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ORIGINAL RESEARCH ARTICLE

EFFECT OF ESCITALOPRAM ON GLYCAEMIC CONTROL IN TYPE 2 DIABETES MELLITUS PATIENTS WITH DEPRESSION

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ABSTRACT

Background: Depression is more common in patients with type 2 Diabetes Mellitus (DM) than patients without type 2 DM. The objective of this study was to study the effect of escitalopram on glycaemic control in type 2 diabetic patients with depression.

Methods: This longitudinal study was conducted in Universal College of Medical Sciences (UCMS), Bhairahawa from September 2019 to March 2020. A total of 137 patients visiting internal medicine OPD and diagnosed with type 2 DM were included. The patients were then referred for psychiatric evaluation. Patient Health Questionnaire -9 was used for the assessment of depression by the consultant psychiatrist. A score of ≥5 was considered as depression. Participants were divided into two groups: Group 1 represented type 2 diabetic patients with depression (n=37) and group 2 without depression (n=100). Escitalopram 10mg daily was prescribed for group 1 patients, keeping the management of DM unchanged for all. The fasting and postprandial blood glucose levels were measured at baseline, two weeks, four weeks, and six weeks interval, respectively, using the automated analyzer.

Results: After the treatment with escitalopram, there was significant ($p<0.05$) reduction in fasting and postprandial blood glucose level in subsequent weeks compared to baseline values. The fasting baseline median blood glucose level in group1 patients reduced from the value of 190.0 to 126.5 mg/dl and postprandial median blood glucose level reduced from baseline value of 295.0 to 201.5 mg/dl at 6 weeks respectively.

Conclusions: Treatment with escitalopram showed a favorable glycemic profile in type 2 DM patients with depression.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia, insulin resistance, defects in insulin secretion, insulin action or both.[1] Type 2 diabetes mellitus is more common than type 1 diabetes mellitus and is associated with comorbid conditions like hypertension, dyslipidemia, depression.[2]

Various studies have shown an increased incidence of depression in patients with type 2 diabetes mellitus.[3-7] Depression is the most common mental disorder that occurs in all ages worldwide. There is a high prevalence of depression with or without comorbid anxiety among patients of DM.[3] Diabetes associated with depression can aggravate both the symptoms of depression as well as diabetes-associated complications.[8] The patients with co-existent diabetes and depression have poorer health outcomes such as poor symptom control, poor glycemic control, more frequent microvascular and macrovascular complications, increased loss of work and higher mortality risk compared to patients with diabetes alone.[9]

Selective Serotonin Reuptake Inhibitors (SSRIs) like Fluoxetine, Escitalopram and Sertraline are commonly prescribed to treat depression associated with diabetes. Among these SSRIs, Escitalopram has high selectivity for the serotonin transporter and has minimal inhibitory effect on cytochrome P-450 2D6 and 3A4 isoenzymes with no risk of hyper or hypoglycemia or weight gain.[10,11]

In the present study, we aimed to observe the effect of Escitalopram in achieving glycemic control in type 2 DM patients with depression.

METHODS

This is a longitudinal follow up study conducted in psychiatry outpatient department (OPD) of Universal College of Medical Sciences (UCMS), Bhairahawa after the approval of the Institutional Review Committee (IRC) of UCMS (IRC No. 189/19).
Sample size was calculated as, $n= Z^2pq/d^2=137$
Where,
p = prevalence of type 2 DM in Nepal[12] =0.084
q =1-p=0.916
d = allowable error at 8%
z = level of significance at 5%

All patients diagnosed with Type 2 DM visiting the internal medicine out-patient department (OPD) of Universal College of Medical Sciences (UCMS), Bhairahawa, Nepal, from September 2019 to March 2020 were referred to psychiatric OPD for evaluation of depression. Informed written consent was obtained from the patients prior to the study. Patients with a history of prior psychiatric illness and/or medication were excluded. Patient Health Questionnaire -9 (PHQ-9) was used for the assessment of depression by the consultant psychiatrist. A score of ≥ 5 was considered as depression. A total of 137 participants were divided into two groups. Group 1 included type 2 diabetic patients with depression (n=37) and group 2 without depression (n=100). Escitalopram 10 mg daily was prescribed for group 1 patients only, keeping the management of diabetes mellitus unchanged for all. The comorbidity conditions identified was referred to respective consultant for further evaluation.

