Insights on the current status and advancement of diabetes mellitus type 2 and to avert complications - An overview

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Highlights

- Type 2 diabetes mellitus type 2 (T2DM) powerful genetic susceptible diseases.
- T2DM leads to high risk with insulin resistance and β-cell dysfunction.
- T2DM complications with possible management strategies were discussed.

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- Recent updates on anti-diabetic drugs were provided
- T2DM treatment of strategies was discussed.

Abstract

Type 2 diabetes mellitus type 2 (T2DM) is an endocrine metabolic disorder, occurring worldwide due to aging, advancement in lifestyle by modernization. T2DM is characterized by higher levels of glucose in the blood due to unresponsive secretion of pancreatic insulin and insulin activity or altogether. T2DM, regarded as a powerful genetic susceptible disease that leads to high risk with insulin resistance and β-cell dysfunction. To manage and overcome type 2 diabetes, physical activity, diet strategies, and other therapeutic medications along with usage of anti-glycemic agents are developed and attempted appropriate. In the present review, attention has been focused on the understanding of T2DM outcomes, complications with possible management strategies, and pathophysiology of T2DM. Further, a detailed note on anti-glycemic agents in use, and other possible drugs of choice was discussed in the light of current preventive strategies are presented in this review.

***Keywords*:** diabetes mellitus type 2, antiglycemic agents, treatment strategies, completions.

Abbreviations: *T2DM, type 2 diabetes mellitus type 2; DKA, diabetic ketoacidosis; GDM, gestational diabetes mellitus; DELA, dual-energy X-ray absorptiometry; BPD/DS, biliopancreatic diversion with duodenal switch; RYGB, laparoscopic roux- en Y gastric bypass; DN, diabetic nephropathy; QOL-DN, quality of life-diabetic neuropathy; PAD, peripheral artery disease; CHD, coronary heart disease; FGF, fibroblast growth factor; CVD, cardiovascular disease; AGE, advanced glycation end-product; RAGE, role of receptor for advanced glycation end-product; DbCM, diabetic cardiomyopathy; ECV, extracellular volume fraction; DPP-4-i, DPP-4 inhibitors; GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide; SGLT2, sodium-glucose transporter-2; CVAE, cardiovascular adverse events; TZD, thiazolidinediones; PPAR, peroxisome proliferator-activated*

receptor; NMDAR N-methyl-D-aspartate receptors; ROCK, Rho-associated protein kinase; PTP1B, protein tyrosine phosphatase 1B; RXR, retinoid X receptor; HATs, histone acetyltransferases; HDACs, histone deacetylases, DNMTs, DNA methyltransferases; FOXO, forkhead box protein O; ACE inhibitors, Angiotensin converting enzyme inhibitors.

1. Introduction

Diabetes mellitus (DM) is known to be a metabolic syndrome since a combination of factors such as deficiencies in insulin secretion or its activity or both have contributed to the development of the hyperglycemic condition. According to the World Health Organization (WHO), diabetes is regarded as a heterogeneous group of disorders and considered it of utmost priority among the non-contagious diseases in the world [1]. International Diabetes Federation (IDF) has reported that diabetes is one of the largest global emergencies of the 21st century, and all over the world, around 422 million people are living with diabetes. It is alarming that type 2 diabetes mellitus (T2DM) dominates 90% of diagnosed subjects [2]. Recent figures from 2015, 415 million people were diagnosed with T2DM, and 318 million people remain glucose tolerant or defective in the conversion of glucose and are at high risk of developing diabetes in the near future [3, 4].

T2DM formally, non-dependent insulin found predominantly worldwide and are characterized by relative insulin inadequacy [5]. T2DM is found to be prevalent and accounts for 90-95% of all diabetic patients. Diminished insulin release due to abnormal fluctuations of basal insulin secretion and elevated glucagon discharge are attributable to developing T2DM [6]. The prevalence of T2DM emerged with profound insulin resistance and relative insufficient secretion of insulin [7] which is predominantly due to the interaction among genetic factors, environment and related risk factors such as high blood pressure, dyslipidemia and central obesity [8]. The implication of the involvement of environment and genetic interactions, increasing risk emerged as an un-resolvable task in the global health care sector.

