ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 13, Issue 7, 2020

Online - 2455-3891
Print - 0974-2441

Research Article

ROLE OF ANTIDEPRESSANT ON THE GLYCAEMIC CONTROL OF UNCONTROLLED TYPE 2 DIABETES MELLITUS PATIENTS

ALLU HARSHAVARDHINI[1], BHANUKUMAR MUTHAIAH[1]*, TIRIN BABU[2], GEORGE MATHEW PANACHIYIL[2], SISIRA SANTHOSH[3], SARAYU SANTHOSH[3]

[1]Department of General Medicine, JSS Medical College and Hospital, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India. [2]Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India. [3]Department of General Medicine, Adichunchanagiri Institute of Medical Sciences, Mandya, B.G Nagara, Karnataka, India. Email: drmbk1961@gmail.com

Received: 20 March 2020, Revised and Accepted: 02 May 2020

ABSTRACT

Objectives: This study aimed to estimate the frequency of depression and the effect of antidepressant on glycemic control in type 2 diabetes mellitus patients.Depression incidence is higher in diabetic patients when compared to the non-diabetic individuals and there exist a two-directional relationship between depression and the development of type 2 diabetes mellitus.

Methods: This prospective interventional study was conducted in type 2 diabetes mellitus patients with a sample size of 100. These patients were diagnosed with depression using WHO-ICD10 criteria. All study patients had uncontrolled blood glucose levels and were on an optimized maximal dose of combination oral hypoglycemic agents with stable glycoregulation (HbA1c 8.4 ±0.5) were taken up for the intervention with antidepressant. These patients were started on with antidepressant after enrollment and followed up for fasting blood sugar (FBS), post-prandial blood sugar (PPBS), and HbA1c at the end of 3 months and 6 months. And also Hamilton depression rating scale scores were estimated at the beginning of the study and at the end of 6 months.

Results: The frequency of depression among the type 2 diabetes mellitus patients was found to be 42%. There were reduction of mean FBS levels from baseline value of 177 mg/dl to follow-up value of 160 mg/dl ($p<0.001$), mean PPBS levels from 251.16 mg/dl to 217.84 mg/dl ($p<0.001$), and mean HbA1c dropped from 8.41 to 7.57 ($p<0.001$) after the treatment with antidepressant.

Conclusion: Our study concluded that patient started on antidepressant showed a reduction in the blood sugar levels and HbA1c levels from their baseline values, which was clinically and statistically significant.

Keywords: Type 2 diabetes mellitus, Depression, Antidepressant, Glycemic control.

 DOI: http://dx.doi.org/10.22159/ajpcr.2020.v13i7.37809

BACKGROUND

Globally, diabetes mellitus is one of the most serious chronic illnesses due to its negative effect on the quality of life of the affected individuals [1]. Nearly 422 million adults had diabetes mellitus according to the 2016 data from the World Health Organization (WHO) and its prevalence is expected to increase to 552 million by 2030 [2]. In India, there are 62.4 million people with type 2 diabetes mellitus and 77 million people with pre-diabetes according to the recent report by Indian Council of Medical Research–India Diabetes national study and these numbers are estimated to rise to 101 million by 2030 [3].

Depression incidence is higher in diabetic patients when compared to the non-diabetic individuals and there exist a two-directional relationship between depression and the development of type 2 diabetes mellitus [4]. The two main currently existing hypotheses explain the causal pathway between depression and the occurrence of diabetes. The first hypothesis showed that depression increases the risk of developing diabetes. The associated chronic stress in depression leads to hypercortisolemia and it may cause centripetal obesity and metabolic syndrome. The physiological alterations like rising in levels of glucocorticoids, catecholamines, growth hormones, modification in the glucose transport function, and secretion of inflammatory cytokines in depression contribute to insulin resistance and abnormal beta islet cell functioning and ultimately become the causal factors for the development of diabetes as well as its complications. The second hypothesis states that psychosocial stressors of having a chronic medical condition (type 1 and type 2 diabetes mellitus) lead to depression [5]. Depression results in increased medical utilization and costs, symptom burden, increased functional impairment, non-compliance to treatment, decrements in quality of life, and increased rates of mortality [6-8]. The rise in the diabetic population in our country and the existence of a significant causative connection between depression and poor glycemic control necessitate the need for studying the effect of antidepressant use on glycemic control of diabetes patients.

