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The Screening of Comorbid Depressive Disorders and Associated Risk Factors in Adult Patients with Type 2 Diabetes

Erişkin Tip 2 Diyabet Hastalarında Depresif Bozuklukların ve İlişkili Risk Faktörlerinin Taranması

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Abstract

Objective: Elevated depressive symptoms and disorders affect one in five patients with diabetes. Current guidelines recommend screening depression in the diabetic population. Turkey has the highest (13.7%) prevalence of diabetes in Europe. However, there are limited data about the prevalence of depressive disorders among diabetic patients in Turkey. We aim to investigate the prevalence of a comorbid depressive disorder in Type 2 diabetic patients who were referred to the Endocrinology outpatient unit of a tertiary hospital. **Material and Methods:** All the Type 2 diabetic patients admitted to our endocrinology department were consecutively included in the study. Their sociodemographics, concomitant diseases and medications, macro and microvascular complications, lifestyle and personal habits, and treatment regimens were obtained by a specifically designed questionnaire. Laboratory data were obtained from the hospital records. The Patient Health Questionnaire-9 (PHQ-9), a depression screening tool, was used as a screening method for depression. Patients with a score of 10 or above determined high risk for depressive disorder according to PHQ-9. The scores were re-evaluated by a psychiatrist to minimize the false negative and positive results. **Result:** A total of 460 patients with Type 2 diabetic were enrolled in this cross-sectional study. 18.9% (n=87) of the participants were found to have depressive disorders according to the psychiatric evaluation done after the PHQ-9 questionnaire. Patients with depressive disorders were predominantly female (69.0% vs. 55.5%; p=0.022), younger (57.2±10.5 vs. 60.0±9.5; p=0.014), had higher HbA1c (8.51±2.51 vs. 7.98±2.05; p=0.042), total cholesterol (205.6±44.2 vs. 194.2±46.0; p=0.045), LDL-cholesterol (123.1±37.8 vs. 113.1±35.4; p=0.026) and non-HDL-cholesterol (158.5±41.61 vs. 146.6±42.7; p=0.024). These patients had frequent neuropathy (37.3% vs. 19.0%, p=0.001), they were less likely to perform exercise (31.8% vs. 53.1%; p<0.001) while smoke in excess (31.4% vs. 14.3%; p<0.001). The analysis showed that female gender (OR=4.4; 95% CI=1.6-12.8; p=0.005) and smoking (OR=7.6; 95% CI=2.8-20.5, p<0.001) are independent determinants of a depressive disorder. **Conclusion:** Approximately one-fifth of diabetic patients had a depressive disorder, and their metabolic parameters were worse than those without a depressive disorder. Therefore, to assess a diabetic patient from all aspects, screening for depressive disorder should be made an indispensable part of the evaluation process.

Keywords: Diabetes; depressive disorders; depression; PHQ-9; Patient Health Questionnaire

