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Body Weight, Serum Insulin, Blood Glucose, Glycated Hemoglobin HbA1C and Insulin Resistance in Escitalopram treated type 2 Diabetic Subjects

Sapna[1], Rahul Roy[2], Pir Naveed Ahmed Ahsan[3], Pir Maroof[3], Rahat Ahmed Memon[3] and Aisha[3]

[1]House Intern, Abbasi Shaheed Hospital, Karachi.

[2]Post-graduate resident, Department of Psychiatry, Lumhs, Jamshoro.

[3]House Intern, Liaquat Universirty Hospital, Jamshoro.

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ABSTRACT

Analyze the body weight, serum insulin, blood glucose, and HbA1C and Insulin resistance in Escitalopram treated type 2 diabetic subjects (T2DM). Observational study. Department of Medicine, Liaquat University of Medical and Health Sciences Jamshoro/Hyderabad from June 2015 to August 2016. A sample of 50 diagnosed cases of T2DM subjects taking Escitalopram 10 mg/kg were selected according to pre-defined criteria. Physical examination was performed. After 3 months of Escitalopram intake, the blood samples were taken for biochemical analysis. Body weight, blood pressure, fasting serum insulin, fasting and random blood glucose, A1C and Insulin resistance (HOMA-IR %) were estimated. *Statistix 10.0* (USA) software for data analysis (95% Confidence interval). Mean ± SD of age was noted as 51.5± 6.5 years (p=0.51). Body weight (kg) at baseline and three months decreased from 79.8±11.6 to 76.0±9.4 kg (p=0.031). Fasting insulin, fasting glucose and insulin resistance (HOMA-IR) at baseline and after 3 months were noted as 133.0±21.7 vs. 128.0±11.7 mg/dl (p=0.0001), 16.0±5.50 vs. 13.5± 3.5 µIU/ml (p=0.0001) and 7.15 vs. 6.09% (p=0.0001) respectively. Escitalopram improves fasting insulin, fasting glucose and insulin resistance and decreases body weight in type 2 DM subjects.

Introduction

Diabetes mellitus has become a challenging health issue of the World. Type 2 DM now counts in majority. Similarly, the socio economic problems of poverty and depravedness are prevailing in the developing countries and have begotten a large number of subjects suffering from anxiety and depression. Depression may run over a sufficient duration to become major depressive disorder (MDD), which is a chronic mental illness.[1,2] The economic constraints put the diabetic subjects at an increased risk of anxiety and depression. Depression interferes with personality, mood, self-care and drug non-compliance.[3,4] Hence, it becomes essential to prescribe the anti-depressants even for the diabetic subjects. T2DM is itself a multi-faceted metabolic disorder of hyperglycemia, hyperinsulinemia, insulin resistance, obesity, and abnormal glucose homeostasis. Altered glycemic control has been correlated with depression. Contrary to this, the most commonly used Specific serotonin reuptake inhibitor (SSRI) anti-depressants are reported to enhance the insulin sensitivity through an increase in serotonin. Serotonin exaggerates the insulin sensitivity, and cases of hypoglycemia are reported.[5-7] Escitalopram is an S-enantiomer of SSRI citalopram which is widely prescribed SSRI because of specificity, selectivity, clinical efficacy, less chances of suicidal tendency, and recurrence of depression. Escitalopram shows near absolute specificity for the serotonin with negligible interactions with other receptors and brain bioamines.[7,8] Escitalopram does not exhibit affinity for the receptors of dopamine, epinephrine and nor-epinephrine unlike to other SSRI for example the fluvoxamine.[9] Majority of SSRIs increase appetite and do weight gain, which may create problems for the glycemic control, however, the Escitalopram has not shown weight gain, hence it may be safer for the diabetic subjects compared to other family members of SSRIs. Drug interactions are also a few for the Escitalopram.[10]

