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Detection of Pancreatic Beta Cell Reserve and Its Relationship with Metabolic Markers and Anthropometric Measurements in Patients with Active Psychotic and Mood Disorders

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Objective: In this research, our objective is to explore how pancreatic beta cell reserve is determined and its correlation with metabolic markers among individuals receiving active treatment for psychotic and mood disorders.

Materials and Methods: The study included 60 healthy controls and 60 psychiatrically treated patients on regular antipsychotic medication. Insulin, c-peptide, cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, vitamin D, HbA1c, parathormone, prolactin, TSH levels were analyzed after anthropometric measurements of all participants.

Results: The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) value was notably greater in the case group compared to the control group, with a significant difference observed (p=0.041). Triglyceride (TG), Very low density lipoprotein (VLDL), Total cholesterol and Low density lipoprotein (LDL) values of the case group were significantly higher than the control group. During the correlation analysis, a noteworthy positive correlation was identified between weight and BMI, waist circumference, waist-to-neck ratio, waist-to-hip ratio, insulin levels, and c-peptide levels.

Conclusion: We believe that individuals with high-risk factors should undergo regular monitoring for conditions such as obesity, insulin resistance, hyperlipidemia, prediabetes, and diabetes, which can be beneficial.

Key Words: *Antipsycohotics, pancreatic beta cell, metabolic disorder*

Aktif Psikotik ve Duygudurum Bozuklukları Olan Hastalarda Pankreas Beta Hücre Rezervinin Tespiti ve Metabolik Belirteçler ve Antropometrik Ölçümlerle İlişkisi

Amaç: Bu araştırmada amacımız psikotik ve duygudurum bozuklukları nedeniyle aktif tedavi alan bireylerde pankreas beta hücre rezervinin nasıl belirlendiğini ve bunun metabolik belirteçlerle ilişkisini araştırmaktır.

Gereç ve Yöntem: Çalışmaya 60 sağlıklı kontrol ve düzenli antipsikotik ilaç kullanan 60 psikiyatrik tedavi gören hasta dahil edildi. Tüm katılımcıların antropometrik ölçümleri sonrasında insülin, c-peptid, kolesterol, trigliserit, LDL kolesterol, HDL kolesterol, D vitamini, HbA1c, parathormon, prolaktin, TSH düzeyleri analiz edildi.

Bulgular: İnsülin Direnci için Homeostatik Model Değerlendirmesi (HOMA-IR) değeri vaka grubunda kontrol grubuna göre belirgin şekilde yüksekti ve anlamlı fark gözlendi (p=0.041). Olgu grubunun Trigliserit (TG), Çok düşük yoğunluklu lipoprotein (VLDL), Toplam kolesterol ve Düşük yoğunluklu lipoprotein (LDL) değerleri kontrol grubuna göre anlamlı derecede yüksekti. Korelasyon analizinde kilo ile BMI, bel çevresi, bel-boyun oranı, bel-kalça oranı, insülin düzeyi ve c-peptid düzeyi arasında pozitif yönde dikkat çekici bir korelasyon tespit edildi.

Sonuç: Yüksek risk faktörlerine sahip bireylerin obezite, insülin direnci, hiperlipidemi, prediyabet ve diyabet gibi faydalı olabilecek durumlar açısından düzenli olarak takip edilmesi gerektiğine inanıyoruz.

Anahtar Kelimeler*:* *Antipsikotikler, pankreas beta hücresi, metabolik bozukluk*

Introduction

Antipsychotics are used for the treatment of sudden-onset bipolar disorder, for psychotic disorders such as schizophrenia, severe anxiety disorders, and depressive states (1). Atypical antipsychotic drugs can cause serious side effects such as weight gain, impaired glucose tolerance, diabetes mellitus, hypertension, coronary artery diseases, neuroleptic malignant syndrome, and pancreatitis (2).

Newer antipsychotic drugs cause less extrapyramidal side effects, less frequent hyperprolactinemia but significantly more weight gain (3). Diabetes mellitus is seen in approximately 16% of patients with schizophrenia. This value increases with age. It is approximately 2 times more common than the general population (4, 5). Based on data from the World Health Organization, clozapine, olanzapine, and risperidone significantly increase the risk of impaired glucose tolerance, and accordingly, the risk of hyperglycemia, diabetes mellitus, exacerbation of existing diabetes, ketosis, diabetic coma, and glucosuria (6).

