https://doi.org/10.31925/farmacia.2024.6.6 **ORIGINAL ARTICLE**

SERUM SEROTONIN LEVEL CAN BE USED AS A PREDICTIVE MARKER FOR DEPRESSION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS. TRUE OR FALSE?

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Abstract

The possible connection between serum serotonin levels and depression in individuals with type 2 diabetes mellitus (T2DM) has gained considerable interest. By examining HAM-D scores, glycated haemoglobin (HbA1c) levels and serum serotonin in T2DM patients receiving antidiabetic medication, with or without antidepressant treatment, we aimed to assess how medication influences depressive symptoms, considering serum serotonin as a possible marker for depression. Our findings indicate that antidiabetic medication, particularly metformin, contributed to an improvement in depression symptoms, its effects-both antidiabetic and antidepressant-being enhanced when combined with an antidepressant. However, these improvements were not correlated with serum serotonin levels, which showed high variability even within the same group of patients. Consequently, our study does not support the use of serum serotonin as a predictive marker for depression in T2DM patients, as numerous other factors, including metabolic abnormalities, insulin resistance and inflammation, impact both conditions.

Rezumat

Posibila legătură între valoarea serotoninei serice și depresie, la persoanele cu diabet zaharat de tip 2, a câștigat un interes considerabil. Prin examinarea scorurilor HAM-D, a nivelurilor de hemoglobină glicată (HbA1c) și a serotoninei serice la pacienții cu T2DM care urmează tratament antidiabetic, singur sau în asociere cu antidepresive, ne-am propus să evaluăm modul în care medicația influențează simptomatologia specifică depresiei, luând în considerare serotonina serică ca posibil marker al depresiei. Rezultatele studiului nostru indică faptul că medicamentele antidiabetice, în special metformina, contribuie la ameliorarea simptomelor depresiei, efectele sale - atât antidiabetice, cât și antidepresive - fiind potențate de medicația antidepresivă. Cu toate acestea, aceste observații nu au putut fi corelate cu valorile serotoninei serice, care au prezentat o variabilitate ridicată chiar și în cadrul aceluiași grup de pacienți. În consecință, studiul nostru nu sprijină utilizarea serotoninei serice ca marker predictiv pentru depresie la pacienții cu DZ2, deoarece numeroși alți factori, inclusiv anomalii metabolice, rezistența la insulină și inflamația, influențează ambele patologii.

Keywords: serum serotonin, depression, type 2 diabetes mellitus, glycated haemoglobin

Introduction

The rising prevalence of chronic conditions poses a significant challenge for health systems globally. The coexistence of multiple chronic conditions often leads to a reduced quality of life and diminished patient functioning [1]. Diabetes mellitus is a disorder marked by glycaemic disturbances due to impaired insulin secretion, the development of peripheral insulin resistance, or both [2]. Most individuals with T2DM also have at least one additional condition that can affect both the management and progression of diabetes.

Piette JD and Kerr EA classified diabetes-related chronic conditions into concordant and discordant [3]. This classification has guided the management of T2DM alongside multiple coexisting morbidities. Concordant comorbidities, such as renal diseases and cardiovascular and metabolic disorders, share similar underlying pathophysiological mechanisms and often require integrated care management with T2DM. For instance, managing blood pressure and lipid levels is crucial for diabetes and cardiovascular disease [4].

Diabetes discordant comorbidities are conditions that do not share the same management, such as asthma,

cancer and psychiatric disorders like depression [5, 6]. Managing these discordant conditions can complicate or counteract chronic antidiabetic treatment. For instance, steroids used to manage asthma may elevate blood glucose levels, while depressive symptoms may reduce a patient's adherence to diabetes self-care [7]. Such conflicting priorities can lead to poorer care outcomes than managing concordant or single conditions. Delayed identification of discordant conditions can negatively impact diabetes management, leading to complications and increasing healthcare costs [8].

Among discordant chronic conditions for T2DM, depression is particularly significant. Research has consistently shown that depression is more prevalent in individuals with diabetes. According to Jones BDM *et al*., patients with T2DM are twice as likely to have major depressive disorder and up to 30% more likely to have symptoms of depression [9].

Diabetes-associated depression remains an under-researched area despite its notable impact on the progression of T2DM. From a neuropathological point of view, a potential link between these conditions involves changes in monoaminergic neurotransmission within specific regions of the central nervous system, particularly the serotonergic system. These changes may lead to mood and behaviour alterations that diminish patients' life quality and can negatively impact the disease evolution [10].

The chemical imbalance theory of depression, particularly the serotonin hypothesis, is widely recognised and has been a focal point in depression research [11-13]. This perspective suggests that depression results from abnormalities in serotonin or other neurotransmitters (norepinephrine, dopamine) levels [14, 15]. Still, it is superficial and can affect the decision to initiate or to continue an antidepressant treatment, sometimes leading to prolonged or lifelong medication use [16, 17].

