Original Article

Effect of Sertraline as an Add-on Therapy in T2DM Patients with Comorbid Depression: An Open Label Randomized Controlled Trial

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Abstract

Objectives: To study the effect of sertraline on depression in type 2 diabetes mellitus (T2DM) patients with comorbid depression. **Materials and Methods:** An open label randomized control study. Patients with T2DM and moderate to severe depression were randomized to sertraline or control therapy for six months. The primary objective was the change in depression score and the secondary objectives were changes in glycemic parameters, wellbeing, and drug adherence scores at three and six months. **Results:** The present study includes 160 T2DM patients with moderate to severe depression. Depression in these patients was evaluated using a self-reporting version of Patient Health Questionnaire (PHQ-9). A total of 80 patients each were randomized to sertraline and control groups. Sertraline significantly improved depression scores in patients with T2DM and moderate to severe depression both at 3 months and 6 months compared to the control group. The wellbeing and treatment adherence scores improved significantly in the sertraline group at 6 months. However, sertraline had no significant effect on glycemic parameters when compared to control group both at 3 months and 6 months. **Conclusion:** Sertraline significantly improves depression and drug adherence in T2DM patients with depression but has no effect on glycemic parameters.

Keywords: Diabetes mellitus, health wellbeing, major depression, medication adherence

Introduction

Diabetes mellitus and depression are two of the most prevalent chronic diseases around the world, which frequently coexist.[1] According to the International Diabetes Federation, 425 million people had diabetes in 2017, and this number was expected to reach 629 million by 2045.[2] In India, it was estimated that 72.9 million people had diabetes in 2017 with a prevalence of 8.8%.[2] Depression, as recognized by "WHO", is the leading cause of disability and the fourth leading contributor to the global burden of disease. The World Health Organization had estimated that 350 million people worldwide were affected by depression in 2017. Evidence suggests that diabetes and depression show bidirectional relationship. Patients with T2DM are 2–3 times more prone to develop depression when compared with general population.[3,4] Similarly, patients with depression are at increased risk of developing T2DM.[5,6] Despite this, depression continues to be underrecognized and undertreated.[7] Diabetes with depression can lead to poor treatment adherence, poor glycemic control, increased risk of complications, and mortality.[8-11]

Psychosociotherapy, pharmacotherapy, or both are the main stay of treatment for depression in people with diabetes. Various pharmacotherapies have been tried in addition to cognitive behavioral therapy with varying success. Sertraline, a selective serotonin reuptake inhibitor (SSRI), might improve depression, treatment adherence, and quality of life in patients with diabetes and comorbid depression. The effect of pharmacotherapy on glycemic control has been conflicting in T2DM. Although some studies showed improvement in HbA1c whereas others showed no benefit.[12-15] The present study is

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an open label randomized control study of sertraline in T2DM patients with moderate to severe depression.

Materials and Methods

This study was carried out by the department of Pharmacology in association with department of Endocrinology and department of Psychiatry of MKCG Medical College Berhampur between March, 2014 to January, 2016. The Institutes Ethics Committee approved the protocol and written informed consent was taken from each of the study participants before including in this study.

Selection of the study subjects

Type 2 diabetes mellitus patients, attending the Endocrinology OPD, MKCG Medical College and Hospital, aged 18–70 yrs, and diagnosed with comorbid depression formed the study subjects. For diagnosing major depressive disorder in T2DM patients, Patient Health Questionnaire PHQ-2 followed by PHQ-9, a self-reporting version of modified Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) was employed.[16] PHQ-2 is a screening tool which involves two questions; such as in the past one month: Have you often been bothered by feeling down, depressed or hopeless and Have you been bothered by little interest or pleasure in doing things. If either of the questions answered affirmatively, PHQ-9 version which assesses the severity of depression was applied. There were nine questions with each grading of 0–3 and a maximum total score of 27. A score of <10 indicated mild depression and ≥10 indicated moderate to severe depression. The present study included those patients with T2DM with a PHQ-9 score of ≥10. Finally, these patients were examined by a psychiatrist to confirm the diagnosis. The diagnosed T2DM cases with PHQ-9 score (≥10) and aged 18–70 yrs were included in the study. Patients with T1DM, schizophrenia, bipolar disorder, dementia, suicidal ideation, psychiatry therapy in past 3 months and raised ALT, and AST >3 times of ULN were excluded from the study. Initially, 2000 adult T2DM patients were screened for depressive disorder by applying PHQ-2, of which 1000 patients were positive for PHQ-2 and were subjected to PHQ-9. A total of 160 patients were included in the study as they had PHQ-9 ≥10. The primary objective was to study the effect of sertraline on depression in T2DM patients with moderate to severe depression. The secondary objectives were the changes in the glycemic parameters including HbA1c, FPG, and PPG, besides the quality of life score (WHO-5 Well being index) and adherence to treatment (Morisky Medication Adherence Scale-MMAS4).

