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The Prevalence of Hypercortisolism in Patients with Type 2 Diabetes and Microvascular Complications: A Prospective Observational Case-Control Study

ABSTRACT

Objective: The goal of this study was to examine the prevalence of hypercortisolism in patients with type 2 diabetes (T2D), and the association of cortisol with microvascular complications.

Materials and methods: This prospective observational case-control, single-center study included 107 patients with T2D. After evaluating their microvascular complications, the patients were divided into 2 groups. Group 1 consisted of 57 patients with complications, and group 2 consisted of 50 patients without. Serum 08h cortisol and adrenocorticotropic hormone (ACTH), 09h cortisol after a short dexamethasone test (DEX cortisol), traditional risk factors, and lipid and inflammatory profiles were determined and correlated among the 2 groups.

Results: Prevalence of hypercortisolism in patients with T2D was 6.3%, in patients with complications it was 10.5%, and 2.0% in patients without complications. In group 1 we found higher basal cortisol and ACTH, and higher low-density lipoprotein cholesterol (LDL-C) and C-reactive protein (CRP) levels when compared to group 2 ($p < 0.05$). A more positive correlation of cortisol with CRP was found in group 1 compared to group 2 (rho = 0.255, p = 0.011). We did not find a significant difference in sex, body mass index (BMI), treatment modality, diabetes duration, triglyceride, or fibrinogen levels among the groups.

Conclusions: Higher serum cortisol levels and higher prevalence of hypercortisolism were significantly associated with diabetic microvascular complications. Systemic inflammation indicators positively correlated with cortisol levels and microvascular complications. This suggests a potential connection between cortisol, inflammation, and microvascular complications in T2D. Further research is needed to clarify the causality of this relationship. (Clin Diabetol 2024; 13, 5: 246–253)

Keywords: type 2 diabetes, microvascular complication, cortisol, dexamethasone, inflammation

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Introduction

Type 2 diabetes (T2D) is expected to become the seventh biggest cause of death by 2030, according to the World Health Organization [1]. Microvascular long-term complications are the leading cause of total eyesight loss, renal failure, and disability [1]. Retinopathy is the most common, occurring in 34.6% of cases [2]. Known risk factors for retinopathy include the duration of diabetes, ethnicity, family history or genetics, age at onset of diabetes, and severity of hyperglycemia [3, 4]. Approximately 22% of patients with T2D are affected by polyneuropathy [5]. Age, smoking, body height, hyperglycemia, and the duration of the disease are among the numerous risk factors that contribute to its development. At an estimated 34.5% prevalence, diabetes-related kidney disease is the primary cause of chronic kidney disease. [6]. Genetic predisposition, blood pressure, obesity, and poor glycemic management are known risk factors [7]. It has been found that inflammation plays a critical role in the pathophysiology of microvascular complications, particularly in their progression [8].

Understanding the underlying pathophysiology and the interaction of metabolic risk factors has advanced significantly in recent years. Multiple strategies have been implemented to address these modifiable risk factors. However, some of these require social changes and public health initiatives, which is a lengthy process. Therefore, it is necessary to continue ongoing research into new risk factors.

One of the investigated contributors to microvascular complications of diabetes is glucocorticoid excess due to hypothalamic-pituitary-adrenal (HPA) axis dysfunction [9, 10]. The association between T2D and long-term complications is suggested to be linked to dysfunction of the HPA axis [11]. An impaired HPA axis causes elevated levels of cortisol, leading to a rise in glucose and insulin. Therefore, amplifying the impact of insulin on adipose tissue leads to the development of visceral obesity, insulin resistance, hyperlipidemia, and hypertension.

This endogenous hypercortisolism has been described using a variety of terms, including "preclinical Cushing's syndrome," "subclinical hypercortisolism," and "subclinical Cushing's syndrome." [12–14]. In 2016, the European Society of Endocrinology (ESE) introduced the term "mild autonomous cortisol secretion (MACS)." It refers to a group of clinical disorders in which patients have an increase in autonomous cortisol secretion but no overt hypercortisolism [15]. Still, it is limited to patients with adrenal incidentalomas. However, endogenous hypercortisolism has also been observed in patients without adrenal incidentalomas, and in the general population it ranges from 0.2% to 2% and even higher, reaching up to 10%. It was particularly observed in some at-risk groups with diabetes and uncontrolled or complex hypertension, obesity, and iatrogenic osteoporosis [16]. The prevalence of hypercortisolism has been reported to be 5.2% in patients with newly diagnosed T2D, and even higher among other, specific categories of patients with T2D (8.4–10.2%) [17].