For a long period of time, depression and diabetes were considered two entirely separate conditions, with research primarily focusing on distinct pathophysiological mechanisms for each. However, recent studies are re-evaluating the comorbidity of these disorders, exploring them together to identify a unified therapeutic target that could effectively address both [10]. Numerous studies have investigated the link between depression and the onset of T2DM [18], proposing several potential explanations for this association.

First, depression may play a direct role in the development of diabetes. Psychological stress and depressive symptoms may be linked to T2D through various pathways. In some cases, depression emerges in adolescence or early adulthood [19, 20], followed by the onset of T2DM later in life [19, 21]. Depressive symptoms are linked to an increased inflammatory state, resulting in elevated inflammatory markers that are also risk factors for diabetes [22]. Moreover, systemic inflammation is linked to elevated stress hormone levels that also promote insulin resistance, representing another pathway connecting depression and T2DM [23, 24].

During a major depressive episode, the hypothalamic-pituitary-adrenal (HPA) axis becomes activated, leading to increase the levels of circulating hydrocortisone. Bjorntorp P proposed that stress causes a specific pattern of fat distribution-central adiposity, which may serve as the connection between stress and diabetes [25]. Furthermore, the Bjorntorp hypothesis suggests that excessive activity of the HPA axis and heightened sympathetic status contribute to metabolic syndrome and insulin resistance in T2DM [26]. In individuals with depression, T2DM may be linked to lifestyle behaviours, including poor health habits, increased caloric intake, excess weight, physical inactivity and smoking, as well as the effects of antidepressant medications, rather than being directly caused by depression itself [27]. When examining the relationship between these two conditions, it is important to consider that antidepressants often lead to weight gain, which can contribute to the development of T2DM [23, 28]. Fortunately, in patients experiencing depressive symptoms, the presence of T2DM may be identified earlier due to frequent visits to the physician's office [29-31].

Secondly, it is acknowledged that diabetes is frequently associated with elevated levels of stress. Patients with T2DM experience significantly higher rates of depression and anxiety compared to the general population [32]. Epidemiological studies indicate an increased risk of depression in individuals with T2DM [33]. Glycated haemoglobin (HbA1c) level has been significantly associated with the development of depression, with higher HbA1c levels increasing the risk of depression. Additionally, intensive glycaemic control has been shown to reduce the risk of diabetic complications and may also play a crucial role in preventing depressive symptoms [34].

Thirdly, hyperglycaemia and hyperinsulinemia are associated with a reduction in serotonergic neuro-transmission, which is crucial for regulating mood and cognition [35].

Considering these three biological pathways – insulin resistance, hyperglycaemia and increased inflammation – that demonstrate the bidirectional relationship between T2DM and depression, and noting that some antidiabetic medications affect these pathways, antidiabetic medications have been explored as potential treatments for depression in patients with diabetes. This approach also offers a solution for reducing polypharmacy [36, 37].

The study's purpose is to evaluate whether there is a correlation between serum serotonin levels, glycated haemoglobin values (as a marker of glycaemic control), and the severity of depression. Additionally, the study aims to assess whether these biochemical parameters are influenced by the type of antidiabetic medication used and the antidepressant treatment administered.

Materials and Methods

Study design

The prospective study was conducted between June and December 2023. One hundred and ten participants were included in the study, and they were divided into three groups based on their medical conditions and treatments.

Participant Selection and Group Assignment.

Group C (Control Group, n = 33): healthy individuals without a diagnosis of diabetes or depression. Group 1 (n = 34): patients with type 2 diabetes mellitus (T2DM) who had been on antidiabetic medications (metformin or others) for at least two years but were not receiving antidepressant treatment. Group 2 (n = 43): patients with T2DM who had been undergoing antidiabetic treatment (metformin or other medications) for at least two years and were also receiving antidepressant treatment.

The exclusion criteria were malignant tumours, type 1 diabetes or gestational diabetes, advanced cardiovascular disease, kidney disease, moderate or severe anaemia, severe neurocognitive disorders or psychiatric diseases (schizophrenia, bipolar disorder), and patients who could not sign the consent form for each investigation performed.

Ethical considerations

The study was carried out with the consent of the Scientific Research Ethics Committee of "G.E. Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mures, Romania, (decision No. 2056/26.01.2023).

Sample and data collection and preparation

Serum serotonin levels exhibit meal-related diurnal fluctuations, with the highest levels observed early in the morning [38]. Following food ingestion [39], two blood samples were collected from each patient in the morning after an overnight fast. One sample was collected in tubes containing a clot activator, centrifuged to separate the serum, and stored at -20°C before the analysis. The second samples sample was collected on EDTA and stored at 2 - 8°C until analysis.

