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An updated review on anti-diabetic agents and their functions: a comparative study

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Abstract

Chronic metabolic disease is characterized by a high concentration of glucose in the blood resulting from imperfections in insulin secretion or insulin action. Currently, it is rapidly becoming an epidemic in several nations around the world affecting millions of people. Hence, it is predicted that the number of affected may double in the next couple of years. This increase may be due to the rise in the aging population, adding to an already existing burden on healthcare providers, particularly in developing countries. Based on the unusual elevation of plasma glucose diabetes is divided into two main types, comprising type (1, 2) DM, gestational diabetes mellitus, neonatal diabetes, maturity-onset diabetes of the young (MODY), and sequelae induced by endocrinopathies, the consumption of steroids, along with other elements. Type 1 diabetes mellitus is considered inadequate insulin synthesis, while Type 2 diabetes mellitus involves the body's cells not responding appropriately to insulin. Type 1 diabetes is a condition that usually affects young people, while type 2 diabetes is more common in older individuals who have unhealthy lifestyles. Both types of diabetes have different causes, symptoms, and treatments due to their distinct differences in how the body processes sugar. The aim of the present study is to learn more specifically pertaining to diabetes mellitus, its complications including clinical appearance, associated risk factors, anti-diabetic regime and its consequences at present.

Introduction

Diabetes mellitus (DM) is a collection of metabolic diseases characterized by hyperglycemia, in which a person does not yield adequate insulin, or the body cells did not respond conscientiously to insulin that is formed [1]. Diabetes is a Greek term meaning “to pass through” suggesting signs of polydipsia, polyuria, and polyphagia, while mellitus is the Latin word meaning “sweetened” proposing glycosuria [2].

Diabetes mellitus usually has been distributed and deal with a number of aspects but the most common three types are: (i) Type 1 diabetes mellitus (T1DM) is as well designated “juvenile diabetes” in which the body becomes unable to harvest insulin also known as insulin-dependent diabetes mellitus (IDDM). (ii) Type 2 diabetes mellitus (T2DM) state in which an insulin utilizing cells fails to respond appropriately this sort mentioned to “adult-onset diabetes” and is non-insulin-dependent diabetes mellitus (NIDDM). (iii) This kind of diabetes commonly occurs in women during her pregnancy and may proceed to T2DM without any history of diabetes known as gestational diabetes [3,4].

In addition, many other varieties of diabetes including exogenous pancreatic disease, monogenetic diabetes syndrome, chemically or drug induced, endocrine diabetic disorder, and diabetes related to infection [5]. Worldwide T1DM is more predominant among children in particular between the ages of (10-14) years [6]. The strongest risk factor for T1DM progression is genetics. In contrast, approximately 25% of individuals who have a family history of diabetes exhibit T2DM, which is more prevalent in adults [7-9].

Clinically, diabetes mellitus is characterized by a high plasma glucose level, weight loss, polyuria, eyesight impairment, and polydipsia while chronic hyperglycemia prominently led to growth retardation and more susceptible to infections [10]. Diabetes can harm blood vessels, nerves, eyes, and kidneys, which can cause many problems. People with diabetes are much more likely to develop heart disease than those without it [11]. Diabetes is a debilitating chronic illness linked to reduced life expectancy, quality of life, and economic costs for patients and society due to healthcare, medications, and early death [12].

Moreover, diabetes has been considered the highest 21st century challenging health distress, with an estimated 285 million individuals affected worldwide in 2010. The incidence of diabetes is expected to increase by more than 20% in adults and up to 69% in seniors in developing countries over the next two decades [13-15]. By 2030, it is expected that over 400 million individuals worldwide will have type 2 diabetes mellitus, including young people living in regions with low- or middle-income [16].

