TPM Vol. 32, No. S7, 2025
ISSN: 1972-6325
https://www.tpmap.org/

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EVALUATING THE NEUROENDOCRINE AND METABOLIC IMPLICATIONS OF SERTRALINE THERAPY IN DIABETIC PATIENTS WITH SEVERE DEPRESSION

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ABSTRACT

Background: Depression and diabetes mellitus are chronic, interlinked conditions that frequently coexist and adversely affect each other's course and prognosis.

Objective: To evaluate the neuroendocrine and metabolic implications of sertraline therapy in diabetic patients with severe depression, focusing on changes in glycemic control, lipid profile, and serum cortisol levels.

Methodology: A cross-sectional analytical study was conducted at Tertiary care hospital from December 2023 August 2024. A total of 205 diabetic patients diagnosed with severe depression were included. Patients aged 30–65 years with type 2 diabetes mellitus and severe depression (diagnosed according to DSM-5 criteria, HDRS score ≥23) who had been on sertraline monotherapy for at least six weeks were enrolled using non-probability consecutive sampling.

Results: The mean age of participants was 51.3 ± 8.6 years; 57.1% were female. Mean fasting glucose and HbA1c were 141.6 ± 33.5 mg/dL and 7.8 ± 1.2%, respectively, while elevated serum cortisol (>18 µg/dL) was observed in 34.6% of patients. A significant positive correlation was found between the duration of sertraline therapy and serum cortisol ($r = 0.32$, $p = 0.01$) as well as HbA1c ($r = 0.21$, $p = 0.04$), indicating mild worsening of glycemic control with prolonged therapy. Lipid parameters showed no significant association with treatment duration ($p > 0.05$).

Conclusion: It is concluded that sertraline therapy in diabetic patients with severe depression may cause mild elevations in HbA1c and cortisol levels with prolonged use, reflecting modest neuroendocrine and metabolic effects. However, no significant adverse impact on lipid metabolism was observed.

Keywords: Sertraline, Diabetes Mellitus, Depression, Cortisol, HbA1c, Neuroendocrine Effects, Metabolic Regulation

INTRODUCTION

Depression and diabetes mellitus are chronic, debilitating conditions that exert profound physical, psychological, and socioeconomic burdens on patients. Both diseases are highly prevalent worldwide and frequently coexist, forming a complex, bidirectional relationship that significantly worsens prognosis [1]. Epidemiological studies have shown that individuals with type 2 diabetes have a two- to threefold higher risk of developing major depressive disorder, while those with depression exhibit a similar increase in the likelihood of developing diabetes. This intricate interrelationship can be attributed to overlapping pathophysiological mechanisms involving neuroendocrine dysregulation, chronic inflammation, oxidative stress, and lifestyle factors such as sedentary behavior, poor dietary habits, and medication non-compliance [2]. As a result, the comorbidity of diabetes and depression represents not only a medical challenge but also a pressing public health concern, especially in low- and middle-income countries where healthcare resources are limited [3]. The neuroendocrine axis plays a pivotal role in linking psychological states with metabolic outcomes. In depressive illness, chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to sustained cortisol secretion, which in turn contributes to insulin resistance, central adiposity, and impaired glucose tolerance [4]. Similarly, the sympathetic nervous system, which is frequently overactive in depression, promotes lipolysis and hepatic glucose output, further aggravating hyperglycemia [5]. The serotonergic system central to mood regulation, also modulates appetite,

pancreatic β-cell function, and energy metabolism [6]. Therefore, antidepressants that target serotonin reuptake, such as sertraline, have the potential to influence these neuroendocrine pathways directly and indirectly. Understanding this crosstalk is essential in diabetic patients, who are already predisposed to metabolic dysregulation [7].

