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CORRELATION OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ACTIVITY WITH CHRONIC COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES

Selma Jusufović[1], Alma Halilčević[2], Šefkija Balić[1], Enra Đešević[1], Alma Horozić[1], Vedad Herenda[3]*

[1]Clinic for Endocrinology and Diabetes, University Clinical Centre Sarajevo, Bosnia and Herzegovina
e-mail: selma.jusufovic@gmail.com; sefkija.balic@gmail.com; enradesevic@gmail.com; ahorozic@gmail.com
[2]Department of Nephrology, Hemodialysis and Transplantation, Internal Medicine Clinic, University Clinical Centre Tuzla, Bosnia and Herzegovina, e-mail: alma.halilcevic007@gmail.com;
[3]Clinic for Nephrology, University Clinical Centre Sarajevo, Bosnia and Herzegovina
e-mail: vedad.herenda@gmail.com

Abstract: For the successful prevention of chronic diabetic complications, it is crucial to identify novel etiopathogenetic factors that contribute to their development. We evaluated the association of hypothalamus pituitary adrenal axis activity (HPA) with the presence of chronic diabetic complications and glycemic control in 107 patients with type 2 diabetes and 29 healthy subjects, matched for age and sex. The study included 107 type 2 diabetic patients and 29 healthy control subjects who were hospitalized at the Internal Medicine Clinic of the University Clinical Center Tuzla. Patients with diabetes were evaluated for chronic complications and divided into two groups according to the presence (group 1, n = 57) and absence (group 2, n = 50) of complications. We determined the parameters of the HPA axis as follows: a level of 08 h cortisol and ACTH and a level of 09 h cortisol after a short dexamethasone test (DEX cortisol) and compared those among the groups. We determined the parameters of glycemic control and compared them with the parameters of the hypothalamus pituitary adrenal axis. In group 1, the values of cortisol were 454 (368–561), ACTH 12.6 (8.7–23), and DEX cortisol 37.5 (23-52), significantly higher compared to group 2 [320 (230–387), 7.9 (3.3–16.4), 26 (22–36), p <0.05, and higher compared to healthy subjects [312 (233–342), p = 0.001, 12 (6–16.7), p = 0.1, 24 (19–29), p = 0.126, respectively]. Evaluating the parameters of glycemic control, we found a higher HbA1C in group 1, 7.9 (6.55-9.45) compared to group 2, 7.5 (5.97-10), p = 0.498, while correlation analyses showed a significant positive relationship between HbA1C and cortisol (R = 0.242, p = 0.012). CONCLUSION: Patients with type 2 diabetes have HPA axis dysfunction. Higher cortisol levels are associated with poor glycemic control and the presence of diabetic complications. To better understand the etiology and provide practical solutions for addressing this issue, additional studies are required.

Keywords: Diabetes type 2, chronic complications, cortisol, dexamethasone, ACTH
Field: Medical Sciences and Health

1. INTRODUCTION

The incidence of diabetes has increased during the past few decades, practically everywhere in the world. The primary cause of mortality and disability among individuals with diabetes are chronic micro- and macrovascular complications (International Diabetes Foundation, 2016).Although hyperglycemia is the most important factor in the etiology and pathogenesis of diabetic complications, other factors also play a significant role. Those other mechanisms in the development of chronic complications are being investigated with increasing interest. Glucocorticoid secretion in Cushing's syndrome is a known pathogenetic mechanism in the development of the metabolic deterioration, such as insulin resistance, hypertension, hyperlipoproteinemia, diabetes, obesity. The question arises whether higher, but below clinical radar, cortisol values could represent the link between the metabolic deterioration and the development of chronic complications in patients with type 2 diabetes. Several studies have recently found hypercortisolemia in patients with type 2 diabetes (Steffenson,2019). Chiodini (2007) and Reynolds (2010) found that in patients with type 2 diabetes with chronic complications, the hypothalamic pituitary adrenal axis (HPA) is disrupted, and cortisol secretion levels are associated to the presence and number of chronic complications. The mechanism behind the link between chronic complications and HPA axis activity has yet to be determined. To further research this topic, we investigated the relationship between HPA axis activity with chronic complications, clinical characteristics, metabolic and glycemic control in patients with type 2 diabetes.

