

PSYCHO-SOCIAL AND CLINICAL VARIABLES ASSOCIATED WITH DEPRESSION IN PATIENTS WITH TYPE 2 DIABETES

Žana Stanković^{1,3}, Miroslava Jašović-Gašić^{1,3,4} & Miroslava Zamaklar^{2,3,4}

¹Clinic for Psychiatry, University in Belgrade, Serbia

²Institute for Endocrinology, Diabetes and Diseases of metabolism, University in Belgrade, Serbia

³Clinical Centre of Serbia, University in Belgrade, Serbia

⁴School of Medicine, University in Belgrade, Serbia

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SUMMARY

Background: Type 2 diabetes (T2DM) doubles the odds of comorbid depression. Depression is a strong predictor of developing T2DM. The aim of the study was to compare depressed patients with T2DM to non-depressed ones with respect to demographic, psycho-social, clinical, anthropometric and metabolic characteristics; to examine the relationship between glycemic control and depression severity in depressed patients; to estimate the risk factors of depression.

Subjects and Methods: A group of depressed diabetic patients comprising those with a Major depressive episode, first or repeated (ICD-10; 1992) and endocrinologist-diagnosed T2DM, duration ≥ 5 years on oral, insulin therapy or both (N=46) and non-depressed ones (N=44) (90 in total) of both genders (<65 years) were included in this cross-sectional study. Laboratory and non-laboratory measures were performed. The patient Health Questionnaire (PHQ-9) and a structured interview (MINI) were used to establish diagnosis, while the Beck Depression Inventory (BDI; cut off ≥ 16) was used to assess the severity of depression. Scaling of Life Events (SLE) for self-assessment of life events and Problem in Areas in Diabetes (PAID) for self-assessment of diabetes distress were also performed.

Results: Statistically significant higher rates of psychiatric heredity, neuropathy, higher level of diabetes related distress and a greater number of life events in depressed patients compared to non-depressed ones were found. There was a statistically significant positive correlation between BDI somatic subscore and the HbA1c level ($r=0.343$; $p=0.020$). The level of diabetes related distress ($OR=1.084$; $p=0.000$), total number of life events ($OR=4.528$; $p=0.001$) and neuropathy ($OR=8.699$; $p=0.039$) were statistically significant predictors of depression using logistic regression.

Conclusions: The results obtained showed that depression in diabetic patients was predicted by both psychological (diabetes related distress, life events) and disease-specific variables (neuropathy). The severity of self-reported somatic depressive symptoms significantly correlated with the HbA1c level in depressed diabetic patients.

Key words: depression - type 2 diabetes – comorbidity - risk factors – neuropathy - diabetes related distress

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INTRODUCTION

Epidemiological data indicate that the number of people with diabetes will be doubled, from the year 2000 (2.8%) to 2030 (4%). Hence one can expect an increase of the total number of cases with 171 million, in 2000 to 366 million people in the world. The data indicate a particularly significant increase in the incidence of type 2 diabetes mellitus (T2DM) (Wild et al. 2004).

T2DM (previously referred to as Non Insulin Dependent Diabetes (NIDD)) occurs in around 85% of cases; usually after 40 years and the largest incidence of occurrence is about 60 years. T2DM is a complex metabolic disorder whose pathogenesis involves varying degrees of insulin resistance (IR) coupled with malfunction of the pancreatic islet beta cells causing insulin deficiency and is defined as fasting serum glucose of >7 mmol/L. T2DM is thought to be a polygenic disorder with environmental factors (age, sedentary life style, Body mass index (BMI) (kg/m^2), obesity and abdominal obesity in particular) also

contributing to disease expression and development (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2003).

Diabetes is associated with potentially life-threatening microvascular (retinopathy, nephropathy and neuropathy or "diabetic foot") (American Diabetes Association 2003, Dalla & Faglia 2006) and macrovascular complications (cerebrovascular and cardiovascular (CVD) diseases) (Wallentin 2004).

Depression is another condition with high prevalence worldwide. Depressive disorders are more frequent in women (4930 per 100,000) than men (3199 per 100,000) and they are the fourth leading cause of disease burden in women and seventh leading cause in men (Ustun et al. 2004). The lifetime prevalence of a major depressive disorder in Europe is 14% (Alonso et al. 2004). Depression is a major cause of morbidity, mortality and disability. The clinical importance of depression is not only in frequency of occurrence, but also in recurrent course, high suicidal risk, comorbidity with other psychiatric and medical diseases and the consequences to the family and society (World Health

Organization. The World Health Report 2001). Cultural influences on the presentation of depression can be significant and the clinician should be aware of differences in the expression of psychological distress in patients from other countries or cultures (Halbreich et al. 2007).

