RESEARCH ARTICLE

F.U. Med.J.Health.Sci.
2024; 38 (1): 07 - 12
http://www.fusabil.org

Determination of Pancreatic Beta Cell Reserve in Antidepressant Users and Evaluation of Its Relationship with Metabolic Parameters: A Cross-Sectional Study*

Kamer KAYA [1, a]
Mehmet Gürkan GÜROK [2, b]
Faruk KILINÇ [3, c]
Bilal ÜSTÜNDAĞ [4, d]
Mehmet Hamdi ÖRÜM [1, e]
Murad ATMACA [2, f]

[1] Elazığ Mental Health and Diseases Hospital, Psychiatry, Elazig, TURKIYE

[2] Fırat University, Faculty of Medicine Department of Psychiatry, Elazig, TÜRKİYE

[3] Fırat University, Faculty of Medicine Department of Endocrinology, Elazig, TÜRKİYE

[4] Fırat University, Faculty of Medicine Department of Biochemistry, Elazig, TÜRKİYE

[a] ORCİD: 0000-0001-6984-9473
[b] ORCİD: 0000-0001-8998-0743
[c] ORCİD: 0000-0002-0198-2558
[d] ORCİD: 0000-0001-6621-2450
[e] ORCİD: 0000-0002-4154-0738
[f] ORCİD: 0000-0003-2772-4124

Received : 08.06.2023
Accepted : 13.10.2023

Yazışma Adresi
Correspondence

Mehmet Hamdi ÖRÜM

Elazığ Mental Health and Diseases Hospital, Psychiatry, Elazig, TURKIYE

mhorum@hotmail.com

Objective: The aim of this study was to determine the pancreatic β-cell reserve by means of homeostatic model assessment for insulin resistance (HOMA-IR) in patients followed up with the diagnoses of major depressive disorder and anxiety disorder and being treated with antidepressants, and to investigate the relationship between the pancreatic β-cell reserve and various metabolic markers.

Materials and Methods: The fasting blood glucose and insulin levels and various biochemical parameters of 60 patients using antidepressants and 60 healthy control subjects were measured and their HOMA-IR values were calculated.

Results: Both the patient and control groups consisted of 32 (53.3%) females and 28 (46.7%) males. There was no significant difference between the groups in terms of age (p=0.275). The median duration of antidepressant use of the patients was 27 (min:12, max:48) months. Weight, body mass index and waist, hip and neck circumferences of the patient group were significantly higher than those of the control group (p<0.05). The insulin, C-peptide and HOMA-IR values of the patient group were also significantly higher than those of the control group (p<0.05). There was no significant difference between the patient and control groups in terms of fasting blood glucose and hemoglobin A1c (HbA1c) values (p>0.05). On the other hand, total cholesterol and low-density lipoprotein (LDL) values of the patient group were found to be significantly higher than those of the control group (p<0.05).

Conclusion: The findings of this study indicated that the use of antidepressants is associated with an increase in C-peptide and HOMA-IR levels, which are positively correlated with insulin resistance.

Key Words: *Antidepressant, insülin, HOMA-IR, beta cell reserve*

Antidepresan Kullanıcılarında Pankreas Beta Hücre Rezervinin Belirlenmesi ve Metabolik Parametrelerle İlişkisinin Değerlendirilmesi: Kesitsel Bir Çalışma

Amaç: Bu çalışmanın amacı majör depresif bozukluk ve anksiyete bozukluğu tanıları ile izlenen ve antidepresan tedavisi gören hastalarda insülin direnci için homeostatik model değerlendirmesi (HOMA-IR) ile pankreas β-hücre rezervinin belirlenmesi ve pankreas β-hücre rezervi ile çeşitli metabolik belirteçler arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Antidepresan kullanan 60 hasta ve 60 sağlıklı kontrol deneğin açlık kan şekeri ve insülin düzeyleri ile çeşitli biyokimyasal parametreler ölçüldü ve HOMA-IR değerleri hesaplandı.