The fasting and postprandial (PP) blood glucose levels were measured at baseline (prior to ESC treatment in group 1), two weeks, four weeks, and six weeks interval, respectively, using the automated analyzer (Huma Star 600, Germany) in central laboratory of UCMS, Bhairahawa. The study Proforma was filled which included socio-demographic parameters, duration of type 2 DM, types of antidiabetic treatment, and co-morbidities (hypertension, Chronic Kidney disease, Diabetic foot, thyroid disorders, and others) present.

Data were entered in Microsoft Excel and analyzed using a statistical package for social sciences (SPSS version 16). Shapiro-Wilk test was done to assess the normality of distribution of the numerical variables. Non-parametric analyses were performed as the distributions were skewed. The Wilcoxon Signed Rank Test was performed to compare blood glucose levels of subsequent weeks with baseline values. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 137 patients diagnosed with type 2 diabetes mellitus were studied, where 37 patients were diagnosed as having depression. Hence, the prevalence of depression in type 2 DM was 27%. Table 1 shows the distribution of socio-demographic variables of the study group. The number of female patients in group 1 was significantly higher (p = 0.019) as compared to males. However, we did not find any significant difference in the age-wise distribution between the two groups.

Table 1: Socio-demographic characteristics of the study group

Variable		Total study population (N=137)	Group 1 (N=37)	Group 2 (N=100)	p-value
Age Group (Years)	25-40	17 (12.4%)	4 (10.8%)	13 (13%)	0.087
	41-60	80 (58.4%)	27 (73%)	53 (53%)	
	>60	40 (29.2%)	6 (16.2%)	34 (34%)	
Sex	Male	66 (48.2%)	10 (27%)	56 (56%)	**0.019**
	Female	71 (51.8%)	27 (73%)	44 (44%)	
Marital status	Married	132 (96.4%)	35 (94.6%)	97 (97%)	0.612 [a]
	Unmarried	5 (3.6%)	2 (5.4%)	3 (3%)	
Education	Illiterate	52 (38%)	17 (46%)	35 (35%)	0.085
	Primary Level	61 (44.5%)	13 (35.1%)	48 (48%)	
	Secondary Level	16 (11.7%)	3 (8.1%)	13 (13%)	
	Higher secondary & above	8 (5.8%)	4 (10.8%)	4 (4%)	
Occupation	Housewife	55 (40.1%)	21(56.8%)	34 (34%)	0.110
	Service	20 (14.6%)	5 (13.5%)	15 (15%)	
	Business	10 (7.3%)	2 (5.4%)	8 (8%)	
	Farmer	30 (21.9%)	5 (13.5%)	25 (25%)	
	Others	22 (16.1%)	4 (10.8%)	18 (18%)	
Socioeconomic status	High	13 (9.5%)	2 (5.4%)	11(11%)	0.554
	Middle	111 (81.0%)	33 (89.2%)	78 (78%)	
	Low	13 (9.5%)	5.4%)	11 (11%)	

p- values obtained from Chi-square analysis. a= Fischer's Exact test. p- values <0.05 considered statistically significant, and are expressed in bold typing

Table 2 shows the diabetic characteristics, duration, management, and co-morbidities present of the study population. The majority of the patients had uncontrolled DM in both groups (73% in Group 1; 67% in Group 2) and were under Oral Hypoglycemic agents for the treatment (67.6% in Group 1; 84% in Group 2).

Figure 1 represents the baseline blood glucose level (both fasting and PP) in the study group. The baseline median values of Group 1 patients are higher compared to Group 2, despite being on anti-diabetic medications.

Table 3 compares the fasting and PP blood glucose levels between the groups at baseline, two weeks, four weeks, and six weeks respectively. Group 1 Patients were prescribed ESC, keeping the treatment of diabetes unchanged. Group 2 patients continued their anti-diabetic treatment as usual. The blood glucose levels (fasting and postprandial) were compared

between the treatment groups in different timelines (baseline, 2, 4, and 6 weeks), respectively, as shown in Table 3. Forty participants (five from Group 1, 35 from Group 2) were lost during follow-up; hence the comparison was made in the remaining study population.

Both group 1 and group 2 patients were under antidiabetic treatment for at least five years. However, the baseline median glucose levels (both fasting and PP) of the Group 1 patients were higher than Group 2 patients. After the treatment of group 1 patients with ESC, this difference was minimized, especially in the 4th and 6th weeks (Table 3). This indicates that antidiabetic drugs alone could reduce blood glucose levels effectively in Group 2 patients, but not in Group 1 patients. However, after the ESC administration, both groups had similar glycemic control, mainly in the 6th week.