Previous studies have reported the Escitalopram are effective in alleviating the mood, and relieving symptoms of depression, with an improvement in the glycated hemoglobin A1 (A1C).[11]. Evidences suggest the serotonin mediated neural pathways might be playing role in the glycemic control through effects possibly on the fasting glucose, fasting insulin, body weight, and insulin sensitivity and resistance. Such effects if really exist for the Escitalopram, then it exploited for improving the glycemic control.[11] Animal mice model studies reported the SSRIs mediated hyper-serotoninemia decreases the hyperglycemia in a dose dependent fashion, such observations may prove promising option for the Diabetics suffering from depressions.[11,12] Interestingly, type 2 diabetics show decreased circulating serum serotonin levels normally because of unknown reasons.[11-13] A search of medical literature shows a few *in-vivo* human studies are reported; hence the gap exists seriously to conduct more research on the topic for evidence based findings.

The present study is the first of its design which was conducted to analyze the effects of three months Escitalopram therapy on body weight, serum insulin, fasting and random

Tele: +92-333-2211220
E-mail address: sapna.dr91@gmail.com

blood glucose, A1C and Insulin resistance in type 2 diabetic subjects

Subjects and Methods

This is an observational study, conducted at the Department of Medicine, Liaquat University of Medical and Health Sciences Jamshoro/Hyderabad from June 2015 to August 2016. Diagnosed cased of T2DM suffering from depression were interviewed for the socio economic problems and depression in detail. Volunteer T2DM suffering from depression not taking SSRI anti-depressants were informed about the purpose of study, its merits and demerits. To get them into confidence many interviews were conducted on different visits. Finally, a sample of T2DM with depression was selected as per criteria of inclusion and exclusion. Study subjects were through non-probability (purposive) sampling technique. Age 30- 60 years, ≥5 years DM duration, depression symptoms, and both genders were the inclusion criteria. Subjects taking anti-depressants, and suffering from chronic systemic disease such as chronic liver disease (CLD), coronary artery disease, and diabetic kidney disease (DKD) were excluded. Subjects were informed of willingness and to sign the consent form and were requested to abide by for follow ups till study is completed. They were asked that the study needs blood sampling and checking of body weight and blood pressure. Blood sampling were to be used for biochemical tests. Volunteers were enrolled and entitled a code for patient confidentiality. Body weight, and systemic blood pressure measurement were performed by a trained nurse and a medical officer followed by a Physician. Body weight was measured on a weighing machine. Blood pressure was measured after five minutes rest according to proper protocol.

- **Diabetes mellitus**

DM was defined in accordance to the criteria set out by the American Diabetes Association (ADA) i.e. blood glucose (fasting) ≥ 126mg/dl and blood glucose (random) (RBG) ≥200 mg/dl.[14]

- **Escitalopram**

Escitalopram (*Cipralex*) was purchased from Pharmacy of the Liaquat University hospital. 10 mg of Escitalopram was given orally for 3 months continuously.

- **Blood sampling**

Overnight fasting of at least 8-12 hours was necessary for the fasting glucose and fasting insulin. Venipuncture was performed by senior nurse. Blood was centrifuged 4000 rpm for 15 minutes. Sera were preserved for biochemical analysis. Storage of sera, if needed, was done at -20^{0}C.

- **Biochemical Analysis**

The serum insulin was assessed by ELISA method and blood glucose by "*glucose oxidase*" method. A1C was assayed per criteria of DCCT guidelines on Hitachi 902 Chemistry analyzer (Roche diagnostics, USA). Insulin resistance (HOMA-IR) % = fasting insulin × fasting glucose/22.5.[15]

- **Ethical clearance and consent form**

Ethical review committee was approved the study protocol and consent form was designed for the volunteers participating in the study.

- **Confidentiality and Proforma**

A structured Proforma was designed for data collection and confidentiality was maintained.