Insulin injections are necessary to control T1DM, while T2DM is managed using insulin-containing or non-insulin-containing drugs. Oral medicines and insulin can cause low blood sugar. Studies have also addressed the use of current pharmaceuticals, alternative treatments, and activity management therapy [17,18]. Various oral insulin secretagogues are currently available for treating type II diabetes mellitus, including Sulfonylureas, biguanides, repaglinide, thiazolidinediones, nateglinide, insulin, pramlintide, alpha-glucosidase inhibitors, and exenatide [19].

These medications work differently, for example, by stimulating insulin secretion, inhibiting hepatic gluconeogenesis, or increasing insulin receptor sensitivity [20]. Personalized medicine advancements have resulted in discovering polymorphisms that affect drug-metabolizing enzymes, drug carriers, targets, and receptors [21]. Therefore, the goal of the present assessment is to learn more specifically pertaining to diabetes mellitus, including its clinical manifestation, statistics on incidence, negative consequences, and treatment regime at present.

Methods

Literature search strategy and selection criteria

We looked into the adherence and compliance of patients with regard to diabetes, hypoglycemic agents, insulin, prescription administration and psychological aspects. We examined a variety of factors, such as administration, unfavorable effects, and diabetic treatment care. We thoroughly looked at several databases, notably Google Scholar, PubMed, and several others to find pertinent material. In order to find relevant material, we searched for these databases from their origin until October 2022. Also, we looked over the bibliographies of each disclose that was acquired and looked for pertinent articles in the fields.

Discussion

Epidemiology

The prevalence of diabetes is increasing worldwide, with more than 80% of adult cases expected to occur in newly established or developing nations by 2030, resulting in a projected total of 438 million cases [22]. As a result of this trend, a growing number of individuals are experiencing significant complications affecting the cardiovascular system, kidneys, eyes, and peripheral nerves. The rise in incidence has also been documented among children and young adults, where T2DM may currently exceed T1DM [23].

In Japan, the incidence of (T2DM) has shown an alarming increase among junior high school students, rising from (7.3/100,000) between (1976-1980) to (13.9/100,000) in (1991-1995) respectively, with T2DM

occurrences surpassing those of T1DM [24]. In cats, male gender has been identified as a common risk factor in the disease progression, with several risk factors in common with T2DM in humans, such as aging, lack of physical activity, and obesity [25]. In 2002, DM was reported as the sixth leading cause of death, accounting for millions of deaths [26].

The genetic predisposition accounts for 70-75% of susceptibility to T1D, with lifestyle factors also playing a role in triggering beta cell loss and diabetes onset. While, T1D prevalence in children aged 0-14 years varies significantly between different countries, with Finland, Sweden, and Norway ranked highest at 57.6, 43.1, and 32.8 cases per 100,000 annually [27-29].

Furthermore, global prevalence of T2D has risen significantly, with the number of affected individuals in 2000 rising commencing (151 to 415 million) presently [30]. In the context of Pakistan, a prior investigation conducted in the Sindh province showed a prevalence rate of 13.9% [31].

Pathophysiology of diabetes

T1DM is a complex immunological illness develops through a combination of immunologic as well as genetic factors [32]. Obesity is a major factor in the development of T2DM as it causes resistance in peripheral tissues and inflammation in metabolic-activated adipose tissue, making it a significant genetic and environmental factor in T2DM development [33]. Reactive oxygen species (ROS) generation is an essential factor in the pathophysiology of macro- and micro-vascular complications related to diabetes, including diabetic nephropathy [34]. Insulin resistance, glucose, free fatty acids (FFA) are linked to increased ROS production and, as a result, oxidative stress, which can impair insulin secretion and efficiency and accelerate the progression to overt T2DM [35]. According to Randle's hypothesis from over three decades ago, FFA and glucose compete for the primary energy source in the heart muscles, resulting in reduced glucose oxidation during high FFA levels [36].

In recent years, researchers have identified a link between T2D and oxidative stress-induced inflammation. Oxidative stress happens when the body can't handle the production of harmful reactive oxygen species. In T2D, there is often increased mitochondrial uncoupling and beta-oxidation, which can lead to higher ROS production. This increased ROS generation can activate inflammatory pathways, leading to a cascade of stress pathways that negatively impact insulin signaling [37,38].