Bulgular: Hem hasta hem de kontrol grubu 32 (%53.3) kadın ve 28 (%46.7) erkekten oluşuyordu. Gruplar arasında yaş açısından anlamlı fark yoktu (p=0.275). Hastaların medyan antidepresan kullanım süresi 27 (min:12, max:48) aydı. Hasta grubunun ağırlık, vücut kitle indeksi ve bel, kalça ve boyun çevreleri kontrol grubuna göre anlamlı olarak yüksekti (p<0.05). Hasta grubunun insülin, C-peptid ve HOMA-IR değerleri de kontrol grubuna göre anlamlı olarak yüksekti (p<0.05). Açlık kan şekeri ve hemoglobin A1c (HbA1c) değerleri açısından hasta ve kontrol grubu arasında anlamlı fark yoktu (p>0.05). Öte yandan hasta grubunun toplam kolesterol ve düşük yoğunluklu lipoprotein (LDL) değerleri kontrol grubuna göre anlamlı olarak yüksek bulundu (p<0.05).

Sonuç: Bu çalışmanın bulguları, antidepresan kullanımının insülin direnci ile pozitif korelasyon gösteren C-peptid ve HOMA-IR düzeylerinde artış ile ilişkili olduğunu göstermiştir.

Anahtar Kelimeler: *Antidepresan, insülin, HOMA-IR, beta hücre rezervi*

Introduction

Following the accidental discovery of the first antidepressant (AD) compounds, new compounds with a similar mechanism of action were synthesized and started to be used in the clinical practice. While the use of reversible monoamine oxidase inhibitors, which have replaced the irreversible monoamine oxidase inhibitors, has decreased over time, the use of selective serotonin reuptake inhibitors has gradually increased. These synthesized compounds visibly reduced the number of patients, especially the ones diagnosed with mood disorder and anxiety disorder, in psychiatry clinics (1).Today, ADs

* This study is derived from the dissertation thesis of the first author published in the field of medicine.

are among the most prescribed drugs in developed countries, and their increasing use in the generalpopulation raises concerns (2). These concerns have increased the interest in investigating the common medical conditions associated with AD use, including metabolic syndrome.

Metabolic syndrome is characterized by obesity, insulin resistance, hypertension, impaired glucose tolerance or type 2 diabetes mellitus (DM), hyperinsulinemia, increased triglyceride (TG) and low-density lipoprotein (LDL) levels, and decreased high-density lipoprotein (HDL) levels (3, 4). The evidence that suggests metabolic syndrome is associated with psychiatric disorders is increasing. Psychiatric disorders may lead to metabolic syndrome also due to the drugs used in their treatment, regardless of the diagnosis of the psychiatric disorder (1).

It is known that long-term use of ADs is associated with an increased risk of DM (5), which is mostly attributed to weight gain, a common side effect of AD drugs. Weight gain is also associated with increased incidence of hypertension, dyslipidemia, coronary artery disease, insulin resistance and type 2 DM (6). Nevertheless, the pathophysiology of ADs associated with insulin resistance has not been fully elucidated. Insulin resistance is a common pathological condition in which target cells do not respond to normal circulating insulin levels (7). Hence, individuals with insulin resistance suffer from impaired insulin action and are prone to develop type 2 DM (8). Beta-cell (β-cell) reserve reflects the insulin-secreting capacity of the pancreas. β-cell reserve becomes important in cases with insulin resistance, since β-cells constantly try to increase insulin secretion in order to prevent hyperglycemia (9). As insulin resistance increases, β-cells increase insulin production to keep blood glucose levels within normal limits. If insulin resistance persists or increases, β-cells will begin to be affected and DM will develop as a result of the decrease in insulin secretion (10). The gold standard test for diagnosing insulin resistance is the hyperinsulinemic-euglycemic clamp. However, given the expensiveness and the difficulty to use hyperinsulinemic-euglycemic clamp in daily clinical practice, homeostatic model assessment for insulin resistance (HOMA-IR) has become widely used in its stead (11).