Epidemiological characteristics of T2DM showed that initially, it kept a steady incidence in developed countries such as the USA and Japan, but subsequently, the trend has changed and became a serious issue in developing countries. Despite aging, a risk factor for T2DM, increasing trends of childhood obesity has resulted in T2DM prevalent among teenagers and adolescents. This caused a new serious problem of significant segments in public health [9]. Complications are usual in people with type1 and type 2 DM. However, differences in pathophysiology and the risks are associated with microvascular and macrovascular disorders [10]. T2DM affects childhood, and its frequency has elevated worldwide. A Canadian national surveillance study report underlined that the occurrence of type 2 in children was found to be maximum, in adolescents <18 years of age 1.54 in 100000 children/year [11]. The latest data from the USA revealed that incidence of T2DM is 8.1/10000 individuals in the (10-24 age groups) per year and 11.8 per 10000 individuals in the (15-19 age group) per annum and this study insisted that the highest rates of incidence observed in American-Indian, African-American, and Hispanic adolescents. However, remarkable segments of adolescents with T2DM patients fall below the poverty line or in developing countries [9]. The present review has tried to focus on the spectrum of ongoing researches with recent advancements in treatment for complications caused by T2DM.

2. Description of T2DM

T2DM encompasses individuals with relative insulin deficiency and peripheral insulin resistance and may not require insulin administration to survive. The appropriate etiologies for T2DM are still unclear. However, autoimmune defect of B-cells is a known factor. Obesity itself causes a certain degree of insulin resistance, but not all patients diagnosed with T2DM are obese, although patients in the absence of obesity due to traditional basis may have an elevated degree of fat distributed profoundly in the abdomen. Diabetic ketoacidosis (DKA) is a life-threatening complication that affects individuals with T2DM. This occurs impulsively and is associated with stress and rampant use of certain drugs such as corticosteroids, atypical antipsychotics and sodium-glucose co-transporter 2

inhibitors [10]. The risk of incidence of T2DM accelerates with age, obesity and physical inactivity. It is prevalent among women with prior gestational diabetes mellitus (GDM), patients with blood pressure or dyslipidemia and in isthmic subgroups. This shows a frequent and close affinity with genetic susceptibility, and it seems to be poorly understood [12].

3. Pathophysiology

T2DM is characterized by a sequence of events such as resistance to insulin, disturbance in insulin and unsuccessful B-cell activation that lead to insulin responsiveness [13]. Addressing the high glycemia in T2DM in crucial as it caused further complications such as onset and gradual development of cardiovascular disorders, neuropathies, retinopathies, and renal dysfunction. Advancement in therapeutic medication confers sufficient alternatives; however, it is unsuccessful with considerable segments of people with T2DM. Rangel et al. have reported that combination therapy approach is suited for addressing micro and macrovascular diseases, covering risk medication of cardiovascular aside from controlling the hyperglycemia, creating a possibility to improve cardiovascular outcomes remarkably [14].

4. Lifestyle Modifications

Lifestyle changes including fewer regular exercises, laziness [15], food habits, stress and sedentary lifestyle [16], smoking and alcohol consumption [17] has taken a toll on maintaining the physique [18] and are the risk factors prominent in the development of T2DM which may result in insulin resistance and T2DM initiation [19]. Obesity, another risk factor associated with T2DM development, is found to have inheritable [20] consequences. The latest study report underlined the need for intake of healthy fats derived from plant and fish sources that are appropriate and reduce the risk of being obese and diabetic. Such paleo-based alterations in the diet and physical activity for 30 minutes a day can achieve considerable results in tackling hyperglycemia and reduce the consequences of T2DM [6].