The high prevalence of T2DM and depression, and the positive relationship between them, suggest the importance of evaluating these two disorders together. In a meta-analysis of Gavard et al. (1993) (20 studies) the prevalence of depression in diabetic population (14.0% (8.5-27.3%) in controlled studies and 15.4% (11.0-19.9%) in uncontrolled ones) was 3 times higher in comparison with those without diabetes. A meta-analysis of Anderson et al. (2001) (42 published studies) (n=21,351) found that the prevalence of major depression in patients with diabetes was 11% and the prevalence of clinically relevant depression was 31%. This study also confirmed that depression in diabetic patients is more prevalent in women. In a study of 143 patients with T2DM and 132 healthy controls in Bahrain, an island country with a high prevalence of T2DM, Almawi et al. (2008) found a higher proportion of patients with T2DM in both the mild-moderate and severe-extremely severe depression categories. Ali et al. (2006) found that the prevalence of depression was significantly higher among patients with T2DM (17.6%) than those without diabetes (9.8%). However, a population-based retrospective cohort study found little evidence that T2DM increases the risk of depression once comorbid diseases and the burden of diabetes complications were accounted for (Brown et al. 2006).

Depression may be an independent risk factor in initiating T2DM. A prospective study of Kawakami et al. (1999) has shown a 2 times greater incidence of T2DM in depressive patients, independently of other risk factors, such as obesity, age, sedentary life style, chronic somatic diseases and a family history of diabetes. There is 37% greater risk of occurrence of diabetes in patients with depression, according to a meta-analysis of Knol et al. (2006) that involved 9 longitudinal studies. A meta-analysis of Cosgrove et al. (2008) confirmed that depression is accompanied by development of T2DM. However, it is estimated that relative risk is small and only 20% of cases of diabetes may be associated with depression in patients with the presence of both disorders. Depression in a young population of patients (20-50 years) increases the risk of development of diabetes around 23%, but not in older adults, based on the results of the population study by Brown et al. (2005). The results of a prospective cohort study of 23 years duration suggested that the risk of occurrence of T2DM in patients with depression is present throughout life, independently of the effects of healthy life style, Body mass index and family history. Educational attainment (>12 years of schooling) is an important moderator of the risk (Mezuk et al. 2008).

Evidence suggests a bi-directional relationship between depression and T2DM. According to a review

by Mezuk et al. (2008) which included studies from the year 1950 to 2007, depression was associated with a 60% increase of T2DM, while T2DM was only associated with a moderate (15%) risk of depression. This bi-directional relationship was confirmed in a study by Golden et al. (2008) in which the authors found that among individuals without elevated depressive symptoms at baseline, patients treated for diabetes had higher odds of developing depressive symptoms during the follow-up period. In contrast, individuals with impaired fasting glucose and those with untreated diabetes had a reduced risk of incidental depressive symptoms. These findings were comparable across racial/ethnic groups. Some antidepressant drugs (tricyclics, irreversible mono-amino oxidase inhibitors (MAOI), and mirtazapine may be accompanied by adverse metabolic effects, weight gain and obesity, increasing the risk of diabetes and other conditions (McIntyre et al. 2006).

The pathophysiological mechanism linking depression and diabetes is still not sufficiently known, but is considered as one of possible physiological dysregulation of multiple systems leading to development of inflammation, dysfunction of the hypothalamus-pituitary-adrenal (HPA) axis accompanied by hypercortisolemia as well as the Metabolic syndrome (MetS) (Musselman et al. 2003). The MetS is a cluster of homodynamic and metabolic abnormalities (hyperglycemia, hypertriglyceridemia, lower HDL cholesterol, hypertension, abdominal obesity) that occur together. It is associated with IR, diabetes (Després et al. 2008) and depression (Koponen et al. 2008, Räikkönen et al. 2007, Jakovljević et al. 2007). Comorbid chronic medical diseases (Egede 2005), diabetic complications (Katon et al. 2004, DeGroot et al. 2000) and a poor glycoregulation (Lustman et al. 2000) are significantly associated with the development and maintenance of depression in patients with diabetes.

Findings are inconsistent regarding the degree to which depression may exert a negative impact on glycemic control in patients with T2DM. Antidepressant treatment brings about improvement of depressive symptoms, prevents recurrences and increases the quality of life in diabetic patients. Some clinical studies show the association of antidepressant effects and improvement of glycemic control (Lustman et al. 2007, Abrahamian et al. 2009), but reduction of depressive symptoms upon antidepressive treatment was not accompanied by simultaneous improvement of glycoregulation, according to the results of other studies (Lustman et al. 1997, Georgiades et al. 2007, Filipčić et al. 2010). Patients with T2DM and concomitant depression are a subset with a worse clinical course and health outcome.