Major depressive disorder (MDD) and anxiety disorder (AD) are among the most commonly observed psychiatric disorders and ADs are substantially used in their treatment (12, 13). In this context, the aim of this study was to determine the pancreatic β-cell reserve by means of HOMA-IR in patients diagnosed with MDD or AD and being treated with ADs, and to investigate the relationship between the pancreatic β-cell reserve and various metabolic markers.

Materials and Methods

Research and Publication Ethics: Ethical approval was obtained from the Firat University Non-invasive Research Ethics Committee and the 1964 Declaration of Helsinki was complied with (Date: 27/02/2019, Number: 97132852/050.01.04). All respondents provided their consent for the information provided to be used for research purposes.

Research Design: The sample of this cross-sectional study consisted of 60 patients who applied to the psychiatry outpatient clinic of Fırat University Hospital and had been using AD for at least 6 months with the diagnosis of MDD or AD. Patients outside the age range of 18-70, patients with DM, hypertension, obesity, liver dysfunction, renal failure, alcohol and substance abuse, mental retardation, and the patients using non-AD psychotropic drugs except for the patients who have shortly used benzodiazepine in the early stages of the treatment were not included in the patient group. On the other hand, the exclusion criteria for both the patient and control groups were as follows: having a history of cholesterol-lowering drug use, presence of any endocrinological condition, having received any drug treatment in the last two weeks before the start of the AD treatment, and the presence of obesity. Consequentially, 60 healthy individuals with characteristics that match those of the patient group in terms of age and gender, who were not diagnosed with any psychiatric or organic disease, and did not use alcohol or substance were included in the control group.

Sociodemographic and Clinical Data Form: A sociodemographic and clinical data form was prepared taking the objectives of this study into consideration by the authors of this study in accordance with the information obtained from the literature and the clinical experience of the authors. The sociodemographic and clinical data form was prepared as a semi-structured form in order to query the sociodemographic data including age, gender, marital status, educational status, occupation, place of residence, economic status, family structure, and the clinical data such as disease duration.

Interventions: Sixty patients who applied to the psychiatry outpatient clinic and whose active treatment were continued were included in the patient group in accordance with study's inclusion and exclusion criteria determined for the patient group. In addition, 60 healthy individuals, who applied to the endocrinology outpatient clinic for routine control and were not diagnosed with any medical condition were included in the control group in accordance with study's inclusion and exclusion criteria determined for the control group. First, patients' sociodemographic and clinical data were collected using the sociodemographic and clinical data form. Subsequently, 12 mL of venous blood samples were taken from all patients and healthy control subjects included in the study between 08:00 am and 09:00 am in the morning in a fasting state. The biochemical analyses of the samples, i.e., insulin, C-peptide, cholesterol, triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), hemoglobin A1c (HbA1c) measurements, were conducted on the same day the samples were taken. Hospital records were used to obtain patients' laboratory and epidemiological data.**Biochemical Analyses:** Serum LDL, TG and HDL

levels were measured with enzymatic colorimetric kits (COBAS 311, Roche Diagnostics GmbH, Mannheim, Germany). LDL values were calculated according to the Friedewald equation [LDL=Total cholesterol–((very low LDL (VLDL)+HDL)), VLDL= TG/5]. HbA1c levels were measured with a COBAS 311 device using the particle-assisted immunoturbidimetric method (Roche Diagnostics, Mannheim, Germany). The HbA1c results were expressed as the percentage of total Hb in accordance with the Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program (DCCT/NGSP) protocol. Insulin levels were measured with an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) and automated Roche Cobas E 411 device (Roche Diagnostics). The HOMA-IR index was calculated based on the HOMA-IR formula [Fasting Glucose (mg/dL)×Fasting Insulin (uIU/mL)/405] using fasting blood glucose and fasting serum insulin levels.

Anthropometric Measurements: Patients' anthropometric parameters including body weight, height, and waist, hip, and neck circumferences were measured. The body weight measurements were performed using a scale and height measurements were performed while leaning against the wall. Waist, hip and neck circumferences were measured by the author in accordance with the relevant measurement technique.