Study procedure

A total of 160 T2DM patients with comorbid depression and a PHQ-9 score ≥10 were enrolled in the study as per predetermined inclusion and exclusion criteria. An informed consent was obtained from each participant in a predesigned informed consent form. After computer-generated randomization, 80 patients (treatment group) received sertraline along with usual antidiabetic drugs and another 80 patients of T2DM served as a control group who received antidiabetic drugs only. Both the groups received general counselling including importance of adherence to treatment, achieving glycemic targets, and aerobic exercises for 30 minutes daily. Patients in the sertraline group were started with 50 mg/d dose and, if needed, the dose was increased to 100 mg/d gradually not more than 25 mg/week. Patients were followed up at three months intervals up to six months. The sociodemographic data of all patients such as age, sex, education, duration of diabetes, and family history of diabetes were recorded. The height, weight, and waist circumference were also measured using standard methods and BMI was calculated as Kg/m^2. Detailed clinical examination for diabetic complications like hypertension, neuropathy, nephropathy, and cardiovascular complications were noted at the time of enrolling and at each point of follow up. The patients were exposed to PHQ-9 questionnaire, WHO-5 (wellbeing index) for quality of life (QOL), and Morisky Medication Adherence scale (MMAS-4) for treatment adherence at entry as well as at all follow up points. The data were collected and recorded in a predesigned case record form.

Laboratory investigations

Fasting and postprandial plasma glucose were measured by auto-analyzer using glucose oxidase method. HbA1c was measured using ion exchange high-performance liquid chromatography on Bio-Rad D10 system.

Statistical analysis

Data were analyzed by using statistical software Graphpad Prism Ver. 0.5. The base line parametric data were analyzed by unpaired student's *t* test and categorical data like sex and complications were expressed in percentages and compared using Chi-square test. The comparison of baseline data with the data obtained at different follow up points in each group as well as the data between two comparator groups like FPG, PPG, and HbA1c were analyzed by one-way ANOVA followed by Tukey's multiple comparison test and nonparametric data like PHQ-9 score, WHO-5 score, and MMAS-4 score were analyzed by Friedman test followed by Dunn's multiple comparison test. Kaplan Meier survival analysis was done to compare the survival proportion of study subjects considering the number of drop out cases using Log rank test. Pearson's correlation test was done to correlate HbA1c% with depression score.

Results

Out of 2000 T2DM patients screened for depressive disorder, 1000 were positive for PHQ2, a prevalence of 50% for depression. However, 160 patients had moderate to severe depression (PHQ-9 ≥ 10) accounting to the prevalence of 8.0% in the present study. A total of 32 patients (15 in sertraline and 17 in control group) lost to follow-up. Therefore, the present study includes 128 patients—65 in sertraline and 63 in control group—for complete analysis [Figure 1].

The baseline characters of the two groups: sertraline and control group are described in Table 1. There was no significant

difference in the baseline parameters between the groups with regard to age, sex, HbA1c, PHQ-9, or WHO-5 score. However, the duration of diabetes was more in control group**.**

The primary outcome measure of change in depression scores improved significantly in both the groups at 3 months and 6 months. However, when compared between groups, the sertraline group had significantly more improvement in PHQ-9 scores both at 3 months and 6 months (*P* value 0.043 and < 0.0001, respectively) [Figure 2 and Table 2].

The secondary outcome measure of change in HbA1c from baseline to 6 months showed significant decrease at 3 and 6 months in both groups. In the sertraline group, it was 8.0 ± 0.12% and 7.2 ± 0.09% at 3 and 6 months, respectively, compared to baseline A1c of 9.1 ± 0.18% which was significant (*P* < 0.01). In the control group HbA1C also decreased both at 3 months (7.6 ± 0.2%) and 6 months (7.2 ± 0.19%) compared to baseline HbA1c of 8.4 ± 0.25%. However, the change in HbA1c level at 3 months and 6 months between the sertraline and control groups [Table 2] did not attain statistical significance either at 3 months (*P* 0.36) or at 6 months (*P* 0.99). The outcome measures like FPG and PPG decreased significantly in both the groups at 3 and 6 months but when compared between the two groups, they were not found to be significant [Table 2]. There was also positive correlation between HbA1c and depression scores in the present study. Pearson's correlation coefficient r = 0.44 (95% CI 0.29–0.57), $R^2 = 0.20$, *P* value < 0.0001 [Figure 3].