5. Complications

5.1. Obesity

T2DM is often associated with an aggregation of risk criteria such as obesity, aging and lifestyle modifications. The main objective of the medication for T2DM is to arrest or slow down the glycemic and ensure a quality life, although such therapeutic medication is very limited to cure obesity individuals with T2DM [21]. Several studies are illustrated recently on obesity-related to T2DM individuals. Shah et al. have proposed the criteria: high plasma glucagon levels in waist-to-hip ratio, suprailiac skinfold thickness and adipose tissue depots in non-obese Asian Indian males with T2DM in India [22]. Investigations were performed by employing anthropometric indices, dual-energy X-ray absorptiometry (DELA) and magnetic resonance imaging (MRI) scan to test the conditions of obesity and to find if any affinity or association remains in glucagon level of plasma and obesity index of the patients with T2DM. Interestingly, findings revealed that non-obese patients with T2DM showed a higher level of glucagon content when compared with control. They inferred that the levels of the glucagon in plasma were positively correlated with obesity and explored mechanisms involved in developing T2DM in non-obese individuals. Purnell et al. executed gastric bypass surgery that resulted in a promising reduction in weight in obese individuals [23]. Similarly, laparoscopic biliopancreatic sleeve gastrectomy (LSG), laparoscopic adjustable gastric banding surgery (LAGB), bilio-pancreatic diversion with duodenal switch (BPD-DS), and laparoscopic roux- en Y gastric bypass (RYGB) are some other surgeries that are performed for obesity in diabetic patients and among the aforementioned, RYGB and BPD-DS are most preferred and effective in obesity correction for T2DM with BMI of >25 kg / m^2 to < 35 kg m^2.

5.2. Microvascular complications

Microvascular complications are characterized by signs of subclinical swelling and are correlated in T2DM with an expression of meprins, a kind of metabolic protein exhibited in renal proximal tubules

that prevented diabetic nephropathy. The role played by meprin in T2DM is well documented. Using meprin α, β knockout mice (KO), investigators tested the impact of meprins in the development of diabetic nephropathy (DN). Authors inferred that mice with normal gene (M) and severe diabetes showed no complications of DN whereas diabetic and meprin α β (KO) animal had the highest mortality rate due to onset of DN characterized by loss of renal function compared with those having normal meprin gene. Study results critically underlined that meprins exhibit a protective function against the DN and the effect is not restricted to the mice. This finding provided helpful clinical applications [24] in controlling the secondary effect of T2DM. Wang et al. have validated the diagnostic accuracy of monofilament test in diabetic peripheral neuropathy (DPN) and concluded that monofilament test showed better sensitivity and favored that such test alone is optimum in identifying DPN [25]. Brown et al. have experimented on the effectiveness of tools applied in the detection of early DPN and inferred that applying 1g monofilament combined with the quality of life-diabetic neuropathy (QOL-DN) questionnaire was promising and cost-effective tool for early detection of DPN in adults with T2DM [26].

5.3. Macrovascular complications

Macrovascular complications are associated with significant influence on the cardiac and neuro aspects of the system. Peripheral artery disease (PAD) is a prevalent complication of diabetic patients affecting the arteries, and the co-existence of foot ulcer with PAD often results in chronic ischemic pain. Tedeschi et al. have assessed the potential and tolerance ability of tapentadol, a drug that serves as both μ-opioid receptor and nor-epinephrine reuptake inhibitor in patients with T2DM and the ischemic pain drug was tested for its analgesic potential. The results proved that it was effective in controlling chronic ischemic pain with T2DM [27]. Authors added that tapentadol PR has slowed down the intensity of pain and it relieved neuropathic indications, thus elevating the quality of life of patients. Shan et al. have illustrated that lifestyle mismanagement remarkably accelerates coronary heart disease (CHD) risk factors [28], [29]. Significant improvement in cardiac performance is

achieved by regular cardiac check-up and follow-up with diet and lifestyle management by refraining from smoking and from consuming alcohol.

5.4. Miscellaneous complications

Complications associated with wound healing in patients with T2DM have observed the coexisting role of pancreatic β-cell dysfunction and sensitive fluctuations in insulin secretion in T2DM and are well documented. A study report revealed that chances for modulating the β-cells sensitivity arise from a signaling network of fibroblast growth factor (FGF) which is a driven force for growth and induce the entire FGF receptor subtypes that remain on both types of cells (beta and peripheral). In preclinical trials, it was interesting to note that when FGF1 was delivered using intracerebroventricular administration, instead of peripheral, no development of obesity or hypoglycemia was observed. The mode of delivery contributes therapeutic benefits to patients with T2DM. Goto et al. reported that T2DM patients with hyperglycemia are at maximum risk of cardiovascular disease (CVD) [30]. Further, it is inferred that advanced glycation end products (AGEs) have played a vital role in defective wound heal in T2DM patients. Wang et al. have proved that they would heal by blocking advanced glycation end-product (AGE)-role of receptor for advanced glycation end-product (RAGE) signaling pathway by applying anti-RAGE antibodies and conspicuously noticed that progress in healing was observed in treated diabetic mice [31]. Further, an improved phagocytic function of macrophages was shown in immune-histo-chemical staining assay. These findings would be probably useful in curing wounds in patients with T1DM and T2DM subjects.