Recent studies have shown that short-term administration of tricyclic antidepressants (TCAs) such as nortriptyline and imipramine may end in reduced fasting blood glucose, but extended use raises the baseline values because of their catecholamine profile. Thus, TCAs can be used for the effective management of depression but it can also lead to deterioration of glucose control [9]. The other class of antidepressant studied was selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, and escitalopram. Apart from the reduction in the severity of depression these drugs can also improve both compliance and glycated hemoglobin (HbA1c) levels [10]. Thus, this study aimed to determine the frequency of depression among the type 2 diabetes patients and also to assess the effect of antidepressant on glycemic control.

METHODS

This prospective observational study was conducted in the Department of General Medicine from November 2016 to September 2018 after

approval from the Institutional Human Ethical Committee of JSS Medical College and Hospital, Mysore, Karnataka.

Study Criteria

Diabetic patients aged more than or equal to 18 years who were free from chronic debilitating conditions and receiving a maximal dose of the combination oral hypoglycemic agents (OHAs) were included in the study after obtaining informed consent from the patients. Patients were excluded from the study if they were on insulin therapy, type 1 diabetic patients, age was more than 60 years of age, diabetes patients having a history of prior psychiatric illness, and/or prior treatment with psychiatric medicines and the patients who were not willing to give the informed consent.

Study procedure

All diabetic patients attending the general medicine outpatient department of the study hospital during the study period who fulfilled the inclusion criteria were enrolled after obtaining informed consent. The enrolled patients were screened for depression using patient health questionnaire and Hamilton depression rating scale (HAM-D) criteria and thereby diagnosed for depression using WHO-ICD 10 criteria. The patients diagnosed with moderate to severe depression and were having uncontrolled blood glucose levels and on an optimized maximal dose of combination OHAs with stable glycoregulation (HbA1c 8.4 ±0.5) were taken up for the intervention with antidepressant tablet escitalopram.

The dose of the antidepressant in each individual patient was titrated to the optimal dose range by the psychiatrist and clinical pharmacist during the treatment course. All antidiabetic medications were kept at the same dose and regimen during the study period. Patients started on antidepressant were followed up twice at the end of 3 months and at 6 months. FBS, PPBS, and HbA1c (FBS and PPBS were measured by glucose oxidase method and HbA1C was estimated by HPLC) were estimated at the beginning of the study and at the follow-up. HAM-D scores were estimated at the beginning of the study and at the end of 6 months.

Table 1: Age distribution of the depressed and non-depressed patients

Age category	Depression			
	No		Yes	
	Count	Column n %	Count	Column n %
<40	16	27.6	3	7.1
41–50	23	39.7	18	42.9
51–60	19	32.8	21	50.0
Total	58	100.0	42	100.0

p=0.03, Chi-square test

RESULTS

A total of 252 type 2 diabetic patients were screened, of which 100 patients fulfilled the inclusion criteria and were screened for depression. Frequency of depression among the type 2 diabetics was found to be 42%. Among depressed patients, 21 (50%) were in the age group of 51–60 years, 18 (42.9%) were in the age group of 41–50 years, and 3 (7.1%) were in the age group of <40 years (Table 1). Among the depressed patients, there was female preponderance with 25 patients (59.5%) being female and 17 patients (40.4%) being male. This data were in line with most major epidemiological studies which reported higher prevalence rates for depression among females and older age groups (Table 2). The duration of diabetes among the depressed was 7.8±3.3 years. About 77% of the diabetic patients were depressed with duration more than 10 years which showed that as the duration of diabetes increases, there is an increased risk of developing depression (Table 3).

Interventional effect of antidepressant on fasting blood sugar (FBS), post-prandial blood sugar (PPBS), and HbA1c levels

There was reduction of mean FBS, PPBS, and HbA1c levels from baseline value of 177 mg/dl, 251.16 mg/dl, and 8.41% to follow-up value of 160 mg/dl (p<0.001), 217.84 mg/dl (p<0.001), and 7.57 (p<0.001), respectively (Table 4).

Interventional effect of antidepressant on depression status

Improvement in depression status by antidepressant therapy was confirmed by the significant decrease of HAM-D scores from 17.3±2.5 to 14.4±2.8 (p=0.0001) over the interventional phase (Fig. 1).

