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Novel therapeutic management strategies for Type II Diabetes

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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. The cause of diabetes continues to be anonymity, although both genetics and environmental factors such as obesity and lack of exercise appear to play roles. Diabetes mellitus is a major and growing public health problem throughout the world, with an estimated worldwide prevalence in 2000 of 150 million people, expected to increase to 220 million people by 2010. Impaired insulin secretion, increased hepatic glucose production, and decreased peripheral glucose utilization are the core defects responsible for the development and progression of type 2 diabetes. However, the pathophysiology of this disease also includes adipocyte insulin resistance (increased lipolysis), reduced incretin secretion/sensitivity, increased glucagon secretion, enhanced renal glucose reabsorption, and brain insulin resistance/ neurotransmitter dysfunction. This chapter focuses on the treatment of hyperglycemia in patients with T2DM. 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, inhibitors of the sodium-glucose co-transporter 2, insulin-releasing glucokinase activators and glucagon receptor antagonists, 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 probably one of the oldest diseases known to man. In 1936, the distinction between type 1 and type 2 DM was clearly made.2 Type 2 DM was first described as a component of metabolic syndrome in 1988.Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. Type 2 DM results from interaction between genetic, environmental and behavioral risk factors. People living with type 2 DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition.

Epidemiology
It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011. It is estimated that 439 million people would have type 2 DM by the year 2030.The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors. Literature search has shown that there are few data available on the prevalence of type 2 DM in Asia as a whole. Studies examining data trends within Asia point to evidence of a dramatic increase in prevalence in both rural and urban setting, and affecting both genders equally.

Pathophysiology
Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure. 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. Studies 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.

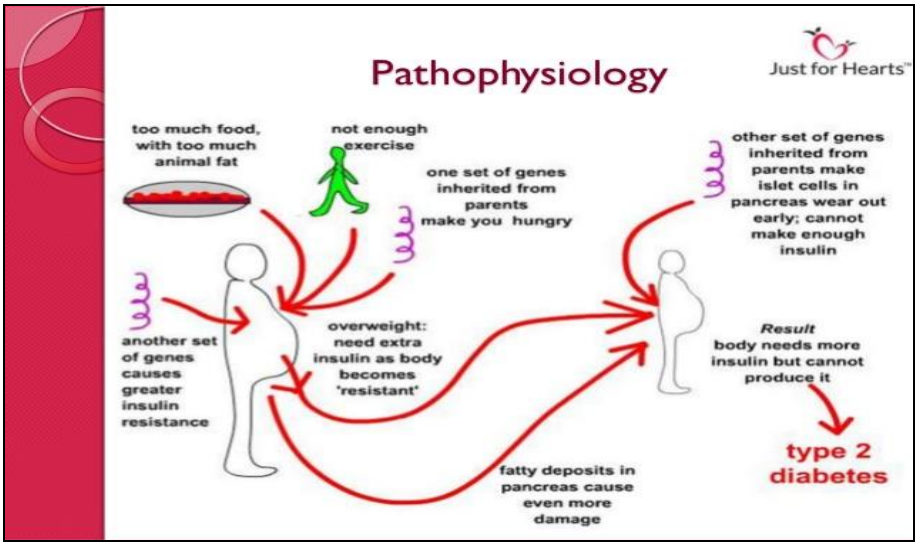

Fig 1

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, and blurred vision. The type 1 DM patients are susceptible to micro vascular complications and macro vascular 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. Most patients with type 2 diabetes die from cardiovascular complications and end-stage renal disease. Geographical differences exist in both the magnitude of these problems and their relative contributions to overall morbidity and mortality.

Treatment Approaches

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 fiber and unsaturated fat and diet low in saturated and trans-fats and glycemic index, regular exercise, abstinence from smoking and moderate consumption of alcohol. 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.

Pharmacological Agents

Biguanide

Biguanide are basic molecules due to the biguanide groups. The biguanides do not induce the release of insulin from the pancreas so they are not classified as secretagogues. Drugs in this class reduce blood glucose levels primarily by either decreasing hepatic glucose production, through inhibiting gluconeogenesis and glycogenolysis, or by stimulating glucose peripheral breakdown through stimulating anerobic glycolysis. The biguanides do not lower normal blood glucose levels so they are not hypoglycemic agents, rather they act only on elevated blood glucose levels, so they are classified as antihyperglycemic agents. Members of the class include metformin, phenformin.