The aims of this study were the following: 1. To investigate differences between the patients with type 2 diabetes and concomitant depression and those with type 2 diabetes alone with respect to demographic, psycho-social, clinical, anthropometric and metabolic

characteristics; 2. To examine the relationship between glycemetic control and severity of depression in the patients with comorbidity of type 2 diabetes and depression; and 3. To estimate risk factors of depression in patients with type 2 diabetes.

SUBJECTS AND METHODS

A total of 90 in- and outpatients of both genders and mean age 56 ± 3 years, with type 2 diabetes mellitus (T2DM) diagnosed by an endocrinologist of at least 5 years duration, were included in this cross-sectional study. They were divided in two groups according to the presence/absence of Major depression: depressed (N=46) and non-depressed (N=44).

Eligibility for the study: Age 30–65 years, preserved vision and hearing, completed at least primary school; ≥ 5 years duration of endocrinologist-diagnosed T2DM in adulthood, treated with either oral hypoglycemic agents, insulin or both.

After collecting demographic data from a self-reported questionnaire we obtained data on depression status using the Patient Health Questionnaire (PHQ), The Beck Depression Inventory (BDI; cut off ≥ 16) and the structured interview MINI to confirm diagnosis of Major depression episode (ICD-10, World Health Organization 1992). The Mini Mental State Examination test was performed to screen cognitive impairment (≤ 23). The Scaling of Life Events (SLE) to assess the presence of life events during the year before to the episode and The Problem in Areas in Diabetes (PAID) to assess the level of diabetes related distress were also performed. The patients with repeated episodes of Major depression included in the study had not been on antidepressant treatment for at least one year before the inclusion in the study or they were at the very beginning of the treatment with antidepressants.

We performed laboratory measures by standard enzymatic methods ((fasting glucose concentration (mmol/L), triglycerides (mmol/L) and HDL cholesterol (High density lipoprotein cholesterol) (mmol/L) level), arterial blood tension (mmHg) as well as anthropometric measure: Waist circumference (WC) (cm) and Body mass index (BMI) (kg/m^2) (body weight in kilograms divided by body height in meters squared) to assess metabolic control and the presence of Metabolic syndrome (MetS).

In consonance with the National Institutes of Health, Adult Treatment Panel III (NCEP ATP-III) definition (2001), the subjects were considered to have MetS if they had any three or more of following: 1) abdominal obesity, defined by waist circumference ≥ 102 cm in men and ≥ 88 cm in women; 2) elevated blood pressure, defined as a systolic blood pressure ≥ 130 mmHg and/or a diastolic blood pressure ≥ 85 mmHg, physician diagnosis, and/or use of antihypertensive drugs; 3) elevated plasma triglyceride concentration (≥ 1.69 mmol/L) or treatment with fibrate medication; 4) Low

HDL cholesterol concentration (men < 1.03 mmol/L and women < 1.29 mmol/L); and 5) elevated fasting glucose concentration (> 6.1 mmol/L ≥ 100 mg/dl) or diagnosed type 2 diabetes.

Diabetes history, most recent glycated hemoglobin (HbA1c) (%) value (a reliable method for estimating glycemetic control over the last 90–120 days), diabetes microvascular and macrovascular complications (angina pectoris, myocardial infarction, heart failure, coronary by-pass), medical comorbidity, antidiabetic therapy and non-antidiabetic pharmacotherapy were obtained from the patients' medical records.

Exclusion criteria: Lifetime presence of depression episodes in patients who were classified as non-depressed; severe depression with agitation, retardation or high level of suicidality; treatment with antipsychotics, mood stabilizers or corticosteroids in the last year; endocrinological diseases other than diabetes; significant cognitive impairment, transient ischemic attack, alcoholism, history of major amputation or other severe chronic medical diseases or complications of diabetes precluding participation (such as renal failure/dialysis, stroke, or widespread malignant disease).

The study was approved by the Ethics committee of Clinical Centre of Serbia. After explanation of the study details and an initial examination for suitability, written informed consent was obtained from all the study participants. This study was carried out at the Clinic for Psychiatry and Institute for Endocrinology, Diabetes and Diseases of metabolism, University Clinical Centre in Belgrade, from March 2008 to March 2010.

Measures

The Patient Health Questionnaire (PHQ)

Depression was measured using the Patient Health Questionnaire (PHQ), the depression section of a patient oriented self-administered instrument derived from the Primary Care Evaluation of Mental Disorders. It lists 9 potential symptoms of depression (e.g., feeling down, depressed, or hopeless, little interest or pleasure in doing things), and asks patients to rate the frequency of experiencing each symptom during the past 2 weeks on a scale ranging from 1, "never" to 4, "almost always". The criteria for the diagnosis of Major depression based on this instrument are the presence of 5 or more of 9 symptoms for at least half a day for the past 2 weeks, and one of them is depressed mood, or anhedonia (Spitzer et al. 1999). Only the patients with score ≥ 10 were included in the study.