Lipid peroxidation is when lipids are broken down by reactive oxygen species (ROS), which can cause damage to tissue and inflammation. In diabetic patients, high levels of iso-prostane indicate increased lipid

peroxidation and can lead to complications. Antioxidants like catalase, glutathione peroxidase, and superoxide dismutase are important for neutralizing ROS and preventing oxidative stress. Diabetic patients with lower or high levels of antioxidants may experience increased ROS generation and complications. The beta islet, which produces insulin, is especially vulnerable to damage because of its low antioxidant defenses [39-41]. The beta islet, which produces insulin, is particularly susceptible to oxidative stress-induced damage due to its low innate antioxidant defenses. Therefore, maintaining a healthy antioxidant status may be essential in protecting against diabetic complications [42]. High blood sugar levels, or hyperglycemia, have recently been linked to the initiation of surplus biochemical pathways, such as stress-activated signaling pathways like nuclear factor- κ B (NF- κ B), NH₂-terminal Jun kinases (JNK)/stress-activated protein kinases (SAPK), p38 mitogen-activated protein (MAP) kinase, and hexosamine. These pathways can lead to oxidative stress, which is caused by NADH-induced reductive stress [43]. Reducing hyperglycemia-induced reductive stress may provide therapeutic options for treating diabetes and its complications [44].

Metabolic diseases, especially diabetes, can be caused by errors in the signaling pathways of IRS-1 and IRS-2 proteins. IRS proteins help regulate glucose absorption, lipogenesis, protein synthesis, and cell viability [45]. Mice with IRS-1 deficiency have hypersecretion of insulin as compensation, while IRS-2 alteration promotes hyperglycemia and can be fatal. IRS-3 and IRS-4 don't show observable phenotypes, but IRS-4 acts as an insignificant function in growth, reproduction, and glucose homeostasis. Insulin resistance in IRS2^{-/-} mice is due to deregulated PI3K activity. Mutations in the GCG-R gene may contribute to T2D in the French population [46], and the significance of Gly972Arg and Ala513Pro variations in the IRS-1 gene in the development of NIDDM is unclear. Glycogen regulates hepatic glucose production and helps regulate glucose homeostasis [47,48].

Medication for diabetes

Biguanides

Metformin hydrochloride (biguanide) is a "first-line therapy" that is widely used to lower blood glucose level in person who have newly been established T2DM. Unlike other synthetic medications, metformin is derived from a natural substance used as part of a natural remedy and was not designed to target a specific route or disease [49]. It is particularly useful in overweight and obese individuals because it inhibits the production of glucose by the liver, increases insulin

sensitivity, and improves glucose uptake by phosphorylating insulin [50].

The medication is chemically constituted of two guanidine groups linked together by the removal of ammonia, making it a member of the biguanide class of medications. Metformin is available in oral formulations ranging from 500 mg/b.i.d. or t.i.d. to a maximum of 2,550 mg/day (roughly 35 mg/kg/day), with 2,000 mg/day being a commonly recommended maximum in some guidelines. Studies have shown that metformin reduces fasting plasma glucose levels by 1.1 mmol/L and HbA1c by 0.9%. At a dosage of 2000 mg, the comparable declines were 4.3 mmol/L and 2.0% (21.9 mmol/mol; $p < 0.01$) [51,52]. Orally administered metformin have been absorbed almost 70% by the small-intestine, while, remaining of the drug passed into colon and eliminated in feces. However, metformin is not recommended for individuals with high blood creatinine levels (1.5 mg/dL in men and 1.4 mg/dL in women) or those with renal function at risk [53].

