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Review Article

The potential role of anti-diabetics in alleviating depression, cognitive disorders, and schizophrenia in diabetes patients

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ABSTRACT

Background and objectives. Diabetes, a prevalent chronic metabolic illness, has been linked to a greater chance of experiencing numerous psychological issues. Recent investigations revealed a potential role for anti-diabetic medications in modifying the pathophysiology of some psychological conditions. However, the exact means for such an action is still to be illustrated. This review has aimed to investigate the underlying molecular mechanisms, clinical trials, and experimental research results to reveal the proposed therapeutic efficacy of anti-diabetic drugs in alleviating the coexistent psychological disorders in type 2 diabetic patients, especially considering depression, cognitive dysfunction, and schizophrenia.

Methods. PubMed, Cochrane Library and Google Scholar were explored by applying the main topic relevant keywords to consider articles that meet our selection criteria up to October 2023.

Results. We exposed a perspective bidirectional correlation between diabetes and psychological illness, where both conditions affect each other directly or indirectly. Additionally, the effect of some anti-diabetic medications on psychological disorders is controversial. Various agents, sometimes through mechanisms beyond their glucose-lowering tendency, were linked to reduced chances of psychological disorders, whereas others were associated with a heightened risk of developing diverse mental health issues.

Conclusion. Clinicians need to be aware of the potential effects of some anti-diabetics on psychological condition; especially when prescribed to diabetic patients with previously determined mental of psychological illness.

Keywords: Diabetes mellitus, Anti-diabetics, Psychological disorders, Depression, Cognitive dysfunction, Schizophrenia.

INTRODUCTION

Psychological disorders (PsD) are conditions characterized by abnormal thoughts, feelings, and behaviors. Individuals with PsD tend to exhibit unhealthy behaviors such as smoking, physical inactivity, and excessive alcohol consumption more frequently than those without such conditions (1,2). All of these behaviors, besides the metabolic side effects of certain antipsychotic drugs, are considered risky for developing type 2 diabetes mellitus (Ty2DM). Furthermore, the changes in biological systems such as elevated stress
conditions may trigger the nervous system for the release of adrenaline and noradrenaline can raise the chance of Ty2DM in patients with PsD (3).
On the other hand, People with Ty2DM are at higher risk of developing PsD due to several mechanisms (4). Accordingly, these disorders share a bidirectional association, influencing each other in multiple ways (5). Brain-derived neurotrophic factors, insulin resistance (InR), and inflammatory cytokines are among the factors

that reflect the role of diabetes complications in developing psychiatric illnesses. Such an interface between DM and PsD has attracted both endocrinologists and mental health professionals for decades. Where simultaneously present, both disorders have been reported to impair the quality of life, have poorer adherence to medication with ineffective self-management, have a greater incidence of DM complications, and predispose to a greater risk of cardiovascular disease (CVD) death (6–8).

Generally, the overlapping in physiological lines between DM and PsD could be present. There is a reported genetic overlap between the risk for the two disorders. Additionally, patients with PsD plus DM exhibit elevated levels of circulating inflammatory mediators, compared with patients with DM alone. Furthermore, InR is a main pathophysiologic feature of DM and is also related to PsD (9). Moreover, the two disorders have many shared lifestyle and environmental risk factors, including diet and physical activity. Lastly, hyperglycemia looks to be closely related to PsD (10).

Anti-diabetic drugs, in a similar scenario, that improve glycemic control through several mechanisms, may have different impacts on PsD. The most reported examples are metformin, thiazolidinediones (TZDs), and glucagon-like peptide 1 (GLP-1) receptor agonists (11–13). On the other hand, some conventional drugs that are useful for resolving PsD may negatively impact the glucose level or hinder the effect of anti-diabetic agents, resulting in a worsening effect on the clinical presentation of patients with Ty2DM (14). Despite this, clinical data that evaluate the effect of anti-diabetic drugs on PsD remains inadequate and controversial. Collaboration between endocrinologists and psychiatrists can improve PsD treatment and reduce the early mortality in at-risk populations with DM (15). Therefore, the aim of this review is to analyze the existing literatures that studied the impact of anti-diabetic medications on psychological health, in addition to identifying any associations between the use of hypoglycemic agents and the development or management of PsD. This review will discuss conditions like depression (DEP), cognitive dysfunction (CD) and schizophrenia (SiZ), considering their influence on treatment decisions for patients with Ty2DM.

Psychiatric disorders in patients with diabetes.