Özet

Amaç: Depresif bozukluk ve artmış depresif durumlar her beş diyabet hastasından birini etkilemektedir. Güncel rehberler, diyabetik popülasyonda depresif semptom ve bozuklukların taranmasını önermektedir. Türkiye, Avrupa'da en yüksek (%13,7) diyabet prevalansına sahip ülke konumundadır. Bununla birlikte, Türkiye'de diyabet hastaları arasında depresif bozukluğun sıklığı hakkında kısıtlı veri bulunmaktadır. Biz bu çalışma ile bir üçüncü basamak Endokrinoloji polikliniğine başvuran Tip 2 diyabetik hasta popülasyonunda eşlik eden depresif bozukluk prevalansını saptamayı amaçladık. **Gereç ve Yöntemler:** Endokrinoloji polikliniğine başvuran tüm tip 2 diyabet hastaları ardışık olarak çalışmaya dâhil edildi. Katılımcıların sosyodemografik özellikleri, eşlik eden hastalıkları ve uygulanan tedaviler, makro ve mikro komplikasyonlar, yaşam tarzı ve kişisel alışkanlıkları hazırlanan sorgu formu ile kayıt altına alındı. Laboratuvar verileri hastane bilgi sisteminden alındı. Depresif bozukluk taraması için "Patient Health Questionnaire-9 (PHQ-9)" depresyon tarama aracı kullanıldı. PHQ-9 puanı 10 ve üzeri olan hastalar, depresif bozukluk açısından yüksek riskli olarak değerlendirildi ve olası yanlış negatif-pozitif sonuçları en aza indirgemek amacıyla bir psikiyatri uzmanı tarafından yeniden değerlendirildi. **Bulgular:** Çalışmaya toplam 460 Tip 2 diyabet hastası dâhil edildi. PHQ-9 skorları ve akabinde yapılan psikiyatri değerlendirmesi sonrası hastaların %18,9 (n=87)'unda depresif bozukluk saptandı. Depresif bozukluk saptanan hastalar ağırlıklı olarak kadın cinsiyette (%69,0'a karşı %55,5; p=0,022), daha genç yaşta (57,2±10,5'e karşı 60,0±9,5; p=0,014), daha yüksek HbA1c (8,51±2,51'e karşı 7,98±2,05; p=0,042), total kolesterol (205,6±44,2'ye karşı 194,2±46,0; p=0,045), LDL kolesterol (123,1±37,8'e karşı 113,1±35,4; p=0,026) ve non-HDL-kolesterol (158,5±41,61'e karşı 146,6±42,7; p=0,024) seviyelerine sahip idi. Ek olarak, bu hastalarda nöropati daha sık (%37,3'e karşı %19,0, p=0,001), egzersiz yapma oranları daha düşük (%31,8'e karşı %53,1; p<0,001) ve sigara içme sıklığı daha yüksek (%31,4'e karşı %14,3; p<0,001) idi. Kadın cinsiyette olmak (OR=4,4; %95 GA=1,6-12,8; p=0,005) ve sigara içmek (OR=7,6; %95 GA=2,8-20,5; p<0,001) depresif bozukluğa sahip olmanın bağımsız öngördürücüleri idi. **Sonuç:** Diyabetik hastaların yaklaşık beşte birinde depresif bozukluk mevcuttu ve metabolik parametreleri depresif bozukluk olmayanlara göre daha kötü idi. Bu nedenle, bir diyabet hastasını kapsamlı bir şekilde değerlendirebilmek için depresif bozukluk taraması hasta değerlendirmesinin ayrılmaz bir parçası olarak uygulanmalıdır.

Anahtar kelimeler: Diyabet; depresif bozukluklar; depresyon; PHQ-9; Halk Sağlığı Anketi

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Introduction

Diabetes is a chronic disease and complicated to manage due to the associated mood and emotional problems. Depression is a frequent comorbidity in Type 1 and Type 2 diabetic patients. Depression affects one in four patients with diabetes (1). In other words, diabetic patients are at 1.4-3 times higher at risk of comorbid depression (1-3). Depressive disorders may complicate the management of diabetes and negatively affect the achieving of glycemic and metabolic targets (4-6). Thus, American Diabetes Association (ADA), US Preventive Services Task Force (USPSTF), and National Institute for Health and Care Excellence (NICE) diabetes guidelines recommend routine screening of depressive symptoms in a high-risk population (2,3,7).
The prevalence of depression is reported as 20.3-29.7% in European countries, and 8.3% in North America (8-10). But there are only a few studies available about the prevalance of depressive disorders for among diabetic patients in Turkey (11-13).
We hypothesize that frequency of depressive symptoms was similar throughout European countries and was associated with metabolic disturbances.
In this cross-sectional study, we aim to determine the frequency of depressive disorders in Type 2 diabetic patients referred to the Endocrinology Outpatient Unit of a tertiary hospital. Our secondary aim was to assess the relationship between comorbid depressive disorder and the metabolic consequences in Type 2 diabetic patients.

