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The Association among Glycemic Control and Depression Symptoms in Patients with Type 2 Diabetes

Elvira Hasanovic[1], Natasa Trifunovic[1,2], Irma Dzambo[1], Hasiba Erkocevic[1,2], Adem Cemerlic[2], Zaim Jatic[1,2], Alma Dzubur Kulenovic[2,3]

[1]Public Institution Health Centre of Canton Sarajevo
[2]Faculty of Medicine University of Sarajevo
[3]Clinical Centre of the University of Sarajevo

Corresponding author:
Natasa Trifunovic, MD. Address: Faculty of Medicine, Cekalusa 90, 71000 Sarajevo, Bosnia and Hercegovina. Phone: +387 61 267 386, E-mail: natasa.trifunovic@mf.unsa.ba. ORCID ID: https://orcid.org/0000-0002-1048-9351 .

ABSTRACT

Introduction: Diabetes and depression are two common and major non-communicable diseases with significant disease burdens worldwide. **Aim:** The aim of this study is to obtain the association among A1C levels and symptoms of depression in patients with type 2 diabetes in family medicine offices. **Methods:** This cross-sectional study was carried out between June 2016 and July 2017. We recruited 150 adults with type 2 diabetes from various family medicine offices. The study questionnaire had two parts; the first one for participants and the second one for family medicine physicians. Participants completed the part of the questionnaire with the PHQ-9 scale and questions regarding demographic data. Family medicine physicians completed the part of the questionnaire with questions concerning clinical data. A univariate and multivariate linear regression analysis was conducted to identify significant predictors of depressive symptoms revealed by the PHQ-9 score. **Results:** Multiple linear regression showed that the level of A1C was a significant predictor of the PHQ-9 score in all three models. Increases in the A1C level were followed by increases in depressive symptoms. Other significant predictors of a positive PHQ-9 score were smoking, level of education and income. **Conclusion:** The level of A1C as an indicator of glycemic control has been shown to have a significant association with the scores of the PHQ-9 questionnaire, which identifies the intensity of symptoms of depression. An increase in the level of A1C is followed by an increase in the intensity of symptoms of depression.

Keywords: diabetes mellitus, glycemic control, depression symptoms, family medicine.

1. INTRODUCTION

Diabetes and depression are two common and major non-communicable diseases with significant disease burdens worldwide. According to the *International Diabetes Federation* more than 425 million people, or 8.8% of adults 20 to 79 years of age, have type 2 Diabetes Mellitus (T2DM), and almost 320 million people have symptoms of some degree of depression. If these trends continue, by the year 2045, 629 million people this age will have diabetes. According to the same report, the number of individuals with diabetes in Europe is 66 million and the prevalence of this disease in Bosnia and Herzegovina is 12% (1).

Depression is a risk factor for the development of diabetes mellitus and it is associated with adverse diabetic outcomes. Conversely, diabetes may worsen the clinical course of depression. Previous studies have demonstrated that depression is more common among people with diabetes than among the general population, and psychological aspects such as diabetes related depressive symptoms have been considered as contributors to poor glycemic control and suggest the bidirectional relationship of these two diseases (2-5).

Many previous studies have reported a high prevalence of depression or depressive symptoms in people with T2DM, which could indicate that depressive symptoms are associated with a significantly increased risk for the incidence of diabetes (2, 6, 7).

Depression screening in primary medical care has been recommended as a first step towards intervention. PHQ-9, one of the most widely used screening tools in primary care, is stan-

dardised to identify the presence and intensity of depressive symptoms. It was developed from the Primary Care Evaluation of Mental Disorders (PRIME MD) of DSM-IV (8).

It has been validated as a screening tool in different population samples, such as the general population, medical students and the elderly (9-12).

PHQ-9 (Patient Health Questionnaire-9) shows good diagnostic properties in various settings, but most typically in primary care. This questionnaire is a measure of nine symptoms of depression according to the DSM-IV and the new DSM-V criteria (13, 14).

