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Type 2 diabetes mellitus and depression

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ABSTRACT
Type 2 diabetes mellitus (DM2) is a chronic non-communicable disease characterized by persistent hyperglycemia due to a deficiency in the synthesis and/or secretion of insulin by pancreatic b-cells, associated with other factors such as insulin resistance in peripheral tissues, hyperglucagonemia, increased hepatic gluconeogenesis, among others (American Diabetes Association, 2023; WHO, 2019). According to the International Diabetes Federation 2021, approximately 8.8% of the world's population of adult individuals has diabetes, of which 79% reside in developing countries. Following this projection, it is estimated that by 2045 around 628.6 million individuals will have the disease.

Keywords: Type 2 diabetes, Hyperglycemia, Public health.

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a chronic non-communicable disease characterized by persistent hyperglycemia due to a deficiency in the synthesis and/or secretion of insulin by pancreatic b-cells, associated with other factors such as insulin resistance in peripheral tissues, hyperglucagonemia, increased hepatic gluconeogenesis, among others (American Diabetes Association, 2023; WHO, 2019). According to the *International Diabetes Federation* 2021, approximately 8.8% of the world's population of adult individuals has diabetes, of which 79% reside in developing countries. Following this projection, it is estimated that by 2045 around 628.6 million individuals will have the disease.

A study conducted in 2017 pointed out that Brazil is the fourth country in the world with the highest number of individuals with the disease. Therefore, in view of the high global prevalence, it is extremely important that there is a mobilization aimed at disseminating information that has an impact on the lifestyle habits of individuals, leading to prevention attitudes, and better management and control of the disease in individuals already diagnosed, as it is a public health problem that impacts the number of hospitalizations and mortality. In 2015, the national average of spending on diabetes by the Unified Health System was US$ 2108 per individual (Javeed; Matveyenko, 2018; WHO, 2019; SBD, 2023).

The etiology of the disease has not yet been fully defined, but some factors have already been determined as a risk for its development. Pancreatic b-cells produce insulin, a hormone responsible for binding to cell receptors, generating a signaling cascade that recruits glucose transporters to the cell membrane, thus enabling the uptake of blood glucose. However, pancreatic b-cells have a low capacity

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for regeneration and the dysfunction of these cells is the main cause of the outcome of DM2. These alterations are associated with genetic factors, in most cases hereditary inheritance, and with environmental factors, such as lifestyle, dietary profile, sedentary lifestyle, epigenetic processes, and insulin resistance (Javeed; Matveyenko, 2018; SBD, 2023; MOREIRA *et al*., 2003).

Therefore, the decreased uptake of blood glucose causes damage both to the various cells of the body, which in the absence of glucose are not able to generate energy in their mitochondria, and to the blood vessels and organs that suffer damage to the vascular walls resulting from hyperglycemia. This situation leads to complications defined as macro and microvascular disorders that lead to the development of other diseases such as nephropathy, retinopathy, neuropathy, cerebrovascular disease, and peripheral arterial disease. Recently, it has also been associated with the onset of other conditions such as cognitive function and mental health (Javeed; Matveyenko, 2018; WHO, 2019; SBD, 2023; Moreira *et al*., 2003).

Regarding mental illnesses, depression is a psychiatric disorder characterized by mood changes resulting from cognitive, psychomotor and vegetative changes. According to the *Diagnostic and Statistical Manual* (DSM-III), the main symptoms are depressed mood, decreased interest and pleasure in activities, significant changes in weight and appetite, insomnia or hypersomnia, agitation or psychomotor retardation, fatigue, feelings of worthlessness or guilt, difficulty concentrating, indecision, and thoughts of death. Depressive disorder occurs when 5 or more of these symptoms occur within a two-week period, of which at least one of the symptoms is depressed mood and/or decreased interest in and enjoyment of activities. The causes of depression are still being studied, and the existing hypotheses are related to neurochemical alterations and neurotransmission systems (Spellman; Liston, 2020).