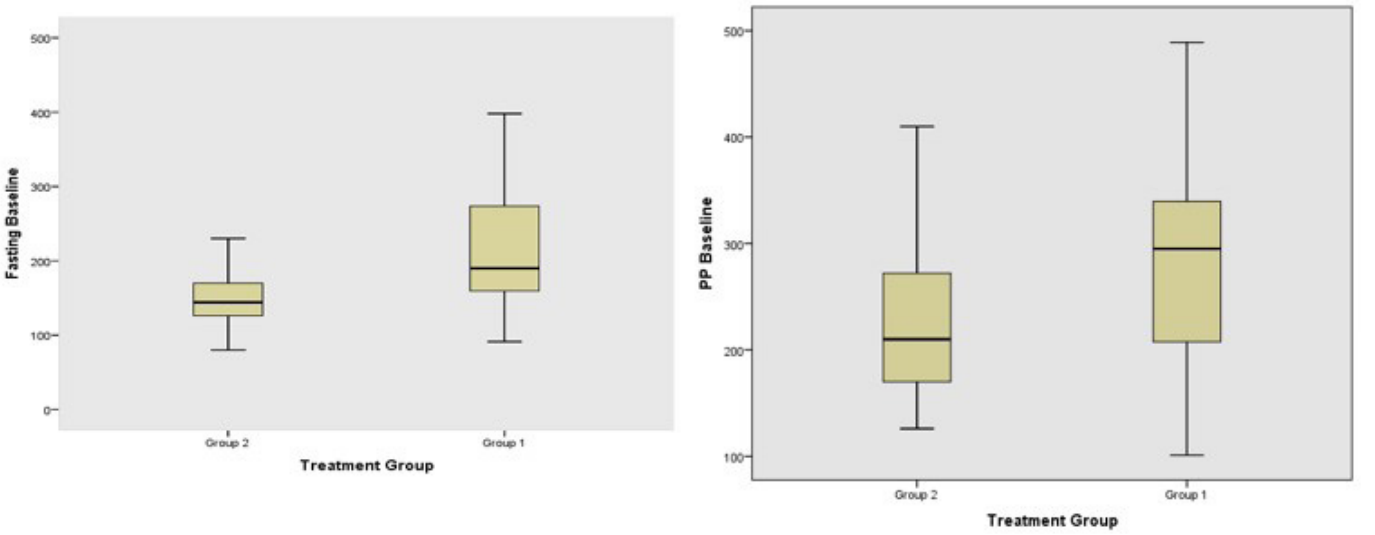

Figure 1: Comparison of baseline blood glucose levels (Fasting and PP) between the groups with depression and without depression

Table 2: Diabetic characteristics of study population

Variables		Total Study Population (N = 137)	Group 1 (N = 37)	Group 2 (N = 100)	p-value
Type 2 DM	Controlled DM	42 (30.7%)	10 (27%)	33 (33%)	0.817
	Uncontrolled DM	95 (69.3%)	27 (73%)	67 (67%)	
Duration Type 2 DM (Years)	≤ 5	85 (62.0%)	17 (46%)	68 (68%)	0.087
	10	24 (17.5%)	7 (19%)	17 (17%)	
	15	13 (9.5%)	7 (19%)	6 (6%)	
	>15	15 (10.5%)	6 (16%)	9 (9%)	
Diabetes treatment	OHA	109 (79.6%)	25 (67.6%)	84 (84%)	0.054
	Insulin	28 (20.4%)	12 (32.4%)	16 (16%)	
Co-morbidities	Present	84 (61.3%)	23 (27.4%)	61 (72.6%)	0.90
	Absent	53 (38.7%)	14 (27.4%)	39 (73.6%)	

Abbreviations: DM-Diabetes Mellitus; OHA- Oral Hypoglycemic Agents; p-values obtained from Chi square analysis. p-values <0.05 considered statistically significant

Table 3: Comparison of fasting and PP blood glucose levels between the study groups

