Future Strategies in Management of Diabetes Mellitus: A Brief Review

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ABSTRACT Diabetes Mellitus is a disorder of altered glucose and lipid metabolism having hyperglycemia as a characteristic feature. Long term uncontrolled Diabetes Mellitus primarily leads to rising in microvascular and macrovascular events involving many organ systems. Strict glycemic control remains the key to avoid such complications. The management of Diabetes and its co-morbid conditions affect patients not only economically but also psychologically. Currently, about nine different varieties of medications are being employed in the treatment of Diabetes Mellitus. Even after having many varieties of drugs available co-morbid conditions associated with Diabetes Mellitus are on the rise as the global burden of disease is also increasing. In last decade drugs against some new targets in the management of Diabetes are approved Glucagon-like Peptide-1 (GLP-1) agonist, Dipeptidyl Peptidase-IV (DPP-IV) inhibitors and Sodium-Glucose linked Transporter-2 (SGLT-2) inhibitors and Peroxisome Proliferator-activated receptor–alpha and gamma agonist. Although numerous drugs are available roughly one-third patient achieve desired glycemic control that is why newer drugs acting on novel targets are required. The objective of the review is to throw light on newer drug targets which are in various stages of development to have latest drugs against Diabetes.

KEYWORDS AMPK, GPR119, Glucokinase activator

Introduction

Diabetes Mellitus (DM) is among most prevalent non-communicable diseases, and virtually every country of the world is facing its epidemic. Once considered a disease of the developed world it has now embraced developing and underdeveloped countries also. Latest data suggests that the worldwide prevalence of diabetes is on rising affecting more than 380 million people in 2013 and likely to affect 592 million people by the year 2035. India is also facing a similar situation having 65.1 million people living with diabetes[1]. The characteristic feature of Type 1 DM is a loss of beta cells, mostly due to autoimmunity leading to severe or absolute insulin deficiency whereas Type 2 DM is characterized by insulin resistance associated with a decrease in insulin secretion[2]. Type 2 DM accounts for the maximum number of cases (90%)[3] and monogenic forms are responsible for 5% cases of DM[4]. Diabetes causes certain pathologic changes in different organs increasing co-morbidities badly affecting individual with diabetes and the health care system. WHO has estimated that the worldwide expenditure for diabetes management would increase from 234 billion in 2007 to 411 billion in the next 20 years[5]. The WHO estimate is based on loss of productivity because of diabetes, and other associated illnesses together show that in the next coming ten years, national income about 336.6 billion USD will be lost[5]. In a study, it was concluded that only nearly 36% of patients having type 2 diabetes achieve satisfactory control of glucose level[6]. Although the study was an old one, and many newer drugs are approved after that, even then the percentage of patients with desired glycemic control is not satisfactory. That's why still the management of DM and its complications is challenging. To decrease the prevalence of DM and its widespread effects, it is necessary to have a better understanding of its aetiopathogen-

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esis and focus on therapeutic and research efforts accordingly. A coordinated approach is required that involves experts from different speciality, exploring and validating new drug targets. Further review will focus mainly on relevant pathophysiology of DM and discussion on targets which can potentially be utilized in the management of DM.

Pathophysiology of Diabetes Mellitus

The decrease in insulin level or insulin resistance leads to inefficient utilization of glucose by insulin-sensitive cells of the body, except those of the brain which does not require insulin for insulin uptake [7]. Important clinical characteristics of patients with type 1 and type 2 diabetes mellitus are enumerated in Table 1 [7].

T1DM is considered an autoimmune disease characterized by destruction of β-cells of the pancreas. T1DM clinically manifests at a very late stage of β-cell destruction. There are certain features which suggest type 1 diabetes mellitus is a result of autoimmunity [8] like the presence of autoantibodies to islet cell; response to immunotherapy and linkage of T1DM with the class II MHC. Currently, there is no pharmacological agent which is approved for this indication targeting autoimmunity.