The Mini international neuropsychiatric interview (MINI)

This is a structured neuropsychiatric interview that is used by clinicians. It provides testing in a standardized way, each criterion necessary to establish the main axis and psychiatric disorders according to DSM-IV to diagnose Major depressive episode (MDE), which is correlated with the ICD-10 (Lecrubier et al. 1997). The

structured interview was applied in all patients who fulfilled screening criteria for Major depressive episode (MDE) for the exclusion of other psychiatric disorders except for depression, as well as to assess sociality.

The Beck Depression Inventory (BDI)

The Beck Depression Inventory (BDI) is a 21-item self-report instrument for measuring severity of depression during the past week. The first 14 items measure psychic (affective-cognitive) depressive symptoms and the last 7 items measure somatic symptoms of depression. Each item is a list of four statements arranged in increasing severity about a particular symptom of depression (Beck et al. 1996). Only the patients with cut off ≥ 16 were included in the study.

The Beck Depression Inventory is the tool most widely used in clinical studies and has been validated in patients with diabetes. A total score ≥ 16 is likely to capture >70% of the patients with Major depression while providing >70% certainty that a person screening positive actually has Major depression (Lustman and Clouse 2004).

Mini Mental State Examination (MMSE)

The Mini-Mental State is a brief mental status test of cognitive functions. The test consists of 13 questions that assess orientation to place and time, learning and memory, construction ability, attention, and calculation skills. The possible range of scores is 0-30 (Folstein et al. 1999). Only the patients without severe cognitive impairment (scores >23) were included in the study.

The Scaling of Life Events (SLE)

This is a self-report scale consisting of 61 items (life events), which are ranged so that catastrophic and upsetting ones are on the top of the scale (death of a child), while favorable and trivial (child's marriage agreed by parents) are on the bottom. It is filled in by ticking the most important event(s) which happened during the last year (Paykel et al. 1971). In this study, we assessed the total number of self-reported life-events.

The Problem Areas in Diabetes (PAID)

This is a self-evaluation questionnaire consisting of 20 questions which measures negative emotions towards diabetes and its treatment. The possible answers are scored from 1-5 on Likert scale from "I strongly disagree" to "I strongly agree". Subscales of the questionnaire related to the emotional problems associated with diabetes (12 items) and problems referring to nutrition (3 items), treatment of diabetes (3 items) and social support (2 items) are also analyzed (Polonsky et al. 1995). Higher score on this scale means higher level of distress related to diabetes.

Statistical analysis

Statistical analyses were carried out using the SPSS software (version 13.0 for Windows). Descriptive statistics for continuous variables (mean value (M) and standard deviation (SD)) and categorical variables (number (N) and percentages (%)) were used.

Comparison of continuous variables of the two study groups of patients was performed either using Student's *t*-test (normal distribution) or Mann-Whitney U test (not normal distribution) (Shapiro-Wilks). Comparison of categorical variables was performed using χ^2 test. Pearson's correlation was used to examine relationship of continuous variables. Logistic regression was performed to estimate risk factors of depression in diabetic patients. In all the analytical methods, the level of significance was $p < 0.05$.

RESULTS

Table 1. presents the demographic characteristics of both patient groups. There were no statistically significant differences between the group of patients with type 2 diabetes and depression and the group of patients with type 2 diabetes alone in gender distribution, marital status, the frequency of employed and smokers, nor were there considerable differences between the two groups of patients in years of age and education.

Table 1. Demographic characteristics of both patients' groups (N=90)

	Type 2 diabetes +depression (N=46)	Type 2 diabetes (N=44)	p
Female gender (N, %)	35; 76.1	24; 54.6	NS†
Married (N, %)	33, 71.7	32; 72.7	NS†
Employed (N, %)	13; 28.3	12; 27.3	NS†
Smoking (N;%)	21; 45.7	12; 27.3	NS†
Age (yrs.) (M±SD)	54.39±6.55	57.18±5.78	NS‡
Education (yrs.) (M±SD)	10.98±2.08	12.11±3.13	NS‡

Note: N-number of patients; %-percentage of patients; M-mean value; SD-standard deviation; NS-Not significant; † χ^2 test; ‡ Mann-Whitney U test.

Table 2. displays the clinical characteristics of both patient groups. We found a statistically significant higher percentage of examinees with a family history of

psychiatric disorders (heredity) ($\chi^2=7.947$; DF=1; $p=0.005$) and the presence of neuropathy in the depressed diabetic patients in relation to the non-

depressed ones ($\chi^2=5.080$; $DF=1$; $p=0.024$). The average age at the first episode of depression onset was 47.57 ± 9.27 years and the average time from the first

episode of depression onset was 6.70 ± 7.52 years in the group of depressed diabetic patients (not shown).