Material and Methods

Study Design and Population

This cross-sectional study was carried out from January 2017 to May 2018 in a tertiary endocrine unit. The study was approved by the local ethics committee (08.02.2017 Keçiören Training and Research Hospital Ethical Committee-Ankara/Turkey/2012-KAEK-15/1338), and the study protocol was designed as per the international agreements (Helsinki Declaration revised 2013). All patients signed informed consent before data collection. Type 2 diabetic patients over the age of 18 were enrolled consecutively in the study. Patients were excluded if pregnant, younger than 18 years, had Type I diabetes, decompensated liver disease, malignancy, chronic inflammatory disorders, or were undergoing renal replacement therapy.

Data Collection

The sociodemographics (age, gender, marital status, education, occupation, and income), concomitant diseases and medications, macro and microvascular complications, lifestyle and personal habits [exercise, smoking, alcohol use], and treatment regimens were obtained by a specifically designed questionnaire given to all the participants by their physicians. Laboratory data were obtained from hospital records.
The following are the evaluations done cross-sectionally,

Anthropometrics and Blood Pressure Measurement

Height, weight, and waist circumferences (WC) of the patients in their underclothes were recorded according to the standard protocol. Body mass index (BMI) was computed as the ratio of weight to the square of height (kg/m^2). WC was measured on the line between the iliac crest and the lower costal margin parallel to the ground, once the patients exhaled. Arterial blood pressure (ABP) was recorded using automatic BP monitors (Omron M2, HEM-7121-E) after at least 5 min of rest in a seated position. Three consecutive measurements were taken from the same arm, and the mean was recorded.

Laboratory Data

For biochemical analyses, all the blood samples were collected from the antecubital vein between 08:00-10:00 AM after overnight fasting. All laboratory parameters were measured using standard procedures. The levels of fasting blood glucose concentration, total, and high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) were measured enzymatically. low-density lipoprotein (LDL-C) was calculated using Friedewald's equation [LDL-C=total cholesterol-(HDL-C+TG/5)] if TG was found less than 400 mg/dL (14). Glycohemoglobin (HbA1c) was measured using high-performance liquid chromatography (HPLC).

Patient Health Questionnaire-9 a Depression Screening Tool

To screen the depressive disorders, Patient Health Questionnaire-9 (PHQ-9), a depres-

sion screening tool was used. PHQ-9 is a valid and reliable tool for screening depressive disorders in diabetic individuals (15,16). All the diabetic patients who were at the risk of a depressive disorder according to PHQ-9 score were re-evaluated by a psychiatrist to minimize the false negative and positive results according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in terms with the major depressive disorder. PHQ-9 is an instrument to perform criteria-based diagnoses of depressive disorders commonly encountered in primary care. A PHQ-9 score of ≥10 has a sensitivity and specificity of 88% in diagnosing depressive disorders (17). Depressive symptoms were screened by the PHQ-9 questionnaire. The PHQ-9 query form consists of 9 questions. The scores obtained by each answer are collected and evaluated on a scale. If the patient has not marked one of the 3 to 4 options given for the first two questions, the questionnaire cannot be evaluated as a depressive disorder regardless of the total score. Patients with a score of 10 or higher as per the rules were referred to a psychiatrist for a re-evaluation of comorbid depressive disorder. The diagnosis of comorbid depressive disorder is made by a psychiatrist according to the DSM-5 criteria. Also, regardless of the PHQ-9 score, all the patients who used prescribed antidepressants were referred to a psychiatrist and re-evaluated for depressive disorder to avoid overdiagnosis.