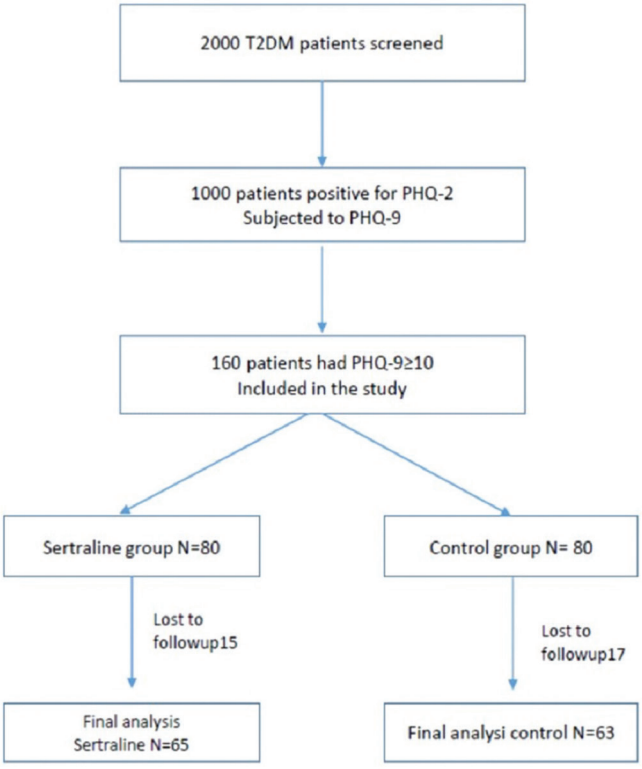

Figure 1: Flow chart of the study (original)

Similarly, the wellbeing scores of WHO-5 showed improvements in both groups but significant improvement observed only in sertraline group at 6 months compared to control group [Figure 4 and Table 2]. The treatment adherence [Figure 5] was better in sertraline group compared to control group at both 3 and 6 months (*P* < 0.0001).

Discussion

In the present study, the occurrence of moderate to severe depression in T2DM was 8.0%. There was significant improvement in the depression scores, wellbeing, and treatment adherence with comorbid depression over 3 to 6 months. It had no significant effect on glycemic parameters including HbA1c, FPG and PPG.

The prevalence of depression in T2DM varies depending on the type of diabetes, age and sex, method of depression assessment, geographic location, and study design. The overall prevalence

Table 1: Baseline characteristics of T2 DM patients with Co-morbid Depression

	Sertraline group *n*=65	Control group *n*=63	*P*
Age (yrs)	49.12±1.04	50.02±1.73	0.65
Sex-M/F (%)	55.3/44.7	68.2/31.8	0.08
BMI	22.79±0.43	24.27±0.49	0.43
Duration of diabetes (yrs)	5.42±0.59	7.61±0.84	0.011*
HbA1c (%)	9.1±0.18	8.65±0.17	0.44
Complications micro or macro (%)	38.46	38.09	1.00
PHQ-9 Score	15.7±0.42	15.4±0.39	0.54
WHO-5 Score	43.5±0.54	43.8±0.58	0.54
MMAS-4 Score	2.1±0.04	2.0±0.02	0.07

Data expressed in mean values in case of parametric data and analyzed by unpaired student's t test. The categorical data expressed in percentages and compared by Chi-square test. **P*<0.05 is considered significant. PHQ-9 Patient Health Questionnaire, WHO-5 World Health Organisation wellbeing score, MMAS-4 Morisky Medication Adherence Scale