The exact pathophysiology of insulin resistance due to atypical antipsychotic drugs is unknown. The first possible mechanism is the reduced level of insulin-sensitive glucose transporters. Other possible mechanisms are the inability to stimulate glucose transporters in microsomes and the reduction of the ability of pancreatic ß cells to respond to blood glucose levels by 5-HT1a antagonism. However, this observation could not be consistently demonstrated in patients taking clozapine and olanzapine (7-9). In addition to weight gain and impaired glucose tolerance, an important side effect of atypical antipsychotic drugs is hyperlipidemia which accelerates atherosclerosis (10, 11).

All known antipsychotic drugs block the D2 receptor. The clinical consequences of this effect in various brain areas are also different. Due to the phase shift in its release, it peaks in plasma earlier than in normal controls. Also, antipsychotic therapy does not improve this disorder. It is not well known enough whether tolerance develops in hyperprolactinemia due to antipsychotic drugs. However, it is known that hyperprolactinemia persists for many years in many cases. With the discontinuation of the drug, the prolactin level returns to normal in an average of 2-4 days (12).

In this research, we aimed to investigate the determination of pancreatic beta cell reserve and its relationship with metabolic markers in patients with psychotic and mood disorders, who are undergoing active treatment.

Materials and Methods

Research and Publication Ethics: This prospective study was started after receiving approval from the ethics committee of Firat University dated 11.04.2019 with the number 06/20.

Case Selection and Study Method: In this study, patient (n=60) and control (n=60) groups were formed. The including criteria of this study were;

Being between 18-70 years of age, not having any psychological disease, not having advanced cardiovascular, metabolic, kidney and liver disease, using antipsychotic drug(s) for at least 6 months not having active diabetes, hypertension, hyperlipidemia, and not having mental retardation or illiteracy. In addition; the presence of alcohol and substance use were excluded from the study.

The study included 60 patients with psychotic and mood disorders who presented to the psychiatry outpatient clinic and are on active treatment, and a healthy control group consisting of 60 individuals selected from those who presented to the endocrinology outpatient clinic for routine check-ups and were not diagnosed with any medical disease. It was ensured that the selected control group was similar to those in the patient group in terms of age and gender. Each patient who participated in the study was informed, their consent was obtained, and they were allowed to participate in the study voluntarily. In addition to the blood requested for routine tests, 4 mL of blood samples were taken from the patients in the psychotic and mood disorder patient group and the control group at the time of admission. All samples were taken in the morning after fasting between 08:00-09:00. The collected samples were studied in the biochemistry laboratory the same day (Insulin, c-peptide, cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, vitamin D, HbA1c, parathormone, prolactin, TSH). Patients' additional laboratory data and epidemiological data were obtained from patients' medical records. Patient's prospective and observational demographic data (age, gender, chronic disease), height-weight-body mass index (BMI), waist circumference measurements (from the midpoint of the distance between the costal arch and anterior superior iliac spine), neck circumference, hip circumference, systolic and diastolic blood pressure measurements and biochemical tests (insulin, c-peptide, cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, vitamin D, HbA1c, parathormone, prolactin, TSH, fasting blood sugar (FBS), AST, ALT, sodium, potassium, urea, creatinine, calcium, phosphorus, LDH, chlorine, uric acid, creatine kinase, hemogram) were recorded.

Biochemical Analyses: Serum cholesterol, triglyceride, and HDL levels were measured by enzymatic colorimetric kits (COBAS 311, Roche Diagnostics GmbH, Mannheim, Germany); LDL was calculated according to Fridewald formula (LDL=Total cholesterol- (VLDL+HDL), VLDL= TG/5). HbA1c levels were measured by a COBAS 311 assay using the particle-enhanced immunoturbidimetric method (Roche Diagnostics, Mannheim, Germany). HbA1c results were expressed as a percentage of total Hb in accordance with the Diabetes Control and Complications Study/National Program for Glycohemoglobin Standardization (DCCT/NGSP) protocol. Insulin level was measured by an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) and automated Roche Cobas E 411 (Roche Diagnostics). HOMA-IR index was calculated using fasting blood glucose and fasting serum insulin level according to the formula: HOMA-IR=Fasting Glucose(mg/dL) X Fasting Insulin(uIU/mL)/405.