Recent studies of metformin have shown an extraordinary concentration in gastrointestinal tract, kidneys, liver and bladder imitating the route of action by positron emission tomography (PET) also a slight agglomeration in muscle tissues [54]. The medication lowers intestinal glucose absorption as well as LDL and VLDL. A reduction in triglycerides and free fatty acids suggests that the medication has a cardio-protective effect and is likely to help improve insulin sensitivity [55]. Metformin lowers glucose production in the liver by suppressing a process called gluconeogenesis. It does this by activating a protein called AMP-activated protein kinase while inhibiting a part of the mitochondrial respiratory chain complex 1, increasing NADH oxidation and ultimately reducing ATP synthesis [52]. Studies have shown that metformin also has an effect on cellular proliferation and inflammation. It has been found to suppress proliferation in keratinocytes via the mitogen-activated protein kinase pathway and reduce proliferative and proinflammatory cytokines in cultured human keratinocytes via the mammalian target of rapamycin signaling pathway [56,57]. Figure 1 represents the structures of Metformin and Phenformin.

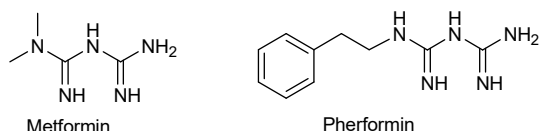


Figure 1: Skeleton of Metformin and Phenformin.

Sulfonylureas

Sulfonylurea (SU) skeleton-containing substances are one of the most prominent organic compounds

displaying promising anti-diabetic properties among their other pharmacological functions [58]. If a patient is unable to take metformin, another oral anti-diabetic drug, such as sulfonylurea, may be administered. The justification for metformin prescribing as the primary-treatment for T2DM relies entirely on its apparent good effect on traditional surrogate outcomes [59]. Tolbutamide was the first SU agent, and it was introduced in Germany during the 1950. Glibenclamide, the second SU agent, which is generally alluded to as a third-generation agent, was launched in 1995 [60]. In individuals with noninsulin-dependent diabetes mellitus, glipizide, a second-generation sulfonylurea, offers a significant anti-diabetic effect [61].

Second- and third-generation sulfonylureas are chosen based on perceived higher efficacy and safety characteristics. Sulfonylureas are still a popular choice for treating diabetes, either on their own or with another drug. They account for about 25% of newly started diabetes treatment [62]. Sulfonylureas lower glucose levels by increasing insulin release from the pancreas and inhibiting the production of glucose in the liver. This is done by blocking K_{ATP} channels [63]. Elderly people with DM treated with sulphonylureas had a 36% greater risk of hypoglycemia than younger people. SUs are the preferred therapeutic agents in diseases such as neonatal diabetes, MODY-3(HNF-1) mutations, and certain Transcription Factor 7-like 2 polymorphisms [64]. K_{ATP} channels are found in a kind of tissues, with neurons, cardiac tissue, also vascular smooth muscle cells. The ATP/ADP ratio regulates them physiologically via nucleotide binding sites on the K_{ATP} channels. This allows the plasma layer to depolarize, subsequent in the prologue of voltage-subordinate calcium channels and the input of calcium particles. Calcium particles bind to calmodulin, causing insulin exocytosis to occur like that observed following glucose stimulation [65,66].

Sulfonylureas have excellent lengthy safety and effectiveness, are inexpensive, and can reduce HbA1c levels by up to 7–16 mmol/mol when taken with metformin [67]. The University Group Diabetes Program (UGDP) study suggested that SU therapy may increase the risk of cardiovascular mortality in patients with type 2 diabetes. This investigation found that SU tolbutamide was linked to an increase in CV mortality [68]. Moreover, some experimental data suggests that SUs may raise the incidence of some cancers, including thyroid, esophageal, pancreatic, colorectal, and hepatic cancer. Possible "Downsides" of sulfonylurea use include Hypoglycemia, weight gain, and perhaps a reduction in myocardial ischemic preconditioning [69,70].