- **Data Analysis**

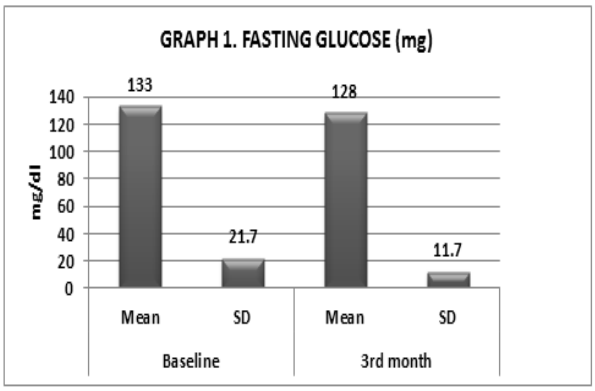
Data analysis was completed on the *Statistix version 10.0* (USA). Continuous and categorical variables were analyzed by paired samples "t" test, one sample t test (age) and Chi-square test. Data was analyzed at 95% CI ($p \leq 0.05$).

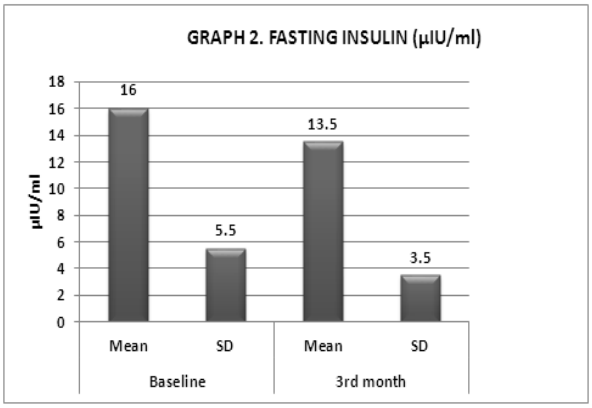
Results

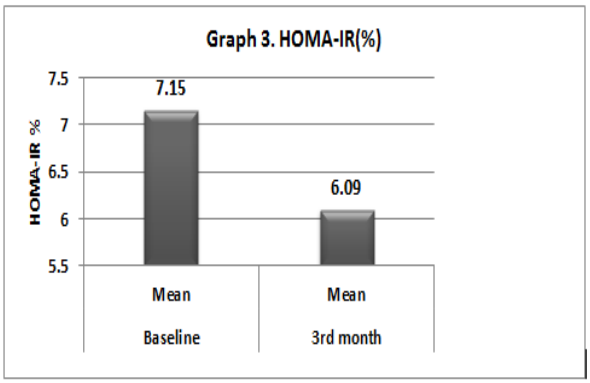
These observational study reports results of 50 diagnosed cases of type 2 DM at baseline and after three months of Escitalopram therapy. Mean ± SD of age was noted as 51.5± 6.5 years (0.51). Body weight (kg) at baseline and three months was reduced from 79.8±11.6 to 76.0±9.4 kg (p=0.031). Of 50 subjects, 31 were male and 19 were female patients. Male to female ratio was 1.63:1. Male subjects pre-dominated in the present study. Systolic and diastolic BP showed no differences at baseline and after three months. Random blood glucose, A1C, fasting glucose, fasting insulin, serum total cholesterol and insulin resistance showed statistically significant improvement after three month Escitalopram therapy (table 1). Fasting insulin, fasting glucose and insulin resistance (HOMA-IR %) at baseline and after 3 months were noted as 133.0±21.7 vs. 128.0±11.7 (p=0.0001), 16.0±5.50 vs. 13.5± 3.5 (p=0.0001) and 7.15 vs. 6.09 (p=0.0001) respectively (table 1, Graphs 1-3).

Table 1. Glycemic control and blood lipids in type 2 Diabetic subjects (n=100).

	Baseline (mean± SD)	3 months (mean± SD)	p-value
Body weight (kg)	79.8±11.6	76.0±9.4	0.031
Systolic BP (mmHg)	144.4±19.3	141.2±20.2	0.53
Diastolic BP (mmHg)	80.4±9.6	79.7±10.0	0.076
Random Blood glucose (mg/dl)	237.0±45.7	233.0±47.0	0.001
A1C (%)	11.7± 5.01	11.03±1.4	0.034
Blood glucose (F) (mg/dl)	133.0±21.7	128.0±11.7	0.0001
Fasting insulin (µIU/ml)	16.0±5.50	13.5± 3.5	0.0001
HOMA-IR (%)	7.15	6.09	0.0001
Total cholesterol (TC) (mg/dl)	201.0±42.0	176.1± 53.7	0.0001