Depression (DEP)

feeling sad, alone, isolated, anxious, or nervous all the time are indications of DEP, which is one of the most prevalent mood disorders, and a major cause of disability worldwide (16). In 2021, the WHO stated that 3.8% of the population is affected by DEP around the world (17). Patients with DM commonly experience DEP, with fourty-one percent suffer from poor mental health and high rates of DEP disorder. Additionally, people with Ty2DM have a 24% higher risk of getting DEP in comparison to normal subjects (18). The condition has a significant negative impact on patients with diabetes and is often linked with poor health outcomes, lower adherence to drugs, unregular glucose levels, and decreased standard of living; therefore, the co-morbid conditions of DEP and DM need careful awareness (19). There are several reported biological pathways that link DM to DEP. The elevation in blood glucose is discovered to be linked to DEP (20). InR acts as a link between diabetes and DEP based on numerous in vivo and in vitro studies (21). High levels of inflammation were established in patients with DM and DEP (22). Hyperglycemia with InR have critical impacts on the brain such as lower the activity of neurotransmitter (NT), hindered neurogenesis, and higher levels of inflammatory mediators with oxidative stress (OxS) (23,24). Because a lot of oral hypoglycemic agents have outcomes on all the above pathways, it is thought that anti-diabetic agents can positively or negatively affect the incidence of DEP (25).

Anti-diabetic therapy and risk of depression

Long-duration usage of metformin improves hippocampal neurogenesis and improves mood by inducing serotonergic neurotransmission (26). Metformin in low doses decreases the risk of DEP but in high doses does not. In addition, low doses protect from neuro-inflammation and OxS (27). Additionally, the large dose of metformin can badly impact mood through altering the composition of the intestinal microbiome (28). Triggering 5'-adenosine monophosphate-6 activated-protein kinase (AMPK) signaling by metformin, cause less adherence of inflammatory cells to the endothelium, resulting in an anti-depressant effect (29). Furthermore, it has

been shown to have anti-depressant potential in individuals with Ty2DM and DEP. Thus, metformin's potential anti-depressant effect indicates that inflammatory mediators and OxS play a major role in DEP through different physiological pathways (30).

Dipeptidyl peptidase IV inhibitors (DPP4-inh), and GLP-1 analogs are incretin mimetics that increase the level of incretin hormone GLP-1 in the circulation. DPP-4 is an enzyme responsible for the degradation of GLP-1, thus its activity is associated with more depressive symptoms, where CD and bipolar disorder are associated with low levels of GLP-1 (31). Incretins increase neurogenesis, cell proliferation, synaptic plasticity, and anti-apoptotic effects, in addition to their ability in lowering the levels of neuro-inflammation, and OxS, besides its modulatory effect on glucose metabolism, which also can explain the preventive effect of DEP (32). The anti-depressant action of incretin-based therapy is still not clear, the changes in functions of GLP-1, peptide YY, and neuropeptide Y can be related to this action. These are gut hormones involved in the brain-gut axis, thus enhancing the signal of GLP-1 and Y-1 receptors to reflect the anti-depressant action (33).

Sodium-glucose co-transporter inhibitors (SGLT2-inh) are another group of anti-diabetics that have a low risk of DEP and dementia (34). SGLT2-inh has a unique ketogenic property that aids in neuro-protective mechanisms (35). Nevertheless, in contrast to other anti-diabetic agents, SGLT2-inh increases ketogenesis, thus associated with an anti-depressant effect (36).

Metformin, GLP-1 analogs, and SGLT2-inh cause weight loss; therefore, they are preferred in obese patients (37). The influence of such drugs on the incidence of DEP can be modulated through a reduction in weight, as obesity and DEP are linked to each other (38).

Insulin therapy, on the other hand, is often used to manage glycemic control in Ty2DM. However, it appears that insulin treatment is not as popular as oral hypoglycemic medications. Approximately 25% of patients with Ty2DM are hesitant to utilize insulin, so it is left as a final option (39). This may be due to the significant psychological difficulties that some patients experience when transitioning from oral anti-diabetic drugs to insulin. Patients who require more

frequent insulin injections per day are more likely to exhibit depressive symptoms. Thus, insulin is positively associated with DEP (40,41).

TZDs (pioglitazone and rosiglitazone), are insulin sensitizers that reduce InR in the brain and peripheral tissues. These drugs can cross the blood-brain barrier (BBB) to increase the sensitivity of insulin in the brain. Despite there is observation about the connection between DEP and InR in the in the brain, using TZDs would not necessarily lead to a reduction in DEP (34).