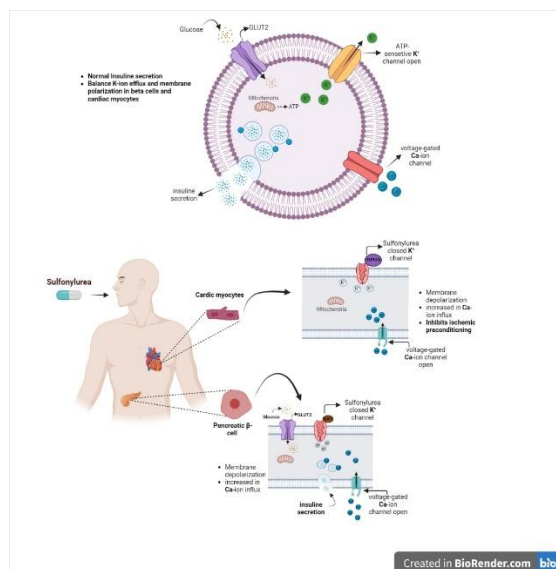


Figure 2: The way sulfonylureas affect pancreatic β-cells and cardiomyocytes is through the sulfonylurea receptor (SUR). This information has been adapted and modified from a source by Gore MO and McGuire DK, which discusses the differentiation of drug effects from class effects in T2DM medications, providing further evidence for cardiovascular outcomes evaluation.

Meglitinides

Meglitinides are drugs against diabetes having an hour-long half-life that are crucial in preventing hypo- and anticipatory hyperglycemia. The two brand name medications most frequently used in this group of drugs are repaglinide and nateglinide. Repaglinide was the first meglitinide variant approved for use in T2DM patients [71]. Meglitinide is a short-acting insulin secretagogue that binds to the sulfonylurea receptor in pancreatic cells, like sulfonylureas but with weaker binding. It increases insulin secretion by inhibiting K_{ATP} channels in cells. Meglitinide responsiveness is linked to various genetic polymorphisms, including SLC01B1, which aids in the hepatic absorption of the medication repaglinide [72].

Repaglinide is an oral medication used for type 2 diabetes, with doses ranging from 0.5 to 4 mg per meal. Meglitinides can cause minor weight gain and hypoglycemia, and individuals with mild renal and hepatic impairment should use them with caution. Repaglinide and nateglinide absorption via liver with repaglinide causing more weight gain and 10% of it eliminated by the kidney. Meglitinide therapy is associated with a 0.5 to 1.5 percent decrease in HbA_{1c}, while repaglinide is better than nateglinide at lowering HbA_{1c} levels [73].

Thiazolidinediones

Thiazolidinediones (TZDs) are medications used for diabetes that improve insulin sensitivity in fat and

muscle tissue. They help control sugar level and reduce the risk of cardio-vascular issues [74]. TZDs activate PPAR-γ, which regulates fatty acid storage and metabolism. They reduce inflammatory cytokines and increase adiponectin levels in adipose tissue, leading to sustained pancreatic beta cell function and reduced insulin resistance [75]. However, the use of TZDs has decreased because of its antagonistic properties over the last decade of fluid retention and edema caused by PPARγ activation on the nephron. TZDs have a high bioavailability and can be used in combination with metformin and sulfonylureas but are prohibited from being used with insulin due to the increased risk of weight gain. Pioglitazone is approved for use with insulin but not alone [76].

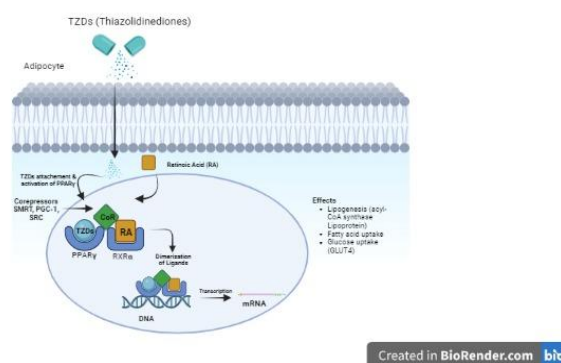


Figure 3: Mechanism of PPARγ activation

The TZDs rosiglitazone and pioglitazone have been effective in preventing and advancing albuminuria and renal fibrosis in type 2 diabetic animals. TZD therapy may retain beta cell activity, and they exhibit both PPAR-γ dependent and independent actions. Pioglitazone has been linked to bladder cancer, and both rosiglitazone and pioglitazone have been related with cardio-vascular consequence and are prohibited in many regions. However, metformin and rosiglitazone together can reduce cardio-vascular risk factors in people with T2DM or insulin resistance [77,78].