Anthropometric Measurements of Individuals: In this phase, anthropometric measurements of individuals such as body weight, height, waist circumference, hip circumference, and neck circumference were inquired. The body weight and height of the individuals were measured with a weighing scale and a wall-mounted height scale. Waist circumference, hip circumference, and neck circumference were measured by the researcher in accordance with the measurement technique.

Statistical Evaluation: Analyses were carried out with SPSS software package version 22 (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). Sample size was calculated using sample size calculating software G*Power version 3.1.9.2 (Universität Kiel, Germany). With 85% power, 0.05 level of statistical significance and effect size of 0.5, sample size for each group was calculated to be 59.

In the study, descriptive data were presented with n and % values for categorical data, and with

mean±standard deviation (mean±SD) and median interquartile range (25-75 percentile values) for continuous data. Chi-square analysis (Pearson Chi-square) was used to compare categorical variables between groups. Normality of continuous variables to normal distribution was tested by the Kolmogorov-Smirnov test. In the comparison of paired groups, the Student t-test was used for normally distributed variables and Mann Whitney U-test was used for non-normally distributed variables. Pearson correlation test was used for normally distributed variables, and Spearman correlation test was used for non-normally distributed variables when examining the correlation between continuous variables. The level of statistical significance was accepted as $p<0.05$.

Results

Of the 60 patients in the case group, 29 (48.3%) were female, with a mean age of 39.6±11.8 years. Similarly, of the 60 patients in the control group, 28 (46.7%) were female, with a mean age of 36.0±12.6 years. There was no significant difference between the groups in terms of gender and age ($p<0.05$). The weight, BMI, waist circumference, neck circumference, hip circumference, waist/neck ratio, and waist/hip ratio of the case group were significantly higher than the control group. However, there was no significant difference in height between the case and control groups. The comparison of sociodemographic characteristics and anthropometric measurements of group measurements is given in Table 1.

In the comparison of laboratory values of case and control groups; HOMA-IR, TSH, Prolactin, Vitamin D, TG, VLDL, Total Cholesterol and LDL levels were found to be significantly different. Laboratory parameter comparisons of the study groups are given in Table 2. Additionally BMI (Figure 1), HOMA-IR values (Figure 2), total cholesterol values (Figure 3), TG values (Figure 4), LDL values (Figure 5) comparisons of the groups of this study were demonstrated.

The correlation analysis showed a positive and significant correlation between insuline and Weight, BMI, Waist circumference and Waist/neck. There was a positive and significant correlation between BMI and Weight and Insulin. Correlation of various parameters of the case group is given in Table 3.

Table 1. Sociodemographic characteristics and anthropometric measurements of groups

	Case	Control	*p*
N (Female/Male)	60 (29/31)	60 (28/32)	0.855
Age (years) (mean±SD)	39.6±11.8	36.0±12.6	0.118
SBP, mmHg	110 (100-123)	115 (109-130)	0.063
DBP, mmHg	70 (69-80)	79 (70-85)	**0.015**
Heart rate, beat/min Mean± SD	84.4±12.7	79.6±8.5	**0.016**
Height (cm)	166.4±8.1	194.3±208.1	0.302
Weight (kg)	76.8±15.2	63.9±9.3	**<0.001**
BMI (kg/m^2)	27.8±5.5	22.6±2.2	**<0.001**
Waist circumference (cm)	96.4±12.3	79.4±9.2	**<0.001**
Waist/neck	0.6±.1	0.5±.1	**<0.001**
Waist/hip	0.9±.1	0.8±.1	**<0.001**
Hip circumference (cm), median (IQR)	105.5 (100.5-111.5)	94.5 (89.0-98.5)	**<0.001**
Neck circumference (cm), median (IQR)	38.0 (34.0-40.0)	36.0 (33.0-37.0)	**0.003**