Sulfonylureas (SUs) are a potent anti-diabetic class; they stimulate insulin secretion in people with TY2DM. Nevertheless, high doses of SUs are associated with a high risk of hypoglycemia, which is correlated to DEP. Therefore, the use of SUs is negatively associated with DEP (42).

Cognitive dysfunction (CD)

Loss of memory, confusion, and difficulties in carrying out daily tasks are all symptoms of diabetic dementia. This is a serious condition of Ty2DM who have a risk of developing cognitive impairment. Alzheimer's disease (AD) can lead to dementia (DEM). In Ty2DM these conditions result from diabetic complications (43). DEM affects about 6% of elderly people and it is a main cause of disability and dependency. Therefore, identification of the risk factors and mechanisms of CD can help to develop new prevention and treatment methods (44).

There are different factors that correlate with DEM and DM. The rise and fall of blood glucose during the day could be linked to CD, independent of HbA1c and fasting plasma glucose (45). Because glucose is the major source of energy in neurons, low levels of glucose can damage the neurons and cause CD, which raises the incidence of DEM (46). low signals of insulin that reach the brain, known as InR, are linked to CD and DEM. This makes InR a potential therapeutic target for AD. Finally, chronic inflammation which is linked to Ty2DM, is regarded as the main cause of InR, and AD. Ty2DM affects the BBB, causing greater inflammation in the brain (47). OxS, atherosclerosis, amyloid β deposition, glycotoxins, dysregulation of fat metabolism, and mitochondrial (Mit) dys-function, are all considered contributors to CD in those with Ty2DM (48).

Recently, new insights into the CD associated with DM and DEM have been revealed and attempts directed to investigate the effectiveness of anti-diabetic agents in preventing CD in diabetic patients (49). With advancements in pharmacology, there are now many different options for lowering blood glucose levels, each with unique benefits. It is important to look at the efficiency of hypoglycemic drugs on diabetes-related CD and DEM, which are serious conditions for the elderly (50).

Anti-diabetics therapy and risk of cognitive dysfunction.

The low risk of Dem was largely associated with the use of metformin in Ty2DM patients (51). Metformin may reduce Dem risk, but the exact reasons remain unclear. It is believed to link the neuro-protective effect to the activation of AMPK dependent signaling in the brain (52). Metformin's capacity to resolve InR, resulting from rising tyrosine kinase activity, and increasing the expression of insulin receptors are other proposed mechanisms (53). In rats, metformin can enhance cognitive function with a significant decrease in OxS and inflammation in the brain (54). Metformin can also lower the formation of glycotoxins by enhancing glycemic control and scavenging glycotoxins (55). Moreover, it may reverse InR, enhance insulin signaling, and improve the metabolism of lipids (56). New studies suggest that metformin has an effect on gut microbiome composition, leading to an increase in InR and a decrease in tissue inflammation. (57). Nevertheless, disagreement exists regarding these findings. A baseline research proposed that the use of metformin over a long period may slightly increase the risk of developing AD and Dem through augmentation of beta-secretase transcription, leading to increase amyloid beta (Aβ)protein production which is crucial in AD onset. (58).

DPP4-inh has valuable features, such as low incidences of hypoglycemia and weight gain, which suggests that this medication can be beneficial for cognitive preservation (50) In a recent human clinical study, it was found that DPP4-inh has several favorable effects on neurodegenerative disorders in different mechanisms, such as the formation of Aβ plaque reduces due to the activity of GLP-1 and GIP, with reduced neuro-inflammation and OxS (59). DPP4-inh can safely be used in

CD, despite that currently marked drugs cannot pass through the BBB, the neuro-protective effects can be achieved indirectly through peripheral bioactivity. Omarigliptin, a novel DPP4-inh, that can penetrate the BBB, opens new possibilities for the development of treatments for neurodegenerative diseases (60).

Ty2DM patients can have double benefits from GLP-1 agonists. Additionally, to enhance glycemic control, some experimental evidence suggests that GLP-1 agonists can be associated with decreased CD in DM (61). Incretins can modulate positive cognitive function in different ways including suppression of inflammation, increased oxidation load, neuro-apoptosis, and Aβ or tau protein accumulation, or by increases in insulin signal transduction, neurogenesis, synaptic plasticity, and neuro-toxicity (62). SGLT2-inh can also be indicated for diabetic patients to prevent cognitive impairment by several direct and indirect effects, as shown in Figure 1 (63,64).