Another complication in T2DM is cardiomyopathy (ChCM) which is diagnosed with a novel technique, employed by Shang et al., of cardiovascular magnetic resonance T1 mapping [32]. Authors calculated myocardial extracellular matrix (ECM) expansion and measuring extracellular volume fraction (ECV) in diabetic cardiomyopathy (DbCM) patients and compared with healthy control. The results revealed that DbCM has induced for an elevation ECV remarkably against control. Besides,

DbCM cluster, ECV value was positively correlated with variable parameters of left ventricular diastolic function. This finding would help in early detection of diabetic cardiomyopathy. Barmpari et al. have analysed on thyroid dysfunction in Greek people with T2DM and T1DM [33]. Investigators have demonstrated that no noticeable change in the incidence of hypothyroidism among T1DM and T2DM patients, whereas nodular goiter was observed often among T2DM individuals. It reveals T2DM persons with hypothyroidism showed maximum glycated hemoglobin (HbA_{1c}) and total cholesterol content compared to control.

6. Management and Preventive Strategies of T2DM

Despite, lifestyle adopted to modernization and diet intake changes in the T2DM individuals, they have shown a remarkable reduction in the persistence of T2DM while the maintenance of body mass index of 25 kg/m^2, uptake of high fiber content food and unsaturated fat, glycemic index, body fitness, restrain from smoking and moderate consumption of alcohol [34]. There is substantial evidence in inhibiting the onset of T2DM and can be slowed down or arrest using several measures, including healthy behavior such as physical activity and weight loss. Particular dietary pattern and advanced pharmacotherapy reduce the risk of developing diabetes.

With a sense of urgency, governmental agencies have to develop and assess strategies to control the increasing rate of obesity. Interestingly, social determinants of health welfare have played a vital role in the risk of diabetes and its complication. National population health survey reported that low-income group was correlated with a 77% higher risk of developing T2DM [35]. Public health intervention to regulate T2DM covering maintenance of physical activity body weight healthy diet, however, patient's ability to cope up this healthy behavior is determined by many other factors such as social environment, cultural and economic condition. There is urgent demand for government to create strategies or policies with objectives addressing poverty and other social system hindrances to the health care sector [36].

7. Recent Updates on Anti-diabetic Drugs

It has been a continuous process for the identification of the "perfect" antidiabetic drug. Because of the complexity of DM and its impact on whole-body hemodynamics, the prescription of drugs varies depends on the physiological status in each case. Below a detailed note about the different classes of antidiabetic drugs available in the market and the mechanisms of action (Fig. 1 and Table 1).

7.1. Dipeptidyl peptidase-4 inhibitors [DPP-4-i]

DPP-4 inhibitors are the most recommended molecule for controlling T2DM-related risks. DPP-4 inhibitors exert the mechanism through the inhibition of the enzyme that degrades incretin hormones such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), which are the major glucose-dependent insulinotropic polypeptides [37, 38]. The administration of these drugs induces the insulin secretion while reducing the glucagon release on the signal from the glucose-levels in the circulation, thereby induces the hypoglycemic effect through the feedback mechanism [39]. Among the major drugs in line for the treatment of diabetes, the DPP-4 inhibitors are the major drug of choice because of its safety profile with less or no side effects related with other diseases [40, 41].

Mannucci and Monami have reported in their systematic review on the safety of DPP-4-i on the cardiovascular system and found to have no association with cardiovascular risks; however, several meta-analyses demonstrated that findings were incompatible with being considered as a class [42]. The evidence accumulated based on the meta-analyses indicated that DPP-4-i were considerably associated with lowering the cardiac risks, whereas the other four studies reported having no association with them. Results were conflicting for drugs such as saxagliptin and sitagliptin. There was evidence that the drug vildagliptin decreases major adverse cardiac event (MACE) risk. Similarly, another drug, alogliptin had no association with MACE risk. Therefore, DPP-4-i were categorised as monotherapy and as synergetic therapy with other antibiotic treatments is recommended.