Sertraline, a selective serotonin reuptake inhibitor (SSRI), is widely prescribed as first-line therapy for major depressive disorder, generalized anxiety disorder, and related affective conditions. Its mechanism of action involves increasing synaptic serotonin availability, thereby improving mood, cognitive function, and emotional regulation [8]. Compared to older antidepressants such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), sertraline is considered metabolically safer and better tolerated, with fewer anticholinergic and cardiotoxic effects [9]. Nevertheless, growing evidence suggests that SSRIs may not be entirely neutral in their metabolic influence. Chronic SSRI therapy has been associated with alterations in glucose metabolism, mild weight changes, and varying effects on lipid profiles. While some studies indicate potential improvements in glycemic control due to enhanced self-care and stress reduction, others report adverse effects such as hyperglycemia or dyslipidemia during long-term treatment [10]. Moreover, depression itself can impair diabetes management through behavioral and physiological pathways. Depressed patients often experience low motivation, poor adherence to diet and exercise regimens, and irregular use of hypoglycemic medications, all of which contribute to suboptimal glycemic control. The resulting hyperglycemia perpetuates fatigue, irritability, and cognitive dysfunction, creating a vicious cycle that intensifies depressive symptoms [11]. From a mechanistic standpoint, SSRIs modulate serotonin receptors not only in the brain but also in peripheral tissues, including pancreatic islets, adipose tissue, and the gastrointestinal tract. This widespread receptor distribution underscores the possibility of systemic metabolic consequences. For instance, serotonin signaling influences glucose homeostasis through regulation of insulin secretion and hepatic gluconeogenesis [12]. Additionally, chronic SSRI use may modify the gut-brain axis, altering nutrient absorption and microbiota composition, which are increasingly recognized as contributors to both mood and metabolic health. Therefore, sertraline therapy in diabetic patients may produce nuanced effects potentially beneficial in some physiological dimensions while detrimental in others depending on duration, dosage, and patient-specific metabolic profiles [13].

Objective

To evaluate the neuroendocrine and metabolic implications of sertraline therapy in diabetic patients with severe depression, focusing on changes in glycemic control, lipid profile, and serum cortisol levels.

METHODOLOGY

A cross-sectional analytical study was conducted at at Tertiary care hospital from December 2023 August 2024. A total of 205 diabetic patients with clinically diagnosed severe depression were enrolled in the study. The sample size was calculated using the OpenEpi software, with a confidence level of 95% and a margin of error of 5%, based on an expected prevalence of depression among diabetic individuals of approximately 20%. Non-probability consecutive sampling was used to recruit eligible participants presenting during the study period. The study included patients aged 30–65 years diagnosed with type 2 diabetes mellitus (as per ADA criteria) and severe depression (as per DSM-5), confirmed by a consultant psychiatrist. All participants had been on sertraline monotherapy for at least six weeks and provided written informed consent. Patients with other psychiatric disorders, severe hepatic, renal, or cardiovascular disease, pregnant or lactating females, and those taking corticosteroids or drugs affecting glucose metabolism were excluded.

Data Collection

All eligible participants were interviewed using a structured questionnaire to collect demographic and clinical data, including age, gender, duration of diabetes, duration of depression, and duration of sertraline use. Physical examination was performed to record anthropometric parameters such as weight, height, and body mass index (BMI). Venous blood samples were collected after an overnight fast to measure fasting blood glucose (FBG), glycated hemoglobin (HbA1c), fasting serum insulin, lipid profile (total cholesterol, triglycerides, HDL, LDL), and serum cortisol levels. Glycemic control was assessed using HbA1c levels, while neuroendocrine activity was evaluated through serum cortisol estimation using the chemiluminescent immunoassay method. Depression severity was evaluated using the Hamilton Depression Rating Scale (HDRS) at the time of assessment.

Statistical Analysis

Data were entered and analyzed using SPSS version 26. Quantitative variables (age, HbA1c, cortisol levels, BMI) were expressed as mean ± standard deviation, while categorical variables (gender, presence of hyperlipidemia, poor glycemic control) were presented as frequencies and percentages. The relationship between sertraline duration and metabolic/neuroendocrine parameters was assessed using Pearson's correlation coefficient and independent t-test. A p-value of <0.05 was considered statistically significant.

RESULTS

Data were collected from 205 patients, mean age of the participants was 51.3 ± 8.6 years, ranging from 30 to 65 years. There were 88 males (42.9%) and 117 females (57.1%), showing a slight female predominance. The average duration of diabetes was 7.2 ± 3.5 years, while the mean duration of depression was 2.8 ± 1.6 years. Patients had

been on sertraline therapy for an average of 4.5 ± 2.1 months. The mean body mass index (BMI) was 27.9 ± 3.4 kg/m², indicating that most of the participants were overweight.