T2DM is a multifactorial disorder resulting from a combination of genetic factors related to insulin secretion and resistance and environmental agents, e.g. overweight, lack of exercise, stress and ageing resulting in β-cell loss[9]. The point at which insulin level fails to compensate rising blood sugar, frank diabetes develops characterized by fasting plasma glucose >126mg/dl on two occasions, 2-hour postprandial glucose >200mg/dl following Oral Glucose Tolerance Test (OGTT) and $\geq$6.5% of HBA_{1c}[10]. There lies a phase of Impaired Glucose Tolerance (IGT) which indicate state between normal and frank diabetes condition corresponding to Fasting Glucose level between 100-125 mg/dl, postprandial glucose 140-199 mg/dl and 5.7-6.4% of HBA_{1c}[10]. The phase of IGT can be a time of active intervention where conversion of IGT into overt diabetes can be prevented or at least can be delayed. This requires the screening of high-risk individuals. The cause of Insulin resistance in type 2 DM is not clear entirely, it may be because of reduced insulin receptor number, or may be secondary to hyperinsulinemia and hyperglycemia[11], or it may result from decreased tyrosine kinase activity[12]. In addition to altered glucose homeostasis, increased lipolysis and glucagon secretion decreased incretin effect, and change in satiety signalling have got an additional yet important role in the pathology of T2DM[13]. As diabetes is having many metabolic derangements mentioned above, they provide molecular targets which are potentially useful to rectify various aspects of DM. The pharmacological agents acting on these potential targets must act in an additive or synergistic manner to current therapies. There are many aspects of metabolism and insulin resistance about which not much is known and currently being explored and are liable for drug intervention.

Current Approaches in Management of Diabetes Mellitus

Strict glycemic control remains key in preventing not only microvascular but also macrovascular complications of both the types of DM[14-16]. Virtually any complication arising in uncontrolled DM can be prevented by achieving a target glucose level. Currently, Medical Nutrition Therapy (MNT) is the first step in the management of T2DM which aims at optimal coordination of caloric intake with other aspects of diabetes therapy. Primary prevention measures of MNT are directed at preventing or delaying the onset of type 2 DM in high-risk individuals[10]. Weight loss and regular exercise lead to improved glucose and lipid control, also help in lowering blood pressure and halting progression of diabetes[17]. Metformin is usually the first choice with or after MNT. Metformin is an indirect AMPK activator that acts primarily by suppressing hepatic glucose production[18] and does not have any effect on beta cell loss. Metformin alone may not be able to achieve target glucose level; hence multiple drugs are added to achieve desired glucose and lipid level. PPAR-γ agonists (Pioglitazone and Rosiglitazone) affect gene expression in various cell types involved in glucose and lipid homeostasis[18]. Rosiglitazone is shown to increase adverse cardiovascular events and banned in India[19]. Both drugs increase the risk of bone fractures, congestive heart failure and weight gain[18]. Saroglitazar is a unique drug approved in India for managing Diabetic dyslipidemia (DD). This is known to be the first dual peroxisome proliferator-activated receptor (PPAR)-α/γ agonist. In clinical studies, Saroglitazar has shown significant improvement in lipid and glycemic parameters. There has been a 46.7% decrease in TG, 32.5% decrease in non-HDL-C, 0.3% absolute reduction in glycosylated haemoglobin (HbA1c) with saroglitazar in patients of Diabetic Dyslipidemia.[20,21]. Insulin secretagogues (Sulfonylurea and Glinide) promote the release of insulin which acts by binding to sulfonylurea receptor[22], a K_{ATP} channel. These drugs close the channel, causing membrane depolarization and calcium ion influx resulting in the release of preformed insulin granules. As they are acting directly on K_{ATP} channel bypassing physiological release of insulin which is due to ATP dependent closure K_{ATP} channel. Activation of the sulfonylurea receptor occurs irrespective of a glucose level which predisposes patients to hypoglycemia. Many patients who respond in the beginning, later on, stop responding to the sulfonylurea. This may occur as a result of a change in drug metabolism or more likely from a progression of β-cell failure[18,23]. In the experimental study, they have been shown to augment β-cell apoptosis[24].

Colesevelam hydrochloride is a bile acid sequestrant capable of lowering low-density lipoprotein (LDL) cholesterol. Bile acid sequestrants could reduce intestinal glucose absorption, which may explain the improved glucose homeostasis in humans[18]. Alpha-glucosidase inhibitors (Acarbose, voglibose and miglitol) act by inhibiting gut membrane-bound alpha-glucosidases which leads to a slowing of absorption of carbohydrates from the GI tract and blunts the rate of rising of postprandial plasma glucose[25].