7.2. Glucagon-like peptide-1 (GLP-1) receptor agonists

GLP-1 is another class of drug involved in the medication of type 2 diabetes. GLP-1 is a type of incretin hormone that has been recognised as a potential target in the treatment of T2DM [43]. GLP-1 is secreted from endocrine L-cells in the small intestine, which is released by signals after a high carbohydrate or fat meal ingestion. The activity of these peptides is wide varied due to the availability of its receptor in the major and minor organs [44]. The major action mediated in the cells is through the activation of adenylate cyclase and cAMP production, which in turn stimulates insulin secretion via protein kinase A (PKA) [45]. On the other hand, GLP-1 exerts a direct inhibitory effect on the ATP-dependent potassium channels. In the pancreas, this peptide activates the insulin granule exocytosis [46].

Recently, a high-quality meta-analysis was conducted by Palmer with 301 trials and 120000 participating adults in a study on GLP-1 receptor agonists and found no association in all-cases of mortality, myocardial infarction and stroke with GLP-1 and other treatments [47]. Similarly, no significant difference was observed in the mortality risks attributed to the cardiovascular adverse events (CVAE) between any single therapies or metformin-based synergistic therapies with a short duration (6 months) but low to moderate quality studies revealed conflicting results. Previously, research trials were analysed and explored that no significant difference was statistically observed in major CVAE between GLP-1 receptor and their control [25, 48, 49]. Another randomised control trial reported that a substantial reduction in the risk factors of major CVAE between semaglutide and control (HRL: 0.74; 95% Cl.0.58-0.95. p<0.001 E and between liraglutide and control (HR: 0.87. [0.78 – 0.97], p=0.001 [50].

7.3. Sodium-glucose transporter-2 (SGLT2) inhibitors

SGLT2 inhibitors are another class of drugs that are used to regulate T2DM. Sodium-dependent glucose co-transporters (SGLTs) are a large class of proteins, which are high-capacity and low-affinity transporters that aid in glucose reabsorption in a variety of tissues [51, 52]. These inhibitors

exert an unprecedented mechanism of action in cells by causing no interference with insulin secretion. While the major action of these co-transporters activates renal glucose reabsorption, the potential intake leads to poor intestinal absorption and, consequently, a low bioavailability. Moreover, some forms of the SGLT2 inhibitors demonstrated the side effects made them less preferable for patients suffering from gastrointestinal disorders [53, 54].

Randomised control trials of meta-analyses conducted [55-58] tested the role of an SGLT2 inhibitor in cardiovascular outcomes. However, several comparisons were made between SGLT2 inhibitors and other antibiotics; special emphasis was focused on SGLT2 inhibitor and its placebo. In their experiment, drugs such as canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, dapagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin were tested. The participated sample was sized from 5936 to 120000 adults period of disease >10 years and follow up <2 years. In sample, a segment of individuals had CVD whereas others were absent. Parameters such as demographics and baseline were showed resemblance in all groups. In contrary, other studies were emphasised and supported the CV outcomes and all-cause mortality for SGLT2 inhibitors, this study reported no statically difference in CV risk and other risks and other active controls. Another meta-analysis study reported that SGLT2 inhibitors had played in a significant elevation in the risk of nonfatal stroke, whereas other reports stated no significant difference.

7.4. Thiazolidinediones (TZD)

Thiazolidinediones were considered as insulin sensitisers, and this has been in use for conditions on genetic insulin resistance. These drugs are the synthetic activators of the nuclear receptor peroxisome proliferator-activated receptor (PPAR), which are abundantly expressed in adipose tissue, muscle, liver, endothelium and pancreatic cells [59, 60]. Furthermore, it is rapidly absorbed and extensively metabolised by hydroxylation and oxidation in the liver, forming active and inactive metabolites. Drug molecules of this group were famous for its antioxidant and anti-inflammatory properties [61, 62]. TZDs regulate normoglycemia by elevating insulin sensitivity chiefly by raising peripheral

glucose disposal and inhibiting hepatic glucose production [63]. TZD accelerates HDL-cholesterol and associated with glucose-lowering medications for glycemic robustness. Lower dose treatment (e.g. pioglitazone 15–30 mg) attenuates weight gain and edema. However, the broader benefits of low dose TZDs effects are still unclear [64]. Even though the bioavailability of these drugs is satisfactory, the retrospection studies illuminated the interbred results such as hepatoxicity with a higher risk of cardiovascular complications while demonstrating excellent hypoglycemic effect [65, 66].