IQR=interquartile range SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: *Body Mass İndex*

Table 2. Comparison of laboratory values of groups

	Case	Control	*p*
Glukoz (mg/dL), Median (IQR)	91.5 (83.0-102.5)	88.0 (83.0-94.0)	0.122
Insulin (µIU/mL) Median (IQR)	8.5 (4.8-13.0)	5.9 (4.2-8.8)	0.07
C-peptide (ng/mL) Median (IQR)	2.2 (1.7-3.1)	1.8 (1.5-2.7)	0.100
HOMA-IR Median (IQR)	2.0 (1.0-3.2)	1.3 (0.9-1.9)	**0.041**
HbA1c (%), Mean±SD	5.4±0.8	6.4±7.8	0.361
TSH (IU/mL), Median (IQR)	2.3 (1.6-3.8)	1.5 (1.1-2.5)	**<0.001**
PTH (pg/mL) , Median (IQR)	48.8 (37.8-64.2)	51.7 (34.0-74.2)	0.987
Prolactin (ng/mL), Median (IQR)	16.3 (10.3-37.0)	8.1 (6.2-10.6)	**<0.001**
Vitamin D (µgr/L), Median (IQR)	15.3 (10.2-23.8)	22.8 (14.8-30.9)	**<0.001**
HDL (mg/dL), Median (IQR)	39.1 (33.3-48)	42.2 (35.6-52.8)	0.110
TG (mg/dL), Median (IQR)	144 (101-207.5)	96.5 (64-152.5)	**0.001**
VLDL (mg/dL), Median (IQR)	29.1 (20.2-41.6)	20.9 (13.9-31.8)	**0.003**
Total Cholesterol (mg/dL), Mean±SD	191.5±42.9	166.9±28.5	**<0.001**
LDL (mg/dL), Mean±SD	126.0±41.9	110.1±32.5	**0.023**

IQR=interquartile range, HDL: High Density Lipoprotein, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, TG: triglyceride, VLDL: Very Low Density Lipoprotein, LDL: Low Density Lipoprotein

Table 3. Correlation of various parameters of the case group

		Weight (kg)	BMI (kg/m^2)	Waist circumference (cm)	Waist/neck	Waist/hip	Insulin (µIU/mL)	C-peptide (ng/mL)
Insulin	r	**.183**	.171	**.198**	**.180**	.121		
(µIU/ml)	*p*	**.045**	.062	**.030**	**.049**	.188		
C-peptide	r	**.179**	.100	.162	.112	.092	**.805**	
(ng/mL)	*p*	**.050**	.278	.078	0.225	.318	**.000**	
HbA1c	r	-.023	-.057	-.092	-.108	-.159	-.044	-.075
(%)	*p*	.803	.540	.315	.239	.082	.635	.415