Table 2. Clinical characteristics of both patients' groups (N=90)

	Type 2 diabetes + depression (N=46)	Type 2 diabetes (N=44)	p
Psych. disord. in family (N; %)	21; 45.7	7; 15.9	0.005†
Diabetes in family (N; %)	27; 58.7	24; 54.5	NS†
Concurr. med. diseases ^a (N; %)	44; 95.7	39; 88.6	NS†
Microvasc. compl. (N; %)	44; 95.7	37; 84.1	NS†
Neuropathy (N; %)	44; 95.7	34; 77.3	0.024†
Retinopathy (N; %)	20; 43.5	18; 40.9	NS†
Nephropathy (N; %)	10; 21.7	9; 20.5	NS†
Macrovasc. compl. (N; %)	15; 32.6	18; 40.9	NS†
Insulin therapy (N; %)	29; 63.0	25; 56.8	NS†
Age at T2DM onset (yrs.) (M±SD)	42.41±7.04	44.93±6.26	NS•
Duration of T2DM (yrs.) (M±SD)	11.96±6.34	12.11±6.04	NS‡
Life events (number)(SLE ^b (M±SD))	1.63±0.80	0.65±0.71	0.000‡

Note: N-number of patients; %-percentage of patients; M-mean value; SD-standard deviation; ^aConcurrent medical diseases (≥ 1); other than diabetes and microvascular diabetic complications) that require chronic treatment; ^bTotal number of life events assessed by The Scale of Life events (SLE); NS-Not significant; † χ^2 test; ‡Mann-Whitney U test; •Student's *t*-test.

We found a statistically significant greater total number of self-reported life events, assessed by the Scaling for Life events (SLE) in the depressed diabetic patients in relation to the non-depressed ones ($U=405.000$; $Z=-5.162$; $p=0.000$) (Mann-Whitney U test).

There were no statistically significant differences with respect to the proportion of examinees with a family history of diabetes, chronic somatic diseases, microvascular complications (≥ 1), presence of retinopathy, nephropathy, macrovascular complications and insulin requirement between the depressed diabetic patients and the non-depressed ones, nor were there statistically significant differences between the two groups of patients in age at T2DM onset and duration of endocrinologist-diagnosed T2DM.

Table 3. provides metabolic and anthropometric parameters of both patients' groups.

There were no statistically significant differences with respect to fasting glucose level (mmol/L), triglycerides level (mmol/L), High density lipoprotein, cholesterol level (HDL) (mmol/L), HbA1c level (%) systolic blood pressure (SP)(mmHg), Body mass index (BMI) (kg/m^2), and waist circumference (WC) (cm) between the depressed diabetic patients and the non-depressed ones, nor were there statistically significant differences in the frequency of examinees with hypertension (HTA), Metabolic syndrome (MetS) and obesity ($\text{BMI}\geq 30 \text{ kg}/\text{m}^2$) between the two examined groups of patients.

There were no statistically significant differences with respect to the proportion of examinees with elevated triglycerides level ($\geq 1.69 \text{ mmol/L}$), lower HDL level ($M<1.03 \text{ mmol/L}$ or $F<1.29 \text{ mmol/L}$) and

abdominal obesity (Waist circumference (WC) (cm): $M>102\text{cm}$, $F>88\text{cm}$) between the depressed diabetic patients and the non-depressed ones (not shown).

Table 4. indicates the psychometric scales (PHQ, BDI, BDI psych. subscale, BDI som. subscale, PAID) mean scores of both patients' groups.

There were statistically significant higher mean PHQ score ($U=0.000$; $Z=-8.202$; $p=0.000$), BDI score ($U=0.000$; $Z=-8.187$; $p=0.000$), BDI psych. subscore ($U=33.500$; $Z=-7.914$; $p=0.000$) (Mann-Whitney U test), BDI som. subscore ($t=-13.511$; $DF=88$; $p=0.000$) (95%CI-7.3155–5.4373) (Student's *t*-test) and PAID score ($U=398.000$; $Z=-4.957$; $p=0.000$) (Mann-Whitney U test) in the depressed diabetic patients in relation to the non-depressed ones.

Statistically considerable positive correlation between BDI som. subscore and the HbA1c blood level (%) ($r=0.343$; $p=0.020$) in the group of depressed diabetic patients was found, but not between BDI total score and the HbA1c blood level (%) using Pearson's correlation.

