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 Taraması

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 sectional study. 18.9% (n=87) of the participants were found to have depressive disorders according to PHQ-9. The scores were re-evaluated by a psychiatrist to minimize the false negative and positive results.

Objectif: Les symptômes dépressifs élevés et les troubles dépressifs affectent un sur cinq des patients diabétiques. Les directives actuelles recommandent de tester la dépression dans la population diabétique. La Turquie a la plus haute (13.7%) prévalence de diabète en Europe. Cependant, il y a des données limitées sur la prévalence des troubles dépressifs liés aux patients diabétiques de type 2 en Turquie. Nous avons cherché à examiner la prévalence d’un trouble dépressif dépendant dans les patients diabétiques de type 2 qui ont été référés au clinique d’endocrinologie d’un hôpital de niveau tertiaire.

Matière et Méthodes: Tous les patients diabétiques de type 2 admis au département d’endocrinologie ont été inclus de manière consécutive dans l’étude. Les sociodémographies, les maladies associées, les médicaments, les complications macro et microvasculaires, le mode de vie et les habitudes personnels, ainsi que les régimes de traitement ont été obtenus grâce à un questionnaire spécifiquement conçu. Les données laboratoires ont été obtenues des dossiers hospitaliers. Le Patient Health Questionnaire-9 (PHQ-9), un outil de dépistage de la dépression, a été utilisé en tant que méthode de dépistage. Les patients avec une note de 10 ou plus ont été déterminés comme à haut risque pour un trouble dépressif selon le PHQ-9. Les scores ont été revérifiés par un psychiatre pour minimiser les résultats faussement négatifs et positifs.

Résultat : Un total de 460 patients avec un diabète de type 2 ont été enrôlés dans cette étude transversale. 18.9% (n=87) des participants ont été trouvés avoir un trouble dépressif selon l’évaluation psychiatrique faite après l’étude. 18.9% (n=87) des participants ont été trouvés avoir un trouble dépressif selon le PHQ-9. Les scores ont été revérifiés par un psychiatre pour minimiser les résultats faussement négatifs et positifs.
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 prevalence 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/m²). 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). Glycemooglobin (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-
A PHQ-9 score of \( \geq 10 \) 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/m² (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 (\( \leq 0.9 \)), 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. \( \geq 30 \) kg/m²), 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-
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 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.

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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 Kirnap, 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 Güzcelik.

References

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The Prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care. 2001;24:1069-1078. [Crossref] [PubMed]

2. American Diabetes Association. Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S1-S153. [Crossref] [PubMed]

3. Siu AL, US Preventive Services Task Force (USPSTF); Bibbins-Domingo K, Grossman DC, Baumann LC, Davidson KW, Ebell M, Garcia AR, Gillman M, Herzstein J, Kemper AR, Krist AH, Kurth AE, Owens DK, Phillips WR, Pignone MP. Screening for depression in adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;26;315:380-387. [Crossref] [PubMed]

4. Van Buren DJ, Wilfley DE, Marcus MD, Anderson B, Abramson NW, Berkowitz R, Landis CL, Trief P, Yasuda P, Hirst K, TODAY Study Group. Depressive symptoms and glycemic control in youth with type 2 diabetes participating in the TODAY clinical trial. Diabetes Res Clin Pract. 2018;135:85-87. [Crossref] [PubMed] [PMC]

5. Schmitt A, Reimer A, Ehrmann D, Kulzer B, Haak T, Hermanns N. Reduction of depressive symptoms predicts improved glycaemic control: secondary results from the DIAMOS study. J Diabetes Complications. 2017;31:1608-1613. [Crossref] [PubMed]

6. Bădescu SV, Tătaru C, Kobylynka L, Georgescu EL, Zahui DM, Zăgorean AM, Zăgorean L. The association between diabetes mellitus and depression. J Med Life. 2016;9:120-125. [PubMed]

7. National Institute of Clinical Excellence (NICE). Depression in adults with a chronic physical health problem: recognition and management. NICE. 2016;31:1-57.

8. Salinero-Fort MA, Gómez-Campello P, San Andrés-Rebollo FJ, Cárdenas-Valladolid J, Abándoce-Herranz JC, Carrillo de Santa Pau E, Chico-Moraleja RM, Bemaud-Victoria D, de Miguel-Yanes JM, Jimenez-Garcia R, López-de-andres A, Ramallo-Fariña Y, de Burgos-Lunar C. Prevalence of depression in patients with type 2 diabetes mellitus in Spain (the DIADEMA Study): results from the MADiabetes cohort. BMJ Open. 2018;24;8:e020768. [Crossref] [PubMed] [PMC]
9. KnoI MJ, HeerEle ER, Egberts ACG, Geerlings MI, Gorter KJ, Numanes ME, Grobbel DE, Klungel OH, Burger H. Depressive symptomEs in subjects with dia-

gnoosed and undiagnosed type 2 diabetes. Psychoso-

m Med. 2007;69:300-305. [Crossref] [PubMed]