Discussion

The present study is the first to analyze the body weight, serum insulin, blood glucose, A1C and Insulin resistance in Escitalopram treated type 2 diabetic subjects (T2DM). After 3 months of Escitalopram, the body weight, serum insulin, blood glucose, A1C and Insulin resistance showed statistically significant differences ($p<0.05$). The body weight (kg) at baseline and at third month decreased from 79.8±11.6 to 76.0±9.4 kg ($p=0.031$). Fasting insulin, fasting glucose and insulin resistance (HOMA-IR %) at baseline and after 3 months were noted as 133.0±21.7 vs. 128.0±11.7 ($p=0.0001$), 16.0±5.50 vs. 13.5± 3.5 ($p=0.0001$) and 7.15 vs. 6.09 ($p=0.0001$) respectively. The study was planned keeping in view the rising frequency of depression and DM, both may aggravate each other. Previous studies[16,17] had reported the Pakistan has great burden of type 2 diabetics which is estimated to multiply by 2035.

Worse economic constraints, worries and anxieties of "non-having", loss of peace, terrorism have badly affected the society. These prevailing social conditions have added many new cases of depression, in particular the diabetics with depression taking SSRIs need continuous surveillance. Escitalopram is now widely used but the effects on the glycemic control are not known.

Previous studies reported the depression is associated with insulin resistance and altered glycemic status. While SSRIs enhance insulin sensitivity through serotonin mediated neural pathways causing hypoglycemia's.[5-7] The finding of glucose lowering effect of Escitalopram is consistent with the above studies. SSRIs not only alleviate the symptoms of depression but also improve the A1C.[11] In present study the A1C was reduced from 11.7± 5.01 at baseline to 11.03±1.4 at third month ($p=0.034$). The findings are in agreement with previous studies.[11,12] Increase serotonin levels by SSRIs have impact on the glycemic control in type 2 diabetics, has been reported previously.[18,19] The observations of present study are in agreement with above studies.

A previous study reported the intra portal infusion of 5-HT[20] or 5-hydroxytryptophan (5-HTP),[21] decreased the blood glucose and increased the glycogen formation in liver as evaluated by the Euglycemic clamp. The findings support observations of our present study. Previous study reported the intra-portal SSRI fluvoxamine lowered blood glucose with an increase in liver glycogen.[21] The findings of present study are in agreement with previous studies conducted on animals[22,23] and type 2 diabetic subjects.[24,25] Another previous study[26] reported the SSRIs increase plasma insulin in rats thereby causing hypoglycemia. The finding of hypoglycemic effect of Escitalopram is a consistent finding.

While other studies had reported the SSRIs increase the insulin sensitivity in diabetic rats[26,27] and in the humans.[24,25] The present study chose Escitalopram because it has low affinity for receptors of other biogenic amines for example adrenergic, histamine, muscarinic, and benzodiazepine receptors, etc.[28]

In a previous study[29] Escitalopram was infused intravenously 10 mg/h (2 µg/ kg/min) in humans, which produced a plasma concentration similar to 20 mg oral dose. They reported hypoglycemic effect with increase in liver glycogen in human beings.[29] The findings of the present study are in agreement with above study.

A previous case report[30] reported of Escitalopram induced hyperglycemia in a diabetic woman. Hyperglycemia was uncontrolled with glibenclamide. It was reported hyperglycemia disappeared once Escitalopram was discontinued.[30] The findings of above study are inconsistent to present and previous studies.[25-27] Other previous studies reported the serotonin neural pathways might be involved in the lipid metabolism.[30,31] The observation of low cholesterol at third month in present study is a supporting finding to above studies.

The limitations of present study are a small sample size; the plasma Escitalopram drug concentration was not measured. However, the effects of Escitalopram on the body weight, serum insulin, blood glucose, HbA1C and Insulin resistance are new observations worth to report.

Conclusion

The present study reports that the Escitalopram improves fasting insulin, fasting glucose and insulin resistance and decreases body weight in type 2 diabetic subjects. A positive decreasing effect on serum cholesterol was also observed.

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