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Original Article

The effects of sertraline on blood lipids, glucose, insulin and HBA1C levels: A prospective clinical trial on depressive patients

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Abstract

BACKGROUND: In this study, we aimed to investigate the possible effects of sertraline on blood glucose and lipid levels as risk factors for cardiovascular disease in depressive patients.

METHODS: Eight male and twelve female depressive patients, diagnosed according to DSM-IV criteria, were included in this study. The subjects aged 19-50 years, did not smoke, and had normal body mass index (BMI), homeostasis model assessment-estimated insulin resistance (HOMA-IR) values, blood pressure, blood glucose, insulin and lipid levels. Sertraline therapy (50 mg/day) was started. Patients with diabetes mellitus, heart disease, pregnancy, and those taking other drugs were excluded from the study. Blood glucose, insulin, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and triglyceride values were measured in patients before, and at the 4th, 8th and 12th weeks after treatment with sertraline. Moreover, HbA1C levels were measured at the beginning and at the end of the treatment (at 12th weeks).

RESULTS: There were no significant differences in physical examination (blood pressure, BMI, body weight, height, waist circumference) and laboratory findings (glucose, HDL-C, LDL-C, HOMA-IR and HbA1C levels) at the 12th week after of treatment with sertraline compared to pretreatment values. However, insulin levels at the 4th, 8th and 12th weeks significantly increased compared with pretreatment values. Likewise, triglyceride levels at the 8th and 12th weeks significantly increased compared with pretreatment values.

CONCLUSIONS: Sertraline-treated patients have to be followed up for blood insulin and triglyceride levels. In addition, their treatment plan needs to be adjusted as necessary to prevent possible metabolic changes.

KEYWORDS: Sertraline, Insulin, Glucose, Lipid, HbA1C.

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Depression, a common disease among the adult population, is also accepted as a risk factor for cardiovascular diseases.[1-5] Clinically apparent cardiovascular disease risk factors are hypertension, hyperlipidemia, hyperglycemia. However, the effects of selective serotonin reuptake inhibitors (SSRI), novel antidepressant drugs, on these risk factors remain unclear.

Fluoxetine has been reported to decrease blood glucose levels in obese non-insulin-dependent diabetics.[6] An 8-week course of treatment with fluoxetine was also shown to decrease fasting blood glucose levels in major depressive disorder patients.[7] Long-term use of antidepressant drugs (paroxetine, citalopram) decreased insulin requirement and glycosylated hemoglobin (HBA1C) levels in diabetic patients.[8] In case of blood lipid levels, while paroxetine did not alter the levels of cholesterol, sertraline, fluoxetine and fluvoxamine increased cholesterol levels in a clinical study.[9]

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In an another study, paroxetine and sertraline increased low density lipoprotein cholesterol (LDL-C) levels in depressive patients.[10] In one case with social phobia severe hypertriglyceridemia was observed as a result of venlafaxine and fluoxetine.[11] While paroxetine increased total cholesterol, high density lipoprotein cholesterol (HDL-C) and LDL-C levels in patients with panic disorder, sertraline increased total cholesterol and LDL-C but did not affect HDL-C, and citalopram increased only HDL-C.[12]

On the basis of these clinically confusing results, we aimed to investigate possible effects of sertraline, a widely used SSRI drug in the treatment of depression, on blood glucose and lipid levels which are risk factors for cardiovascular disease in depressive patients.

Methods

This was a prospective clinical trial conducted on patients applied to the Psychiatry Clinic of Farabi Hospital in School of Medicine, Karadeniz Technical University. Patients (8 male and 12 female) diagnosed as depressive according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria who aged between 19-50 years, did not smoke, and had normal body mass index (BMI), homeostasis model assessment-estimated insulin resistance (HOMA-IR) values, blood pressure, blood glucose, insulin and lipid levels were included in our study. Afterwards, sertraline therapy (50 mg/day) was started (Table 1). At the beginning of the study, informed consents were taken from the patients. The study was approved by the Local Ethics Committee of School of Medicine, Karadeniz Technical University (approval number: 2007/10). Patients with diabetes mellitus, heart disease, pregnancy, or those taking other drugs were excluded from the study.

Study protocol:

Blood glucose, insulin, HDL-C, LDL-C, and triglyceride values were measured in patients before treatment with sertraline, and at the 4th, 8th and 12th weeks. HbA1C levels were measured at the beginning and at the end of the treatment (the 12th weeks). All blood samples were taken at the same time of the day. Drug dose for each patient was determined by the psychiatrist. The study terminated at the end of the 12th week and patients were treated by a psychiatrist afterwards.