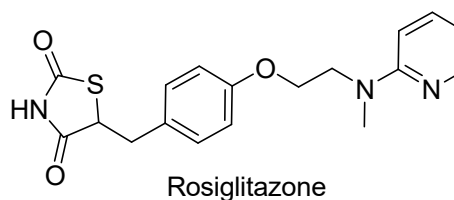


Figure 4: Structure of Rosiglitazone.

Alpha-Glucosidase Inhibitors

Alpha-Glucosidase (AG) inhibitors are a type of medication for diabetes that work by slowing the breakdown and absorption of carbohydrates in the small intestine. This is achieved by inhibiting the activity of the enzyme alpha-glucosidase, which breaks

down complex sugars into simple sugars that can be absorbed by the body [79]. Three AGIs, including Acarbose, Miglitol, and Voglibose, are currently used in the management of diabetes. These drugs have been revealed to decrease post-prandial plasma glucose level, enhance cholesterol concentrations, blood pressure, and other cardiovascular risk factors [80]. AGIs work by blocking brush border enzymes sucrose-isomaltase and maltase-glucoamylase, which are involved in carbohydrate digestion [81]. Voglibose is commonly used to treat T2DM. AGIs have a lower risk of causing potentially fatal side effects compared to other diabetes drugs such as sulphonylureas and biguanides. In addition, the use of Acarbose has been found to lower the risk of developing T2DM in people with impaired glucose tolerance. AGIs offer an effective long-term therapy option for type 2 diabetes patients while lowering cardiovascular risk and enhancing insulin sensitivity [82].

The structure of Acarbose is presented in figure 5.

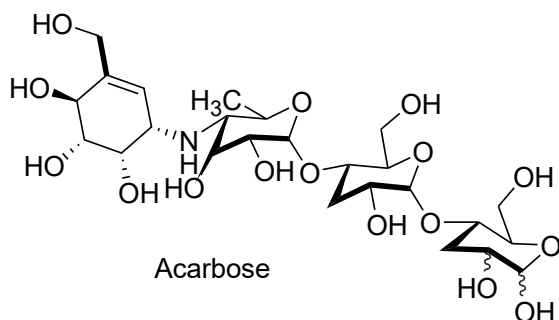


Figure 5: Acarbose skeleton

Incretin-Based Therapies

Incretin hormones are released after eating and control the release of insulin and glucagon and slowing stomach emptying and reducing the number of calories. Incretin-based medications are a recent addition to the arsenal of diabetes treatments and work by increasing beta-cell activity and insulin production while decreasing glucagon secretion. Incretin-based therapeutics are classified into two; glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors [83]. GLP-1 receptors are found not only in the pancreas but also in cardiovascular tissues, suggesting that GLP-1 may have cardioprotective effects. Some of the currently available drugs in this category include sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin. Adverse effects of incretin-based therapies include nasopharyngitis, hypersensitivity, nausea, headache, and skin reactions [84,85].

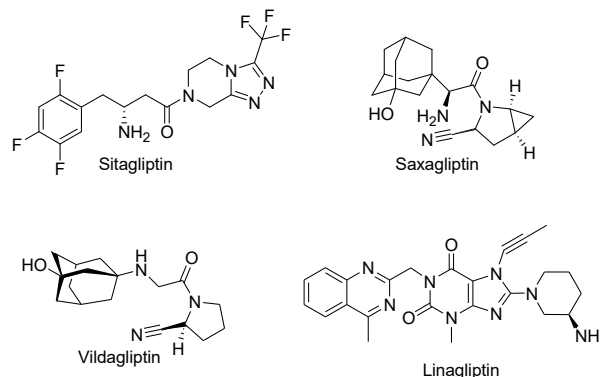


Figure 6: Structures of Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin.