Recent studies associate diabetes with psychiatric aspects, due to the need to change routine and habits after diagnosis, and due to the microvascular and neurochemical changes that diabetes can cause. In view of the above, it is hypothesized that type 2 Diabetes Mellitus is related to the onset and/or worsening of depressive symptoms, which reinforces once again the importance of glycemic control, and the attention of health professionals in direct contact with these individuals regarding signs of depression, aiming to ensure the improvement and maintenance of patients' quality of life (Spellman; Liston, 2020).

OBJECTIVE

The objectives of this study were to conduct a narrative review on the relationship between type 2 diabetes mellitus and depression, and to describe and discuss the mechanisms that lead to the association between these diseases.

METHODOLOGY

This is a narrative-type scientific review work, carried out between the months of April and July 2023. Narrative review is characterized as a synthesis of evidence in the literature based on a descriptive and interpretative approach (GALVÃO, T. F., & PEREIRA, M. G, 2014). Data collection was performed using the following databases: US National Library of Medicine (NLM) – PubMed; Scientific Electronic Library Online – SciELO; and Google Scholar. For the search, the terms "type 2 diabetes", "glycemic control" and "depression" were used, as identified by the vocabulary of Health Sciences Descriptors – Decs, associated with the Boolean operators "and", "or", and "and not" for further refinement in the search.

Clinical trials and systematic reviews conducted in humans that related type 2 diabetes mellitus and depression were selected. Articles in English and Portuguese published in the last five years were included in the study. Articles that addressed type 1 diabetes, made use of animal models, or that were published in years prior to the ten-year period were excluded.

DEVELOPMENT

By using the descriptors in the databases, 65 articles were selected and, when applying the exclusion criteria, the total number of articles selected for review and discussion was 10. Of the selected articles, 8 are reviews, of which four are systematic reviews; an observational, cross-sectional and analytical study; and a cross-sectional study. Table 1 shows the selected papers with their respective titles, authors, journal of publication, methodology, and year of publication.

Depression is an emotional disorder that affects more than 300 million people worldwide, of which approximately 17 thousand are in Brazil (IBGE 2019). This figure represents 10.6% of the country's population, which is the first in number of diagnoses in Latin America, and the second in all of the Americas, behind only the United States (PAHO).

According to data from the *International Diabetes Federation* (IDF) 2021, 537 million people in the world have Diabetes, of which approximately 90% have Type 2 Diabetes Mellitus. In Brazil, approximately 16 million adults live with the disease (IDF 2021). Thus, it is suggested that approximately 10.6% of individuals with DM2 have depression, and that around 17% have mild to moderate depressive symptoms (Mukherjee; Chaturvedi, 2019).

Studies also state that individuals with type 2 diabetes mellitus are twice as likely to develop depression as the general population (Felisberto *et al*., 2017; Genis-Mendoza *et al*., 2022; Mukherjee; Chaturvedi, 2019), which would mean values between 24 and 30% of patients with diabetes (Nguyen *et al*., 2021; Pinho *et al*., 2021). However, the reasons that explain this relationship still remain under hypotheses, which require further investigation and assertive results.

Table 1. Data of selected articles

Title	Authors	Magazine	Methodology/ Year of publication
Depression in Type 2 Diabetes Mellitus or Type 2 Diabetes Mellitus in Depression? – A Review	Felisberto, V. *et al*.	Portuguese Journal of Diabetes	Revision/ 2017
Depressive symptoms and disorders in type 2 diabetes mellitus	Mukherjee, N.; Chaturvedi,S.	Current Opinion in Psychiatry	Revision/ 2019
Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression	Van Sloten, T. T. *et al*.	The Lancet Diabetes and Endocrinology	Review/ 2020
The Association among Glycemic Control and Depression Symptoms in Patients with Type 2 Diabetes	Hasanovic, E. *et al*.	Socio-medical matter	Cross-sectional study/ 2020
Depression in type 2 diabetes: A systematic review and meta-analysis of blood inflammatory markers	Nguyen, M. M. *et al*.	Psychoneuroendocrinology	Systematic Review and Meta Analysis/ 2021
Type 2 Diabetes Mellitus and Depression: Is there a relationship between these pathologies?	Pinho, S. *et al*.	Psychology, Health & Disease	Observational Study, Cross-Sectional and Analytical/ 2021
Psychiatric disorders as risk factors for type 2 diabetes: An umbrella review of systematic reviews with and without meta-analyses	Lindekilde, N. *et al*.	Diabetes Research and Clinical Practice	Systematic review//2021
Biopsychosocial and Nutritional Factors of Depression among Type 2 Diabetes Mellitus Patients: A Systematic Review	Amsah No.; M. D. S., J.; Ahmad, no.	International Journal of Environmental Research and Public Health	Systematic review//2022
Increased Levels of HbA1c in Individuals with Type 2 Diabetes and Depression: A Meta-Analysis of 34 Studies with 68,398 Participants	Genis-Mendoza, A. D. *et al*.	Biomedicines	Systematic review//2022