Table 5. presents the results of logistic regression of predictors of depression in the patients with comorbidity of T2DM and depression. Logistic regression was performed to assess the impact of family history of psychiatric disorders, total number of life events, PAID total score and presence of neuropathy (independent variables) on the likelihood of presence of depression in patients with T2DM (dependent variable). The full model containing all predictors was statistically significant ($\chi^2=53.871$; $p=0.000$) and explained 60.1% of the variance of dependent variable (Nagelkerke $R^2=0.601$). The model correctly classified 87. 8% of cases.

Table 3. Metabolic and anthropometric variables of both patients' groups (N=90)

	Type 2 diabetes + depression (N=46)	Type 2 diabetes (N=44)	p
FGL(mmol/L) ^a (M±SD)	11.35±4.12	10.60±2.92	NS•
TRG(mmol/L) ^b (M±SD)	2.95±2.15	2.87±1.80	NS‡
HDL(mmol/L) ^c (M±SD)	1.05±0.27	1.14±0.29	NS‡
HbA1c(%) ^d (M±SD)	8.69±1.92	9.11±1.65	NS•
WC(cm) ^e (M±SD)	102.15±14.06	102.18±14.77	NS•
SP(mm Hg) ^f (M±SD)	136.09±17.32	138.98±23.66	NS‡
BMI(kg/m ²) ^g (M±SD)	31.42±6.49	30.02±5.99	NS‡
HTA ^h (N;%)	43; 93.5	34; 77.3	NS†
MetS ⁱ (N;%)	42; 91.3	36; 81.8	NS†
BMI≥30kg/m ² ^j (N;%)	27; 58.7	23; 52.3	NS†

Note: N-number of patients; %-percentage of patients; M-mean value; SD-standard deviation; ^aFGL-Fasting glucose level (mmol/L); ^bTRG-Triglycerides (mmol/L); ^cHDL-High density lipoprotein cholesterol (mmol/L); ^dHbA1c-Glycosylated hemoglobin A1c (%); ^eWC-Waist circumference (cm); ^fSP-Systolic pressure (mmHg); ^gBMI-Body mass index (kg/m²); ^hHTA-Hypertension; ⁱMetS-Metabolic syndrome (NCEP ATP-III criteria); ^jBMI-Body mass index ≥30kg/m²; NS-Not significant; †χ² test; ‡Mann-Whitney U test; •Student's *t*-test.

Table 4. Mean PHQ, BDI and PAID score of both patients' groups (N=90)

	Type 2 diabetes + depression (N=46)	Type 2 diabetes (N=44)	p
PHQ ^a (M±SD)	17.22±4.75	3.55±2.53	0.000‡
BDI ^b (M±SD)	25.63±6.86	6.34±2.65	0.000‡
BDI psy. ^c (M±SD)	15.28±5.86	2.50±1.75	0.000‡
BDI som. ^d (M±SD)	10.22±2.60	3.84±1.82	0.000•
PAID ^e (M±SD)	56.10±11.99	39.47±14.96	0.000‡

Note: N-number of patients; %-percentage of patients; M-mean value; SD-standard deviation; ^aPHQ-Patient Health Questionnaire; ^bBDI-Beck Depression Inventory; ^cBDI psy.-Subscale of psychic (cognitive-affective) symptoms of depression (items 1-14.); ^dBDI som.-Subscale of somatic symptoms of depression (items 15-21.); ^ePAID-Problem Areas in Diabetes; ‡Mann-Whitney U test; •Student's *t*-test.

Table 5. Logistic regression of predictors of depression in patients with Type 2 diabetes+depression^a

	B	S.E.	Wald	DF	p	OR	95.0% C.I. for OR	
							Lower	Upper
Family history of psych. disorders ^b	0.119	0.724	0.027	1	0.869	1.127	0.273	4.652
Total number of LE ^c	1.510	0.435	12.028	1	0.001	4.528	1.929	10.630
PAID ^d	0.081	0.022	13.254	1	0.000	1.084	1.038	1.133
Neuropathy ^e	2.163	1.048	4.258	1	0.039	8.699	1.115	67.885
Constant	7.565	1.744	18.822	1	0.000	0.001		

Note: Variables- ^aType 2 diabetes and Type 2 diabetes+depression (Type 2 diabetes-1, Type 2 diabetes+depression-0); ^bFamily history of psychiatric disorders (present-1, not present-0); ^cTotal number of life events assessed by The Scaling of Life events (SLE); ^dPAID total score; ^ePresence of neuropathy (present-1, not present-0).

Three of the four independent variables made a unique statistically significant contribution to the model: PAID total score (OR=1.084; 95%CI=1.038–1.133; p=0.000), total number of life events, assessed by The Scale of Life events (SLE) (OR=4.528; 95%CI=1.929–10.630; p=0.001) and presence of neuropathy (OR=8.699; 95%CI=1.115–67.885; p=0.039). Family history of psychiatric disorders did not make a statistically significant contribution to the model (OR=1.127; 95%CI=0.273–4.652; p=0.869).