Reference ranges of the measured parameters were as follows: glucose (60-110 mg/dl), insulin (2.6-25 μU/ml), HDL-C (30-70 mg/dl), LDL-C (60-130 mg/dl), HBA1C (4.2-6.4%), and triglyceride (50-175 mg/dl). Insulin levels were measured by electrochemiluminescence immunoassay method using Elecsys 2010 autoanalyzer. Glucose, HDL-C, LDL-C, triglyceride, and HbA1C were measured by a Roche-/Hitachi 912/917 autoanalyzer

Statistical analyses:

The data is expressed as mean ± SD. Statistical analyses were performed using $SPSS_{17}$. Due to violations of parametric test assumptions (non-normal distribution and low number cases), comparison of changes in measured values over time was carried out using Freidman test. Wilcoxon Signed Ranks test was then performed to show the significance of pairwise differences. The level of significance was set at $p < 0.05$.

Results

There were no significant differences in physical and laboratory examination findings between the 12th week of treatment with sertraline and pretreatment values. The only significant difference was detected in insulin and triglyceride levels (Table 2). In addition, blood glucose values during treatment with sertraline did not significantly differ from pretreatment values (Figure 1).

A significant increase was seen in blood insulin values obtained at the 4th, 8th and 12th weeks of treatment with sertraline compared to pretreatment values ($p < 0.05$) (Figure 2). There was no significant difference in HDL-C and LDL-C values during treatment with sertraline compared to pretreatment values (Figure 3). However, triglyceride levels were

Table 1. Demographic, physical and laboratory examination findings of patients

	Study findings	Normal range values
Age (year)	19-50	-
Sex (male/female)	8 / 12	-
Body weight (kg)	82.31 ± 4.01	-
Height (cm)	163.5 ± 3.58	-
Waist circumference (cm)	97 ± 3.58	-
BMI (Body mass index)	25.27 ± 1.61	20-25.9
Systolic blood pressure (mmHg)	116.67 ± 5.09	< 140 mmHg
Diastolic blood pressure (mmHg)	82.50 ± 1.02	< 90 mmHg
HOMA-IR	2.30 ± 0.21	< 2.5
Glucose (mg/dl)	94.13 ± 4.20	60-110
Insulin (µU/ml)	9.91 ± 0.86	2.6-25
HDL-C (mg/dl)	45.40 ± 2.82	30-70
LDL-C (mg/dl)	109.47 ± 7.90	60-130
Triglyceride (mg/dl)	120.93 ± 10.76	50-175
HbA1C (%)	5.55 ± 0.10	4.2-6.4

HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment-estimated insulin resistance.

significantly increased at the 8th and 12th weeks of treatment compared to pretreatment values ($p < 0.05$) (Figure 3). No significant difference was observed in HbA1C values compared to pretreatment value (Figure 4).

Discussion

There were not any differences in blood glucose and HbA1C levels between pre- and post-values in sertraline-treated patients with depressive disorder in our study. However, insulin levels were significantly increased at the 4th, 8th and 12th weeks compared with pretreatment values.

Erenmemisoglu et al. have shown that sertraline did not change insulin level but reduced blood glucose level in mice.[13] Gomez et al. demonstrated that sertraline increased glucose-stimulated insulin secretion in rats.[14,15] However, clinical studies indicated sertraline

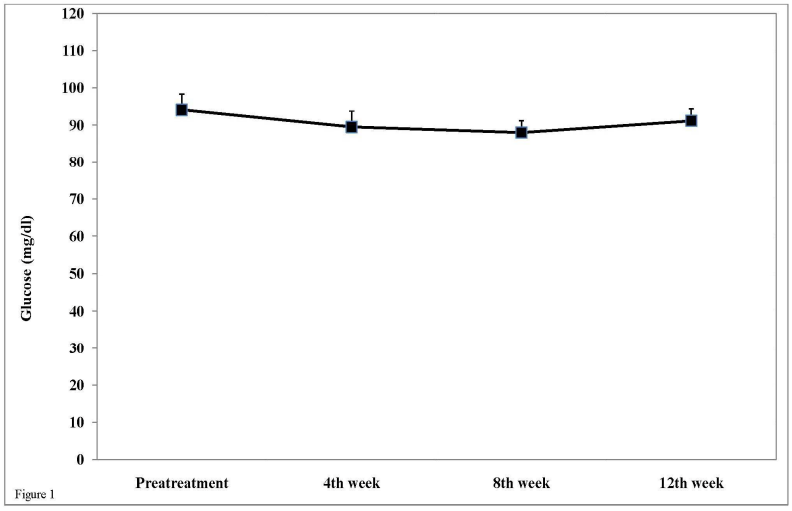

Figure 1. Pretreatment and post-treatment blood glucose levels at the 4th, 8th and 12th weeks of sertraline treatment
*: Compared with pretreatment values ($p < 0.05$).