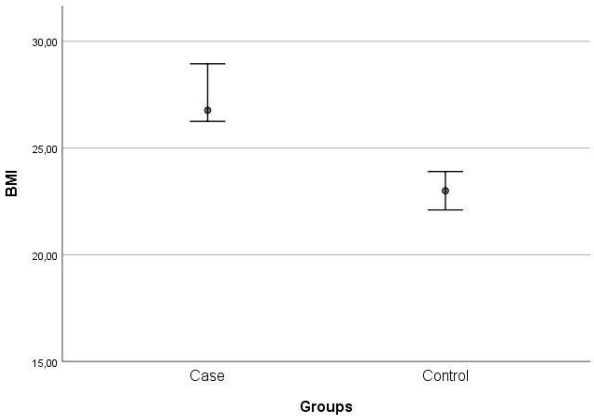

Figure 1. Comparison of BMIs of the case and control groups

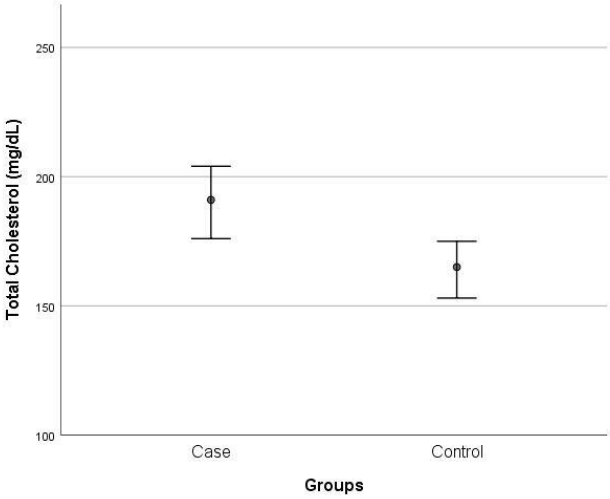

Figure 3. Comparison of total cholesterol values of the case and control group

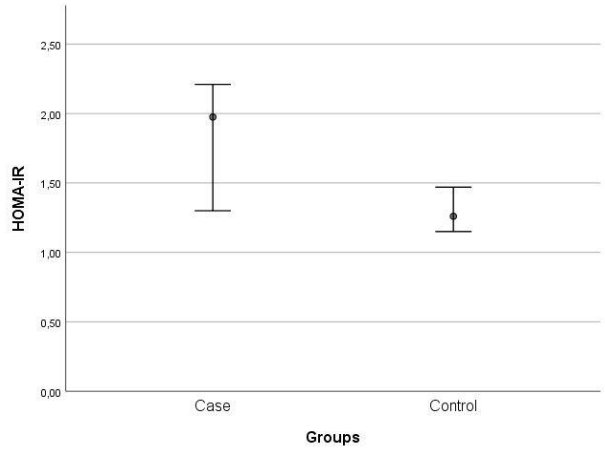

Figure 2. Comparison of the HOMA-IR values of the case and control groups

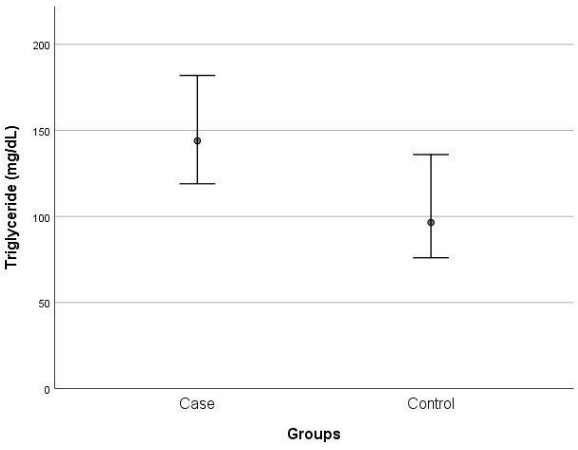

Figure 4. Comparison of TG values of the case and control groups

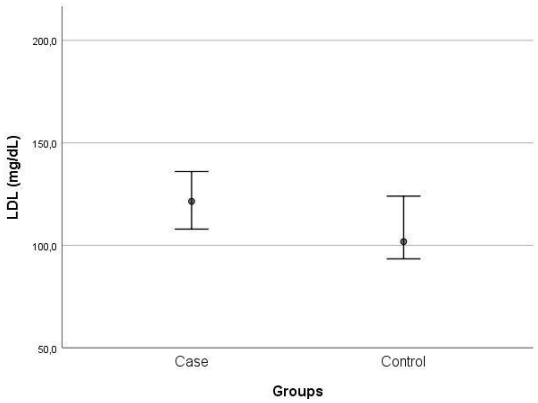

Figure 5. Comparison of LDL values of the case and control groups

Discussion

A growing body of evidence shows a bidirectional link between mood disorders and some physical diseases (13). However, atypical antipsychotics are associated with varying degrees of weight gain, and metabolic abnormalities such as diabetes and hyperlipidemia (14). It is known that metabolic syndrome, which has a multifactorial pathogenesis, is also associated with atypical antipsychotic drugs commonly used in psychiatry (15, 16).