Table 1: Baseline Characteristics of Patients (n = 205)

Variable	Mean ± SD / n (%)
Age (years)	51.3 ± 8.6
Gender	Male: 88 (42.9%) / Female: 117 (57.1%)
Duration of Diabetes (years)	7.2 ± 3.5
Duration of Depression (years)	2.8 ± 1.6
Duration of Sertraline Therapy (months)	4.5 ± 2.1
Body Mass Index (kg/m²)	27.9 ± 3.4

The mean fasting blood glucose was 141.6 ± 33.5 mg/dL, which is higher than the normal range of 70–110 mg/dL, reflecting poor glycemic control. The mean HbA1c level was 7.8 ± 1.2%, exceeding the target threshold of 7.0%. Fasting insulin levels averaged 14.7 ± 5.3 µIU/mL, remaining within the reference range (2–25 µIU/mL). Total cholesterol averaged 204.8 ± 36.9 mg/dL, and triglycerides were 186.2 ± 45.7 mg/dL—both mildly above normal limits. The mean HDL cholesterol was 43.5 ± 9.8 mg/dL, which is acceptable but on the lower side, while LDL cholesterol averaged 129.4 ± 29.6 mg/dL, near the upper limit of normal.

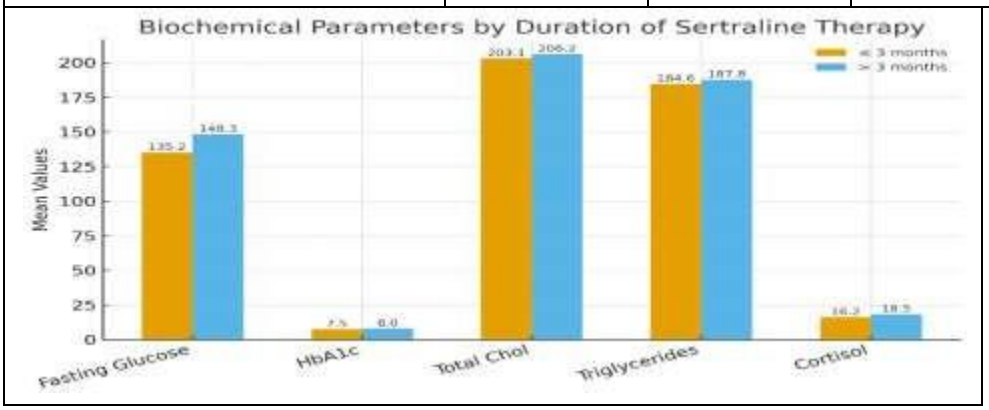
Table 2: Metabolic and Neuroendocrine Parameters in Patients on Sertraline (n = 205)

Parameter	Mean ± SD / n (%)	Reference Range
Fasting Blood Glucose (mg/dL)	141.6 ± 33.5	70–110
HbA1c (%)	7.8 ± 1.2	< 7.0
Fasting Insulin (µIU/mL)	14.7 ± 5.3	2–25
Total Cholesterol (mg/dL)	204.8 ± 36.9	< 200
Triglycerides (mg/dL)	186.2 ± 45.7	< 150
HDL Cholesterol (mg/dL)	43.5 ± 9.8	> 40
LDL Cholesterol (mg/dL)	129.4 ± 29.6	< 130
Serum Cortisol (µg/dL)	17.5 ± 5.1	5–18

Among the 205 participants, 138 (67.3%) had elevated HbA1c levels, while 67 (32.7%) maintained normal control. Abnormal lipid levels were also common: 122 (59.5%) had elevated total cholesterol, 126 (61.5%) had raised triglycerides, 114 (55.6%) had low HDL cholesterol, and 103 (50.2%) had elevated LDL cholesterol. Elevated cortisol levels (>18 µg/dL) were observed in 71 patients (34.6%), whereas 134 (65.4%) had values within the normal range.

Table 3: Distribution of Patients by Glycemic and Lipid Status (n = 205)

Parameter	Normal	Abnormal	Percentage Abnormal
HbA1c	67 (32.7%)	138 (67.3%)	67.3%
Total Cholesterol	83 (40.5%)	122 (59.5%)	59.5%
Triglycerides	79 (38.5%)	126 (61.5%)	61.5%
HDL Cholesterol	91 (44.4%)	114 (55.6%)	55.6%
LDL Cholesterol	102 (49.8%)	103 (50.2%)	50.2%
Elevated Cortisol (>18 µg/dL)	134 (65.4%)	71 (34.6%)	34.6%