Bio-psycho-socio-environmental factors have been strongly associated with the outcome of depression in DM2 patients. Amsah; Md Isa and Ahmad (2022) developed a systematic review that evaluated 19 articles, seeking to point out biopsychosocial and nutritional factors. related to depression in patients with T2DM. The statistically relevant factors found were gender; age; the existence of chronic diseases other than diabetes; unsatisfactory sex life, since these patients are more prone to sexual dysfunctions; type of hypoglycemic treatment; individuals with DM2 complications such as neuropathy, nephropathy and retinopathy, their own fear of complications, denial of the diagnosis and dissatisfaction with the results of the treatment; also patients from emerging countries; low-income families, with low schooling, dietary pattern; sleep quality; inappropriate habits such as smoking and excessive alcohol use; loneliness from the absence of a partner and even divorce have been associated with a higher risk of depression in T2DM patients.

In general, women are more likely to develop chronic and metabolic diseases, such as T2DM (Nguyen *et al*., 2021). Pinho *et al*. (2021) observed in their observational, cross-sectional, and analytical

study in two Family Health Units (FHU) in Coimbra, Portugal, that women with diabetes were approximately three times more likely to have depression than men with this pathology; This result corroborates the findings of Siddiqui (2013) and Mukherjee and Chaturvedi (2019). The cross-sectional study by Hasanovic *et al*. (2020) with 150 adults from Sarajevo in Bosnia and Herzegovina, did not find a statistically significant result between gender and depression in individuals with DM2, but stressed that on a global scale the chance is twice as high that women with diabetes have depression.

Age is still a controversial factor, as various findings show different results. Amsah; MD Isa and Ahmad (2022) observed that women with T2DM under the age of 65 are more likely to have depression. This leads to the understanding that age and the aging process in individuals with DM2 are related to the onset of depressive symptoms and depression itself (Felisberto *et al*., 2017). On the other hand, Pinho *et al*. (2021), in their sample, did not find a statistically relevant value that would relate age to the onset of depression in individuals with DM2. They also highlighted the ambiguity of the results of studies sometimes showing a higher probability of depression in young patients and sometimes in the elderly.

There was evidence that BMI and the presence of other chronic diseases are related to the occurrence of depression in patients with type 2 diabetes (Amsah; MD Isa; Ahmad, 2022; Felisberto *et al*. 2017; Nguyen *et al*., 2021). As described by Felisberto et al. (2017), Hasanovic *et al*. (2020) observed in their sample a positive association between BMI and higher values related to depressive symptoms determined by the *Patient Health Questionnaire* (PHQ). Studies conducted in Brazil also showed a strong relationship between obesity and depression in these patients (Diderichsen, Andersen, 2019).

The occurrence of other comorbidities and chronic diseases, such as hypertension and heart disease, in general, have been reported to have a higher incidence of depression in individuals with DM2 (Amsah; MD Isa and Ahmad, 2022; Felisberto *et al*. 2017; Hasanovic *et al*., 2020). In addition to the aforementioned comorbidities, the existence of complications of DM2 and the fear of these complications were identified as predictors of a higher incidence of depression in these patients (Amsah; MD Isa and Ahmad, 2022; Pinho *et al*., 2021,Genis-Mendoza *et al*., 2022.