Interventional effect of antidepressant: Association between improvement in depression status and improvement in glycemic control

Association and directional nature between changes in depression and diabetes status were addressed by checking the relationship between the change of HAM-D score (delta HAM-D) and the change in HbA1c levels (delta HbA1c) during the interventional phase by means of Pearson's correlation testing. A positive linear correlation between improvement in depression scale and improvement in glycemic control was observed, with corresponding p=0.015 (Fig. 2).

DISCUSSION

Frequency of depression among type 2 diabetes mellitus

In this study, the frequency of depression among type 2 diabetes patients was found to be 42%. Among the study patients, 71.42% were

Table 2: Gender distribution among diabetic patients with and without depression

Age category	Diabetic patients without depression					
	Female		Male		Total	
	Count	Column n %	Count	Column n %	Count	Column n %
<40	6	12.8	13	24.5	19	19
41–50	20	42.6	21	39.6	41	41
51–60	21	44.7	19	35.8	40	40
Total	47	100	53	100	100	100
Age category	**Diabetic patients with depression**					
	Female		**Male**		**Total**	
	Count	**Column n %**	**Count**	**Column n %**	**Count**	**Column n %**
<40	1	4	2	11.8	3	7.1
41–50	11	44	7	41.2	18	42.9
51–60	13	52	8	47.1	21	50
Total	25	100	17	100	42	100

moderately depressed and 28.5% were severely depressed. Das *et al*. study showed the rate of major depressive disorder to be 46.15% in type 2 diabetes mellitus and among them 32.2% were mildly depressed, 36.7% were moderately depressed, 14.4% had severe depression (n=13), and 16.7% had very severe depression according to the HAM-D scale [11]. Mushtaque *et al*. study revealed that there were a total of 38.75% type 2 diabetes mellitus patients suffered from depression. Out of them, the majority were moderately depressed (48.38%) and none were found to be suffering from very severe depression by HAM-D scoring [12]. Overall, our findings were comparable with most of the studies showing an increased prevalence of depression among type 2 diabetics which needs to be screened for depression.

Table 3: Duration of diabetes among depressed and non-depressed patients

Duration of diabetes	Depression			
	No		Yes	
	Count	Row n %	Count	Row n %
<5 year	32	76.2	10	23.8
6–10 year	24	49.0	25	51.0
>10 year	2	22.2	7	77.8

p=0.002, Chi-square test

Table 4: Baseline FBS, PPBS, and HbA1c levels among the depressed and effect of antidepressant on FBS, PPBS, and HbA1c levels

FBS value	Mean	Standard deviation	p value
Baseline	177.00	7.44	(p<0.001)
At 3 months	169.74	8.02	
At 6 months	160.03	12.78	
PPBS value			
Baseline	251.16	8.49	(p<0.001)
At 3 months	237.11	14.54	
At 6 months	217.84	25.53	
HbA1c value			
Baseline	8.41	0.50	(p<0.001)
At 3 months	8.02	0.39	
At 6 months	7.57	0.47	

p<0.001, each point, <0.0001, repeated measure ANOVA. FBS: Fasting blood sugar, PPBS: Post-prandial blood sugar, HbA1c: Glycated hemoglobin

Age and sex distribution

In our study, among depressed patients 21(50%) were in the age group 51–60 years. There was a female preponderance among depressed patients with 25 patients (59.5%) being female and 17 patients (40.4%) being male. In Mushtaque *et al*. study, the mean age of the depressed group was 50.90±7.73 years and that of the non-depressed group was 48.88±9.54 years. The difference in the age of both groups was not statistically significant (t=0.993, p=0.301). Although depression was more prevalent in the female age group, gender was not found to be significantly associated with depression (p=0.920) [12]. In a systematic review and meta-analysis by Ali *et al*. designed to estimate the prevalence of clinically depressed patients with type 2 diabetes, found that the prevalence of depression was significantly higher among patients with type 2 diabetes (17.6%) than those without diabetes (9.8%). They also found that the prevalence among females with diabetes (23.8%) was higher than their male counterparts with diabetes (12.8%) [13]. In most of the studies, socio-demographic factors of age and gender did not seem to have any significant influence on the occurrence of depression, neither did the duration of diabetes.