Table 2. Pretreatment and post-treatment physical examination findings at the 12th week of sertraline treatment

	Pretreatment values	Post-treatment values	p
Systolic blood pressure (mmHg)	116.67 ± 5.09	118.33 ± 6.42	> 0.05
Diastolic blood pressure (mmHg)	82.50 ± 1.02	78.33 ± 4.36	> 0.05
Body weight (kg)	82.31 ± 4.01	82.35 ± 3.76	> 0.05
Height (cm)	163.5 ± 3.58	163.5 ± 3.58	> 0.05
Waist width (cm)	97 ± 3.58	95.75 ± 2.81	> 0.05
BMI (Body mass index)	25.27 ± 1.61	25.27 ± 1.50	> 0.05
HOMA-IR	2.30 ± 0.21	5.83 ± 1.91	> 0.05
Glucose (mg/dl)	94.13 ± 4.20	91.14 ± 3.19	> 0.05
Insulin (µU/ml)	9.91 ± 0.86	22.98 ± 3.56	< 0.02
HDL-C	45.40 ± 2.82	42.43 ± 3.10	> 0.05
LDL-C	109.47 ± 7.90	104.29 ± 7.29	> 0.05
Triglyceride (mg/dl)	120.93 ± 10.76	205.43 ± 22.89	< 0.02

HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment-estimated insulin resistance.

to cause different incremental or decremental effects on blood glucose level.[16,17] A 180-day sertraline treatment reduced insulin requirement and HbA1C levels in diabetic patients.[8] Sertraline, as a SSRI, may increase insulin secretion since serotonin increases insulin secretion in pancreas.[18] In our study, while an increase in insulin levels was obtained, no change in blood glucose level was measured. Long-term use of SSRIs, e.g. fluoxetine and paroxetine, has been reported to decrease blood glucose levels in diabetic patients and major depressive disorder patients.[6,7] The difference between the results of these studies and our results might be explained by the difference in chemical structure, metabolism and pharmacokinetics of SSRI drugs which are a heterogeneous group of antidepressants. In addition, although we observed increased insulin levels, the levels were still in normal range and therefore did not affect blood glucose level. It should also be noted that the duration of this

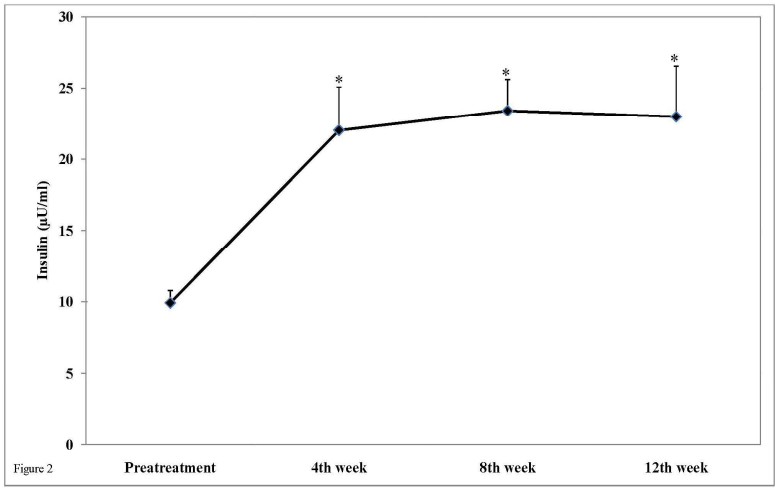

Figure 2. Pretreatment and post-treatment blood insulin levels at the 4th, 8th and 12th weeks of sertraline treatment
*: Compared with pretreatment values (p < 0.05).