The samples were analysed using standard analytical methods at a local health clinic. To assess the serum serotonin levels, serum samples were analysed using high-performance liquid chromatography (HPLC). At the same time, glycaemic control was evaluated by determining the HbA1c value [40] from whole blood samples collected in EDTA tubes using an ion-exchange HPLC method. According to the medical results, the standard reference ranges were 4.8 - 6.0% for HbA1c and 40 - 200 µg/L for serotonin.

The assessment of depression severity at the time of blood sampling was mandatory. In this regard, the psychiatrist used a standardised depression rating scale, the HDRS (HAM-D) scale, consisting of 17 items and which assesses the symptoms of depression in the previous week [41].

Statistical analysis

Descriptive statistics assessed the data's frequency, percentage, mean, median and standard deviation. The Shapiro-Wilk test evaluated the distribution of the data sets under consideration. For comparing two data sets with a Gaussian distribution, the unpaired Student's t-test was employed; for non-Gaussian distributions, the Mann-Whitney test, a non-parametric method, was used. When comparing more than two non-Gaussian data sets, the Kruskal-Wallis test was applied, along with the Dunn test for multiple comparisons. The Chi-squared test was used to evaluate the association between qualitative variables. Multiple linear regression was performed to examine the relationship between several predictor variables and the outcome variable. A significance threshold of 0.05 was established for the p-value. The statistical analysis was conducted using version 29.0 of the SPSS software trial (SPSS, Chicago, IL, USA).

Results and Discussion

The three groups were homogeneous regarding gender distribution, with no statistically significant differences observed, as presented in Table I.

Table I

Gender Distribution Between Groups

	T2DM patients without antidepressant treatment	T2DM patients with antidepressant treatment	Control	p
Feminine	19 (55.88%)	22 (51.16%)	15 (45.45%)	0.6940
Masculine	15 (44.12%)	21 (48.84%)	18 (54.55%)	
Total	34 (100.00%)	43 (100.00%)	33 (100.00%)	

Patients with depression who were undergoing chronic treatment were prescribed either duloxetine (58.14%) or venlafaxine (41.86%). For managing T2DM, they were treated with metformin (51.95%) or other anti-diabetic medications (48.05%).

Both antidepressants inhibit the reuptake of nor-epinephrine and serotonin from the synaptic cleft, which increases the concentration of these neuro-transmitters and explains their beneficial effects in alleviating the symptoms of depression [42, 43]. Although, venlafaxine is classified as a serotonin (5-HT) and norepinephrine reuptake inhibitor, it primarily inhibits serotonin transporters at therapeutic doses; significant inhibition of norepinephrine reuptake occurs only at higher doses [43]. Serotonin, a monoamine with various functions in both neuronal and non-neuronal

systems, is involved in the dynamics of depressive affective disorders and helps regulate mood and eating behaviours [44].

In addition to inhibiting serotonin transporters in the central nervous system, serotonin reuptake inhibitors also affect serotonin transporters (SERT) activity in the periphery, particularly in blood platelets, leading to increased blood serotonin levels. Typically, platelets take up plasma serotonin, which is stored and released as needed [45].

Serotonin is believed to regulate pancreatic β-cell proliferation and insulin secretion [46], and it has even been linked to glucose regulation [47]. Pancreatic β-cells produce serotonin during two critical physiological conditions of β-cell proliferation: the perinatal period and pregnancy. Serotonin is stored in the same vesicles as insulin and has been linked to regulating blood glucose levels [47, 48].

Although literature data are controversial, Wium-Andersen IK *et al*. in a comparative analysis of data from 232,707 patients (116,699 of whom had a T2DM diagnosis), concluded that patients with T2DM have an elevated risk of depression. Furthermore, he found that antidiabetic medication may reduce this risk [36].

Our study confirmed these findings. Table II summarises the comparative data, indicating that both antidiabetic and antidepressant treatments show lower HAM-D scores, better glycaemic control (lower HbA1c) and higher serotonin levels than those not receiving antidepressant treatment.

Table II

Comparison of HAM-D scores, HbA1c [%] and serotonin levels in T2DM patients with and without antidepressant treatment

Parameter	T2DM patients without antidepressant treatment (n = 34)	T2DM patients with antidepressant treatment (n = 43)	p
HAM_D	24.06 ± 2.29	16.33 ± 3.17	< 0.0001
HbA1c (%)	6.52 ± 0.92	5.73 ± 0.74	< 0.0001
Serotonin (µg/L)	25.23 ± 19.24	47.46 ± 54.65	0.1107

Although serum serotonin levels (as shown in Table II) were not statistically significantly different between the experimental groups, Table III highlights that serum serotonin levels tend to be higher in patients treated with duloxetine compared to those treated with venlafaxine, potentially reflecting duloxetine's more potent inhibition of serotonin reuptake.