Duration	Total study population (N=97)	Group 1 (N=32)	Group 2 (N=65)	p-value
Fasting Blood Glucose level				
Baseline	155.0 (130.0- 192.5)	190.0 (159.25-276.75)	144.0 (125.5-171.0)	**<0.001**
2 weeks	143.0 (121.0-185.0)	163.5 (130.25-233.75)	138.0 (118.5-166.5)	**0.020**
4 weeks	135.0 (112.0-167.0)	142.0 (120.0-193.75)	133.0 (111.0-154.0)	0.119
6 weeks	125.0 (107.0-156.0)	126.5 (108.0-175.75)	125.0 (106.0-148.0)	0.773
Post Prandial Blood Glucose level				
Baseline	222.0 (177.5-306.5)	295.0 (203.75-339.75)	210.0 (170.0-275.0)	**0.002**
2 weeks	222.0 (169.5-291.5)	266.5 (195.25-308.75)	197.0 (166.5-268.0)	**0.031**
4 weeks	200.0 (156.5-269.0)	235.0 (160.75-283.75)	191.0 (154.5-261.0)	0.388
6 weeks	195.0 (152.5-253.0)	201.5 (140.25-260.0)	193.0 (157.0-250.5)	0.741

Values expressed in Median with 25th and 75th percentile given in parentheses. Mann Whitney U test was performed to compare mean ranks between Group 1 and Group 2. p- values <0.05 were considered statistically significant, and are expressed in bold typing.

We also compared whether a reduction in fasting and PP blood glucose levels was significant in subsequent weeks when compared to baseline values. Both groups had significantly lower blood glucose concentration (both fasting and PP) than baseline values after 2, 4, and 6 weeks of respective medications (Table 4).

Table 5: Blood glucose levels of 2, 4, and 6 weeks compared to baseline values in group 1 and 2

Blood glucose Levels (mg/dl)	Timeline	Median (25 -75 percentile)	p-value
Fasting - Group 1 (Antidiabetics + ESC)	Baseline	190.0 (159.25-276.75)	
	2 weeks	163.5 (130.25-233.75)	**<0.001**
	4 weeks	142.0 (120.0-193.75)	**<0.001**
	6 weeks	126.5 (108.0-175.75)	**<0.001**
Fasting - Group 2 (Antidiabetics)	Baseline	144.0 (125.5-171.0)	
	2 weeks	138.0 (118.5-166.5)	**0.019**
	4 weeks	133.0 (111.0-154.0)	**0.007**
	6 weeks	125.0 (106.0-148.0)	**0.002**
Postprandial - Group 1 (Antidiabetics + ESC)	Baseline	295.0 (203.75-339.75)	
	2 weeks	266.5 (195.25-308.75)	**<0.001**
	4 weeks	235.0 (160.75-283.75)	**<0.001**
	6 weeks	201.5 (140.25-260.0)	**<0.001**
Postprandial - Group 2 (Antidiabetics)	Baseline	210.0 (170.0-275.0)	
	2 weeks	197.0 (166.5-268.0)	**<0.001**
	4 weeks	191.0 (154.5-261.0)	**<0.001**
	6 weeks	193.0 (157.0-250.5)	**<0.001**

All the values were compared with baseline values. p- values were obtained from Wilcoxon Signed Rank test. p- values < 0.05 considered to be statistically significant, and are expressed in bold typing.

DISCUSSION

This longitudinal study was conducted among 137 patients with type 2 diabetes mellitus under antidiabetic medications. The prevalence of depression among diabetic patients in the present study was 27%. Various other studies have reported a higher prevalence of depression in type 2 DM patients at 34%[13], 39%[14], and 34.4%.[15] However, the relationship of diabetes and depression is unknown. The higher prevalence of depression in diabetic patients may be related to severe chronic illness, psychological factors associated with diabetes, and diabetic complications. Most of the diabetic patients with depression were females (27; 73%) and most of them are housewife (Table 1), in accordance with other studies. [10,14] Majority (73%) of the depressive patients belonged to the age group 41-60 years. The mean ages from the other studies also fell within same age group. [10, 14, 15] The reason for this is unclear and further study is required in future to rule out the cause of depression in diabetic patients.

In the present study, the baseline blood glucose levels (both fasting and PP) were higher in patients with diabetes and depression compared to patients with diabetes alone. A similar finding by De la Roca- Chiapas JM et al. [16] and Groot et al. [9], Lustman PJ et al. [17] also have indicated that depression is associated with a patient with a higher blood glucose level. This may be due to poor adherance to diabetic medications, poor adherance to dietary habits, poor glycemic control and more diabetic complications. However, the exact mechanism is unknown.