DISCUSSION

According to the results obtained in this study, the depressed patients with T2DM considerably differed from the non-depressed ones by a higher frequency of family history of psychiatric disorders, greater total number of life events, higher level of distress related to diabetes and higher frequency of polyneuropathy.

The results regarding psychiatric heredity could be expected, considering that genetic susceptibility (in

interaction with environmental factors) plays a role in the development of major depressive disorder. Individuals with a family history of affective disorders, panic disorder, and alcohol dependence carry a higher risk for major depressive disorder (Bhalla & Moraille-Bhalla 2010).

The two examined groups of patients had comparable demographic, disease-related and metabolic and anthropometric characteristics. These findings are in concordance with the results of a study by Yoshida et al. (2008), which included a mixed sample of patients with T2DM (n=105) and T1DM (n=24). In that study it was shown that there were no significant differences in clinical variables between depressed and non-depressed diabetic patients. In a study by Collins et al. (2009), the depressed and non-depressed diabetic patients did not differ by level of glycoregulation and in the most recent study of Egede & Ellis (2010) (n=201) no significant differences were observed in patients with T2DM by depression status in the level of HbA1c, LDL (Low density lipoprotein) cholesterol, and HDL cholesterol. The results of a prospective longitudinal study (n=3,762) of 5 years duration which was carried out in patients with T2DM shown no significant differences in the HbA1c level, systolic blood pressure and LDL cholesterol level between the patients with comorbidity (major or minor depression) and those with T2DM only (Heckbert et al. 2010). In considering the results regarding clinical variables, we should keep in mind that our study was carried out in an institution of tertiary level and included the more complex patients with T2DM.

The total number of self-reported life events which happened during a year before the episode of depression was one of the predictors of depression in patients with T2DM based on the results obtained in this study. These findings pointed to the importance of cumulative effects of stressful events in the development and maintenance of depression in patients with T2DM. A study by Fisher et al. (2001) which included different ethnic groups (patients born in Europe and patients from Latin America), showed significant contribution of life events (financial stress in both ethnic groups and marital conflicts, more significant in patients of European origin) to the association of depression and T2DM, not only in patients with Major depression, but also in those with only depressive symptoms, without fulfilling criteria for Major depression. Besides other sociodemographic correlates, depression in patients with T2DM was associated with a poor relationship with partners, according to the results of a study by Agbir et al. (2010).

In considering contribution of life events to depression in both patients with T2DM and patients without T2DM, we should have in mind the significant influence of early traumatic experiences (these referring to lost and lack of control, in particular) in development of a “depressive nucleus” (Ingram 1984) in childhood, which could activate epigenetic processes and

preexisting vulnerability to stress and development of disorder, particularly during exposure to stressful events later in life. This has clinical significance in both the prevention of depression, and in psychotherapeutic interventions.

We should take into consideration that the time of examination (period of decompensation) could affect self-report of life events because of the need of the patients to explain their troubles by environmental factors (Zimmerman et al. 1986). Furthermore, it is often difficult to decide whether life events are dependent (secondary to depression) or independent (do not occur as a result of depressive symptoms).

It is necessary, however, to emphasize that life events (both acute and chronic), although they may precede the episodes of depression, may not be the cause of the episode. This dilemma can be clarified by comparing the number and quality of life events that preceded the episode of depression with the life events during the year after the episode of the disease.

According to the model of logistic regression used in our study, distress related to diabetes (negative emotions towards diabetes and its treatment) was the second psycho-social factor which predicted depression in patients with T2DM.

Emotional problems associated with T2DM are more frequently presented in patients with Major depression (49%) in relation to those with subclinical forms of depression (42%) and patients without depression (Kokoszka et al. 2009). Distress related to diabetes is more frequent in patients with severe depressive symptoms compared with those with mild and moderate depressive symptoms (Power et al. 2005). Emotional problems associated with T2DM are also one of predictors of maintenance of depression in patients with diabetes (Pibernik-Okanović et al. 2008). Patients' attitude that diabetes is a serious problem as well as depression, strongly correlated with high levels of HbA1c (Daly et al. 2009). Fisher and colleagues (2007) reported that diabetes-specific distress was a better predictor of diabetes self-care than symptoms of depression or a diagnosis of Major depressive disorder. However, in a study of Gonzales et al. (2008) which included the patients with T2DM treated in primary care (n=848) was found that symptoms of depression had a greater negative impact on self-control of diabetes than distress related to diabetes, even in patients not fulfilling criteria for Major depression. The findings of that study also suggested that while symptoms of Major depression and diabetes-specific distress are related, sharing 29% of their variance in the overall sample and 13% among those who did not meet screening criteria for Major depression, they are independent constructs. Younger age, female gender and diabetes complications/comorbidity were associated with depression and diabetes related distress, according to a study by Fisher et al. (2008). These results indicate the need for disclosure of distress associated with diabetes during all contacts with the patient, not just occasionally.