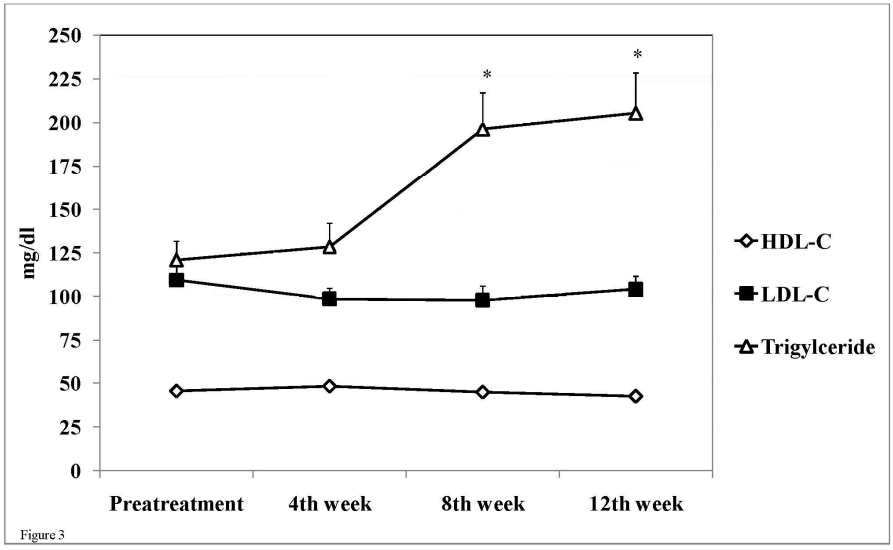

Figure 3. Pretreatment and post-treatment blood HDL-C, LDL-C and triglyceride levels at the 4th, 8th and 12th weeks of sertraline treatment
*: Compared with pretreatment value ($p < 0.05$).

study could have been too short to show the chronic effects of sertraline on blood glucose level. Moreover, as hypothesized in literature,[19] our results might also be explained by hepatic insulin-sensitizing substance (HISS). HISS is released from the liver by insulin. It acts selectively for skeletal muscles and leads to uptake and storage of glucose as glycogen in the large skeletal muscle masses. In the absence of HISS release, the response to insulin is reduced and more insulin has to be secreted from the pancreas.[19,20] Sertraline might prevent the release of HISS from the liver and may cause an increased insulin secretion to regulate glucose.

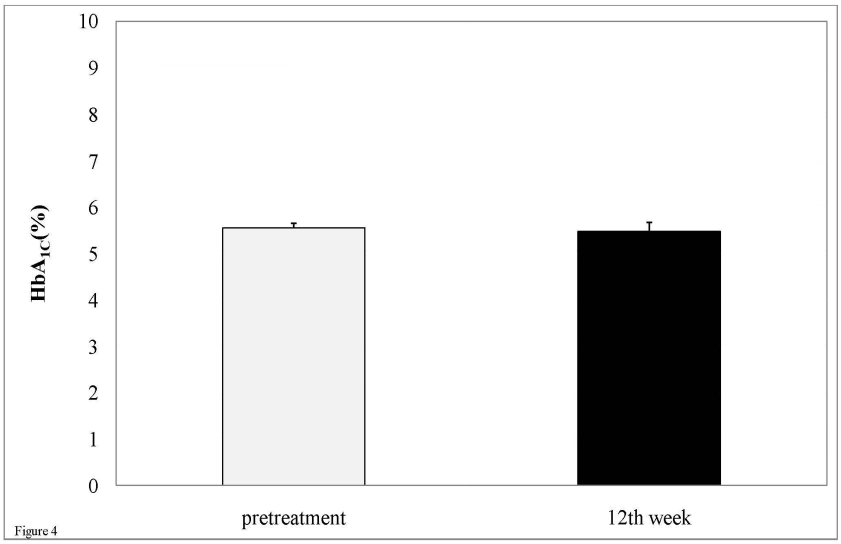

Figure 4. Pretreatment and post-treatment blood HbA1C levels at the 12th week of sertraline treatment
*: Compared with pretreatment values ($p < 0.05$).

In the present study, although HDL-C and LDL-C levels in sertraline-treated patients with depressive disorder did not significantly differ from pretreatment values, triglyceride levels significantly increased at the 8th and 12th weeks. Several studies have reported the effects of sertraline on blood lipid levels in literature. Sertraline increased cholesterol levels in patients receiving psychiatric treatment.[9-12] Increased blood triglyceride levels during sertraline treatment in our study might have been due to increased insulin secretion and insulin's anabolic effects. Furthermore, HISS-dependent insulin resistance might also have been responsible. HISS causes the entrance of glucose into muscle cells resulting in triglyceride conversion to very low density lipoprotein (VLDL) by the liver. Blockade of HISS release prevents this usage of glucose in muscle cells. The excess amount of glucose enters adipose tissue and becomes a nutrient storage as lipids. However, during the blockage of HISS, the conversion of triglyceride to VLDL in the liver might be inhibited by sertraline.[19-21] So sertraline treatment may cause hypertriglyceridemia.

Unfortunately, there was a limitation in this study. The patients who were treated with sertraline and had no other health disorders were included in this study. Thus, the number of patients was limited.

Conclusion

Based on our results and available literature, sertraline-treated patients have to be followed up for blood insulin and triglyceride levels. Their treatment plans need to be revised in order to adjust possible metabolic changes.

Acknowledgements

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

All authors planned and conducted the study procedure and performed data analyses and wrote. All authors read and approved the final draft of the manuscript.

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