This questionnaire was chosen due to its good psychometric properties, quick administration and availability in the Croatian and Serbian languages, two of the three official languages used in Bosnia and Herzegovina, which are understandable to the general population.

2. AIM

The aim of the study was to obtain the association among glycosylated haemoglobin A1C level (A1C level) and symptoms of depression in patients with type 2 diabetes in family medicine offices.

3. METHODS

This cross-sectional study was carried out between June 2016 and July 2017. We recruited 150 adults with type 2 diabetes from various family medicine offices in the Public Institution Health Centre of Sarajevo Canton in the city of Sarajevo. G*Power 3.1 was used to estimate the required sample size for multiple regression analyses (14). When assuming a two-tailed test, the effective size f^2 of 0.10 with an alpha level of 0.05 at 0.95 power and 11 predictors, a minimum of 133 participants were required. In this study, the sample size was 150 participants and that was sufficient to detect a statistically significant relationship.

The study questionnaire had two parts; the first one for participants and the second one for family medicine physicians. Participants completed the part of the questionnaire with the PHQ-9 scale and questions regarding demographic data (age, gender, marital status, education, smoking, employment and self-reported income). Family medicine physicians completed the part of the questionnaire with questions concerning clinical data [Body mass index (BMI), duration of the T2DM, type of the T2DM management and glycosylated haemoglobin A1C level (A1C level)] based on patient health records. According to the American Diabetes Association (ADA) the cut off of seven is used for glycemic control, where ⩾7 indicates poor glycemic control (15) (ADA guidelines from that period). A PHQ-9 score of ⩾10 indicated a classification of significant depressive symptomatology. The inclusion criteria were the following: already diagnosed T2DM at least one year before the questionnaire, age 18 and above, both genders, a capability to answer the questionnaire, and willingness to take part in this study. Exclusion criteria were previously diagnosed mood disorders, psychotic disorders, cognitive impairment, malignant disorders, previous coronary heart disease, stroke, end stage chronic diabetic kidney disease and refusal to give written consent for the study.

The Patient Health Questionnaire (PHQ) is a diagnostic tool for mental health disorders used by health care professionals, created by Drs. Spitzer, Williams and Kroenke, staff from Columbia University in collaboration with researchers at the Regenstrief Institute at Indiana University and with the support of an educational grant from Pfizer Inc., during the development of PRIME-MD. The PHQ-9 is a tool specific to the diagnosis of depression, which simply scores each of the nine DSM-IV criteria based on the mood module from the original PRIME-MD. It includes nine questions to be rated by subjects on a four-point Likert-type scale (8, 16, 17).

Characteristics	
Age (M, ±SD)	65.09 (±9.69)
Gender, n (%)	
Females	95 (63%)
Males	55 (37%)
Marital status n (%)	
Single /never married	12(8.0%)
Married/partner	90 (60.0%)
Widowed	48 (32.0%)
Education (years) n (%)	
⩽12	128 (85.3%)
>12	22 (14.7%)
Employment n (%)	
Employed	24 (16%)
Unemployed	126 (84%)
Income n (%)	
Sufficient	108 (72%)
Insufficient	42 (28%)
Smokers, n (%)	40 (27%)
Body mass index, mean (SD)	27.45 (5.09)
<25	51 (34%)
25.0-29.9	48 (32%)
⩾30	51 (34%)
Duration of diabetes in years, mean (SD)	10.81 (6.08)
Type of DM management n (%)	
OHA	81 (54.0%)
OHA + Insulin	32 (21.3%)
Insulin	37 (24.7)
A1C level, mean (SD)	7.8 (1.347)
<7%	44 (29.3%)
7%-8%	49 (32.7%)
>8%	57 (38.0%)
PHQ-9 score, mean (SD)	18.75 (13.97)
Minimal depression (0-4)	61 (40.7%)
Mild depression (5-9)	37 (24.7%)
Moderate depression (10-14)	23 (15.3%)
Moderately severe depression (15-19)	17 (11.3%)
Severe depression (20-27)	12 (8.0%)