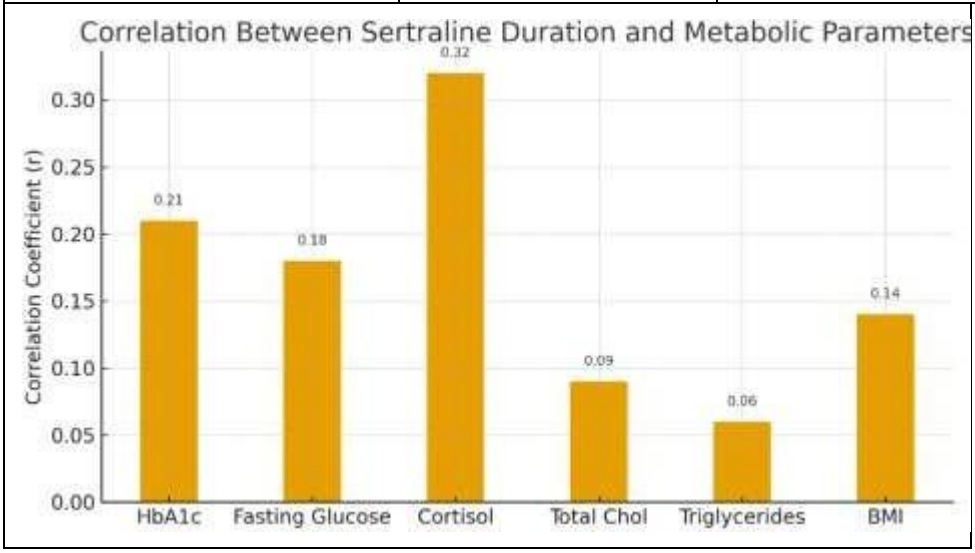


Patients with a therapy duration exceeding three months had higher mean fasting glucose (148.3 ± 35.7 mg/dL) compared to those treated for less than or equal to three months (135.2 ± 30.9 mg/dL), with a statistically significant p-value of 0.03. Similarly, HbA1c was higher in the long-term group (8.0 ± 1.3%) versus the short-

term group (7.5 ± 1.1%), with p = 0.04. Mean serum cortisol was 18.5 ± 5.3 µg/dL in the longer therapy group and 16.2 ± 4.8 µg/dL in the shorter therapy group (p = 0.02). Differences in total cholesterol (206.2 ± 36.5 vs. 203.1 ± 37.4 mg/dL, p = 0.52) and triglycerides (187.8 ± 45.2 vs. 184.6 ± 46.3 mg/dL, p = 0.61) were not significant.

Table 4: Comparison of Mean Biochemical Parameters by Duration of Sertraline Therapy

Parameter	≤ 3 months (n = 92)	> 3 months (n = 113)	p-value
Fasting Glucose (mg/dL)	135.2 ± 30.9	148.3 ± 35.7	0.03*
HbA1c (%)	7.5 ± 1.1	8.0 ± 1.3	0.04*
Total Cholesterol (mg/dL)	203.1 ± 37.4	206.2 ± 36.5	0.52
Triglycerides (mg/dL)	184.6 ± 46.3	187.8 ± 45.2	0.61
Serum Cortisol (µg/dL)	16.2 ± 4.8	18.5 ± 5.3	0.02*



Duration of therapy showed a significant positive correlation with HbA1c (r = 0.21, p = 0.04) and serum cortisol (r = 0.32, p = 0.01), indicating that longer use was associated with higher blood glucose and cortisol levels. The correlation with fasting glucose (r = 0.18, p = 0.07) was weak and not statistically significant. Correlations with total cholesterol (r = 0.09, p = 0.28), triglycerides (r = 0.06, p = 0.41), and BMI (r = 0.14, p = 0.11) were also statistically insignificant.

Table 5: Correlation Between Duration of Sertraline Therapy and Metabolic/Neuroendocrine Parameters

Parameter	Correlation Coefficient (r)	p-value
HbA1c (%)	0.21	0.04*
Fasting Glucose (mg/dL)	0.18	0.07
Serum Cortisol (µg/dL)	0.32	0.01*
Total Cholesterol (mg/dL)	0.09	0.28
Triglycerides (mg/dL)	0.06	0.41
BMI (kg/m²)	0.14	0.11