It is supposed that in these conditions, the HPA axis is persistently activated, causing the release of corticotrophin-releasing hormone (CRH). CRH stimulates the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH), which causes an increase in cortisol release [17].

However, the link between cortisol levels and microvascular complications in T2D is still being debated.

This study aimed to emphasize the role of cortisol in microvascular complications, in patients with T2D.

Materials and methods

Study design

A prospective observational case-control, single-center study was performed among 107 patients with T2D as participants for a duration of 12 months. All subjects were admitted to Tuzla University Clinical Center Internal Medicine Clinic.

Study population

After an assessment of their microvascular diabetes-related complications, we divided the patients into 2 groups. Group 1 consisted of 57 patients with manifest chronic microvascular complications, and group 2 consisted of 50 patients without chronic complications, serving as the control group. We established the following inclusion criteria: T2D, age of 30 years and older at the time of diagnosis, and body mass index (BMI) between 20 and 35 kg/m^2. Exclusion criteria were 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; chronic renal failure; sleep cycle disorder; depression; alcoholism; glucocorticoid therapy; and therapy with drugs that affect the HPA axis (beta blockers, alpha blockers, cholinergic agonists, and antagonists).

Prior to inclusion in the study, and independently of the study, outpatient therapy with insulin, oral antidiabetics, lipid-lowering drugs, and antihypertensives were not excluded or corrected for the needs of the study.

Ethical approval

The study protocol was approved by the Ethical Committee of the University Clinical Centre Tuzla, under

the number 02-09/2-50/14. The researcher explained to each participant the goal of the study. Furthermore, all participants were informed of their right to refuse or cease participation in accordance with the ethical norms of the 1983 Helsinki Declaration.

Data collection

Complete medical history was obtained, including the type, onset, age at diagnosis, modality of treatment, and related comorbidities. Body weight, height, and blood pressure were recorded. BMI was calculated as weight divided by height squared (kg/m^2), and data regarding glycated hemoglobin (HbA1c) levels and use of oral hypoglycemic agents and insulin treatment were collected. Comprehensive clinical examinations and standard investigations were performed on the third day after admission. Blood samples were taken at 9 a.m. after fasting for at least 8 h. The samples were collected by puncturing the median elbow vein, preserved at a low temperature, and centrifuged within one hour. They were then promptly sent to the central laboratory for testing. In the Department of Biochemistry, University Clinical Tuzla, fasting blood glucose, HbA1c, urea, creatine, potassium, sodium, total proteins, albumin, globulin, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, serum creatinine, C-reactive protein (CRP), fibrinogen were determined by the standard laboratory method on an Architect c 8000 Abbott device, and complete blood count by standard laboratory method on a SISMEX device. Urinary albumin creatinine ratio (UACR) was measured by immunoturbidimetry.

Serum cortisol was measured at 08 h using radio immune assay. Immulite 1000 cortisol is an enzyme-labeled, competitive immunoassay (normal value < 207.0 nmol/L). Plasma ACTH levels at 08 h were measured by radio immune assay. Immulite 1000 ACTH is a solid phase two-site sequential chemiluminescence immunoassay (normal value 2.2–11.0 pmol/L). A low-dose overnight dexamethasone suppression test was carried out by taking 1 mg of dexamethasone orally at 11 p.m. and measuring the cortisol level the next morning at 9 a.m. A revised criterion for cortisol suppression < 60 nmol/L was used to improve the sensitivity of the procedure, and unsuppressed ACTH level was used as a confirmatory test [14].

Assessment of microvascular long-term complications

Kidney disease, based on the classification suggested in the Kidney Disease: Improving Global Outcomes guidelines (KDIGO), was defined as persistent albuminuria (UACR > 300 mg/d or > 200 μg/min) confirmed on at least 2 occasions, 3–6 months apart [11]. Diabetes-related polyneuropathy was defined based on clinical examination combined with neurophysiologic testing performed using conventional surface electromyography (EMG) examination and nerve conduction tests on the right knee joint for the tibial nerve and common peroneal nerve [18]. Retinopathy was assessed with ophthalmoscopy with the pupil dilated, in which detection of microaneurysms in the posterior pole is the earliest clinical sign [19].

Statistical analysis

The correct sample size is critical to ensure statistical accuracy in order to detect real differences, if any. The sample size for the participants was estimated using the GPower software version 3.1 with power (1-error) set at 0.80 and error (a) set at 0.05. Our sample pool of 50 patients per group (total 100) provides an achieved statistical accuracy of 84.39%, which is above the recommended minimum of 80%. This ensures that the research results are representative of the population being studied, which contributes to the reliability of the established findings.