Improvement of glycemic control during the treatment for depression

Our study showed a beneficial effect of antidepressant on glycemic control beyond standard diabetic treatment practice. There was reduction of mean FBS levels from baseline value of 177 mg/dl to follow-up value of 160 mg/dl (p<0.001), mean PPBS levels from baseline value of 251.16 mg/dl to follow-up value of 217.84 mg/dl (p<0.001) and mean HbA1c dropped from 8.41 to 7.57 (p<0.001). In Nicolau *et al*. study, 48 type 2 diabetes patients treated with citalopram were screened for determining its effect on depressive symptoms and metabolic control. Patients were followed for 6 months. There were significant improvement in depression scores and in almost all areas of the quality of life; however, no differences were found in glycemic control assessed by HbA1c [14]. Dhavale *et al*. study investigated the effect of escitalopram in 100 type 2 diabetes mellitus with increased blood glucose levels. Depressed patients were then started on escitalopram while their diabetes treatment remained unchanged. They were reviewed 6 weeks later and blood glucose levels were repeated. At the follow-up, 47% of patients started on escitalopram showed clinically and statistically significant lower fasting and postprandial blood glucose levels [9].

Finally, bearing in mind the results of our study, as well as the data from other publications that we have reviewed and believed that further investigations in this field are needed to produce definitive results on

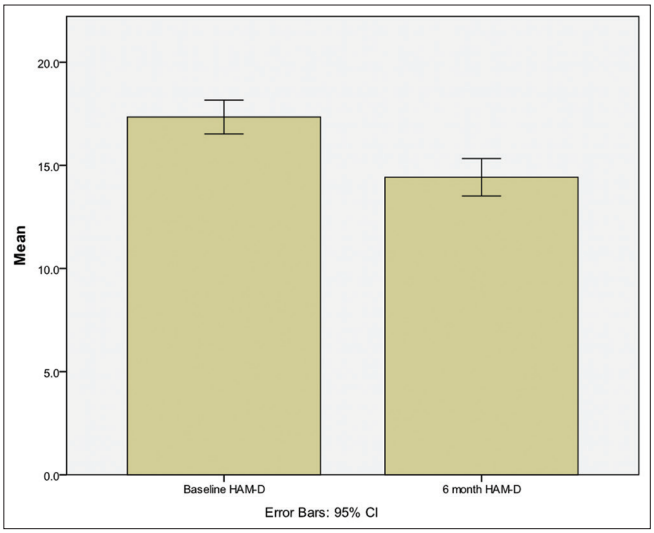

Fig. 1: Mean baseline and follow-up values of Hamilton depression rating scale scores

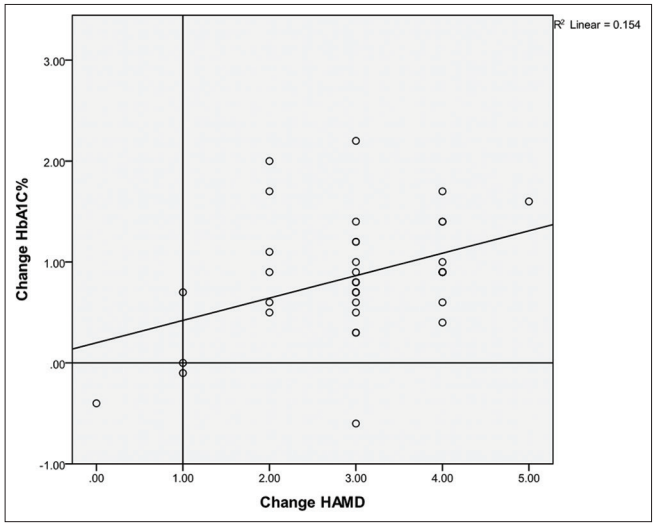

Fig. 2: Correlation between delta Hamilton depression rating scale and delta HbA1c

the significance and range of psychiatric treatment in patients with diabetes and comorbid depression, including the development of more comprehensive and collaborative models for treating both depression and diabetes.

Association between changes in depression status and glycemic control

Our study reports a linear association between improvement in HAM-D scores (delta HAM-D) and improvement in HbA1c values (DHbA1c) in diabetic patients with comorbid depression treated with SSRI antidepressant. It indicates the reciprocal interaction between depression and glycoregulation, suggesting that treatment of depression may be beneficial to both mood and glycemic control. Wiltink *et al.* study showed a linear and consistent association to the intensity of depression in the presence of diabetes (increasing from 6.9% in no or minimal depression to 7.6% in mild, 9% in moderate, and 10.5% in severe depression), i.e., the prevalence of diabetes was elevated substantially (1.5 fold) in severe versus non-depressed patients [15].