DISCUSSION

This study evaluated the neuroendocrine and metabolic implications of sertraline therapy in diabetic patients with severe depression. The findings reveal that while sertraline remains an effective and generally well-tolerated antidepressant, its prolonged use may modestly influence metabolic and neuroendocrine parameters, particularly glycemic control and cortisol regulation. These results underscore the importance of individualized monitoring and interdisciplinary management when treating depression in diabetic populations. In the present study, the majority of patients (67.3%) exhibited poor glycemic control with HbA1c levels exceeding 7%, despite ongoing diabetic management. A significant positive correlation was observed between the duration of sertraline therapy and both HbA1c (r = 0.21, p = 0.04) and serum cortisol levels (r = 0.32, p = 0.01), suggesting that prolonged sertraline exposure might exacerbate hyperglycemia through neuroendocrine modulation. Elevated cortisol levels were present in approximately one-third of the patients (34.6%), a finding that supports the hypothesis that SSRI-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis contributes to mild hypercortisolemia [14]. This hypercortisolemic state can impair insulin sensitivity, stimulate hepatic gluconeogenesis, and promote central adiposity, thereby worsening glycemic parameters in diabetic individuals. These findings align with prior studies that have demonstrated the neuroendocrine impact of antidepressant therapy in diabetic patients. Similarly,

Lustman et al. (2016) found that patients with type 2 diabetes treated with SSRIs showed variable changes in HbA1c levels depending on treatment duration and individual metabolic responsiveness [15].

Interestingly, while sertraline showed a slight impact on glycemic control, its effect on lipid metabolism appeared minimal. No significant correlations were observed between the duration of sertraline therapy and total cholesterol, triglycerides, or LDL levels ($p > 0.05$). The relatively stable lipid profiles in our cohort suggest that sertraline's serotonergic mechanism may exert a neutral or even protective effect on lipid homeostasis by reducing stress-mediated sympathetic activation. Another important observation from this study is the gender distribution and its lack of association with metabolic variation [16]. Despite a female predominance (57.1%), no significant gender-based differences were found in HbA1c, lipid, or cortisol levels ($p > 0.05$). This indicates that sertraline's neuroendocrine effects are likely independent of sex hormones, although prior studies have proposed that estrogen modulation may influence serotonin sensitivity and metabolic outcomes. The absence of a gender effect in this cohort supports the general applicability of the findings across both sexes [17].

The observed rise in serum cortisol and modest deterioration of glycemic parameters with longer sertraline therapy durations (>3 months) have potential clinical implications. Chronic activation of the HPA axis and subsequent cortisol elevation can contribute to long-term metabolic complications such as insulin resistance, weight gain, and dyslipidemia. These changes may counteract the benefits of improved mood and mental function achieved through antidepressant therapy [18]. Therefore, while SSRIs like sertraline remain a cornerstone of depression management in diabetic patients, clinicians should remain vigilant regarding metabolic monitoring. Routine follow-up of HbA1c and cortisol levels, along with adjustment of diabetic therapy when necessary, can help maintain optimal metabolic balance without compromising psychiatric outcomes. The complex interplay between depression, antidepressant therapy, and metabolic control is further complicated by behavioral factors. Improvement in depressive symptoms following sertraline therapy may enhance patient adherence to diabetic medications, diet, and exercise regimens, potentially offsetting the mild metabolic disturbances caused by the drug [19]. This dual effect may explain why some studies, such as those by McIntyre et al. (2019) and Pan et al. (2020), reported improved glycemic control in depressed diabetics treated with SSRIs due to overall improvement in lifestyle behaviors and stress reduction. Thus, the net metabolic effect of sertraline may vary based on the balance between physiological alterations and behavioral improvements [20].

Limitations of the present study include its cross-sectional design, which restricts causal inference between sertraline exposure and metabolic outcomes. The absence of a control group of diabetic patients with depression not receiving antidepressants limits comparative analysis. Furthermore, confounding factors such as diet, physical activity, and concurrent use of hypoglycemic agents were not fully standardized. The study also relied on single-time-point cortisol measurements rather than diurnal profiling, which might underestimate the complexity of HPA-axis alterations.

CONCLUSION

It is concluded that sertraline therapy, while effective in alleviating severe depressive symptoms, may exert subtle yet clinically meaningful neuroendocrine and metabolic effects in diabetic patients. Prolonged use of sertraline was found to be associated with mild elevations in serum cortisol and HbA1c levels, indicating a possible interaction between serotonergic modulation and hypothalamic-pituitary-adrenal (HPA) axis activity that can influence glycemic control. However, lipid parameters remained largely unaffected, suggesting that sertraline has a limited impact on lipid metabolism compared to its effects on glucose regulation.

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