7.5. Other anti-diabetic drugs on cellular metabolism

7.5.1. Inhibitors of α-glucosidases

Apart from the above-mentioned drug molecules targeting the glucose metabolism, the use of drugs targeting the digestion of carbohydrates is apprehensible. Hence, the use of α-glucosidases inhibitors received attention because of their ability to competitively and reversibly inhibit glucosidases present in the brush border membrane intestinal villi. On the other hand, adverse effects such as flatulence, diarrhea, and abdominal discomfort and potential elevation in liver hepatic enzymes are reported [67]. However, these inhibitor molecules are majorly appreciated because of its dual role in stimulating the increase of endogenous glucagon-like peptide-1 (GLP-1) [68, 69].

7.5.2. Biguanides

These drug molecules were identified 100 years ago, and these were ignored completely due to the direct availability of insulin therapy. Unlike other molecules which target the cellular metabolism, these glucose-lowering guanidine derivatives were reported to have an insulin-sensitising effect via blocking liver gluconeogenesis while increasing skeletal muscle uptake of glucose, and reducing the absorption of glucose in the intestinal mucosa. While research reports evidenced its action similar to the TZD and inhibitors of α-glucosidases through activation of PPAR and GLP-1. Despite documented adverse effects of this drug, these molecules were the prime prescription for the first-line pharmacological agent for T2DM individuals [70, 71].

7.5.3. Sulfonylureas

A mishap observation during the 1940s leads to the development of sulfonylureas which was reported to have hypoglycemic effect in tissues. These molecules stimulate receptors of sulfonylurea in the β-cell of the pancreas leading to the closure of ATP-dependent potassium channels causing the translocation of secretory granules to the cell surface and extrusion of insulin through exocytosis and the release of insulin. The major side effects reported were into the extracellular space to hypoglycemia, weight gain, and hyperinsulinemia if the treatment goes unattended [72, 73].

7.5.4. Meglitinides

Meglitinides are another group of drug molecules that are insulin secretagogues similar to the action to sulfonylureas. These drug attracted attention due to the rapid action in the receptor in releasing the insulin, and better bioavailability. These molecules are the drug of choice due to its major metabolism in the liver tissues and its excretion via the bile into the feces. Hence, it is a viable option for patients with renal failure. However, cautions should be taken in patients with liver disease due to the same advantage that the pharmacokinetics of this drug may be significantly developing adverse reactions [74, 75,]. Thus with the lack of evidence on the sudden hypoglycemia, this drug has been made as a friendly selection for the individuals suffering from T2DM.

7.6. Other choices of inhibitors

The rising contemporary treatments for the disease treatment, new molecular targets have been developed targeting various unmet signaling mechanisms, and these details have been discussed below. Amongst, the development of inhibitors of fructose-1,6-bisphosphatase (FBPase) gained attention because these drug molecules limit the gluconeogenesis. In addition, these drugs were reported to ameliorate both fasting and postprandial hyperglycemia without the incidence of hypoglycemia, or major perturbation of lactate or lipid homeostasis [76, 77].

The emergence of various natural molecules and the identification of small-molecule inhibitor paved the way for the alternate thinking for novel drug development for the management of metabolic disorders. In that category, the transcription factors belonging to the forkhead/winged-helix box gene, group O (FOXO) subfamily have been found to be crucial in downstream suppression of insulin/insulin-like growth factor-I receptor signaling pathways. Hence, an idea of developing the inhibitor to FOX group of proteins can hypothetically be a regulator of hepatic glucose metabolism; hence it would be a novel drug target in the future [78, 79].