Our research design includes a continuous variable of cortisol values and a qualitative outcome of the presence of chronic complications of diabetes. We analyzed the differences between the 2 groups using the t-test for independent samples, adjusted for the cortisol referral threshold as a clinically significant value.

The statistical analysis was conducted using IBM Corp.'s SPSS version 22, an application software released in 2013 (Version 22.0 of IBM SPSS Statistics for Windows, NY/Armonk: IBM Corp.). The following descriptive statistical methods were applied: relative numbers, interval of variation, standard deviation, interquartile range, range, and measures of central tendency (arithmetic mean and median). Of the analytical methods, the following were used:

A) checking general and specific assumptions for the performance of statistical procedures: identification of the empirical distribution, verification of the empirical versus hypothetical distribution, verification of the least expected cell frequency as an assumption for the chi-square test of independence;
B) assessing the significance of the difference: Student's t test, rank sum test, and Kruskal-Wallis analysis of variance, the chi-square test of independence (2×2 or $2 \times k$) or Fisher's exact test was used in case of unmet testing presumptions. The usual level of significance "$\alpha < 0.05$" was chosen.

Table 1. Baseline Clinical Characteristics

Variables	All patients (n = 107)	Without complications (n = 50)	With complications (n = 57)	P-value
Sex M (%)	46 (43.0%)	22 (44.0%)	24 (42.1%)	0.843**
Sex F (%)	61 (56.9%)	28 (56.0%)	33 (57.8%)	0,783**
Age [years]	55 (49–62)	51 (39–61)	56(53–62)	0.026*
Diabetes duration [months]	22 (3–58)	22 (4–58)	20 (3–61)	0.960*
Hypoglycemic agents (insulin) (%)	14 (13.0%)	6 (12.0%)	8 (14.0%)	
Hypoglycemic agents (OAD) (%)	28 (26.1%)	13 (26.0%)	15 (26.3%)	0.947**
Hypoglycemic agents combined (%)	65 (60.8%)	31 (62.0%)	34 (59.6%)	
CRP [mg/dL]	5.50 (3–11)	4.70 (2.3–7.2)	7.60 (4.4–12.4)	0.001*
Fibrinogen [g/L]	6.0 (4.4–9.9)	5.10 (4.4–7.7)	6.60 (3.9–11.1)	0.202*
TGL [mmol/L]	2.40 (1.5–3.3)	2.27 (1.5–3.2)	2.54 (1.5-4.2)	0.631*
HDL-C [mmol/L]	0.99 (0.83–1.2)	0.89 (0.7–1.2)	1.10 (0.9–1.31)	0.002*
LDL-C [mmol/L]	3.10 (2.67–3.7)	2.99 (2.4–3.3)	3.23 (2.82–3.73)	0.015*
BMI [kg/m^2]	29 (25–31)	29 (25–30)	29 (25–32)	0.272*
Cortisol [mmol/L]	387 (307–496)	320 (230–387)	454 (368–561)	**0.001***
DEX cortisol [mmol/L]	31 (22–51)	26 (22–36)	37.5 (23–52)	**0.019***
ACTH [pmol/l]	10.8 (4.6–22)	7.9 (3.3–16.4)	12.6 (8.7–23)	**0.002***
Unsuppressed DEX cortisol [mmol/L] (%)	25 (22.8%)	7 (14.0%)	18 (31.6%)	
Unsuppressed ACTH [pmol/L] (%)	7 (6.3%)	1 (2.0%)	6 (10.5%)	

Data are presented as median, N, or %, median Q1–Q3 — interquartile range; Mann-Whitney* and chi-square tests** were used with a significance level of $p < 0.05$

ACTH — plasma adrenocorticotropic hormone; BMI — body mass index; CRP — C-reactive protein; DEX — serum cortisol after dexamethasone test; HDL-C — high-density lipoprotein cholesterol, LDL-C — low-density lipoprotein cholesterol; OAD — oral antidiabetic drugs, TGL — triglycerides

Comparisons between the control and patient groups were conducted using either a t-test or a Mann-Whitney U test, depending on the nature of the data. For categorical variables, a χ^2 test was done. General linear modeling was employed to compare the data obtained from the control group, group 1, and group 2, while taking into account the effects of age and sex. The relationships between variables were assessed using either the Pearson correlation coefficient or Spearman's rank correlation test, depending on the circumstances.