It is known that the prevalence of obesity is high in patients with schizophrenia and the use of atypical antipsychotics causes significant weight gain. However, it has been shown that first-episode schizophrenia patients who have never used antipsychotic drugs before are also prone to abdominal adiposity (17). The results of anthropometric and tomographic evaluations have shown that these patients have higher waist/hip ratios and approximately three times more visceral adipose tissue compared to controls (18). In our study, the weight, BMI, and waist-to-hip ratios of the case group were found to be significantly higher compared to the control group (Figure 1).

In another study conducted with olanzapine treatment, significant increases were recorded in fasting insulin levels, C-peptide, and fasting glucose levels (19). The results of our study showed that the weight, BMI, and waist/hip ratios of the case group were significantly higher than the control group (Table 1). However, there was no significant difference between the case and control groups in terms of FPG, insulin, c-peptide, and HbA1c values (Table 3). We concluded that this may vary depending on patient-based, pre-psychotic weight status, familial characteristics, concomitant diseases, education, and socioeconomic levels.

In individuals considered to be in the risk group for DM, antipsychotic drugs may cause hyperglycemia by inducing peripheral insulin resistance or by suppressing insulin secretion from pancreatic beta cells. While some views argue that atypical drugs reduce insulin secretion, there are also studies reporting that these drugs cause hyperinsulinemia (20, 21). In our study, the significantly higher HOMA-IR value of the case group compared to the control group indicates the development of peripheral insulin resistance due to the medications used.

However, it should be known that not all antipsychotic drugs that cause hyperglycemia are 5-HT receptor antagonists, and weight gain is not a prerequisite for the development of hyperglycemia and diabetes (22). In our study, weight gain in cases was found to be higher compared to the control group; however, there were no significant differences in FPG, insulin, C-peptide, and HbA1c values, which is consistent with previous studies.

It has been suggested that weight gain, glucose intolerance, multiple drug use, and diet may be responsible for the development of dyslipidemia due to atypical antipsychotic drug use (23). Other studies conducted with atypical drugs have reported that only hypertriglyceridemia, one of the components of dyslipidemia, is significantly associated with insulin resistance and hyperinsulinemia (24). However, the development of dyslipidemia seems to be associated with weight gain. A study comparing clozapine, olanzapine, risperidone, and haloperidol showed increased mean cholesterol levels in the group using clozapine and olanzapine with significant weight gain (25). In our study, the TG, VLDL, total cholesterol, and LDL values of the case group were found to be significantly higher than the control group (Figure 3-5). However, there was no significant difference between the case and control groups in terms of HDL (Table 2). This parameter with no significant difference was emphasized in a study as attributable to insulin resistance, which is known to play a role in lipid metabolism and lower HDL levels (26).

There are only a few reports in the literature regarding the prevalence of hypertension that can occur with the use of atypical antipsychotic drugs. It has been reported that among these drugs, especially clozapine is associated with the development of hypertension, and antipsychotic drugs other than clozapine rarely increase blood pressure (27). Studies have shown that the incidence of hypertension in schizophrenic patients using atypical antipsychotic drugs or placebo is close to each other. Therefore, it is generally considered that atypical antipsychotics do not cause hypertension. However, it has been reported that hypertension may develop as a result of specific atypical antipsychotic treatments in some susceptible patients (28). In our study, the diastolic blood pressure of the case group was found to be significantly lower than the control group (Table 1). There was no significant difference between the case and control groups in terms of systolic blood pressure.

A study found that prolactin and thyroid-stimulating hormone levels did not change with olanzapine treatment. The absence of a significant change in prolactin levels is consistent with other studies reporting minimal effects of olanzapine on prolactin levels compared to haloperidol and risperidone (19). In our

study, the HOMA-IR value of the case group was found to be significantly higher than the control group. TSH values were found to be higher in the case group but were not statistically significant.

The lack of metabolic data in our study before the initiation of treatment, the inability to evaluate each antipsychotic agent differently in itself, and the relatively low number of cases can be considered the limitations of the study.

In conclusion, the results of our study showed a significant increase in most metabolic markers, especially insulin resistance, body mass index, lipid profile, and prolactin levels of patients with psychotic and mood disorders and ongoing active treatment. We believe that close follow-up of patients with high-risk factors for obesity, insulin resistance, hyperlipidemia, prediabetes, and diabetes would be beneficial, and larger studies are needed.

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