*Corresponding author: selma.jusufovic@gmail.com

2. PATIENTS AND METHODS

Participants

The prospective observational case-control study included 107 patients with type 2 diabetes in study group and 29 healthy subjects in the control group. All subjects were hospitalized at the Tuzla University Clinical Center, Internal Medicine Clinic. The study group was divided into two subgroups according to the presence/absence of chronic complications. Group with chronic complications (group 1) consisted of 57 patients with complications. The group without chronic complications (group 2) consisted of 50 patients. The inclusion criteria were: age at the time of diagnosis > 30 years; BMI ≥20 and ≤40 kg/m2. Exclusion criteria: acute complications of diabetes in the last 3 months, acute illnesses in the last 3 months; previously established functional disorders of the adrenal glands and pituitary gland. Twenty nine nondiabetic patients were selected as control subjects according to the above-mentioned selection criteria (control group). The control subjects were admitted to the hospital for evaluation as potential donors for kidney transplantation. The Ethical Committee of University Clinical Centre Tuzla approved of the study protocol. Participation in the study was contingent on individual consent.

Methods

Waist circumference, body weight, body height was measured for all patients. RIA method was used to determine the cortisol and ACTH parameters. A low-dose overnight dexamethasone suppression test was performed by taking 1 mg of dexamethasone orally at 11 pm and determining the cortisol level at 9 am. A normal response cortisol < 50 nmol/L(Chiodini, 2005). Good glycemic control was defined with values of HbA1c<7%, fasting blood glucose 3.9–7.2 mmol/l, blood glucose 2h after a meal <10 mmol/L. Poor glycemic control is defined as Hba1>7%, fasting glucose >7.2, glucose 2h after a meal>10 mmol/L (American Diabetes Association, 2019). Neuropathy was evaluated by measuring the diabetic neuropathy score (Feldman, 1994); retinopathy by an ophthalmological examination of the eye fundus (Wong, 2011). Incipient nephropathy is proven by a serum microalbumin level of 30–299 mg/day; nephropathy with microalbumin > 300 mg/day (Kidney Disease: Improving Global Outcomes, 2012). The criteria for defining myocardial infarction were: previously established diagnosis of myocardial infarction; previously established diagnosis of angina; ECG findings of ischemia. Ischemic heart disease is defined in those patients who meet both MI and angina criteria. Cerebrovascular insult (CVI) ischemic or hemorrhagic is defined by the previously established diagnosis by the findings of computed tomography.

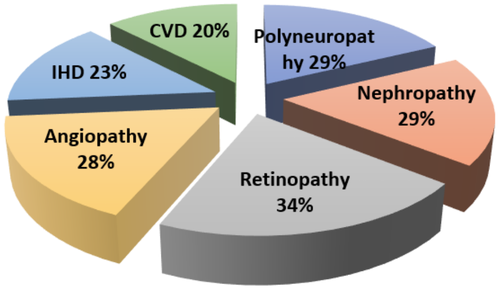
Statistical analysis

Statistical analysis was performed with the application software SPSS version 22, IBM Corp. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Descriptive statistics methods were used: measures of central tendency, measures of variability, and relative numbers. Analytical statistics: A) methods of checking general and specific assumptions for the performance of statistical procedures, B) methods for assessing the significance of the difference. For the analysis of categorical (nominal) variables, the Chi-square test of independence (2 x 2 or 2 x k) or Fisher's exact test was used in case of violated testing assumptions. The usual level of significance "α < 0.05" was chosen.