Logistic regression analysis was conducted to assess the relationship between the presence of chronic complications of diabetes and cortisol secretion in patients with T2D. This analysis took into account potential confounding factors including age, sex, BMI, hypertension, disease duration, and metabolic control.

Results

According to the inclusion and exclusion criteria, a total of 107 adult patients with T2D were included in this research study. The baseline clinical characteristics of the research are described in Table 1. The median age was 55 (49–62) years; 46% were men, and 61% were women. Duration of diabetes in months was 22 (3–58) months. In our sample, 14 patients were treated with insulin, 28 patients with oral hypoglycemic drugs, and 65 patients had combined treatment. We found a prevalence for polyneuropathy 29%, retinopathy 34%, and nephropathy 29%. Evaluating the association of the traditional risk factors with long-term microvascular complications, we found higher median age, CRP, HDL-C, and LDL-C levels in the group of patients with complications. We did not find a significant difference in sex, BMI, treatment modality, duration of diabetes, triglyceride, or fibrinogen levels among these groups.

Parameters of HPA axis are shown in Table 1. Among patients with diabetes, 25 (22.8%) were unable to suppress DEX cortisol levels less than 60 nmol/L. Seven of those patients (6.3%) also had unsuppressed plasma ACTH levels. In the group of patients with microvascular complications, 18 (31.6%) were unable to suppress DEX cortisol levels below 60 nmol/L. Six of those patients (10.5%) had unsuppressed plasma ACTH levels. In the group of patients without microvascular complications, 7 (14%) were unable to suppress plasma cortisol levels below 60 nmol/L, and one of these patients (2%) showed unsuppressed plasma ACTH levels. These findings indicate that the prevalence of hypercortisolemia with unsuppressed DEX cortisol

Table 2. HPA Axis Activity Parameters in T2D Patients with and without Long-Term Microvascular Complications

Polyneuropathy	With complication (n = 31)	Without complication (n = 76)	P-value
Cortisol [nmol/L]	493 (395–589)	359 (263–424)	0.0001
ACTH [pmol/L]	22.0 (17.8–30.6)	10.8 (4.0–22.2)	0.0001
DEX cortisol [nmol/L]	27.85 (3.25–52.7)	25.86 (23.0–36.7)	0.626
Retinopathy	(n = 40)	(n = 67)	
Cortisol [nmol/L]	499 (418–589)	329 (250–399)	0.0001
ACTH [pmol/L]	22 (17.8–30.6)	9.81 (3.12–15.3)	0.0001
DEX cortisol [nmol/L]	37.85 (3.19–55.0)	25.86 (23.0–36.7)	0.765
Diabetes kidney disease	(n = 31)	(n = 76)	
Cortisol [nmol/L]	466 (397–542)	359 (280–440)	0.0001
ACTH [pmol/L]	22 (17.8–30.6)	10.04 (2.21–22.25)	0.0001
DEX cortisol [nmol/L]	37.8 (2.9–52.0	28.8 (23.0–36.7)	0.581

Parameters are expressed as median Q1–Q3 — interquartile range; Mann-Whitney test was used with a significance level of $p < 0.05$
ACTH — plasma adrenocorticotropic hormone; DEX cortisol — serum cortisol after dexamethasone test; HPA — hypothalamus pituitary adrenal; T2D — type 2 diabetes

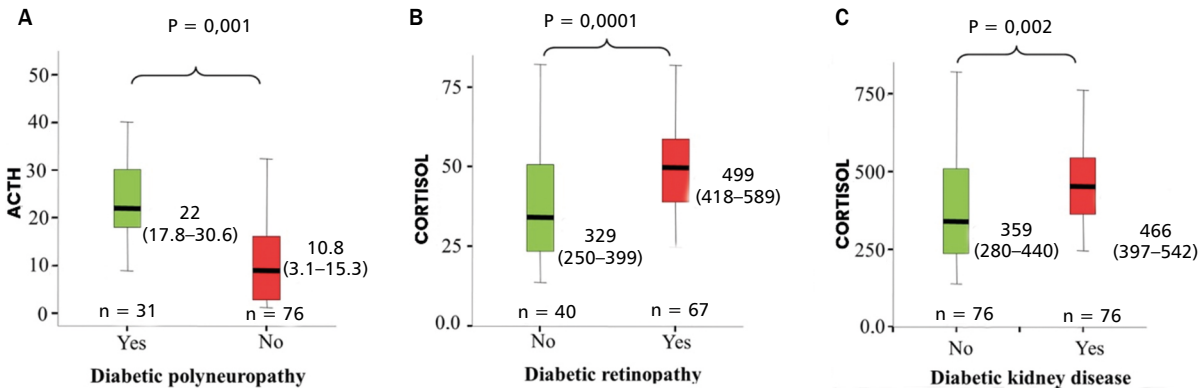

Figure 1. (A.) ACTH levels in patients with and without diabetes-related polyneuropathy; (B.) Cortisol levels in patients with and without diabetes-related retinopathy; (C.) Cortisol levels in patients with and without diabetes-related kidney disease
ACTH — adrenocorticotrophic hormone

and ACTH levels in patients with diabetes was 6.3%, in patients with microvascular complications it was 10.5%, and in patients without microvascular complications it was 2%.