In addition, the growing body of evidence to suggest that inflammatory molecules are associated with the hyperglycemia and hence, pharmacological strategies targeting inflammation reduction may be therapeutically useful in type 2 diabetes. It was reported that the raised level of TNF-α induces insulin resistance in adipocytes and peripheral tissues while impairing the insulin signaling through serine phosphorylation [80-82]. Hence, the potential use of combined anti-inflammatory drugs such as tumor necrosis factor-alpha inhibitors with hypoglycemic molecules would certainly improve insulin resistance, and insulin secretion may represent a valuable option to tackle the double-edged complication.

In the modern approach to treat diseases, the research aims at restoring the cellular functions demonstrated the promising approach, especially in treating diabetes. In that way, N-methyl-D-aspartate receptors (NMDARs) gained attention; these are glutamate-gated ion channels increases glucose-stimulated insulin secretion in the pancreatic islets, improves glucose tolerance in mice. And it has an action in modulating the glucagon, insulin and somatostatin secretion in the tissues. Further, these cellular signaling promotes islet cell survival under diabetogenic conditions. Hence, drug molecules that are NMDAR antagonists could serve as an adjunct treatment for diabetes mellitus could act as better blood-glucose-lowering and β-cell-protective medication in current diabetes treatment [83-85].

Clinical interest on the small GTPase RhoA and its downstream effector, Rho kinase (ROCK) have gained importance due to its innumerable functions in the major organs. Various reports evidenced the

increased activity and gene expression of Rho-kinase in animal models of type 1 or type 2 diabetes and in in vitro hyperglycemic conditions. Hence, the inhibitors of Rho-kinase are speculated to could prevent or ameliorate diabetic complications. Moreover, the evidence of statins Rho/Rho-kinase signaling inhibitory pathway by statins may also play a role in the prevention of diabetic complications providing a novel target for the treatment of long-term diabetic complications [86, 87].

Further, a pre-eminent place has been attained by the protein tyrosine phosphatase 1B (PTP1B), an enzyme that negatively regulates insulin signaling leads to insulin resistance. The enzyme tethered to the cytosolic surface of the endoplasmic reticulum (ER), initiates folding, modification, and trafficking of proteins in the ER homeostasis. Murine models targeting protein-tyrosine phosphatase 1B (PTP1B), PTP1B(-/-) demonstrate enhanced insulin sensitivity without while sensitizing peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists and hence focuses on the potential therapeutic exploitation of PTP1B inhibitors for the management of these conditions is under trial [88, 89].

In addition to the hypoglycemic drugs to control blood glucose, the release of glucose from the liver was found to be more in T2DM. Hence, strategies targeting glycogenolysis is an altered way of controlling the sudden surge of glucose in circulation. A notable controlling enzyme glycogen phosphorylase has been brought into a trail for the regulation of hyperglycemia. The major function of the enzyme is found to be the release of monomeric glucose from the glycogen polymer from the storage. Hence, cumulative information has bolstered interest for glycogen phosphorylase inhibitors as potential new hypoglycaemic agents for the treatment of type 2 diabetes mellitus in terms of regulation of the hepatic glucose output [90, 91].

Aldose reductase (ALR2), an NADPH-dependent reductase, is the first and rate-limiting enzyme of the polyol pathway of glucose metabolism and is implicated in the pathogenesis of secondary diabetic complications. Hence, this enzyme has been a target in recent years to treat or prevent the development of secondary complications in diabetes [92, 93]. Retinoid X receptor (RXR) antagonists are one among drug candidates for the treatment of T2DM. In cells, peroxisome proliferator-activated

receptor gamma (PPARγ) is a ligand-dependent transcription factor that plays an important role in regulating glucose metabolism. It has been identified that the functional activity of PPARγ is manifested by heterodimers of PPARγ with retinoid X receptors (RXRs). Researchers have found that the agonists of PPARγ, such as thiazolidinediones executed the hypoglycemic effect in an animal model of T2DM, and are thought to improve insulin resistance through antagonism to the PPARγ/RXR heterodimer [94, 95].