The time since diagnosis of diabetes seems to be associated with the onset of depressive symptoms (Genis-Mendoza *et al*., 2022). Hasanovic *et al*. (2020) and Pinho *et al*. (2021) did not observe significant associations between these factors in their samples; However, it is worth noting that these are cross-sectional studies and that their samples may demonstrate a possible local impact, however they may not necessarily reflect the global panorama. Reddy *et al*. (2010) observed a strong connection between the occurrence of depressive symptoms in individuals diagnosed with T2DM 5 years ago or more.

Mukherjee and Chaturvedi (2019) also report this correlation, however, they observed the predominance of depression in newly diagnosed patients, progressing to a decrease in cases over time,

followed by a new increase after long-term diagnoses due to greater chances of diabetes complications. They also highlighted the occurrence of cases in which patients remain for an indeterminate period, often for more than years, presenting gradual signs of improvement or worsening, but do not completely recover from depression.

The diagnosis, the changes in routine and habits acquired after the diagnosis, the acceptance of the disease, the type of treatment, the dissatisfaction with the results of the treatment and the possible appearance of complications cause suffering and stress to both newly diagnosed and long-term patients. These consternations have recently been conceptualized with the term *Diabetes Distress*. *Diabetes Distress* is defined by Fisher *et al*. (2012), such as: "unique emotional burdens and often hidden concerns that are part of the spectrum of the patient's experience when managing a serious and demanding chronic disease such as diabetes" and can easily be confused with depression in both definition and diagnosis, and is present in the Diabetes-Depression relationship (Wardian *et al*., 2019). However, *Diabetes Distress,* when not welcomed and properly supported, can generate depressive symptoms, evolving to depression itself (Mukherjee; Chatuvedi, 2019).

Diabetes distress and depression are also related to the type of hypoglycemic treatment being used by the patient. Individuals on more incisive oral hypoglycemic therapy, with various classes of medications, and more severe dietary restrictions tended to show more depressive symptoms when compared to individuals on milder treatment (Mukherjee; Chaturvedi, 2019). In agreement with this finding, Hasanovic *et al*. (2020) also demonstrated, in a research sample, that patients on insulin therapy obtained higher scores on the *PHQ-9 depression screening tool*, demonstrating a higher incidence of depressive symptoms. It is worth noting that the conduct of the professional prescribing diabetes control therapy is determined based on their technical knowledge, the severity of the patient's health condition and their peculiarities. Therefore, more intense treatments should not be disregarded, but the doctor should be aware of the signs of stress and depressive symptoms.

A previous history of depression also becomes a risk factor for recurrence after the diagnosis of T2DM. This is due, in addition to the possible recurrence of the disease, to the characteristics of the disease that affect several areas of the individual's life, such as diminished self-care that leads them not to feel the need to develop healthy habits, reflecting in losses in adherence to DM2 treatment (Felisberto *et al*., 2017; Mukherjee; Chaturvedi, 2019); changes in appetite and food choices. Greater affinity for foods rich in saturated fat has been reported in patients with depression and T2DM; as well as a low-protein, high-fat and high-calorie diet, and high sugar intake (Amsah; MD Isa; Ahmad, 2022; Mukherjee; Chaturvedi, 2019 Nguyen *et al*., 2021).

A sedentary lifestyle is also related to glycemic control, and the practice of physical exercise plays a role in the prevention and improvement of depressive symptoms and depression (Amsah; MD Isa;

Ahmad, 2022; Mukherjee; Chaturvedi, 2019; Nguyen *et al*., 2021). However, excessive and very intense physical exercise can cause fatigue, which appears to be a predictor of depressive symptoms, in addition to causing lower adherence to activities, which can affect diabetes control (Amsah; MD Isa; Ahmad, 2022; Mukherjee; Chaturvedi, 2019).