10. Li C, Ford ES, Srinne TW, Mokdad AH. Prevalence of de-

pression among U.S. adults with diabetes: fin-

ings from the 2006 behavioral risk factor surveil-

lance system. Diabetes Care. 2008;31:105-107. [Crossref] [PubMed]

11. Eker S. Prevalence of depression symptoms in dia-

beticus: the maastricht study. J Am Geriatr Soc. 2000;6;173:458-461. [Crossref] [PubMed]

12. Evrak S, Deficien and classification of diabetes melli-

tus: the maastricht study. J Am Geriatr Soc. 2001;6:302-308. [Crossref] [PubMed] [PMc]

13. Altnok A, MarakoÊlu K, Kargin NÇ. Evaluation of quali-

ty of life and depression levels in individuals with Type 2 diabetes. J Family Med Prim Care. 2016;5:302-308. [Crossref] [PubMed] [PMc]

14. Friedewald WT, Levy RJ, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cho-

lesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499-502. [Crossref] [PubMed]

15. van Steenbergen-Weijenburg KM, de Vroege L, Ploeger RR, Brals JW, Vloedmgd MG, Veneman TF, Hakkaart-van Rrojen L, Rutten FFJ, Beekman ATF, van der Feltz-Cornelis CM. Validation of the PHQ-9 as a screening instrument for depression in dia-

beteEs in specialIzed outpatient clinics. BMC Health Serv Res. 2010;12;205. [Crossref] [PubMed]

16. Jansen EPCJ, Köhler S, Stehouwer CDA, Schaper NC, Dagnelie PC, Sep SJS, Dagnelie PC, Henry RMA, van der Kallen CJH, van den Heuvel P, Graaf RD, Vollebergh W, Dragomirecka E, Kohn R, Kessler M, Kessler RC, Kawakami N, Klic C, Offord D, Ustun TB, Ulrich Wittchen H. The epidemiology of major depressive episodes: results from the Interna-

tional Consortium of Psychiatric Epidemiology (ICPE) Surveys. Int J Methods Psychiatr Res. 2006;29:2539-2548. [Crossref] [PubMed] [PMc]

17. Kronenke K, Spitzer RL, Williams JBW. The PHQ-9: va-

lidity of a brief depression severity measure. J Gen Intern Med. 2001;16:606-613. [Crossref] [PubMed] [PMc]

18. Definition, diagnosis and classification of diabetes melli-

tus and intermediate hyperglycemia: report of a WHO/IDF consultation. World Health Organization Report. 2006.

19. Obesity: preventing and managing the global epi-

demic. Report of a WHO consultation. World Health Organization technical report series 894, 2000.

20. Satman İ, İmamoğlu S, Yılmaz C, Akalin S, Salman S, Dinçcağ N. TEMD Diabetes Mellitus Çalışma ve Eğitim Grubu (Ed). Diabetes Mellitus ve Komplikas-
yonlarının Tani, Tedavi ve İzlem Kilavuzu-2019. Türkiye Endokrinoloji ve Metabolizma Derneği (TEMD) Yayınları, Batı Matbaaçılık, Ankara, 2019. ISBN: 978-605-4011-38-4.

21. McManus P, Mant A, Mitchell PB, Montgomery WS, Marley J, Auland ME. Recent trends in the use of an-
tidepressant drugs in Australia, 1990-1998. Med J Aust. 2000;6:173:458-461. [Crossref] [PubMed]

22. Hemels MEH, Koren G, Einarsen TR. Increased use of antidepressants in Canada: 1981-2000. Ann Pharmacother. 2002;36:1375-379. [Crossref] [PubMed]

23. Lépine JP, Gastpar M, Mendlewicz J, Tylee A. Depres-

sion in the community: the first pan-European study DEPRES (Depression Research in European Society). Int Clin Psychopharmacol. 1997;12:19-29. [Crossref] [PubMed]

24. Carta MG, Cariolino B, Kovess V, Porcedda R, Zedda A, Ruds N. Lifetime prevalence of major depression and dysthymia: results of a community survey in Sardinia. Eur Neuropsychopharmacol. 1995;5:103-107. [Crossref] [PubMed]

25. Egede LE, Simpson K. Epidemiology, treatment and costs of depression in adults with type 2 diabetes. Expert Rev Pharmacoeconomics Outcomes Res. 2003;3:251-262. [Crossref] [PubMed] [PMC]

26. Andreulakis E, Hyphantis T, Kandylis D, Lacroix S. Depression in diabetes mellitus: a comprehensive review. Hippokratia. 2012:16:205-214. [PubMed]