On a contrary note, the mTOR signaling inhibitors were found to induce severe hyperglycemia. The mammalian target of rapamycin (mTOR) inhibitors is primarily used as immunosuppressors after transplantation and now frequently used as antineoplastic therapies in various cancers. These drug molecules play a key role in regulating cell growth as well as lipid and glucose metabolism. The deleterious effect of mTOR inhibitors on glucose metabolism is due to an increased insulin resistance secondary to a reduction of the insulin-signaling pathway within the cell and a reduction of insulin secretion via a direct effect on the pancreatic beta cells [96, 97]. Despite its promising strategy in the cardiac disease of T2DM, a crucial watch is suggested for treating secondary complications in diabetes. In addition, an activator of mTOR is suggested to be a promising drug in the treatment of hyperglycemic conditions.

Conclusively, in the above-mentioned list of drugs, we have excluded the use of inhibitors of epigenetic enzymes such as histone acetyltransferases (HATs), class II histone deacetylases (HDACs) and DNA methyltransferases (DNMTs), miRNA, phytochemical inhibitors and nanoparticles drugs. As we would cover these topics in another science review elaborately, we have restricted with the present literature.

8. Perspectives

Overall, the present review would serve as an introductory package about the treatment strategies from ancient to till date for the threatening health care issue that leads to intolerable damage in the economy of the world. Despite novel pharmacotherapy that is well developed for regulating T2DM,

approaches on lifestyle diet system, physical fitness is regarded as the driven forces and major criteria to manage T2DM and can extend quality of life with T2DM.

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FIG. 1 Treatment strategies of type 2 diabetes (T2DM).

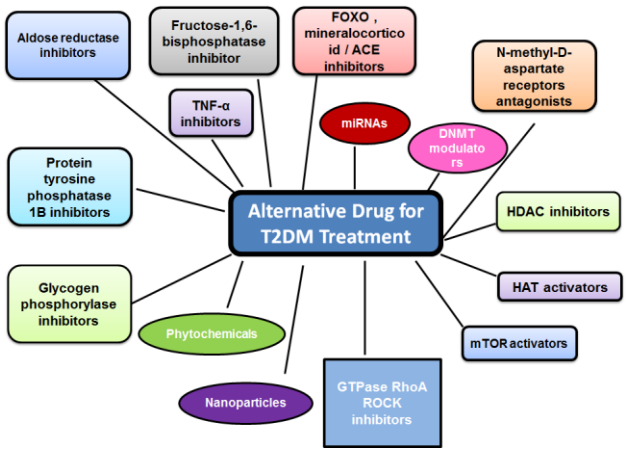

Table 1 Treatment strategies for diabetes mellitus.

Class	Mechanism of action	Adverse effects
Sulfonylureas	Closure of ATP-dependent potassium channels, stimulate the pancreas to produce more insulin	Sudden hypoglycemia
Meglitinides	Stimulate the pancreas to produce	Sudden hypoglycemia but less than sulfonylurea. The adverse effect in liver failure conditions.
Biguanides	Reduce the production of glucose by the liver. Insulin-sensitizing effect via blocking liver gluconeogenesis.	Diarrhea, metallic aftertaste, nausea

Thiazolidinediones (TZD)	Increase insulin sensitivity of the body cells and reduce the production of glucose by the liver. Activators of the nuclear receptor peroxisome proliferator-activated receptor (PPAR)	• Swelling due to water retention, weight gain • Pioglitazone : increased risk of bladder cancer • Rosiglitazone : increased risk of non-fatal heart attack
Alpha-glucosidases inhibitor	Slow the absorption of carbohydrates ingested. Stimulating the increase of endogenous glucagon-like peptide-1 (GLP-1) and induces pancreas to produce more insulin	Flatulence, diarrhoea, and abdominal discomfort and potential elevation in liver hepatic enzymes
Dipeptidyl-peptidase-4 (DPP-4) inhibitors	Intensify the effect of intestinal hormones (incretins) involved in the control of blood sugar	Pharyngitis, headache
Glucagon-like peptide-1 (GLP-1) agonist	Mimic the effect of certain intestinal hormones (incretins) involved in the control of blood sugar	Nausea, diarrhea, vomiting
Sodium-glucose cotransporter 2 (SGLT2) inhibitors	Glucose reabsorption in a variety of tissues. Help eliminate glucose in the urine	Genital and urinary infections, more frequent urination. Adverse effects in gastrointestinal conditions.