Table III

Comparison of serum serotonin levels in relation with the antidepressant used

	Duloxetine (n = 25)	Venlafaxine (n = 18)	No treatment (n = 34)	p
Serotonin (µg/L)	61.62 ± 66.05	27.79 ± 22.69	25.23 ± 19.24	0.0030
Dunn's Multiple Comparison Test	✓	✓	X	0.0438
	✓	X	✓	0.0035
	X	✓	✓	0.7364

Among oral antidiabetic drugs, studies have indicated that metformin, unlike other agents, has additional favourable effects on patients' mental health. Metformin is widely regarded as a preferred treatment due to its combined antidiabetic and antidepressant effects and is currently the first-line pharmacological therapy for T2DM [49, 50]. It decreases hepatic gluconeogenesis, enhances insulin sensitivity, reduces intestinal glucose absorption and promotes peripheral glucose uptake [51, 52].

Possible neuroprotective mechanisms of metformin, as reported in the literature, include increasing serotonin and norepinephrine levels in the central nervous system (CNS), stimulating AMP-activated protein kinase (AMPK) to reduce reactive oxygen species production, and inhibiting serotonin reuptake from the synaptic cleft [53, 54]. Additionally, numerous studies indicate that T2DM and depression share common biological mechanisms, including an overactive immune response marked by elevated levels of interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) and C-reactive protein (CRP). These pro-inflammatory cytokines can impact serotonin levels by promoting the breakdown of its precursor, tryptophan, through the activation of indoleamine 2,3-dioxygenase [55, 56]. Metformin's neuroprotective properties – anti-inflammatory, anti-apoptotic and antioxidant – have demonstrated anti-depressant effects in diabetic patients with depression and may boost cognitive function by inhibiting cytokine production and increasing serotonin levels [56, 57].

By promoting serotonergic neurotransmission, this antidiabetic drug could potentially enhance the efficacy of antidepressants that increase serotonin levels in the central nervous system, either by inhibiting its reuptake, reducing its metabolism, or through receptor-mediated mechanisms [58-60].

In our patients, although the differences in plasma serotonin levels were not statistically significant between those who received metformin and those treated with other antidiabetic drugs (AD), there was a statistically significant difference in the median values of HAM-D scores. The HAM-D score was lower in the metformin-treated group, both in patients receiving or not receiving antidepressants. Furthermore, a potentiation of metformin's

antidiabetic effect was observed with concurrent antidepressant administration, reflected in a statistically significant reduction in HbA1c levels (Table IV).
The analysis of data correlations revealed that HbA1c levels fluctuate based on both treatments (antidepressant and antidiabetic, $r^2 = 0.263$). Additionally, changes in HAM-D scores are influenced by the antidepressant ($r^2 = 0.337$), with statistically significant lower HAM-D scores being observed in patients treated with duloxetine and venlafaxine ($p < 0.01$).

Table IV

The influence of metformin on the HAM-D score, serum serotonin level and HbA1c in patients with treated and untreated depression

Parameter	Treated depression			Untreated depression		
	Metformin (n = 23)	Other AD (n = 20)	p	Metformin (n = 17)	Other AD (n = 17)	p
Serotonin (µg/L)	67.31 ± 67.84	24.64 ± 15.72	0.0625	25.65 ± 17.42	24.81± 21.43	0.6794
HAM-D	14.43 ± 2.64	18.50 ± 2.19	< 0.0001	23.12 ± 2.12	25.00 ± 2.12	0.0144
HbA1c (%0	5.34 ± 0.42	6.17 ± 0.79	0.0003	6.35 ± 0.60	6.68 ± 1.15	0.5690

Serum serotonin levels increased in subjects receiving antidepressant treatment, though this was not statistically significant ($p = 0.0567$). Additionally, plasma serotonin concentrations varied widely between individuals, even those on the same treatment regimen.

Conclusions

While serotonin is known to play a key role in mood regulation, its relationship with depression in diabetic patients is complex. Some studies suggest that lower serotonin levels may be associated with increased depressive symptoms and that it can be used as a predictive marker for depression. Our findings show that metformin improves depressive symptoms, even when administered on its own. Additionally, anti-depressants enhance glycaemic control in patients on long-term antidiabetic treatment, particularly in those taking metformin. However, no significant relationship was found between serum serotonin and medication. Therefore, while serum serotonin levels may provide some insights, relying on them as a predictive marker for depression in T2DM patients may be too superficial. Further research is needed to clarify the role and implications of serotonin in this context.

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Conflict of interest

The authors declare no conflict of interest.

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