Statistical Analyses: Statistical analyses ofthe collected data were conducted using the SPSS 22.0 (Statistical Package for Social Sciences for Windows, version 22.0, IBM Corp., Armonk, NY, U.S., 2013) software package. The descriptive data were expressed as numbers (n) and percentage (%) values in the case of categorical data, and as mean±standard deviation (mean±SD) and median (interquartile range between the 75^{th} and 25^{th} percentiles) in the case of continuous data. Pearson's chi-squared test was used to compare the categorical variables between the groups. Kolmogorov-Smirnov test was used to determine whether the continuous variables conformed to the normal distribution. In comparison of paired groups, independent t-test was used in the case of normally distributed variables and the Mann-Whitney U-test was used in the case of non-normally distributed variables. In the analysis of the relationships between continuous variables, Pearson's and Spearman's correlation analyses were used in the case of normally and non-normally distributed variables, respectively. Probability (p) values of <0.05 were deemed to indicate statistical significance. Power analysis was performed using ClinCalc LLC software (for type I/II error rate; alpha 0.05, power 80%) and it was seen that there should be at least 27 cases in each group.

Results

Of the patients included in the study, 32 (53.3%) were female and 28 (46.7%) were male, and the mean age of the group was 43.6±10.7 years. Similarly, the control group consisted of 32 (53.3%) females and 28 (46.7%) males, with a mean age of 41.2±12.8 years. The median duration of AD use of the patients was 27 (min. 12, max. 48) months.

Weight, body mass index (BMI), waist, hip circumference and neck circumferences of the patient group were significantly higher than those of the control group (p<0.05) (Table 1). In addition, insulin, C-peptide and HOMA-IR values of the patient group were also found to be significantly higher than those of the control group (p<0.05). There was no significant difference between the groups in terms of fasting blood glucose (FBG) and HbA1c values (p>0.05) (Table 2). Total cholesterol and LDL values of the patient group were significantly higher than those of the control group (p<0.05). On the other hand, there was no significant difference between the groups in terms of HDL, TG and VLDL values (p>0.05) (Table 3).

Table 1. Comparison of anthropometric measurements of the patient and control groups

	Patient Group (Mean±SD)	Control Group (Mean±SD)	p value
Height (cm)	164.4±17.0	166.3±8.8	0.455
Weight (kg)	75.6±12.6	67.5±13.2	0.001*
BMI (kg/m^2)	27.5±4.6	24.3±3.9	<0.001**
Waist Circumference (cm)	93.7±10.0	83.8±13.9	<0.001**
Hip Circumference (cm)	106.2±15.4	95.9±11.3	<0.001**
Neck Circumference (cm)	37.5±3.6	34.5±4.8	<0.001**
Waist Circumference/Neck Circumference Ratio	2.5±0.2	2.5±0.4	0.371
Waist Circumference/Hip Circumference Ratio	0.9±0.1	0.9±0.1	0.855

*p<0.05, **p<0.001; independent t-test was used; SD: Standard deviation, BMI: Body mass index

Table 2. Comparison of FBG, insulin, C-peptide, HOMA-IR and Hba1c values of the patient and control groups

	Patient Group [Median (IQR)]	Control Group [Median (IQR)]	p value
FBG (mg/dL)	90.0 (97.0-84.5)	89.0 (96.0-84.5)	0.983
Insulin (µLU/mL)	11.5 (19.3-7.5)	6.3 (11.9-4.8)	**<0.001****
C-Peptide (ng/mL)	2.5 (3.7-2.1)	2.0 (2.8-1.6)	**0.005***
HOMA-IR	2.5 (4.5-1.6)	1.4 (2.5-1.0)	**<0.001****

*p<0.05, **p<0.001; Mann-Whitney U test and independent t-test; IQR: Interquartile range, FBG: Fasting blood glucose, HOMA-IR: Homeostatic model assessment for insulin resistance

Table 3. Comparison of Lipid Panels of the Patient and Control Groups

	Patient Group (Mean±SD)	Control Group (Mean±SD)	p value
Total Cholesterol (mg/dL)	200.8±45.3	173.1±54.9	**0.003***
HDL (mg/dL)	45.8±12.8	44.5±11.2	0.541
TG (mg/dL)	164.6±84.3	142.8±248.2	0.520
LDL (mg/dL)	129.2±38.6	114.2±34.5	**0.026***
VLDL (mg/dL)	34.2±17.2	29.8±49.8	0.514
HbA1c (%)	5.7±0.6	5.5±0.6	0.224