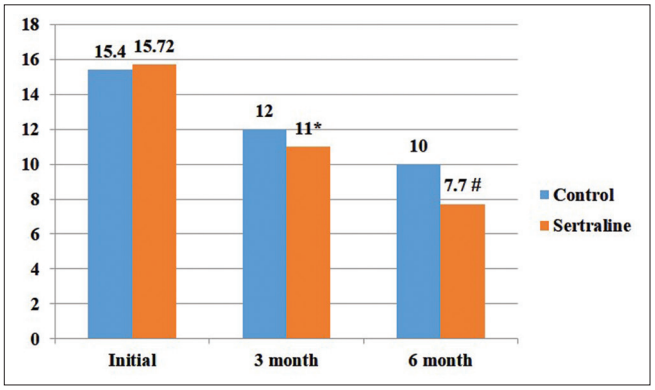

Figure 2: Effect of sertraline on PHQ-9 score (original). Data expressed as mean and was analyzed by Friedman's test and Dunn's multiple comparison test. *n* = 65 (antidepressant group) and *n* = 63 (control group). *#indicates *P* < 0.05 between control and sertraline group at 3 and 6 months respectively

Table 2: Effects of Sertraline in T2DM patients with depression

	Baseline	3 months	6 months	*P*-trend Baseline vs 3 months	*P*-trend 3 months vs 6 months
PHQ-9 Score					
Control	15.4±0.51	12±0.40	10±0.36	0.002	<0.001
Sertraline	15.7±0.42	11±0.24	7.7±0.20	<0.001	<0.001
P-trend		0.043*	0.0008*		
HbA1c					
Control	8.4±0.25	7.6±0.20	7.2±0.19	<0.001	<0.001
Sertraline	9.1±0.18	8.0±0.12	7.2±0.09	<0.001	<0.001
P-trend		0.36	0.99		
FPG (mg/dl)					
Control	178±6.8	150±4.9	138±5.3	0.05	0.78
Sertraline	215±12	155±5.3	126±2.7	<0.001	<0.001
P-trend		0.99	0.81		
PPG (mg/dl)					
Control	233±11	186±7.7	162±6.9	<0.001	<0.001
Sertraline	277±12	195±6.9	145±4.3	<0.001	<0.001
P-trend		0.95	0.35		
WHO-5 Score					
Control	43.8±0.58	56±0.39	64±0.48	<0.001	<0.001
Sertraline	43.5±0.54	64±0.22	88±0.26	0.001	<0.001
P-trend		0.08	<0.001*		
MMAS-4 Score					
Control	2.04±0.02	3.2±0.09	3.2±0.09	<0.001	<0.001
Sertraline	2.13±0.04	3.9±0.05	4.0±0.04	<0.001	<0.001
P-trend		<0.001*	<0.001*		

Data expressed in mean values with standard deviation. Parametric data analyzed by One way ANOVA followed by Tukey's multiple comparison test. PHQ-9 score, MMAS-4, and WHO-5 score were analyzed by Friedman test followed by Dunn's multiple comparison test. *indicates *P*<0.05. PHQ-9 Patient Health Questionnaire; WHO-5 World Health Organisation wellbeing score; MMAS-4 Morisky Medication Adherence Scale

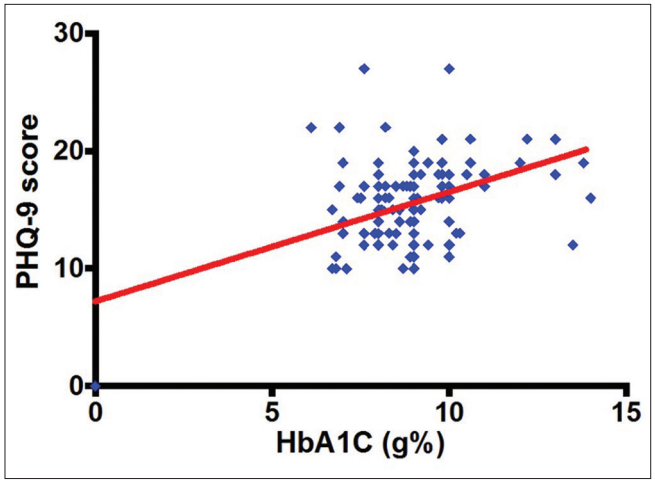

Figure 3: Correlation between HbA1c and PHQ-9 scores (original). Pearson's correlation coefficient r = 0.44 (95% CI 0.29-0.57), R^2 = 0.20, *P* value <0.0001