Figure 1: The influences of SGLT2-inh on CD. These inhibitors may help to improve cognitive impairment by reducing OxS, neuro-inflammation, levels of amyloid in the brain, and overall brain injury. They may also have a positive impact on the mTOR pathway, Mit function, insulin signaling, and vascular aspects. These are the possible core mechanisms.

Intranasal insulin (INI) is being studied as a potential management for CD related to Ty2DM. The administration of INI at a low dose over time improves delayed memory and preserves general cognition compared to acute administration at higher doses. (65). Another clinical study showed that systematic insulin therapy helps lower CD in patients with DEM (50). While high incidences of DEM occur in some Ty2DM patients treated with systemic insulin (66). Additionally, peripheral insulin use can lead to harmful effects on the brain due to its tendency to cause

hypoglycemia, where long-term episodes of hypoglycemia have been linked to an increased risk of DEM (67).

InR and inflammation can be improved by TZDs. Chronic use of TZD has a potential preventive effect against DEM in patients with Ty2DM. This protective effect could potentially aid in developing preventative measures for diabetic DEM (65). Additionally, pioglitazone only may have therapeutic benefits for AD in improving cognition (68).

Research on the impact of SUs on brain health is limited. However, available studies show no negative effects on cognitive function or increased risk of dementia (69). SUs may have a potential neuro-protective benefit and provide a protective effect compared to other diabetic medications (70).

Schizophrenia (SiZ)

SiZ is a mental disorder that affects people of all cultures, starting at an early age and causing misery for patients and families. SiZ is characterized by hallucinations, delusions, and disorganized thinking (71). Sadly, people with SiZ have a mortality rate two times higher than the general population and a shorter lifespan of 10 or 20 years (72). Although over 10% of excess mortality can be attributed to suicidal and other abnormal behavior, the increased comorbidity of medical illnesses in patients with SiZ also contributes to this excess mortality (73). SiZ patients are at greater risk for having Ty2DM. The incidence of Ty2DM in patients with SiZ is 2-3 times higher (6%-21%) than in the general population. (74).

The rise in Ty2DM cases among individuals with SiZ has several contributing factors. Both Ty2DM and SiZ share common causes. Lifestyle factors such as physical inactivity, unhealthy diet, smoking, and obesity all can contribute to evolve both conditions (75). On the other hand, SiZ also has specific risk factors such as lower socioeconomic status, cognitive impairment, and potential risks associated with antipsychotic treatments. Reduced hormonal regulation of appetite, characterized by low leptin and high insulin levels, is often present at the beginning of SiZ before starting with antipsychotic medicines (76). Genetic etiology plays an important role in pathogenesis, The risk of Ty2DM in patients with SiZ is raised 2-

4fold concerning a positive family history of diabetes (77). Figure 2 illustrates the main mechanisms for the association between SiZ and Ty2DM.

Figure 2: mechanisms underline the relation between SiZ and Ty2DM. SiZ and Ty2DM are linked due to factors such as poor diet, lack of physical activity, antipsychotic treatments, and shared genetic vulnerabilities and biological pathways. SiZ; schizophrenia, Ty2DM; type 2 diabetes mellitus.

Cognitive impairments are also a hallmark of SiZ. SiZ with comorbid DM has more cognitive impairments than those without DM or DM only. Diabetes risk factors such as hyperglycemia, InR, and lipid metabolic disorders can affect cognitive functions (78).

Many anti-diabetic drugs have been evaluated for their efficacy, tolerability, and compliance in preventing metabolic syndromes (obesity, diabetes, hypertension, and dyslipidemia) among psychiatric patients (79,80). The high degree of InR is linked with the severity of SiZ; therefore, oral glucose-lowering agents that boost the action of insulin in the brain provide favorable cognitive improvement options in Ty2DM and SZ. (81).

Anti-diabetic therapy and risk of Schizophrenia

There is evidence suggesting that metformin can improve psychiatric and cognition symptoms in schizophrenic patients (82). In SiZ, metformin may help reduce weight and InR in patients with antipsychotic therapy (83,84). Furthermore, metformin was shown to decrease the shift from pre-diabetes to diabetes (85), and in those with pre-diabetes and SiZ, the progression of Ty2DM can be delayed or inhibited using metformin (mainly in patients treated with olanzapine and clozapine, anti-psychotics that cause glucose dysregulation) (86).