*p<0.05; independent t-test was used; SD: Standard deviation, HDL: High-density lipoprotein, TG: Triglyceride, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, HbA1c: Hemoglobin A1c

The heart rate of the patient group [median: 86 (min.78, max. 92.5)] was found to be significantly higher than that of the control group [median 79.5 (72-82)] (p<0.001). There was no significant difference between the groups in terms of systolic and diastolic blood pressures (p=0.874 and p=0.270, respectively).

The correlation analyses revealed a positive and significant relationship between weight and BMI values, waist circumference, waist circumference/neck circumference ratio, waist circumference/hip circumference ratio, insulin and C-peptide levels. Additionally, there was a positive and significant relationship between BMI value and waist circumference, waist circumference/neck circumference ratio, and C-peptide level. There was also a significant positive correlation between waist circumference and waist circumference/neck circumference ratio, waist circumference/hip circumference ratio, and insulin and C-peptide levels. It has been determined that there was a positive and significant relationship between waist circumference/hip circumference ratio and insulin and C-peptide levels. Lastly, there was a positive and significant relationship between insulin and C-peptide levels as well.

Discussion

The findings of this study indicated that HOMA-IR, insulin, C-peptide and total cholesterol values of patients using ADs were significantly higher than those of the control group, and that their body weight-related parameters increased significantly. On the other hand, there was no significant difference between the patient and control groups in terms of FBG, HbA1c, HDL, TG and VLDL values. However, the heart rate of the patient group was found to be significantly higher than that of the control group.

Individuals with psychiatric disorders are thought to be at metabolic risk regardless of their use of psychiatric drugs. Lifestyles, dietary choices, activity habits and genetic characteristics of people with psychiatric disorders put them at higher risk for weight gain, diabetes and cardiovascular diseases. Although it is widely accepted that patients taking antipsychotic drugs have a higher risk of metabolic syndrome than those not taking antipsychotic drugs, the relationship between ADs and metabolic syndrome is still a matter of debate (14). Regardless of the psychiatric disorder diagnosis, ADs may also directly affect the components of the metabolic syndrome. There are many studies which demonstrated that the use of ADs increased weight gain (15,16). Similarly, in this study, abdominal obesity-related anthropometric measurements were found to be significantly higher in the patient group than in the control group.

DM, insulin resistance, and hyperglycemia are among the most common metabolic risk factors seen in the psychiatric patient population. On the other hand, it is known that psychiatric disorders and anxiety and depression symptoms are more commonly seen throughout lifetime in diabetic patients with impaired metabolic control (17). The findings of the studies on the effects of ADs, which are used as the primary method of treatment in depression, on insulin sensitivity and glucose homeostasis are contradictory. The large-scale epidemiological studies conducted in recent years have provided indirect evidence that AD use increases the risk of weight gain and DM (18, 19). It has been shown that insulin signalling has been impaired and cellular insulin

resistance increased in patients using sertraline and paroxetine (20). Chang et al. (21) found that HOMA-β levels of drug-naive depression patients increased after six weeks of venlafaxine and fluoxetine treatment. On the other hand, there are also studies that did not detect any relationship between the use of ADs and various HOMA parameters. In the cohort study of Azevedo Da Silva et al. (22) conducted with 4700 men and women, the fasting plasma glucose, HbA1c, HOMA2-%B (beta-cell function) and HOMA2-%S (insulin sensitivity) values of the subjects were recorded at three-year intervals. The follow-up tests revealed that the mean fasting plasma glucose and HbA1c levels of the patients increased, whereas the HOMA2-%B and HOMA2-%S values decreased. In addition, no significant difference was detected in fasting plasma glucose, HOMA2-%B and HOMA2-%S values between those who used ADs and those who did not use ADs, both at the beginning of the treatment and during the follow-ups. Longitudinal analyses of Azevedo Da Silva et al. (22) indicated that AD use was not associated with altered glucose metabolism. In comparison, in this study, insulin, C-peptide and HOMA-IR values, which are the leading indicators in the development of diabetes and metabolic syndrome, were found to be significantly higher in the patient group than in the control group. Nevertheless, there was no significant difference between the groups in terms of FBG and HbA1c values. It is known that insulin resistance is observed in the early stages of type 2 DM, whereas the diagnosis of type 2 DM and advanced pancreatic involvement occur after many years (23). In parallel, the findings of this study demonstrated that patients using AD are at risk for the development of type 2 DM and metabolic syndrome.