Sulfonylureas

These generally well tolerated but because they stimulate endogenous insulin secretion, they carry a risk of hypoglycemia. Elderly patients, with DM who is treated with sulfonylureas have a 36% increased risk of hypoglycemia compared to younger patients. Glyburide is associated with higher rates of hypoglycemia compared to glipizide. 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. 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.

Mitiglinide

(Non-Sulfonylurea Secretagogues) Knowledge that sulfonylureas act as insulin secretagogues through blocking the potassium channels prompted the idea of testing more selective potassium channel blockers for antidiabetic activities. The mitiglinide family of oral antidiabetic agents acts purely by such mechanism and its members are generally described as the nonsulfonylurea secretagogues. The mitiglinide are carboxylic acid derivatives (benzoic or phenylacetic); characterized by being 5-10 times more potent than sulfonylurea drugs, having faster onset but shorter duration of actions, and show no hyperinsulinemia. Like the sulfonylureas, the mitiglinide are not appropriate to treat Type I patients and are useful only for the treatment of Type II diabetes.

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, 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.

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.

Insulin and insulin analogue

Insulin is a protein with about 6000 molecular weight, produced by the beta cells of the pancreas. The hormone is chemically composed of 2 polypeptide chains designated as chain "A," comprised of 21 amino acids, and chain "B," comprised of 30 amino acids. The 2 chains are connected through 2 intermolecular disulfide bridges. Insulin derived from animal sources differs from human insulin in 1 or more of the amino acids. The interspecies structural differences of insulin products do not significantly affect the biological activities; however, the antigenic properties increase with the number of amino acids changes. In all species, insulin is biosynthesized in the pancreas as a precursor form (proinsulin) of continuous single peptide chain in which the carboxyl-terminal of chain A (A30), and the amino-terminal of chain B (B1) are connected through a 35 amino acid chain C. Proinsulin is stored in the pancreas as a complex with zinc ions. At times when insulin is physiologically needed, chain C cleaves off by certain proteolytic enzymes to produce the active form of insulin. Insulin facilitates glucose entry into adipose tissues, muscles, and liver by stimulating several enzymatic reactions that start at the insulin receptors. The stimulation of an intrinsic tyrosine kinase of the insulin receptor results in an increase in membrane phosphorylation that consequently increases the membrane permeability to glucose through a complicated cascade of intracellular events.

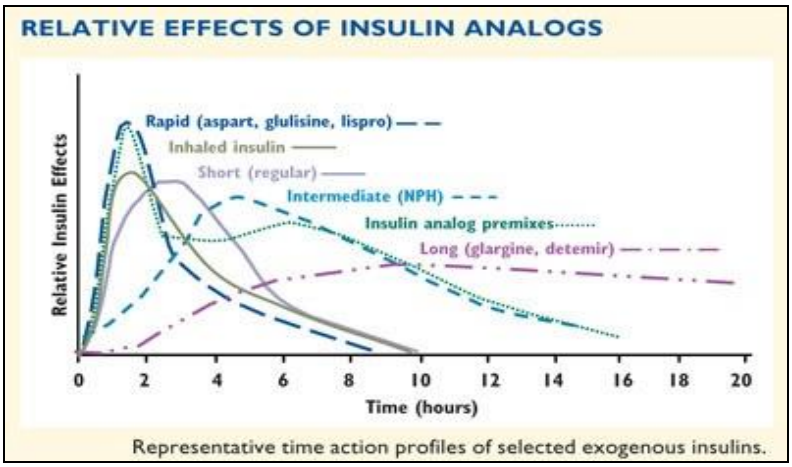

Fig 2

Novel Approaches in Treatment of Type Ii Diabetes

The number are newer targets are identified and huge research work going on in the development of newer and effective drugs for the management of Type II diabetes.

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.GLP-1 also acts as a postprandial satiety signal through neurohormonal networks that signal the brain to suppress appetite and food intake. Furthermore, GLP-1 also has direct effects on the β cells. 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. Albiglutide and Dulaglutide also approved by USFDA in 2014. 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. Oxyntomodulin (OXM) is a peptide activates both GLP-1 receptor (GLP-1R) and glucagon receptor (GCGR). 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, and somatostatin secretion.