Definitions

An internationally accepted definition for Type 2 diabetes was used by the physicians (18). Hypertension was defined as an average office BP>140/90 mmHg on two different visits or an individual undergoing antihypertensive treatment. Dyslipidemia was defined as TG>150 and/or LDL-C>100, and/or low HDL-C (men <40, women <50 mg/dL), or receiving medications for dyslipidemia. Obesity was defined as BMI>30 kg/m^2 (19). Treatment targets were defined as HbA1c<7%, office ABP<140/90 mmHg, and LDL-C<100 mg/dL according to the national (20) and international (2) diabetes guidelines. Achieving all the goals, such as glycemia, BP, and lipid levels by an individual patient, indicate triple metabolic control being established. The exercise was defined as meeting both these criteria, performing exercise more than two days per week, and more than thirty minutes per day. Marital status was dichotomized as married and unmarried. Self-reported income status was categorized according to their ability to meet up basic needs and save. A low education level was defined as less than eight years of formal education. Macrovascular complications were either self-reported: having a history of coronary artery disease, angina, heart attack, cerebrovascular event or peripheral artery disease; or recorded by the physicians according to their findings such as non-palpable extremity pulses, low ankle-brachial index values (≤0.9), positive findings on coronary or peripheral arteriography, and carotid or peripheral arterial duplex ultrasound examination. Retinopathy was self-reported by the patients based on being identified with an eye problem related to diabetes mellitus. Nephropathy was recorded by the physicians if the patients had albuminuria and/or decreased estimated glomerular filtration rate. Neuropathy was also self-reported or recorded by the physicians if the patients had symptoms related to bilateral symmetric distal neuropathy or other autonomous neuropathies attributed to diabetes mellitus.

Statistical Analyses

Statistical analyses were performed in SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean±SD and median (minimum-maximum value) for continuous variables or as a percentage for categorical variables. To identify the variables associated with depression state (depressive/not depressive), the univariate analyses were performed using Chi-square, Fisher exact, Student's t, and Mann-Whitney U tests, where ever appropriate. For the multivariate analysis, binomial logistic regression was performed to ascertain the association of different variables. The criteria for inclusion in the model were having statistical significance ($p<0.05$) in the univariate analysis and a clinical rationale to have a potential association with glycemic control. The variables were gender, BMI (<25 vs. 25-29.9 vs. ≥30 kg/m^2), BP (<140/90 mmHg vs. higher), having microvascular and

macrovascular complications, smoking, exercise (≤2/week vs. higher), alcohol consumption, statin treatment, insulin usage, education level, and monthly income. The odds ratios with 95% confidence intervals (CI) are given in Figure 1. The p-value is two-tailed with a significance level of 0.05.

Results

A total of 460 patients with Type 2 diabetes were enrolled in the study. Based on the predefined criteria, 18.9% (n=87) of the participants had comorbid depressive disorders. The clinical and demographical characteristics of the patients are given in Table 1.

The patients with comorbid depressive disorders were predominantly female (69.0% vs. 55.5%; p=0.022), younger (57.2±10.5 vs. 60.0±9.5; p=0.014), had higher HbA1c (8.51±2.51 vs. 7.98±2.05; p=0.042), total cholesterol (205.6±44.2 vs. 194.2±46.0; p=0.045), LDL-C (123.1±37.8 vs. 113.1±35.4; p=0.026) and non-HDL-C (158.5±41.61 vs. 146.6±42.7; p=0.024) (Table 1, Table 2). Additionally, these patients had frequent neuropathy (37.3% vs. 19.0%, p=0.001) and were less likely to perform exercise (31.8% vs. 53.1%; p<0.001) while smoke in excess (31.4% vs. 14.3%; p<0.001) (Table 1).

According to the multivariate analyses, being female [odds ratio (OR)=4.4; 95% CI=1.6-12.8; p=0.005] and smoking (OR=7.6; 95% CI=2.8-20.5; p<0.001) were independent determinants of comorbid depressive disorders in type 2 diabetic patients (Figure 1).

Discussion

The result shows that approximately one-fifth of Type 2 diabetic patients have comorbid depressive disorders. Patients with depressive disorders were predominantly fe-

Table 1. The demographic parameters of patients with and without depressive disorders.