Regarding social factors, chronic diseases, in general, are more recurrent in developed countries, with evidence in diabetes, which is one of the most prevalent chronic diseases (Felisberto *et al.*, 2017; Pinho *et al*., 2021). However, DM2 has shown a considerable increase in developing countries (Amsah; MD Isa; Ahmad, 2022). Low income, unemployment, and lower level of education also contribute to the emotional outcome, since diabetes inevitably requires financial expenses for treatment and follow-up; and a low level of education makes it difficult to understand the disease, its importance and treatment scheme, changing habits, among other inherent issues (Hasanovic *et al*., 2020; Mukherjee; Chaturvedi, 2019).

Sexual problems can be related to both diseases, and have been correlated, among others, to marital problems, and consequently to divorce and loneliness. All of these factors have been determined as possible triggers for depressive symptoms (Amsah; MD Isa; Ahmad, 2022; Hasanovic *et al*., 2020).

The literature points to evidence that both diseases share the same pathophysiological mechanisms, such as inflammatory processes and their biomarkers, alterations in the hypothalamic-pituitary-adrenal (HPA) axis, macro and microvascular dysfunctions, and insulin resistance. This reinforces the conception that the relationship between DM2 and depression is bidirectional (Mukherjee; Chaturvedi, 2019; Nguyen *et al*., 2021; Pinho *et al*., 2021; Van Sloten *et al*., 2020).

The hypothalamic-pituitary-adrenal axis is responsible for the production of the hormone cortisol and changes in the axis are directly associated with depression and diabetes, which leads to consequent hypercortisolemia. The high concentration of cortisol causes an increase in circulating glucose, free fatty acids, insulin resistance, and inflammation. In excess, the hormone also impairs hippocampal neurogenesis, a region that encompasses the limbic system that is responsible for regulating emotions, implying the outcome of depression. Changes in the circadian cycle have also been pointed out as a factor in this relationship, since, when dysregulated, it can interfere with the production and release of cortisol (Felisberto *et al*. 2017; Mukherjee, Chaturvedi, 2019; Pinho *et al*., 2021).

Insulin and its signaling play a role in neuromodulation, neuroprotection, neurotransmission, prevention of apoptosis, reduction of inflammation, maintenance of serotonin levels and monoamine oxidase (MAO) activity, so insulin resistance, due to changes in neuronal function, plays a role in the onset of depressive symptoms (Mukherjee, Chaturvedi, 2019). Felisberto *et al.* (2017) also highlight that in healthy individuals, it has been noted that the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis can occur by cytokine-mediated inflammatory processes, generating oxidative stress and consequent

decrease in serotonin synthesis, resulting in the pathophysiology of depression.

The action of the immune system and the inflammatory state also help to clarify the link between diabetes and depression. Blood concentrations of certain inflammatory markers are usually moderately increased in both disorders alone, especially in diabetes, given the pro-inflammatory characteristics of hyperglycemia and insulin resistance. However, the findings show that the levels of these markers are considerably increased in individuals with both pathologies when compared to those diagnosed with only one of them (Felisberto *et al*., 2017; Nguyen *et al*., 2021).

Interleukin 6 (IL6) has been shown to be increased in DM2 patients, and at increased levels, it interferes in the long term with neurotransmission, neurogenesis and neuroplasticity and, according to findings, has been shown to be related to the reduction of the prefrontal cortex, possibly explaining the pathogenesis of depression. IL6 has also been shown to be associated with biopsychosocial factors such as Body Mass Index (BMI), diet, sedentary lifestyle, smoking, which are in themselves predictors of both DM2 and depression (Nguyen *et al*., 2021).

CD40, a protein of membrane and cells of the immune system and also of the vascular wall, has been found to be increased in patients with diabetes and depression. The signaling of its ligands, coming from adipose tissue cells, causes an increase in the synthesis of tumor necrosis factor (TNF) and IL6, being a possible explanation for the pattern of systemic inflammation in individuals with diabetes and depressed individuals (Felisberto *et al*., 2017; Nguyen *et al*., 2021).