3. RESULTS

Evaluating the prevalence of certain diabetic complications, we found that in our sample prevalence for polyneuropathy was 29%, nephropathy 29%, retinopathy 34%, prevalence of patients with some form of ischemic heart disease was 23, peripheral angiopathy 28%, and cerebrovascular disease 20% (Graph 1)

Graph 1. Prevalence of chronic diabetic complications in the study groups



Source: Author Jusufović, S. at. all. (2024), "Correlation of hypothalamic-pituitary-adrenal axis activity with chronic complications in patients with type 2 diabetes."

The clinical characteristics of the groups are shown in table 1.In the group of patients with complications treatment modality and duration of diabetes were equally distributed, while age was unequally distributed compared to patients without chronic complications. We found a higher age in the group of patients with complications (60.24 vs 46.89) (Mann-Whitney U test 069.500, Z -2.222, Wilcoxon W 2344.500, p<0.026).

Table 1. Clinical characteristics of the patients among groups

		All patients (n=107)	Without complications (n=50)	With complications (n=57)	Healthy subjects (n=29)	P value
Sex	M F	46 (43%) 61(56%)	22(44%) 28(56%)	24 (41%) 33(58%)	12(41%) 17(59%)	0.843
Age	Median Q1-Q3	55(49-62)	51(39-61)	56(53-62)	43(37-55)	**0.026**
Diabetes duration	Median Q1-Q3	22 (3-58)	22(4-58)	20 (3-61)	-	0.960
Treatment	Insulin OAD Combined	14 28 65	6 13 31	8 15 34	-	0.847
Diet	Diet No diet	89 18	45 5	44 13	-	0.077
Legend: Parameters are expressed as n-absolute number, percentage value. Central value: Median Q1-Q3 – interquartile range; The Mann Whitney test and the Chi square test were used with a significance level of p< 0.05. Duration of diabetes expressed in months, Abbreviations: OAD- Oral antidiabetics						

Source: Author Jusufović, S. at. all. (2024), "Correlation of hypothalamic-pituitary-adrenal axis activity with chronic complications in patients with type 2 diabetes."

The characteristics of metabolic comorbidities and glycemic control in the groups are shown in table 2. No statistically significant difference was found in the distribution of BMI, HLP and obesity in the entire sample. A higher prevalence of hypertension was found in the group of patients with chronic complications. Bipolar Chi- square matching test confirms this (Goodness-of fit Chi-Square =64.383, df-1) p=0.001.

Table 2. The characteristics of metabolic comorbidities and glycemic control among groups

Diabetic patients					
		All patients (n=107)	Without complications (n=50)	With complications n=57	P value
HbA1c	Median Q1-Q3	7.8 (6.4-9.5)	7.5 (5.97-10)	7.9 (6.55-9.45)	0.498
Glycemic control	Good Poor	58 49	34 16	24 33	**0.007**
BMI	Median Q1-Q3	29 (25-31)	29 (25-30)	29 (25-32)	0.272
HLP	Yes No	79 28	38 12	41 16	0.633
Obesity	Yes No	69 38	30 20	39 18	0.364
AH	Yes No	95 12	42 8	53 4	**0.001**
Uncontrolled AH Controlled AH		50 57	22 28	28 29	0.596
Legend: Parameters are expressed as an n-absolute number. Pearson Chi-Square (Yates' Correction for Continuity) χ^2= 0.291, df-1, p <0.05 was used. Abbreviations: BMI - Body mass index; HLP - hyperlipoproteinemia, AH - arterial hypertension, HbA1C - glycosylated hemoglobin.					

Source: Author Jusufović, S. at. all. (2024), "Correlation of hypothalamic-pituitary-adrenal axis activity with chronic complications in patients with type 2 diabetes."

Biochemical parameters of HPA axis function from the whole diabetic and control group are summarized in Table 3.