DDP-4 Inhibitors

By competing for GLP-1 binding to DPP, DPP-4 inhibitors block the breakdown of naturally secreted GLP-1 and extend its duration of effect in the body. Five DPP-4 inhibitors are available on the international market: sitagliptin, saxagliptin, linagliptin, vildagliptin, and alogliptin. The first three are approved for use in the United States and are administered orally and once daily. Sitagliptin and saxagliptin require dosage adjustment with kidney impairment, whereas linagliptin does not. These agents appear to have a larger effect on reducing postprandial than fasting glucose concentrations. Many clinical studies of varying design are reported in the literature, and each agent has not been studied to the same degree, particularly with respect to comparisons with other T2DM drugs. Meta-analyses suggest that DPP-4 inhibitors, when used as monotherapy, do not provide the same degree of glycemic control as metformin. In combination therapy with metformin, DPP-4 inhibitors provide an A1C decrease slightly smaller than that with sulfonylureas, about the same as that with pioglitazone, and significantly less than that with GLP-1 agonists. From a safety standpoint, DPP-4 inhibitors are very well tolerated. In one comparative study, the incidence of hypoglycemia with sitagliptin was low (4.9%), whereas that with the sulfonylurea glipizide was much higher (32%) (Nauck 2007). In contrast to sulfonylureas and pioglitazone, both of which are associated with weight gain, DPP-4 inhibitors appear to be weight neutral. A concern with this class upon postmarketing surveillance is case reports of pancreatitis.

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. The most common side effects of canagliflozin are the vaginal yeast infection and urinary tract infection because it has a diuretic effect. Dapagliflozin also approved in October 2014 by US FDA in a fixed dose combination with metformin. Empagliflozin most recently USFDA approved drugs of SGLT2 inhibitor class of anti-diabetic medications.

Delayed Release Metformin

Metformin is one of the prescribed oral antidiabetic agents 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. 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.

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

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. Patients with type 1 diabetes may develop an absolute deficiency of both insulin and amylin, and those with type 2 diabetes have impaired beta-cell secretion amylin in response to a meal. Amylin suppresses post-prandial arginine and stimulated glucagon secretion, and slows gastric emptying time. When added to pre-prandial insulin, pramlintide improves post-prandial sugar control and promotes weight loss in patients with both type of diabetes, Effects on HbA1c reduction are humble.

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.

Fibroblast growth factor 21 Analog

Fibroblast growth factor 21 (FGF21) is a metabolic hormone 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. 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.

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. IONIAGCGRRx is an anti-sense drug designed to reduce the amount of glucagon receptor. 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

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. Leptin suppresses hyperglucagonemia, normalizes HbA1c, and lowers (in contrast to insulin monotherapy) both lipogenic and cholesterolemia 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. The leptin effects are only a few patients who are obese (with leptin defect) would respond

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. 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. 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.

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. 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.

Diacylglycerol Acyltransferase-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. 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.

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

Other Oral Antidiabetic Therapies

Some other oral antidiabetic therapies have shown some assure in improving glycemia in type 2 diabetes, including, AMPK activators, modulators of the gut microbiota, activators of the bile acid farnesoid X receptor, activators of glycogen synthase, inhibitors of glycogen phosphorylase, and ranolazine. Ranolazine is antianginal drugs currently approved by the FDA that works by inhibiting the late sodium current in cardiac myocytes.

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 sympathomimetic appetite-suppressant drug, whereas topiramate is a γ -aminobutyric acid receptor modulator, although its mechanism of action in promoting weight loss is poorly understood.

Anti-inflammation target to reduce CVS Complications

Type 2 diabetes and obesity can be characterized as low grade inflammation states. 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.

Conclusion

There is a pressing need for improvement in diabetes care. The prevalence of diabetes is increasing at an alarming rate, and diabetes mellitus is presenting an enormous economic burden in terms of direct health care expenditures and costs of treating diabetic complications. Although there are a number of relatively new classes of therapeutic agents, none is optimal and none alone achieves satisfactory glycemic control that can be sustained. Thus the development of newer agents aimed at additional targets should enhance our ability to effectively treat this important disease. The most active areas of diabetes research are PPARα/γ receptor agonists, GLP-1 analogues, 11 67 dipeptidyl peptidase 4 (DPP4) inhibitors, protein tyrosine phosphatase 1B (PTP1B) inhibitors, liver selective glucocorticoid inhibitors and hormone sensitive lipase (HSL) inhibitors and these agents will be treating diabetes effectively in near future.

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