Brain-derived neurotrophic factor (BNDF) is a neurotrophin of great importance that is part of processes of modulation of plasticity, growth, differentiation, synapse and repair of neurons in the hippocampus and prefrontal cortex region. And, in addition to the other factors already discussed, findings indicated a decreased concentration of BNDF in processes of intense inflammatory state, which results in depression (NGUYEN *et al*., 2021). C-reactive protein (CRP), a marker of inflammation, is considered a vascular risk factor, consequently, it is a risk factor for individuals with DM2 and/or depression (Felisberto *et al*., 2017; Nguyen *et al*., 2021).

Van Sloten *et al*. (2020), in a review article, described the cerebral microvascular dysfunctions in type 2 diabetes that cause increased permeability of the blood-brain barrier, resulting from hyperglycemia, insulin resistance, increased cytokines, and inflammatory mediators. These dysfunctions also aggravate the entry of inflammatory molecules and white blood cells, causing damage to brain tissue; reduction of vasoreactivity and, consequently, a deficient cerebral perfusion, which also implies insufficient oxygenation; in addition to the reduction of self-regulation, also related to cytokines and inflammatory mediators. Among other consequences of these dysfunctions, atrophy of the hippocampal region, which is commonly found in patients with depression, has been consistently related to T2DM.

In addition, insulin resistance decreases the internalization of glucose, which is the main energy

source of brain cells, causing their functions to be compromised. Hyperglycemia is pointed out as a reason for the malfunction of endothelial cells and increased formation of glycation end products (EFA's), which cause oxidative stress and the synthesis of pro-inflammatory cytokines. All of these changes were related to the outcome of depression (Mukherjee; Chaturvedi, 2019; Nguyen *et al*., 2021; Van Sloten *et al*., 2020).

Findings also indicated that certain indicators of the diabetes-depression relationship were already detectable during prediabetes, and that it would already be a possible factor for the occurrence of this association, if the disease were to become established. The period called prediabetes by some authors occurs when the values of glycemic and metabolic control markers are considerably altered, but are still not sufficient for the final diagnosis of diabetes. Prediabetes is usually characterized by a phase of insulin resistance followed by a compensatory increase in hormone release, however unable to resolve insulin resistance, leading to consequent loss of β cell function (Felisberto *et al*., 2017). Van Sloten *et al*. (2020) also pointed out that related cerebral microvascular processes may begin well before the diagnosis of diabetes, contributing to mental and mood changes not only during, but for a long time preceding the disease.

Hasanovic *et al*. (2020) observed a significant correlation between high glycated hemoglobin (HbA1c) values and higher scores of the *Patient Health Questionnaire* (PHQ) in the patients evaluated, evidencing once again that uncontrolled glycemic control increases the chances of depression. The data is in agreement with the systematic review by Genis-Mendoza *et al*. (2022) who observed higher HbA1c values in patients with diabetes and depression than in those with diabetes alone. Felisberto *et al*. (2017), Mukherjee and Chaturvedi (2019) and Pinho *et al*. (2021) also got the same response.

Increased HbA1c and depressive symptoms were also more present in patients less than 10 years after diagnosis. Individuals with good adherence to drug treatment often continue to have a lack of metabolic control, which is reflected in glycated hemoglobin values, thus Genis-Mendoza *et al*. (2022) highlighted that the treatment of depressive symptoms can be of great value in the results of diabetes treatment.

Mukherjee and Chaturvedi (2019) pointed out that genetic factors can relate depression to diabetes. According to their findings, 34 polymorphisms in several chromosomes were associated with diabetes, and a higher count of these polymorphisms was related to depression.

As seen, several consequences can occur when there is no adequate treatment of one disease to the detriment of the other. Therefore, the treatment of both diseases is of great value for a general improvement of the patient's physical and emotional health. For both, early diagnosis and treatment is extremely important for the prevention of aggravations, complications, and the chance of a better response to interventions.

As for diabetes, the initial drug treatment for type 2 initially consists of oral hypoglycemic agents that stimulate pancreatic insulin production, such as biguanides and sulfonylureas, alone or in combination, and when the results are unsatisfactory (Brasil, 2020), concomitant use is made with insulin therapy. However, authors raise evidence of the use of other medications. Genis-Mendoza *et al*. (2022) suggest the use of GLP-1 agonists such as dulaglutide and semaglutide, and dipeptyl-peptidase-4 (DDP-4) inhibitors such as sitagliptin, vidagliptin, and saxagliptin. In addition to these medications, Mukherjee and Chaturvedi (2019); Nguyen *et al*. (2021) and Van Sloten *et al*. (2020) raise the proposal for the intranasal use of insulin and insulin-like growth factor 1 (IGF-10) and insulin sensitizers.