Dyslipidemia, one of the metabolic syndrome parameters, is another risk factor that contributes to mortality and morbidity in psychiatric patients. The effects of AD use on lipid levels have not been fully elucidated (24,25). However, many studies have shown that the use of AD may be associated with an increase in total cholesterol levels. A significant increase in serum total cholesterol levels has been shown after selective serotonin reuptake inhibitor (SSRI) treatment in patients with a diagnosis of panic disorder (26). Bradwejn et al. (27) found an increase in total cholesterol and LDL levels with venlafaxine treatment. Similarly, the total cholesterol and LDL values of the patient group were found to be significantly higher than those of the control group in this study. However, there was no significant difference between the groups in terms of HDL, TG and VLDL values. In general, the results of this study are consistent with the relevant results reported in the literature. Nevertheless, further large-scale studies are still needed to shed more light on the subject.

Limitations of the Study: The limitations of this study primarily included the absence of pre-treatment FBG, blood lipid levels, and body anthropometric measurements. Secondary limitations of the study included the relatively low number of cases, the difficulty in communication experienced by some of the psychiatric patients who meet the study inclusion criteria, and the fact that a small number of these the psychiatric patients did not volunteer to participate in the study. Another limitation of the study is that the AD subtypes used by the patients are not known. Pre- and post-treatment studies with drug-naive patient groups are needed. It is suggested that patients' disorder characteristics be detailed (diagnosis, duration of disorder, severity of disorder, etc.). MDD increases the risk of metabolic syndrome independently of ADs. In this sense, it would be more appropriate to select the control group from patients who were followed up with a diagnosis of MDD and did not use ADs. It is a limitation that the psychiatric symptom severity of the patient group was not measured using a scale.

In conclusion, the findings of this study demonstrated that the use of AD leads to high C-peptide and HOMA-IR values, which are positively associated with insulin resistance. Therefore, it is important the patients using ADs are monitored and stratified in terms of the risk of metabolic syndrome both before and during treatment. On the other hand, it should not be forgotten that ADs are not the only factor that play a role in the development of metabolic syndrome and that individual differences and lifestyle may be important as well. That is, a multidisciplinary approach may also be beneficial in cases where necessary.

References

1. Vetulani J, Nalepa I. Antidepressants: Past, present and future. Eur J Pharmacol 2000; 405(1-3): 351-363.
2. Azevedo Da Silva M, Dugravot A, Balkau B, et al. Antidepressant medication use and trajectories of fasting plasma glucose, glycated haemoglobin, β-cell function and insulin sensitivity: A 9-year longitudinal study of the D.E.S.I.R. cohort. Int J Epidemiol 2015; 44(6): 1927-1940.
3. Crichton GE, Elias MF, Robbins MA. Association between depressive symptoms, use of antidepressant medication and the metabolic syndrome: The Maine-Syracuse Study. BMC Public Health 2016; 16: 502.
4. Chokka P, Tancer M, Yeragani VK. Metabolic syndrome: Relevance to antidepressant treatment. J Psychiatry Neurosci 2006; 31(6): 414.
5. Brown LC, Majumdar SR, Johnson JA. Type of antidepressant therapy and risk of type 2 diabetes in people with depression. Diabetes Res Clin Pract 2008; 79(1): 61-67.
6. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006; 444(7121): 881-887.
7. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000; 106(4): 473-481.
8. Reaven G. Insulin resistance, type 2 diabetes mellitus, and cardiovascular disease: The end of the beginning. Circulation 2005; 112(20): 3030-3032.
9. Weyer C, Bogardus C, Mott DM, et al. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999; 104(6): 787-794.