Table 1. Baseline demographic and clinical characteristics of participants

	PHQ-9	A1C	BMI	Smoking	Type of DM therapy	Employ-ment	Income
PHQ9	1						
A1C	0.210**	1					
BMI	0.265**	0.187*	1				
Smoking	-0.236**	-0.062	-0.133	1			
DM therapy	0.209*	0.283**	-0.007	0.076	1		
Employment	0.328**	0.038	0.248**	-.189*	0.062	1	
Income	-0.364**	-0.109	-0.186*	0.007	-0.053	-0.232**	1
** p < 0.01 (2-tailed).							
* p < 0.05 (2-tailed).							

Table 2. Correlation Between PHQ-9 Score and Demographic and Clinical Characteristics of Study Participants

Ethics Board of the Faculty of Medicine, at the University of Sarajevo.

4. RESULTS

Of all the 150 participants, the mean (SD) age was 65.09 (9.69) years, 63% of participants were women and 60% were married. A large majority of the participants were unemployed (66%), had completed high school (85%), and had a self-reported sufficient income (72%). 27% of participants were smokers. The mean (SD) BMI was 25.28 (3.39) kg/m^2. The mean (SD) duration of T2DM was 10.81 (6.08) years. Also, most of the participants took oral hypoglycaemic agents (75%) and had two (37%) or three (25%) co-morbid conditions. Only 44 (29%) participants had an A1C below 7%.

	M1			M2			M3		
	B	Std. Error	β	B	Std. Error	β	B	Std. Error	β
(Constant)	-4.66	3.09		-4.31	3.12		-2,88	3,92	
A1C	1,62	0,39	0,32**	1,52	0,41	0,30**	1,10	0,37	0,22**
Type of DM therapy				0,59	0,66	0,07	0,71	0,59	0,09
BMI							0,13	0,10	0,09
Smoking							-2,46	1,09	-0,16*
Employment							2,94	1,36	0,16*
Income							-4,83	1,09	-0,32**
R2		0.103			0.108			0.321	
F for change in R2		17.02**			8.87**			11.26**	
Dependent Variable: PHQ-9									
*p <0.05. **p <0.001.									

Table 3. Summary of Multiple Regression Analysis for Variables Predicting the PHQ-9 score (N = 150)

The PHQ-9 items estimate 4-point symptom frequency, ranging from 0 ("not at all") to 3 ("every day"), and classifies the symptoms of depression according to the score obtained by summing up the values. Values from 0 to 4 indicate an absence of depression; from 5 to 9 mild depression; from 10 to 14 moderate depression; from 15 to 19 moderately severe depression and from 20 to 27 severe depression. In addition, at the end of the questionnaire, there is a tenth question, related to how participants cope with problems and how those problems impact their daily work, operation, and relationships with other people

Statistical analyses were carried out by mean and standard deviation for continuous variables and frequency, and percentage of categorical ones to assess the demographic characteristics of participants. The Spearman correlation coefficient was conducted to reveal the relationship between the PHQ-9 score and A1C levels, as well as demographic and clinical characteristics of participants. Bivariate correlations, with $p < 0.25$, were included in a univariate and multivariate linear regression analysis to identify significant predictors of depressive symptoms revealed by the PHQ-9 score. Statistical Package of Social Science (SPSS version 23.1; IBM Corporation, Armonk, NY, USA) was used for the statistical analysis. The study was approved by the

The internal reliability of the PHQ-9 score was excellent with an $\alpha = 0.95$. The majority of the participants (64%) had a PHQ-9 score below 10 (minimal depression and mild depression) which clinically meant no depression. 52 (36%) participants had depression. Among participants with depression, severe depression (PHQ-9 score of 20-27) was found in 8% of cases. Detailed demographic and clinical