Patients with chronic medical conditions, such as type 2 DM, are more likely to suffer from depression. Depression can interfere with self-care in diabetes and increase the risk of micro and macrovascular complications. [14] The relation between depression and diabetes is still not clear as they seem to be intricately linked. Whatever be the causal association, the presence of one can significantly impact the other. Various studies have indicated that depression is associated with hyperglycemia.[10, 14,15] Depressed patients have poor glycemic control, despite medication, compared to the patients without any mood disorders like anxiety, depression etc.[9, 16, 18] Depression is associated with increased activity of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system resulting in increased release of cortisol, catecholamines, and glucagon. This results in increased glucose production, decreased insulin sensitivity, and reduced insulin secretion.[19] Also, the patients with depression are less attentive towards a healthy lifestyle and increase the risk for type 2 DM. Similarly, the presence of depression in diabetic patients may be due to chronic antidiabetic treatment, diet restriction, increase financial burden, and various diabetes-related complications. Hypo or hyperglycemia induces negative emotional states in patients with diabetes resulting in depressive symptoms.[18]

In our study, we measured the fasting and PP blood glucose levels across various timelines (baseline, 2, 4, and 6 weeks). The baseline median blood glucose values in diabetic patients with depression were higher than diabetic patients without depression, as mentioned above. This suggests insufficient glycemic control in group 1 patients despite similar anti-diabetic treatment as the other group. After ESC treatment in this group, the difference in median blood glucose levels between the two groups diminished and was even comparable by the sixth week. Also, the reduction in blood glucose values was highly significant in both groups when compared with baseline values. While this reduction can be attributed to the ongoing anti-diabetic therapy in the patients without depression, the

significant reduction in group 1 patients cannot be accredited solely to the anti-diabetic medications given the high baseline blood glucose values. A similar decrease in fasting and post-prandial blood sugar level was also found in the study done by Gehlawat et al [10] ($p<0.05$) and Dhavale et al [14] (FBSL $p\leq0.029$; PPBSL $p\leq0.004$). Another study done by Mathews J et al. [15] also found a statistically significant difference in fasting and post-prandial blood sugar level compared to baseline blood sugar levels after escitalopram treatment ($p<0.05$).

Whether the glycemic control achieved in group 1 patients after ESC treatment is simply due to the adequate management of the depression, an important type 2 DM risk factor, or due to specific glycemic control achieved by the drug cannot be hypothesized from this study. Various commonly used antidepressants, such as tricyclic antidepressants (TCAs), have shown to increase the risk for hyperglycemia.[15] The selective serotonin reuptake inhibitors (SSRIs) like ESC, on the other hand, have demonstrated favorable glycemic control effects in type 2 DM patients with depression on both short term and long term use.[14, 15, 20] It has been suggested that serotonergic activities of SSRIs result in increased insulin sensitivity and consequent reduction in blood sugar levels. Various studies have also shown that ESC treatment restores the hypothalamic-pituitary-adrenal axis and improved glucose uptake and insulin stimulation [21], reduce the risk of poor glycemic control [22] and have a synergistic effect on both mood and glycemic level in depressed diabetic patients.[23] Furthermore, ESC is a new SSRI with better-tolerated side effects in elderly patients and also has a rapid onset of action (1-2 weeks). These properties have made ESC the most prescribed antidepressant medication in depressive patients with diabetes.[14] The findings from our study also favor the use of this drug in depressed diabetic patients to achieve the desired glycemic control, in addition to antidiabetic medications. However, larger studies with proper assessment of comorbid conditions and other confounders are recommended for validation.

This is a single-center study with a small number of patients, so results could not be generalized. There is a need for further multicenter studies for establishing effective treatment options for the patients of comorbid diabetes and depression. The effects of comorbid conditions on glycemic control, as well as depression, were not evaluated. Thus, large studies should be done to find out the depression in type 2 diabetes patients and their comorbid complications. More studies are required to compare the role of antidepressants in treating depression in diabetic patients.

CONCLUSION

This study suggests that depression is common in patients with type 2 DM. Thus, the assessment of depression should be done in patients with type 2 DM. The present study showed a significant reduction in fasting and post-prandial blood glucose level from baseline to six weeks after the treatment with Escitalopram in patients with diabetes mellitus and depression. Thus, Escitalopram can be considered as an efficacious drug for treating depression in patients suffering from type 2 diabetes mellitus. Further large-scale studies, including comparison with other antidepressants, are recommended.

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CONFLICT OF INTEREST: None

FINANCIAL DISCLOSURE: None

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