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), together known as incretins, are the essential hormones contributing to glucose tolerance. They are secreted in proportion to the nutrient load ingested and relay this information to the islet as part of a feed-forward mechanism that allows an insulin response appropriate to meal size. GLP-1 analogues (Exenatide and Liraglutide) result in improvement in glycemic control and body weight. They may be prescribed as monotherapy, as a supportive drug to lifestyle modification or in combination with oral hypoglycemics in patients with type 2 DM. Also, upcoming evidence suggests incretin-based therapies may have a favourable impact on inflammation, cardiovascular and the central nervous system[18,26].

Dipeptidyl-Peptidase IV Inhibitors (DPP IV Inhibitors) increase the AUC of GLP-1 and GIP causing more than 2-fold rise in plasma concentrations of active GIP and GLP-1. This leads

Table 1 Clinical characteristics of patients with Type 1 and Type 2 diabetes mellitus [7].

S.No.	Features	Insulin Dependent DM	Non-Insulin Dependent DM
1.	Age	Usually <20yrs.	Usually >30yrs.
2.	Body Weight	Low to normal	Obese
3.	Insulin level	Low or absent	Normal
4.	Glucagon level	High, can be suppressed	High, resistant to suppression
5.	Glucose level	Increased	Increased
6.	Insulin sensitivity	Normal	Reduced
7.	Therapy	Insulin	Weight Loss, Oral hypoglycemics, Insulin

to an increase in insulin secretion, reduced glucagon levels, and betterment in both fasting and postprandial glucose level. The DPP-4 inhibitors are usually well tolerated, having a low risk of hypoglycemia but they are comparatively expensive[27].

Sodium-glucose co-transporter-2 inhibitors work by inhibiting SGLT2 in the Proximal Convoluted Tubule, to inhibit reabsorption of glucose and increase its excretion with urine. As glucose is excreted, its plasma levels decrease resulting in an improvement in glycemic parameters[28,29]. There is minimal risk of hypoglycemia and no risk of overstimulation or fatigue of the beta cells[30]. Uro-genital tract infections (UTIs) are the most commonly observed adverse drug events in subjects on SGLT2 inhibitors[31]. These treatment modalities are available nowadays. Further, we will discuss newer drug targets which are in various phases of development.

Newer Targets in Management of Diabetes Mellitus

- Immunomodulatory approaches were being explored to prevent the autoimmunity in type 1 diabetes. Some immunomodulators, like monoclonal antibodies directed against the lymphocyte receptors CD3[32,33] and CD 20[34,35] were tried as a treatment option for T1DM. Studies have shown that immunosuppression probably results in a slowing of β-cell loss, but toxicities associated with them remain a concern. In type 2 diabetes there are also many new targets which are being explored.
- The enzyme 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) is mainly expressed in the hepatocytes and adipocyte. There exist two forms of this enzyme. Type 1 is involved in the bidirectional conversion of cortisol to cortisone and vice versa. Type 2 catalyzes the one-way conversion of cortisol to cortisone[36]. Cortisol has got a significant role in counter-regulation of insulin action, but at higher doses, it can cause an increase in weight, visceral adiposity, insulin resistance, and hyperglycemia[18]. Inhibition of 11β-HSD1 leads to decreased cortisol level restoring insulin sensitivity proven in preclinical studies leading improved glucose tolerance and weight reduction in animal studies[37,38]. The results were replicated in Phase I and II clinical trial[39]. 11β-HSD1 inhibitor INCB13739 inhibits 11β-HSD1 in doses of 100 and 200 mg once daily for 12 weeks, leading to falling in HBA_{1c} by 0.47 and 0.56%[40].
- Glucokinase is an essential enzyme acting as a glucose sensor involved in glucose homeostasis increasing insulin in response to the rising concentration of glucose[41]. In β-cells of pancreas, glucokinase is a very important enzyme in insulin release, and this enzyme in hepatocytes regulates hepatic gluconeogenesis. This role of glucokinase was confirmed by targeted deletion of the glucokinase gene in animal models[42]. Animal studies also proved that beta cell glucokinase is a significant determinant of glucose homeostasis than liver glucokinase. In genetically modified animals overexpression of glucokinase was associated with better glucose tolerance, with the comparable plasma insulin levels in the normal non-transgenic mice animals. These findings suggest that overexpression of glucokinase helps in lower basal plasma glucose concentration[42]. Inactivating mutations in the glucokinase gene in humans lead to the development of maturity-onset diabetes of the young type 2 (MODY2)[43]. Glucokinase activators (GKAs) are in different phases of clinical trials. Piragliatin has been found to lower fasting, and postprandial glucose levels, improved β-cell sensitivity to glucose, and a decrease in hepatic glucose output in patients with T2DM[44] were discontinued. AZD6370 and AZD1656 were evaluated to act as Glucokinase activator and completed phase 2 clinical trials[45,46]. Phase3 clinical trials for these compounds are in the queue. Glucokinase activators are efficacious in

managing both postprandial and fasting plasma glucose in patients of T2DM in phase 2 clinical trial. They can be used in combination with currently approved drugs.