Distress related to diabetes could mediate the relationship between depression and glycaemic control (Fisher et al. 2009, Van Bastelaar et al. 2010). Lowering of diabetes-related distress might help to enhance diabetes self-management, thereby attaining better glycaemic control. These findings stress the importance of acknowledging and addressing diabetes-related issues in the context of depression treatment to help improve diabetes outcomes. Distress associated with diabetes and depression should be viewed as separate constructs, for proper clinical assessment of patients, as well as the implementation of appropriate therapeutic interventions.

Neuropathy was a disease-specific predictor of depression in patients with T2DM, according to the results obtained in our study. This diabetes complication was highly prevalent in both groups of patients with T2DM included in the study, but considerably higher in depressed diabetic patients. In the patients included in our study, the diagnosis of neuropathy was established on the basis of clinical and neurophysiologic examinations, not only by self-report or subjective complaints. The results of the study regarding high rate of neuropathy could be expected, since the study included great number of in-patients with T2DM and worsening of the illness (poor glycaemic control). Diabetic peripheral neuropathy is common, affecting up to 50% of patients, and predisposes patients to severe functional limitations through symptoms of unremitting pain and unsteadiness (Boulton et al. 2000).

The meta-analysis of de Groot et al. (2001) (27 studies) shown a consistent and significant association between depression and diabetes complications. Neuropathy in patients with T2DM was associated with a higher frequency of mental disorders, particularly anxiety disorders and major depression. Severity of depressive symptoms was positively correlated with severity of neuropathic symptoms, but not with clinical status, according to a study of Moreira et al. (2007). Neuropathy tended to add to the prediction of depression, other comorbidities did not, based on a study of Lee et al. (2009). In a recent prospective study of 5 years duration, Major depression proved to be a risk factor for the development of microvascular complications. Glycaemic control and life style did not significantly affect the risk of microvascular complications (Lin et al. 2010).

In our study, which included patients with T2DM, the significant correlation of severity of self-reported somatic symptoms of depression (BDI somatic subscore) and the level of HbA1c was found in the group of diabetic patients with concomitant depression. In a study of Van Tilburg et al. (2001) significant correlation of severity of depressive symptoms (BDI score) and glycaemic control (the level of HbA1c) was found only in patients with T1DM. In a study by Aikens et al. (2008) the association between depression severity and HbA1c was found only in diabetic patients on insulin therapy, but not in those on oral hypoglycaemic drugs. One of the

findings of a study by Daly et al. (2009) (n=253) was a significant correlation of intensity of self-reported depression (PHQ score) and HbA1c level.

It is important that the presence of depression is accompanied by self-report of more symptoms of the illness (fatigue, paresthesia, feeling faint), independently of glycoregulation (Lustman & Clouse 2005). A study of Pouwer & Snoek (2001) (174 outpatients and 1437 patients, members of the diabetes association) confirmed the existence of significant association between depression severity and HbA1c level in the three of four samples of women and in one of the four samples of men, regardless of the number of complications, level of education and Body mass index. Only in ambulatory patients with T2DM was there a significantly higher correlation of HbA1c and depression severity.

Possible advantages of this study are that the diagnosis of Major depression was established using a structured neuropsychiatric interview (MINI), not only by using a self-report instrument. Furthermore, we separately assessed life events and emotional problems related to diabetes and its treatment, and the diagnosis of neuropathy was established by using clinical and neurophysiologic tests, not by self-report or subjective complaints.

The most important limitations of this study include its cross-sectional design, insufficient number of patients in order to explore the impact of gender and kind of therapy (insulin vs. oral therapy alone) on the examined variables and inclusion of a great majority of diabetic patients with poor glycaemic control and deteriorating course of the illness.

CONCLUSION

The depressed diabetic patients had a higher rate of psychiatric heredity, the presence of neuropathy, a higher level of diabetes related distress and a greater number of life events in comparison with the non-depressed ones. Self-reported somatic depressive symptoms significantly positively correlated with the HbA1c level in the group of depressed diabetic patients. Level of distress related to diabetes, total number of life events and presence of neuropathy were predictors of depression in patients with T2DM.

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Correspondence:

Žana Stanković
Clinic for Psychiatry, Clinical Centre of Serbia
Pasterova 2, 11000 Belgrade, Serbia
E-mail: stankovic.zana@gmail.com