10. Fletcher B, Gulanick M, Lamendola C. Risk factors for type 2 diabetes mellitus. J Cardiovasc Nurs 2002; 16(2): 17-23.

11. Turner RC, Holman RR, Matthews D, et al. Insulin deficiency and insulin resistance interaction in diabetes: Estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. Metabolism 1979; 28(11): 1086-1096.

12. Derijks HJ, Meyboom RH, Heerdink ER, et al. The association between antidepressant use and disturbances in glucose homeostasis: Evidence from spontaneous reports. Eur J Clin Pharmacol 2008; 64(5): 531-538.

13. Isaac R, Boura-Halfon S, Gurevitch D, et al. Selective serotonin reuptake inhibitors (SSRIs) inhibit insulin secretion and action in pancreatic β cells. J Biol Chem 2013; 288(8): 5682-5693.

14. Kivimäki M, Hamer M, Batty GD, et al. Antidepressant medication use, weight gain, and risk of type 2 diabetes: A population-based study. Diabetes Care 2010; 33(12): 2611-2616.

15. Chiwanda L, Cordiner M, Thompson AT, et al. Long-term antidepressant treatment in general practice: Changes in body mass index. BJ Psych Bull 2016; 40: 310-314.

16. Blumenthal SR, Castro VM, Clements CC, et al. An electronic health records study of long-term weight gain following antidepressant use. JAMA Psychiatry 2014; 71: 889-896.

17. Levkovitz YB, Shushan G, Hershkovitz AIsaac. Antidepressants induce cellular insulin resistance by activation of IRS-1 kinases. Moll Cell Neurosci 2007; 36: 305-312.

18. Dannon P II, Lowengrub K, Gonopolsky Y, et al. A naturalistic long-term comparison study of selective serotonin reuptake inhibitors in the treatment of panic disorder. Clin Neuropharmacol 2007; 30: 326-334.

19. Warnock JK, Mutzig EM. Diabetes mellitus and major depression: considerations for treatment of Native Americans. J Okla State Med Assoc 1998; 91: 488-493.

20. Amsterdam JD, Shults J, Rutherford N. Safety and efficacy of s-citalopram in patients with co-morbid major depression and diabetes mellitus. Neuropsychobiol 2006; 54: 208-214.

21. Chang HH, Chi MH, Lee IH, et al. The change of insulin levels after six weeks antidepressant use in drug-naïve major depressive patients. J Affect Disord 2013; 150(2): 295-299.

22. Azevedo Da Silva M, Dugravot A, Balkau B, et al. Antidepressant medication use and trajectories of fasting plasma glucose, glycated haemoglobin, β-cell function and insulin sensitivity: A 9-year longitudinal study of the D.E.S.I.R. cohort. Int J Epidemiol 2015; 44(6): 1927-1940.

23. Gallwitz B, Kazda C, Kraus P, et al. Contribution of insulin deficiency and insulin resistance to the development of type 2 diabetes: Nature of early stage diabetes. Acta Diabetol 2013; 50(1): 39-45.

24. Ma Y, Balasubramanian R, Pagoto SL, et al. Relations of depressive symptoms and anti-depressant use to body mass index and selected biomarkers for diabetes and cardiovascular disease. Am J Public Health 2013; 103: 34-43.

25. Gabriel A. Changes in plasma cholesterol in mood disorder patients: does treatment make a difference? J Affect Disord 2007; 99: 273-278.

26. Bailey DL, Le Mellédo JM. Effects of selective serotonin reuptake inhibitors on cholesterol levels in patients with panic disorder. J Clin Psychopharmacol 2003; 23(3): 317-319.

27. Bradwejn J, Ahokas A, Stein DJ, Salinas E, Emilien G, Whitaker T. Venlafaxine extended-release capsules in panic disorder: Flexible-dose, double-blind, placebo-controlled study. Br J Psychiatry 2005; 187: 352-359.