- Fructose 1,6-bisphosphatase (FBPase) is a tightly controlled, rate-limiting enzyme that catalyzes the critical step in hepatic gluconeogenesis which converts fructose-1,6-bisphosphate to fructose 6-phosphate[47]. As FBPase enzyme is located near at the end of cycle inhibition of FBPase leads to inhibition of gluconeogenesis from all substrates and minimally affecting other metabolic pathways. FBPase inhibitors must have sufficient safety margin as suggested by patients with deficient FBPase usually have near normal clinical profile[48]. MB07803 is an inhibitor of FBPase that has reached into Phase II trial in T2DM patients[49].
- Protein tyrosine phosphatase (PTPases) is a large family of enzymes which remove phosphate groups from phosphorylated residues (tyrosine and others) on proteins. Protein tyrosine phosphatases control tyrosine phosphorylation in the cell — insulin signals by tyrosine phosphorylation[50]. The PTPases control cellular growth, the cell cycle, and cytoskeletal integrity[51]. Phosphorylation of tyrosine residue is regulated by PTP1B which acts as a negative regulator of the insulin signal transduction[52]. PTP1B was the first PTP to be purified from human placental tissue[53]. PTP1B inhibitor can be an option in the management of T2DM and may improve insulin sensitivity.
- The G protein-coupled receptor 119 (GPR119) and GPR120 have evolved as a newer target for a new potential oral management of T2DM. GPR119 is also known as a glucose-dependent insulinotropic receptor, primarily expressed in the β-cells of the pancreas, L-cells of the intestine. GPR119 agonists can increase insulin release and induce GLP-1 secretion [54,55]. GPR119 receptor agonist leads to an increase in intracellular c-AMP level by activating Gαs which acts via adenylate cyclase. With this rationale GPR119 considered as a potential therapeutic target in T2DM. GPR120 is a member of the rhodopsin family of GPCR that is also present in the intestinal tract and adipocytes which gets activated by medium to long chain fatty acids resulting in insulin-sensitizing effects of omega three fatty acids[56]. Dysfunction of GPR120 is responsible for altered fat metabolism, predisposing to obesity[57]. Hence GPR120 is considered to be a potential drug target for T2DM and obesity.
- One of the critical regulators of cellular metabolism is the AMP-activated protein kinase (AMPK), which gets activated as intracellular ATP level go down. AMPK plays many roles such as regulation of growth, metabolism, autophagy[58-60]. Trigger for AMPK activation is cellular stress like low ATP, prolonged exercise etc. Few pharmacological agents are supposed to activate AMPK, e.g. Metformin and is supposed to act by inhibiting complex I of the respiratory chain leading to falling in ATP[61,62]. Resveratrol also activates AMPK similar to Metformin by inhibiting the F1F0 mitochondrial ATPase[63] and may have similar metabolic effects. Metformin acts primarily by inhibiting hepatic gluconeogenesis, and the role of AMPK in metformin action is debatable[64]. Activators of other peripheral nutrient sensors are in development.

Conclusion

The key to managing diabetes is a tightly regulated blood glucose level which prevents the development of complications. Classical drugs like sulfonylurea and metformin are highly effective in managing diabetes, but with time they lose their effectiveness, resulting in simultaneous administration of multiple drugs. Some drugs discontinued due to the adverse effects. Newly approved drugs seem promising, but few are associated with adverse effects which lead to stopping of medication. In long-standing T2DM, ultimately patients may require insulin preparations for adequate control of blood glucose. The problem is that targets and lead compounds are there but not have succeeded clinically. The reason may be an incomplete understanding of the pathophysiology of T2DM with a variety of factors underexplored. Target validation which has a profound effect on the pathology of diabetes is one of the keys to having the master drug. Even after tedious effort, many potential drugs fail in different phases of a clinical trial which may be because of uncertainty in response to the human body. We need a more predictable approach in drug development so that the cost and time can be saved. As diabetes is a leader in non-communicable disease pandemic, similar basic principles of drug development should be applied to have wonder drug.

Competing Interests

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