Table 3. Comparation of HHA axis parameters between groups

		Diabetic patients (n=107)	Healthy subjects (n=29)	p value
Cortisol	Median (Q1-Q3)	387 (307-496)	307 (219-355)	0.017
ACTH	Median (Q1-Q3)	10.8 (4.6-22)	27 (23.5-42.25)	0.126
DEX cortisol	Median (Q1-Q3)	31 (22-51)	27 (24-42)	0.681
		Diabetic without complications (n=50)	Diabetic with complications (n=57)	p value
Cortisol 08h	Median Q1-Q3	320 (230-387)	454 (368-561)	0.001
ACTH	Median Q1-Q3	7.9 (3.3-16.4)	12.6 (8.7-23)	0.002
DEX cortisol	Median Q1-Q3	26 (22-36)	37.5 (23-52)	0.019
		Healthy subjects (n=29)	Diabetic without complications (50)	p value
Cortisol	Median (Q1-Q3)	312 (233-342)	320 (230-387)	0.45
ACTH	Median (Q1-Q3)	12 (6-16.7)	7.9 (3.3-16.4)	0.47
DEX cortisol	Median (Q1-Q3)	24 (19-29)	26 (22-36)	0.18
		Healthy subjects (n=29)	Diabetic with complications (n=57)	p value
Cortisol	Median (Q1-Q3)	312 (233-342)	454 (368-561)	0.001
ACTH	Median (Q1-Q3)	12 (6-16.7)	12.6 (8.7-23)	0.101
DEX cortisol	Median (Q1-Q3)	24 (19-29)	37.5 (23-52)	0.126
Legend: Parameters are expressed as Median Q1-Q3 – interquartile range. The Mann-Whitney test was used with a significance level of p< 0.05. Abbreviations: ACTH - adrenocorticotropic hormone; DEX cortisol - cortisol after dexamethasone test.				

Source: Author Jusufović, S. at. all. (2024), "Correlation of hypothalamic-pituitary-adrenal axis activity with chronic complications in patients with type 2 diabetes."

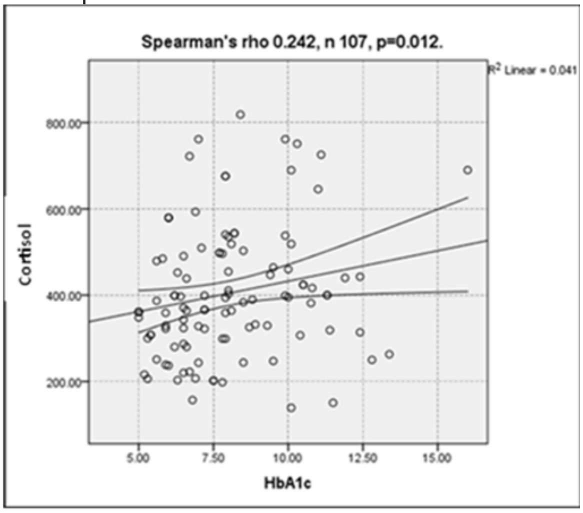
We found statistically significant higher cortisol levels in diabetic patients compared healthy subjects (p =0.017), lower ACTH levels and higher DEX cortisol levels but without statistical significance. In diabetic patients with chronic complications we found statistically significant higher cortisol levels (p =0.001), higher ACTH levels (p =0.002) and higher DEX cortisol levels but without statistical significance. Levels of cortisol, ACTH, and DEX cortisol were comparable between the diabetic patients without complications and healthy subjects.

By comparing the HHA axis parameters of patients with complications and healthy subjects, we found a significantly higher value of cortisol in patients with complications (p=0.00012). Levels of ACTH, and DEX cortisol were comparable between the two groups (HbA1c in the sample of patients with diabetes is 8.01 ± 2.16 percent. We found a higher mean rank in the group of patients with complications (55.90 vs 51.83).