Variables	Total patients (n=460)	Without depressive disorder (n=373; 81.1%)	With depressive disorder (n=87; 18.9%)	p
Gender (female) (n, %)	267 (58.0%)	207 (55.5%)	60 (69.0%)	0.022
Age (years)	59.48±9.72	60.02±9.46	57.17±10.48	0.014
Higher education (n, %)	217 (48.3%)	171 (47.3%)	46 (52.9%)	0.345
Patients with lower income (n, %)	324 (75.7%)	262 (75.3%)	62 (77.5%)	0.677
Marital status (married) (n, %)	366 (82.2%)	303 (83.9%)	63 (75.0%)	0.054
Smoking (n, %)	79 (17.6%)	52 (14.3%)	27 (31.4%)	<0.001
Alcohol intake (n, %)	7 (1.6%)	6 (1.7%)	1 (1.2%)	0.766
Regular exercise (n, %)	217 (49.0%)	190 (53.1%)	27 (31.8%)	<0.001
Diabetes duration (year)	10.94±8.14	10.69±8.16	12.15±8.02	0.186
Macrovascular complications (n, %)	85 (22.4%)	68 (21.7%)	17 (25.8%)	0.516
Coronary artery disease	100 (23.8%)	79 (23.0%)	21 (27.3%)	0.422
Peripheral artery disease	8 (1.9%)	6 (1.8%)	2 (2.7%)	0.578
Cerebrovascular disease	10 (2.3%)	9 (2.6%)	1 (1.3%)	0.497
Microvascular complications (n, %)	107 (36.8%)	83 (34.6%)	24 (47.1%)	0.093
Retinopathy	61 (17.3%)	50 (17.1%)	11 (18.3%)	0.813
Nephropathy	45 (13.6%)	36 (13.3%)	9 (15.0%)	0.734
Neuropathy	95 (22.2%)	67 (19.0%)	28 (37.3%)	0.001
Obesity (n, %)	256 (57.7%)	207 (57.3%)	49 (59.0%)	0.778
Hypertension (n, %)	338 (73.5%)	280 (75.1%)	58 (66.7%)	0.110
Dyslipidemia (n, %)	303 (78.0%)	264 (76.5%)	69 (84.1%)	0.134
Insulin treatment (n, %)	191 (41.5%)	148 (39.7%)	43 (49.4%)	0.097
Statin treatment (n, %)	110 (23.9%)	89 (24.3%)	21 (22.3%)	0.689
Treatment with anti-depressants (n, %)	61 (13.3%)	0 (0.0%)	61 (70.1%)	< 0.001

Table 2. The PHQ-9 scores, laboratory parameters, and rates of achieving metabolic targets of patients with and without depressive disorders.

Variable total (n=460)	Total patients (n=460)	Without depressive disorder (n=373; 81.1%)	With depressive disorder (n=87; 18.9%)	p
PHQ-9 score	7.04±5.14	5.88±3.96	11.97±6.51	<0.001
BMI (kg/m^2)	31.71±5.97	31.50±6.06	32.62±5.55	0.126
SBP office (mmHg)	130.84±18.96	131.41±18.95	128.37±18.91	0.191
DBP office (mmHg)	79.43±10.19	79.55±10.42	78.89±9.11	0.599
HbA1c (%)	8.08±2.15	7.98±2.05	8.51±2.51	0.042
Total-C (mg/dL)	196.46±45.84	194.23±46.01	205.61±44.25	0.045
HDL-C (mg/dL)	47.56±13.23	47.69±13.53	47.05±11.95	0.697
LDL-C (mg/dL)	115.10±36.07	113.17±35.42	123.11±37.82	0.026
TG (mg/dL)	184.51±105.45	180.61±102.87	200.83±114.87	0.121
Non-HDL-C (mg/dL)	148.99±42.76	146.62±42.77	158.56±41.61	0.024
Achieving metabolic targets				
ABP (<140/90 mmHg)	266 (60.6%)	211 (59.1%)	55 (67.1%)	0.183
LDL-C (<100 mg/dL)	151 (36.2%)	130 (38.7%)	21 (25.9%)	0.032
HbA1c (<7%)	162 (36.3%)	136 (37.4%)	26 (31.7%)	0.336
Triple target	34 (7.7%)	32 (8.9%)	2 (2.4%)	0.042

PHQ-9: Patients Health Questionnaire-9; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Glycated hemoglobin; Total-C: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; TG: Triglycerides; ABP: Arterial blood pressure.