Van Sloten *et al*. (2020) explain that the use of intranasal insulin favors the improvement of cerebral microvascular factors, since this means of administration passes directly through the blood-brain barrier. Nguyen *et al*. (2021) raise the issue that it is already seen that high CRP values in individuals with type 2 diabetes and depression and, therefore, it is of great value to study a possible antidepressant effect in anti-inflammatory drugs.

Depression is as complex as diabetes when it comes to intervention. First, because it is often underdiagnosed because the symptoms are similar to those of *Diabetes Distress*, especially after the beginning of treatment, and especially because of the lack of professionals properly prepared to identify depressive signs and symptoms, especially in DM2 patients (Felisberto *et al*., 2017; Pinho *et al*., 2021). Thus, it is pertinent to differentiate the diagnosis of depression according to the DSM-IV criteria, thus allowing a more appropriate choice of treatment according to the patient's needs, often avoiding drug treatments that would obtain satisfactory results with psychological intervention (Mukherjee; Chaturvedi, 2019).

Cognitive-behavioral therapy (CBT), for example, has been shown to be effective in treating depressive symptoms. CBT with protocols specifically aimed at patients with diabetes, in which therapists underwent specialized training for the care of DM2 patients, showed results as effective as traditional CBT, in addition to better glycemic and dietary control results, and lower insulin resistance (Felisberto *et al*., 2017; Mukherjee; Chaturvedi, 2019).

Pharmacological treatment can often be indispensable for an effective treatment of depression. Selective serotonin reuptake inhibitors (SSRIs) are usually the first and main indication because they are associated with decreased insulin resistance and HbA1c, and weight loss, especially escitalopram, sertraline, and fluoxetine (Felisberto *et al*., 2017; Genis-Mendoza *et al*., 2022; Mukherjee; Chaturvedi, 2019). Bupropion, which is a dopamine reuptake inhibitor, and agomelatine, which is a selective serotonin reuptake inhibitor (SSRI) and melatonin receptor agonist, also have such benefits in addition to being less associated with sexual dysfunction when compared to other classes of antidepressants. Tricyclic antidepressants and monoamine oxidase (MAO) inhibitors should be avoided as much as

possible in these patients since they are characterized by insulin resistance, hyperglycemia, and weight gain (Felisberto *et al*., 2017; Mukherjee; Chaturvedi, 2019).

Thus, it is considerable to state that there is a relationship between diabetes and depression, and that this relationship is bidirectional. This association is explained by several factors that demonstrate that this correlation is not only causal, but can also result from the same pathophysiological mechanisms in both diseases, such as inflammatory processes and their biomarkers, alterations in the hypothalamic-pituitary-adrenal (HPA) axis, macro and microvascular dysfunctions, and insulin resistance.

Sex; age; the existence of chronic diseases other than diabetes; unsatisfactory sex life; type of hypoglycemic treatment; complications of DM2, fear of complications, denial of diagnosis, and dissatisfaction with treatment results; patients from emerging countries; low-income families, with low schooling, dietary pattern; sleep quality; inappropriate habits such as smoking and excessive alcohol use; loneliness from the absence of a partner and even divorce are associated with a higher risk of depression in T2DM patients.

FINAL THOUGHTS

It is inevitable that there is a relationship between type 2 diabetes mellitus and depression, whether it is a causal, bidirectional or inter-pathophysiological mechanisms. However, the search for answers that guide the elucidation of questions and problems related to the relationship between these two pathologies is still under the responsibility of academia and health professionals; since they cause great physical and emotional suffering, and in isolation are matters of public health responsibility. This work was intended to be part of this search through a small compendium of findings and information, highlighting elucidated discoveries and still open questions.

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