Analyzing the factorial variable of the glucose control parameter, we found that 58 patients had good glucose control, and 49 patients had poor glucose control, with a statistically significant association of poor glucose control and the group with diabetic complications.

The correlation between cortisol and HbA1c measured on the same measuring scales was investigated using correlation analysis and shown in graph 1. The obtained Spearman's rho coefficient of non-parametric correlation is 0.242, n 107, p=0.012, explaining the significant positive relationship between these two variables, which means that more cortisol values follow higher HbA1c values (Graph 2).

Graph 2. Correlation of cortisol levels and HbA1C



Source: Author Jusufović, S. at. all. (2024), "Correlation of hypothalamic-pituitary-adrenal axis activity with chronic complications in patients with type 2 diabetes."

4. DISCUSSION

The activity of the HPA axis in patients with type 2 diabetes has been investigated as one of the factors in the pathogenesis of deterioration metabolic control in patients with type 2 diabetes (Joseph, 2015; Shengnan, 2023).

Our study aimed to examine the association of cortisol levels with the occurrence of chronic complications, with parameters of metabolic control and the degree of glycemic regulation in patients with type 2 diabetes.

We compared the parameters of HPA axis activity in patients with and without chronic diabetic complications, and healthy subjects. We further compared HPA axis parameters with glycemic control parameters and other metabolic dysfunctions, such as hyperlipoproteinemia, obesity and hypertension.

We examined the relationships between patients with type 2 diabetes and traditional risk factors for the emergence of chronic complications, including age, length of diabetes, type of treatment, and glycemic control.

We found a significantly higher age in patients with complications. According to the results of the study by Shamshingaram (2017) elderly patients with diabetes had a higher percentage of complications. In the study by Fei (2019) found older age as an independent risk factor for diabetic peripheral neuropathy.

We found a longer mean duration of the diabetes in the group of patients without complications, but the obtained result is not statistically significant. By analyzing treatment modalities, we did not find a significant association of different treatment modalities and BMI with chronic complications. Our result is in agreement with the previous study and with the meta-analysis results of Zhou et al. (27) who found no association of diabetic complications with BMI. In our study, the prevalence of hypertension was 88%. According to our results, hypertension and hyperlipidemia were more common in patients with complications, which is in agreement with the results of the UKPDS 50 study (28). It is important to note that in 53% of patients in our study, hypertension was uncorrected by therapy, which is in agreement with the study by Arambewela (2018). When we evaluated the prevalence of complications, our results were consistent with the results of studies on the prevalence of chronic complications (De Boehr, 2007).

By comparing the parameters of the HHA axis in patients with diabetes and healthy subjects, we found higher values of cortisol and DEX cortisol in patients with diabetes compared to healthy subjects, with no significant difference. Our results are in agreement with the study of Chiodini (2007) where the values of cortisol, DEX cortisol and ACTH were found in the normal range in the group of subjects with diabetes and in agreement with studies done on healthy subjects. By comparing the parameters of the HHA axis in the group of patients with chronic complications compared to healthy subjects and patients without complications we found significantly elevated cortisol values of patients with complications. Another significant result of our study is that we did not find significant differences in the values of the HHA axis parameters in the group of subjects without complications and healthy subjects Our results are consistent with results of Roy (1998) who demonstrated elevated cortisol levels in patients with diabetic retinopathy and cardiovascular complications.

In our study, poor glycemic control is associated with higher prevalence of chronic complications, which is consistent with previous study results (Sharen, 2021). By correlating glycemic control and HHA axis parameters, we obtained a significant positive relationship between higher cortisol values and higher HbA1C values.This finding is consistant with previous studies (Chiodini, 2007; Joseph, 2015; Doing, 20212). In conclusion higher cortisol levels are associated with chronic diabetic complications. Additional studies are necessary to clear the pathophysiology of the dysfunction. If future studies establish a causal relationship between the HPA axis and diabetic complications, strategies to reduce cortisol could be developed for the prevention of complications.

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