LIMITATIONS

Our study did not include a control group because it would mean deterring psychiatric consultation and consecutive treatment in patients with a high HAM-D score corresponding to moderate to severe depression.

CONCLUSION

Our study concluded that patients started on antidepressant showed a reduction in the blood sugar levels and HbA1c levels from their baseline values, which was clinically and statistically significant. This underscores the need for screening and treatment of depression in patients with diabetes, particularly so if the duration of diabetes is 10 years and beyond.

ACKNOWLEDGMENTS

The authors would like to thank the staffs and the postgraduate students of the Department of General Medicine and Clinical Pharmacy, JSS Hospital, Mysore, for their support and encouragement.

AUTHORS CONTRIBUTION

Dr Allu Harshavardhini and Dr Bhanukumar Muthaiah were involved in the concept, design, collection of data, interpretation of data, and manuscript reviewing. Dr Tirin Babu and Dr George Mathew Panachiyil were involved in manuscript preparation, manuscript editing, and dafting of the manuscript. Sisira Santhosh and Sarayu Santhosh were involved in the data collection of the study.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL APPROVAL

Approved by the Human Ethical Committee, JSS Medical College and Hospital, Mysore, Karnataka.

AUTHORS FUNDING

Nil

REFERENCES

1. Da Silva JA, De Souza EC, Böschemeier AG, Da Costa CC, Bezerra HS, Feitosa EE. Diagnosis of diabetes mellitus and living with a chronic condition: participatory study. BMC Public Health 2018;18:699.
2. Hu FB. Globalization of diabetes: The role of diet, lifestyle, and genes. Diabetes Care 2011;34:1249-57.
3. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, *et al*. The Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study: Methodological details. J Diabetes Sci Technol 2011;5:906-14.
4. Alzoubi A, Abunaser R, Khassawneh A, Alfaqih M, Khasawneh A, Abdo N. The bidirectional relationship between diabetes and depression: A literature review. Korean J Fam Med 2018;39:137-46.
5. Egede LE, Ellis C. Diabetes and depression: Global perspectives. Diabetes Res Clin Pract 2010;87:302-12.
6. Avasthi A, Grover S, Bharadwaj R. Clinical practice guidelines for management of depression in elderly. Indian J Psychiatry 2018;60:S341-62.
7. Vishnupriya R, Ezhilramya J, Meenakshi B. Metformin in the prevention of metabolic syndrome associated with initiation of atypical antipsychotic therapy in adolescents and young adults-a randomized, open labelled, single centered study. Int J Pharm Pharm Sci 2016;8:200-6.
8. Ogbonna BO, Ezenduka CC. Drug use indicators in patients with Type 2 diabetes in a teriary healthcare facility in Nigeria. Int J Pharm Pharm Sci 2014;6:493-5.
9. Dhavale HS, Panikkar V, Jadhav BS, Ghulghule M, Agari AD. Depression and diabetes: Impact of antidepressant medications on glycaemic control. J Assoc Physicians India 2013;61:896-9.
10. Gehlawat P, Gupta R, Rajput R, Gahlan D, Gehlawat VK. Diabetes with comorbid depression: Role of SSRI in better glycemic control. Asian J Psychiatr 2013;6:364-8.
11. Das R, Singh O, Thakurta RG, Khandakar MR, Ali SN, Mallick AK, *et al*. Prevalence of depression in patients with Type II diabetes mellitus and its impact on quality of life. Indian J Psychol Med 2013;35:284-9.
12. Mushtaque A, Gulati R, Hossain MM, Azmi SA. Prevalence of depression in patients of Type 2 diabetes mellitus: A cross sectional study in a tertiary care centre. Diabetes Metab Syndr 2016;10:238-41.
13. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: A systematic review and meta-analysis. Diabet Med 2006;23:1165-73.
14. Nicolau J, Rivera R, Francés C, Chacártegui B, Masmiquel L. Treatment of depression in Type 2 diabetic patients: Effects on depressive symptoms, quality of life and metabolic control. Diabetes Res Clin Pract 2013;101:148-52.
15. Wiltink J, Michal M, Wild PS, Schneider A, König J, Blettner M, *et al*. Associations between depression and diabetes in the community: Do symptom dimensions matter? Results from the Gutenberg health study. PLoS One 2014;9:e105499.