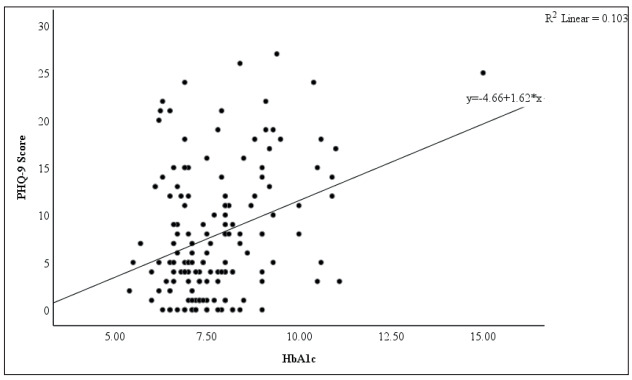

Figure 1. The scatterplot shows that the A1C level was a significant predictor of the PHQ-9 score. The regression equation was: PHQ-9 score = 4.66 + 1.62 * A1C, R2 = 0.103, F (1, 148) = 17.02, p = 0.000.

characteristics of the participants are shown in Table 1.

The Spearman correlation was conducted for the PHQ-9 score and demographic and clinical variables (age, gender, marital status, education, employment, income, smoking, BMI, duration of diabetes in years type of T2DM management, and A1C level). Significant correlations are presented in Table 2.

Associations between glycemic control (A1C) and PHQ-9 score were examined using unadjusted and adjusted multiple linear regression analyses modelling. In the unadjusted model 1 (M1), the total score of PHQ-9 score was significantly associated with glycemic control ($\beta = 0.32$, $p < 0.000$). After controlling for the type of diabetes management, the regression model 2 (M2) showed that the glycemic control was still revealed to be a significant predictor of the total score of the PHQ-9 score ($\beta = 0.30$, $p = 0.000$). In the adjusted model 3 (M3), glycemic control was a significant predictor of the PHQ-9 score ($\beta = 0.22$, $p = 0.004$). Smoking ($\beta = -0.16$, $p = 0.025$), education ($\beta = 0.16$, $p = 0.033$) and income ($\beta = -0.32$, $p = 0.000$) were significant predictors of the PHQ-9 score. All three models were significant for the PHQ-9 score. Table 3.

A scatterplot summarizes the results of the univariate linear regression conducted to reveal a relationship between A1C levels and the PHQ-9 score (Figure 1). Overall, there was a strong, positive association of A1C levels and the PHQ-9 score of depressive symptoms. Increases in A1C level were followed by increases in depressive symptoms.

5. DISCUSSION

As a part of our research, 35% of individuals with T2DM had a positive PHQ-9 score, meaning a certain degree of depression, which is a significantly larger percentage than which may be found in research conducted in developed countries (18, 19). However, this is similar or somewhat smaller of a percentage of individuals with symptoms of depression, than in research conducted in less developed nations (20, 21).

More than two thirds of those researched in our study had an A1C > 7%. The A1C, as an indicator of glycemic control, was significantly correlated with the results of the PHQ-9 in almost all of the models. According to the results of the univariate linear regression relationship between the levels of A1C and the PHQ-9 score, there exists a substantial positive correlation between the two, meaning that an increase in A1C is followed by an increase in depressive symptoms. The results of several large studies and meta-analyses showed poor glycemic control to be a significant factor associated with symptoms of depression (22-25) while Reddy and associates, using the same questionnaire for the detection of symptoms of depression did not find glycemic control to be related to symptoms of depression according to data from patient charts (26).

The age of questionnaire respondents in our research was similar as in other studies which included individuals with diabetes (27), but age did not have a significant impact on the appearance of symptoms of depression, and neither did gender, even though almost two thirds of our respondents were women and despite that fact that symptoms of depression, on a global scale, are found two times more often among the female gender (28-30).