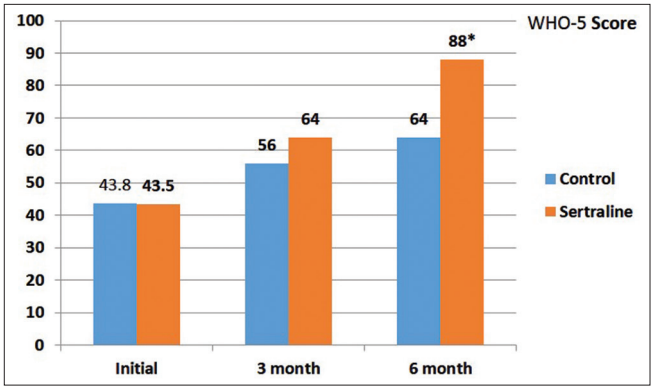

Figure 4: Effect of sertraline on WHO-5 scores (original). Data expressed as mean and was analyzed by Friedman's test and Dunn's multiple comparison test. *n* = 65 (antidepressant group) and *n* = 63 (control group). *indicates *P* < 0.05 at 6 months between control and sertraline groups

of major depression in the present study was 50% which is in accordance with studies from India which found prevalence of 35–46%.[17,18] Meta-analysis of 42 studies by Anderson *et al*., and 10 studies by Ali *et al*. showed that the overall prevalence of depression in T2DM was 27% and 17.6%, respectively.[3,19] The prevalence of moderate to severe depression in the present study was 8% only. One of the reasons for low prevalence in the present study could be the inclusion of only moderate to severe depression patients.

Sertraline showed significant improvement in depression scores which as expected due to the antidepressant medications. However, it also improves treatment adherence. Treatment adherence in patients with diabetes and depression is often challenging. The present study showed that sertraline significantly improves treatment adherence which was

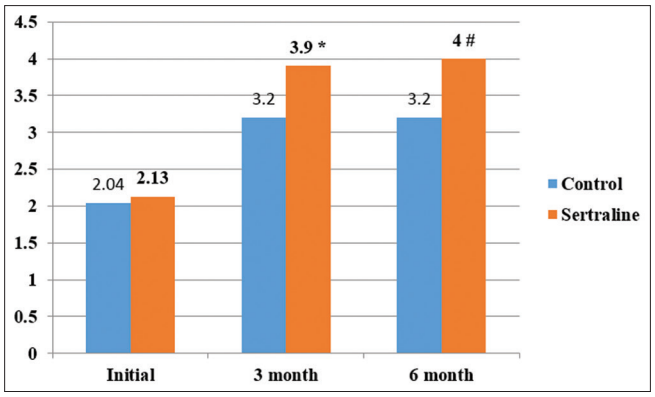

Figure 5: Effect of sertraline on MMAS-4 score (original). Data expressed as mean and was analyzed by Friedman's test and Dunn's multiple comparison test. $n = 65$ (antidepressant group) and $n = 63$ (control group). *#indicates $P < 0.05$ between control and sertraline group at 3 and 6 months respectively

observed at 3 months of initiation of therapy. Similar to present study, Bogner *et al*.; found that 60% patients receiving pharmacotherapy for depression had >80% drug adherence to antidiabetic medicines compared to only 35% in the usual care group of patients with diabetes and depression.[20]

There was no statistically significant difference in HbA1c in the present study between control and sertraline groups. Studies have shown that sertraline improves HbA1c in type 1 diabetes mellitus but they are not consistent in T2DM.[21] A retrospective study found that use of antidepressant medication in T2DM patients with depression was twice likely to achieve good glycemic control than the control group.[22] Similarly, an integrated approach to diabetes and depression therapy found improved glycemic control in 60.9% patients compared to 35.7% in control group.[20] In DAD (Diabetes and Depression) study, they found a nonsignificant decrease in HbA1c in sertraline group compared to cognitive behavioral therapy.[23] These findings are in line with the present study.

There was a positive correlation between hyperglycemia and depression scores in the present study. Therefore, as observed in the control group of present study, controlling hyperglycemia might improve depression levels. Identifying and treating depression in patients with diabetes is beneficial as it improves the quality of life. Sertraline is an SSRI, which acts by inhibiting the reuptake of sertraline. It improves depression scores, treatment adherence, and wellbeing but it has no significant effect on glycemic indices in T2DM patients with depression.

The limitations of the present study are the possible, unintended bias due to being an open label study and failure to evaluate the behavioral therapy or other forms of therapy in these patients.

Conclusion

Sertraline significantly improves depression, treatment adherence, and wellbeing in patients with diabetes and moderate to severe depression.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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