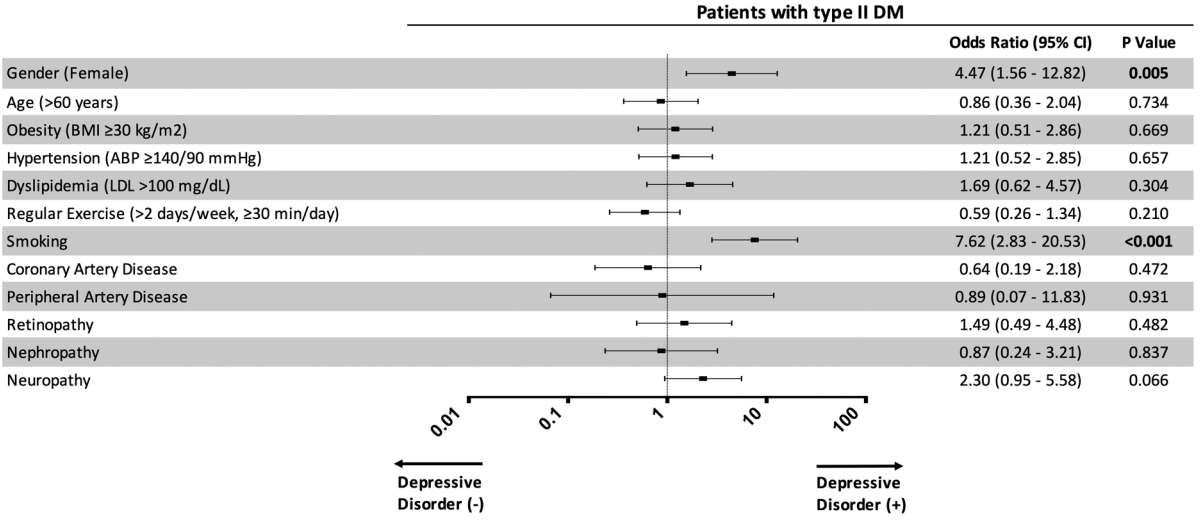

Figure 1: The factors associated with depressive disorder in patients with Type 2 diabetes.
BMI: Body mass index; ABP: Arterial blood pressure; LDL: Low-density lipoprotein.

male, younger, and had poor lipid levels. Being a female or a smoker were predictors of a depressive disorder.

A depressive disorder has a broad and heterogeneous diagnosis, where depressed mood and/or loss of pleasure are the most characteristic features. Many factors, including chronic diseases, can cause or exacerbate depressive disorders. Incidentally, the concomitant depressive disorder may also adversely affect the course of chronic diseases. The frequency of depressive dis-