Trial data for DPP4-inh in SiZ is currently unavailable. Useful data can be inferred from general population studies. The DPP4-inh, sitagliptin, and vildagliptin have cognitive improvement effects in SiZ patients through enhancing the incretin effect. (87). An analytical review showed that GLP-1 receptor agonists improve fasting

glucose and HbA1c and cause weight loss in SiZ patients on treatment who have body mass index > 25 kg/m² (88).

SGLT2-inh causes reducing toxicity of glucose, improving β cell function, decreasing oxidative damage and inflammation, and promoting weight loss which can improve sensitivity to insulin and glucose homeostasis. (89). Dapagliflozin can enhance the sensitivity of insulin in the brain, alleviate brain Mit dysfunction, preserve hippocampal synaptic plasticity, and reduce brain apoptosis and cerebral inflammation (90). However, there are no clear studies about the cognitive benefit of SGLT2-inh in SiZ. On the other hand, the risk of hypoglycemia that is associated with insulin, especially with increasing dose frequency, makes its use risky in SiZ patients (86). Also, because TZDs have a high risk of developing CVD and heart failure (91), besides their tendency to cause weight gain, they are not preferred to use in SiZ (86). Similarly, limited data are available for the effectiveness of SUs in SiZ patients. Nevertheless, because of their higher risk of weight gain and hypoglycemia (92), they are not the preferred option in SiZ.

Clinical implications of anti-diabetics on PsD

The importance of the collaboration between endocrinologists and mental health professionals was involved with the aim of this review. In terms of clinical implications, achieving the patient's benefit from the best choice of the right medicine for each condition separately. Accordingly, for diabetic patients with a high incidence of DEP disorder, their best choice is to start with a low dose of metformin as a first line treatment of diabetes. DPP-4 inh, GLP-1 agonist, and specifically SGLT2-inh can be used alone or in combination with metformin if glycemic control does not reach the target with metformin alone. All these anti-diabetic agents can reduce the chance of DEP in diabetic patients or alleviate the symptoms and progression of DEP compared to insulin, SUs, and high doses of metformin which are very risky in such conditions (93).

As mentioned, DEM is risky for diabetic patients due to CD and high glucose levels. So, it is important for an endocrinologist to avoid it as possible as he can. Glucose-lowering therapy and insulin signaling improvement can help preserve cognitive

function, but the effectiveness of diabetic medications in preventing DEM is still unclear. Despite SUs and TZDs are considered to be safe in preventing diabetic DEM (43,70). Metformin, DPP4-inh, GLP-1 agonists, and SGLT2-inh are the best choice for preserving cognition (50,64). Peripheral insulin is not recommended for a patient with a high incidence of DEM due to its serious side effect such as hypoglycemia (67).

Preserving cognition in diabetic patients with SiZ disorder is one of the most important points for saving a patient's life and prolonging longevity. Thus, prescribing the appropriate anti-diabetics drugs will prevent the high mortality rate among SiZ patients. Metformin is the first-line medication for treating Ty2DM in SiZ patients (82). Additionally, drugs with a low incidence of hypoglycemia and weight loss tendency, like GLP-1 receptor agonists, SGLT2-inh, and DPP4-inh are preferred choices as second-line medications for treating Ty2DM in SiZ patients. Table 1 summarizes the effects of anti-diabetic medications on PsD, some of them are positively affecting PsD but some are negatively affecting which are not the drug of choice for diabetic patients with such conditions.

CONCLUSION

PsD and DM are mutually connected in a bidirectional way, where one condition may have an impact on the other in various ways. Furthermore, there is still debate on how some diabetes medications affect psychological illness. While some of these medications have been significantly correlated with a lowered risk of psychological disorders, others have been shown to predispose to a higher likelihood of a variety of mental health issues, occasionally through mechanisms that proceed beyond their primary function. Accordingly, healthcare professionals need to be aware of the potential effects of some anti-diabetics on psychological condition; especially when prescribed to diabetic patients with previously determined mental of psychological illness.

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Table 1: The positive and negative impact of anti-diabetics on the incidence of DEP, CD, and SiZ.

Anti-diabetic agent	Risk of DEP	Risk of CD	Risk of SiZ
Metformin	-	-	-
DPP-4 inh	-	-	-
GLP-1 agonist	-	-	-
SGLT2-inh	-	-	-
Insulin	+	+	+
TZDs	-	-	+
SUs	+	-	+