Marital status in our interviewed individuals did not have a significant impact neither on glycemic control nor on the appearance of symptoms of depression. Additionally, the results from other research showed no significant differences between respondents who had the presence of symptoms of depression and those with or without minimally expressed symptoms of depression in relation to marital status (31).

In our research there is no statistically significant relationship between the duration of education and the appearance of symptoms of depression in individuals with diabetes. Other similar research contains completely different results in comparison with ours. A recent epidemiological analysis conducted by Diderichsen and Andersen, showed the relationship of both diseases, diabetes and depression, with education levels and income levels in respondents of the female gender, meaning that an individual researched with lower levels of education had a 3.3% larger prevalence of diabetes and a 4.7% larger prevalence of depression (32).

Work status had a significant impact on the appearance of depressive symptoms in those interviewed with diabetes in our research as well as other similar studies (21, 33).

The levels of monthly income along with work status in the adaptive Model 3 in our interviewed individuals, showed it to be a predictor of a positive PHQ-9 score. Similar results were found in other studies when monthly income levels of individuals were analyzed, which showed a significant negative correlation. Thus, according to the PHQ-9 questionnaire, respondents with lower monthly levels of income were found in a larger percentage to exhibit some form of depression (21).

A positive correlation between levels of BMI, the results of the PHQ-9, and glycemic control was also found. Research from Reddy and associates, conducted with a larger sample size and on a wider geographic territory, showed an even larger statistical significance ($p = 0.001$) in the positive correlation between obesity and the PHQ-9 score, meaning with expressed symptoms of depression (26).

In study Skopljak et al 2011, positive symptom score test of depression is present at 36% of respondents (N=100); 32% men and 39% women (2).

Recent studies conducted in Brazil showed that obesity and education had a synergistic interactive effect on the regulation of diabetes in both genders, and that obesity has a positive correlation with depression in both males and females (32).

Reddy and associates, in contrast to our results, found that length of duration of diabetes was significantly related with the results of PHQ-9 questionnaires, meaning that duration of diabetic disease five years or longer is associated with more expressed symptoms of depression (22). Respondents in our study who were on insulin had higher PHQ-9 scores, meaning larger expressed symptoms of depression. In study Skopljak et al 2011 there were a significant difference for a positive score for depression is at the patients who use insulin in the treatment of diabetes in relation to the group using oral therapy –73% vs. 20% (2).

Reddy and associates attained similar results in their study. Respondents who were on insulin therapy had more

highly expressed symptoms of depression compared to respondents who were on oral therapy or without therapy completely. (p=0.004) (26).

Epidemiological analysis of statistics from large studies on the control of cardiovascular risk factors in individuals with T2DM and the influence of depression on the outcome of disease, is similar to our results and shows a statistically significant correlation between smoking and higher results on the PHQ-9 score (33).

6. CONCLUSION

The results of our study showed a significant positive association between the levels of A1C as an indicator of glycemic control and the scores of the PHQ-9 questionnaire which identifies the intensity of symptoms of depression. In addition, we found that an increase in levels of A1C is followed by an increase in the intensity of symptoms of depression. Among individuals with T2DM, positive predictors of symptoms of depression were found to be obesity, type of therapy utilized in the treatment of DM2, income, and work status. Use of insulin in therapy is a predictor of depression, which is not surprising, and can be indicative of the degree of disease progression.

- **Declaration of Patient Consent:** The authors certify that they obtained all appropriate patient consent forms.
- **Author's contribution:** Conception and design: Elvira Hasanović, Alma Džubur Kulenović and Irma Džambo; Acquisition, analysis and interpretation of data: Zaim Jatić; Drafting the article: Nataša Trifunović, Hasiba Erkočević and Adem Cemerlic; Revising it critically for important intellectual content: Zaim Jatić and Alma Džubur Kulenović; Approved final version of the manuscript: Elvira Hasanović, Alma Džubur Kulenović, Irma Džambo, Nataša Trifunović, Hasiba Erkočević, Adem Cemerlic, Zaim Jatić.
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