27. Egede LE, Ellis C. The effects of depression on meta-
bolic control and quality of life in indigent patients with type 2 diabetes. Diabetes Technol Ther. 2010;12:257-262. [Crossref] [PubMed] [PMC]

28. Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl RV, Graaf RD, Vollebergh W, Dragomirecka E, Kohn R, Kessler M, Kessler RC, Kawakami N, Kilic C, Offord D, Ustun TB, Ulrich Wittchen H. The epidemiology of major depressive episodes: results from the Interna-
tional Consortium of Psychiatric Epidemiology (ICPE) Surveys. Int J Methods Psychiatr Res. 2003;12:3-21. [Crossref] [PubMed] [PMc]

29. Clouse RE, Lusman PJ, Freedland KE, Griffith LS, McGill JB, Carney RM. Depression and coronary heart disease in women with diabetes. Psychosom Med. 2003;65:376-383. [Crossref] [PubMed]

30. M de Groot, Anderson R, Freedland KE, Clouse RE, Lusman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med. 2001;63:619-630. [Crossref] [PubMed]

31. Chen S, Zhang Q, Dai G, Hu J, Zhu C, Su L, Wu X. Association of depression with pre-diabetes, undi-

agnosed diabetes, and previously diagnosed dia-

betes: a meta-analysis. Endocrine. 2016;53:35-46. [Crossref] [PubMed]

32. Harte van B, de Leew FE, Weinstein HC, Schel-

tens P, Biessels GJ. Brain imaging in patients with diabetes: a systematic review. Diabetes Care. 2006;29:2539-2548. [Crossref] [PubMed]

33. Gold SM, Dziobek I, Sweat V, Tisi A, Rogers K, Bru-

ehl H, Tsui W, Richardson S, Javier E, Convit A. Hippocampal damage and memory impairments as possible early brain complications of type 2 dia-

betes. Diabetologia. 2007;50:711-719. [Crossref] [PubMed]

34. Gary TL, Crum RM, Cooper-Patrick L, Ford D, Bran-
cati FL. Depressive symptoms and metabolic control in African-Americans with type 2 diabetes. Diabetes Care. 2000;23:23-29. [Crossref] [PubMed]

35. Stordal E, Myklebust A, Dahl AA. The association be-

tween age and depression in the general population: a multivariate examination. Acta Psychiatrica Scandanvica. 107:132-141. [Crossref] [PubMed]
36. Weiss Wiesel TR, Nelson CJ, Tew WP, Hardt M, Mohile SG, Owusu C, Klepin HD, Gross CP, Gajra A, Lichtman SM, Ramani R, Katheria V, Zavala L, Hurria A, Cancer Aging Research Group (CARG). The relationship between age, anxiety, and depression in older adults with cancer. Psychooncology. 2015;24:712-717. [Crossref] [PubMed] [PMC]

37. Rothermund K, Brandstädter J. Depression in later life: cross-sequential patterns and possible determinants. Psychol Aging. 2003;18:80-90. [Crossref] [PubMed]

38. Lawton MP, Kleban MH, Dean J. Affect and age: cross-sectional comparisons of structure and prevalence. Psychol Aging. 1993;8:165-175. [Crossref] [PubMed]

39. Kessler RC, Foster C, Webster PS, House JS. The relationship between age and depressive symptoms in two national surveys. Psychol Aging. 1992;7:119-126. [Crossref] [PubMed]

40. Chaiton M, Cohen J, O’Loughlin J, Rehm J. Use of cigarettes to improve affect and depressive symptoms in a longitudinal study of adolescents. Addict Behav. 2010;35:1054-1060. [Crossref] [PubMed]

41. Boden JM, Fergusson DM, Horwood LJ. Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. Br J Psychiatry. 2010;196:440-446. [Crossref] [PubMed]

42. Clyde M, Smith KJ, Gariépy G, Schmitz N. The association between smoking and depression in a Canadian community-based sample with type 2 diabetes. Can J Diabetes. 2013;37:150-155. [Crossref] [PubMed]

43. Rai D, Zitko P, Jones K, Lynch J, Araya R. Country- and individual-level socioeconomic determinants of depression: multilevel cross-national comparison. Br J Psychiatry. 2018;202:195-203. [Crossref] [PubMed]

44. Cyranowski JM, Frank E, Young E, Shear MK. Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model. Arch Gen Psychiatry. 2000;57:21-27. [Crossref] [PubMed]

45. Baxter AJ, Scott KM, Ferrari AJ, Norman RE, Vos T, Whiteford HA. Challenging the myth of an “epidemic” of common mental disorders: trends in the global prevalence of anxiety and depression between 1990 and 2010. Depress Anxiety. 2014;31:506-516. [Crossref] [PubMed]