led to a search for activators of the enzyme in hepatocytes or β-cells or both [99]. More than 100 patents for glucokinase activators have been filed, but results to date have been disappointing. Initial encouraging results were observed with Roche and Merck glucokinase activators, but the efficacy waned over time, leading to discontinuation of the clinical development programs. A similar waning of efficacy has been observed with AZ D1656 in a 6-month trial and with AMG 151. A novel, hepatic-specific activator, TTP 399, which does not interfere with binding of glucokinase to the glucokinase regulatory protein, has shown promise in a 6-week phase 2a study in people with type 2 diabetes, reducing A1C by 0.92% versus baseline and 0.53% versus placebo [100]. It is anticipated that the development of novel glucokinase activators will continue because of the pivotal role of the enzyme in the regulation of glucose homeostasis [101–103].

18. Fructose-1, 6-Bisphosphatase Inhibitors:

The enzyme fructose 1,6-biphosphatase catalyzes the conversion of fructose-1, 6-bisphosphate to fructose-6-phosphate and back to fructose-1,6-bisphosphate and plays a central role in the regulation of glycolysis and gluconeogenesis. When the bifunctional protein is phosphorylated, the negative charge causes a conformational change of the enzyme to favor Fructose-1,6-Bisphosphatase activity otherwise, phosphofructokinase 2 activity is favored [104]. In patients with type 2 diabetes, the basal rate of HGP is increased because of an accelerated rate of gluconeogenesis. In animal models of type 2 diabetes, inhibition of Fructose-1,6-Bisphosphatase activity effectively lowers HGP from a variety of gluconeogenic substrates without causing hypoglycemia [105, 106]. In a 14-day study in 42 patients with type 2 diabetes demonstrated a modest reduction in FPG concentration and Preliminary results with MB07803 (Metabasis Therapeutics) [107].

19. Acetyl-CoA Carboxylase Inhibitors:

The Acetyl-CoA carboxylase catalyzes the irreversible carboxylation of malonyl-CoA for the biosynthesis of fatty acids. Circulating FFAs and increased levels of intracellular lipotoxic metabolites of fatty acids (FACoAs, DAG, and ceramides) cause insulin resistance in liver and skeletal muscle and inhibit insulin secretion. The Acetyl-CoA Carboxylase inhibitor NDI-630 (Nimbus) has been shown to enhance insulin sensitivity, lower plasma Free Fatty Acid and glucose levels, and correct dyslipidemia in animal models of obesity and type 2 diabetes [108].

20. Other Oral Antidiabetic Therapies:

Some other oral antidiabetic therapies have shown some assure in improving glycemia in type 2 diabetes, including [109], AMPK activators, modulators of the gut microbiota [110], activators of the bile acid farnesoid X receptor [111], activators of glycogen synthase, inhibitors of glycogen phosphorylase [112], and ranolazine [113]. Ranolazine is antianginal drugs currently approved by the FDA that works by inhibiting the late sodium current in cardiac myocytes. How this is related to the decrease in A1C observed in patients with type 2 diabetes is unclear, although, at higher doses than achieved clinically, the ranolazine has been shown to inhibit fatty acid oxidation. In vitro studies have demonstrated that ranolazine inhibits glucagon secretion by the pancreatic α-cells by inhibiting sodium channels [114, 115].

21. Anti-Obesity Medications:

The current diabetes is being determined by the obesity epidemic, which represents overload tissue fat. Accumulation of lipotoxic metabolites in the β-cell inhibits insulin secretion, whereas increased levels of Fatty ACoA, DAG, and ceramides in the liver and muscle cause insulin resistance. Recently, a combination of phentermine or topiramate XR (Qsymia) and lorcaserin (Belviq) have been approved by the FDA as treatments for weight loss in obese individuals. Lorcaserin is a selective 5-hydroxytryptamine 2C agonist that decreases food intake through the proopiomelanocortin system. Phentermine is asympathomimetic appetite-suppressing drug, whereas topiramate is a γ -aminobutyric acid receptor modulator, although its mechanism of action in promoting weight loss is poorly understood [116]. lorcaserin reduced body weight by ~ 5% and mean A1C by ~ 1.0%, even though the use of diabetes medications was decreased. In the 2-year SEQUEL study [117].

22. Anti-inflammation target to reduce CVS Complications:

Type 2 diabetes and obesity can be characterized as low-grade inflammatory states [118]. Since the inflammatory processes include the key organs involved in the metabolic dysregulation in diabetes (eg liver, β cells, adipose tissue), attempts are being made to target the inflammation associated with type 2 diabetes. Since this approach does not, primarily, intend to improve glycemic or lipid control. A number of IL-1 and IL-18 modulators are in clinical trials with the intent to evaluate safety along with the reduction of risk of cardiovascular events [119].

CONCLUSION

The Type 2 DM is a metabolic disease that can be prevented through lifestyle modification, diet control, and control of overweight and obesity. The oral and injectable non-isulin drugs used in the treatment of type 2 DM and some newer approaches mention in this article have been directed improving currently available anti-diabetic drugs and finding the new compounds. Novel drugs are being developed like GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors, 11-β- HSD-1 inhibitors, DGAT-1 inhibitors, glucagon receptor antagonists, glucokinase activators, FBPase inhibitors, ACC inhibitors, anti-inflammatory medications, yet no cure is available in sight for the disease, despite new insight into the pathophysiology of the disease. Management should improve the quality of life of individuals with type 2 DM.

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