Dipeptidyl-Peptidase IV Inhibitors

Drugs that block the enzyme DPP-IV (dipeptidyl peptidase IV) are showing potential as effective treatments for diabetes. DPP-IV is responsible for breaking down GLP-1 (Glucagon-like peptide 1), a key hormone involved in regulating blood sugar levels. By inhibiting DPP-IV, GLP-1 stays active longer and can better regulate glucose levels. By inhibiting DPP-IV activity, GLP-1 and glucose-dependent insulintropic peptide (GIP) degradation can be reduced, leading to improved incretin function and glucose homeostasis. DPP-IV cleaves the NH₂-terminal amino acids of bioactive peptides, shortening GLP-1 and inactivating it. DPP IV inhibitors, such as sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin, improve metabolic control in type 2 diabetes, alone or in combination with other drugs [58]. Clinical studies have shown that these drugs are rapidly absorbed with high oral bioavailability and are well-tolerated with minor adverse effects [86].

Bromocriptine

Bromocriptine mesylate is an FDA-approved drug for the treatment of T2DM. The drug has been revealed a prominently lessen complete blood glucose, plasma-insulin/growth hormone concentrations during a 50 g oral glucose tolerance test in acromegaly patients when administered orally in doses of 5 mg every 6 hours for a mean of 12 months [87]. The drug acts as a postsynaptic dopamine receptor agonist and serotonin modulator and is used to treat Parkinson's disease, hyperprolactinemia, and acromegaly [88]. It is hypothesized that bromocriptine reduces post-prandial blood glucose and hepatic glucose production by increasing low hypothalamic dopamine levels and impeding high sympathetic activity in the central nervous system by limiting serotonin turnover [89]. Daily oral doses of bromocriptine were administered to obese menopausal females, and their body fat storage was measured. In animal models, bromocriptine has been found to reset circadian rhythms and decrease

body fat levels. However, an overdose of bromocriptine can lead to various symptoms, including nausea, constipation, dizziness, severe hypotension, disorientation, delusions, lethargy, and hallucinations, among others. Therefore, it is essential to monitor fluid intake and excretion closely [90].

Conclusion

We have highlighted the important classes of anti-diabetic agents and their role as oral hypoglycemic medications in the treatment of diabetes mellitus T2. Untreated diabetes can cause various problems, so it is essential to address it quickly with the right medication. Untreated diabetes can lead to complications, including diabetic retinopathy, nephropathy, and neuropathy. Other cardiovascular risk factors must also be addressed in type 2 diabetic patients. Diabetes is defined as a major chronic health disease that needs frequent self-management and an interdisciplinary team approach comprising healthcare experts, dietitians, patients understanding, and their caregivers. Diabetic patients must develop a lifestyle that allows them to control obesity and depression. Treatment choices may be personalized, or advice established on the affected risk factors, current HbA1C level, and drug efficacy, ease of use, financial situation/insurance/costs, and risk of side effects such as hypoglycemia and weight gain. The efficacy of medication must be monitored and evaluated as early as possible using diagnostic blood tests (HbA1C) and one-on-one counseling for the progression of diabetes problems such as retinopathy, nephropathy, neuropathy. Individuals with diabetes mellitus T2, an endocrine abnormality, can be managed via lifestyle modifications, careful nutrition management, and weight control. Overall, evidence from pharmacogenomics-based trials may aid in presenting a better image of any involved molecular pathways on the way to selecting pharmaco-economically feasible and applicable treatment methods for the complex multifactorial illness that is diabetes.

Competing Interest

The authors declare that there is no conflict of interest.

Author Contributions

AH, AL, MA, and MR wrote the manuscript. MA, ZR planned the proposal of the study. MR and NJ critically reviewed the manuscript. All authors contributed to the writing and editing of the manuscript. All authors have read and approved the final manuscript.

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