orders is increasing all over the world (8,21-24). It is reported that the prevalence of depressive disorders in people with chronic diseases is twice higher than in the healthy population (25). Various studies have reported the prevalence of depressive disorders from 8% to 30% in diabetic patients (25-27). However, studies also show that only half of the patients with depressive disorders are diagnosed (25). The data on the prevalence of depressive disorders among diabetic patients in Turkey is limited. An international study that used the PHQ-9 questionnaire reported the prevalence of depressive disorder as 21% for both Type 1 and Type 2 diabetes, in Turkey (11). Another study found a prevalence of 26.4% by using Beck's Depression Inventory in 440 adult patients with Type 2 diabetes (13). The prevalence of depressive disorders in our study (18.9%) was similar to that of the reports of other national (11,13) and international studies (4,27,28). Depressive disorders may affect the course of diabetes, while it may also be affected by diabetes as well. It may also increase the risk of macro and microvascular complications in diabetic patients (29,30). Therefore, it is very important to determine the risk factors that develop depressive disorders in diabetic patients. Evidence shows that the prevalence of depression is moderately increased in prediabetic patients and significantly increased in diabetic patients (31). There may be a few reasons for an increased risk of depression in diabetic patients, such as diabetes, causing structural changes in the brain leading to atrophy (32). Studies show that atrophic changes may involve the hippocampus and that HbA1c may be an important determinant of hippocampal volume (33). Our study supports these findings by showing a higher HbA1c level in patients with depressive disorders. The patients with depressive disorder in our study had higher total cholesterol, LDL-C, and non-HDL-C levels. These findings are also consistent with the previous studies that reported higher cholesterol levels in Type 2 diabetic patients with depressive disorders (27,34). Lack of diet, medication adherence, and inadequate self-care in depressive patients may be the most important reasons for the poor metabolic features. Patients with depressive disorders in our study were younger than patients without depressive disorders. However, several studies show conflicting results of the effect of aging on depressive disorders, where many show a linear rise in the frequency of depressive disorders with increasing age (35-37), while others show a negative correlation (38). Also, different studies suggest a U-shaped relationship between age and depressive disorders (39).

Further, we showed that female gender and smoking were the independent determinants of depressive disorders in Type 2 diabetic patients. Patients with depressive disorders have poor self-care behaviors, such as overeating, drinking alcohol, smoking, limited physical activity, and poor medication adherence. For these reasons, it is not surprising that smoking is a determinant of a depressive disorder in this study. Studies also show that there may be a dose-dependent relationship between depressive disorder and smoking (40,41). In a study of Type 2 diabetic patients, heavy smokers were twice as likely as to experience major depression compared to nonsmokers (42). Diabetic patients may have more problems in quitting smoking because of the physical and emotional burdens associated with diabetes, where smoking may act as a stress-coping behavior (42). Many studies have also reported that depressive disorders are more common in women (43-45). The findings of a similar global female predominance suggest that the differential risk may primarily stem from the biological sex difference and is less dependent on race, culture, diet, education, and many other potentially confounding social and economic factors. Therefore, it was expected from our study to identify that the female gender is a risk factor in the development of depressive disorders.

This study may have several limitations. Firstly, as described in the definitions, PHQ is an instrument in performing criteria-based diagnoses of depression and other mental disorders. However, it is not a gold standard method for diagnosing depressive disorders. Also, in order to prevent an overdiagnosis, all the patients with high PHQ scores are further referred to a psychiatrist, with their progress being fully

monitored. Secondly, the study does not represent the whole country as it is performed in a local health center. Thirdly, we did not question erectile dysfunction in male patients, which is an important factor that causes depression in male diabetics. Additionally, the cross-sectional design of the study may preclude a causal relationship between predictive risk factors and depressive disorder in diabetic patients. There may also be a selection bias in our study since all the enrolled patients were followed-up in a tertiary endocrine unit, and also the enrollment of patients with multiple comorbidities and complications may have affected the results. Nevertheless, the result of our study is remarkable because it is one of the rare studies in our country that reports the prevalence and characteristics of depressive disorders in diabetic patients.

In conclusion, the prevalence of depressive disorders is considerably high in Type 2 diabetic patients, although they are being followed up in a tertiary outpatient endocrinology unit. To assess a diabetic patient from all aspects, screening for depressive disorders should be made an indispensable part of the evaluation process. The risk is higher if the patient is a female or a smoker. Further, prospective studies with a larger sample size may be required to reveal the relationship between depressive disorders and diabetes.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: İbrahim Demirci, Alper Sönmez; Design: Cem Haymana; Control/Supervision: Ömer Azal; Data Collection and/or Processing: Nazlı Kırnap, Orhan Demir, Aydoğan Aydoğdu; Analysis and/or Interpretation: Coşkun Meriç, Güven Oysul; Literature Review: Abdullah Bolu; Writing the Article: İbrahim Demirci, Cem Haymana; Critical Review: Alper Sönmez; References and Fundings: Neşe Ersöz Gülçelik.

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