Table 2 summarizes the cortisol, ACTH, and DEX cortisol levels among patients with and without microvascular chronic complications. In patients with polyneuropathy, we found higher levels of basal cortisol 493 (395–589) and ACTH 22 (17.8–30.6) compared to patients without polyneuropathy 359 (263–424); 10.8 (4.0–22.2), ($p < 0.05$), respectively (Fig. 1A). In patients with retinopathy, we found higher cortisol levels 499 (418–589) and ACTH 22 (17.8–30.6), compared to patients without retinopathy 329 (250–399) 9.81 (3.12–15.3) ($p < 0.05$), respectively (Fig. 1B). Also, in patients with chronic kidney disease, we found higher levels of cortisol 466 (397–542) and ACTH 22 (17.8–30.6), in comparison to patients without 359 (280–440) 10.04 (2.21–22.25) ($p < 0.05$), respectively (Fig. 1C). There was no significant difference in levels of DEX cortisol among groups.

We correlated cortisol levels with inflammatory and lipide profiles in patients with and without complications. We found a positive correlation of cortisol with CRP rho = 0.255, p = 0.011. Patients with higher CRP had higher cortisol values. Cortisol was not correlated with fibrinogen TGL, HDL-C, and LDL-C. In the group of patients without microvascular complications, we did not find a correlation between these parameters (Tab. 3).

Table 3. Correlation of Cortisol Levels with Inflammatory and Lipide Profile

		Spearman's rho	CRP	Fib.	TGL	HDL-C	LDL-C
Cortisol	Patients With complications	Correlation coefficient	0.255	0.019	0.193	0.139	0.148
		P	0.011	0.853	0.183	0.337	0.306
		N	57	57	57	50	50
Cortisol	Without complications	Correlation coefficient	0.169	0.109	0.214	0.148	0.243
		P	0.241	0.451	0.136	0.306	0.108
		N	50	50	50	50	45

Data are presented as Spearman rho correlation coefficient
CRP — C-reactive protein; Fib — fibrinogen; HDL-C — high-density lipoprotein; LDL-C — low-density lipoprotein; TGL — triglyceride

Discussion

In our study, we initially evaluated the prevalence of long-term microvascular complications in patients with T2D. Following which, we assessed the levels of cortisol, ACTH, and cortisol after the dexamethasone suppression test in patients with and without microvascular complications. To evaluate the relationship between traditional risk factors and complications we examined age, BMI, treatment modality, and diabetes duration in groups. Finally, to investigate the relationship between inflammation and cortisol as a potential link to microvascular complications, we correlated lipid and inflammatory markers with cortisol levels.

We found the prevalence of long-term diabetes-related complications to be 37% for retinopathy, 29% for diabetes-related kidney disease, and 29% for polyneuropathy. Our findings are consistent with studies on the prevalence of chronic complications. According to study data, the overall prevalence of any form of retinopathy is 34.6% [8, 19], diabetes-related kidney disease of any degree is 25–34.5% [20, 21], and polyneuropathy is 22% [5, 18].

We found significantly higher levels of cortisol and ACTH in patients with polyneuropathy, retinopathy, and diabetes-related kidney disease compared to patients without these complications. We did not find a statistically significant difference in cortisol levels following the dexamethasone suppression test between these groups. Our findings align with previous research [22] that discovered elevated cortisol levels in individuals with long-term diabetes complications. The elevated ACTH levels in our study suggest central HPA axis dysfunction. Prior research revealed similar findings of inadequate ACTH suppression and absent correlation with DEX cortisol. The hypothesized mechanism is that the HPA axis is chronically active, which results in the release of CRH, in turn increasing the secretion of ACTH. ACTH is therefore responsible for the increased release of cortisol from the adrenal cortex [22].

Our findings indicate that the prevalence of hypercortisolemia with unsuppressed DEX cortisol and ACTH levels in patients with diabetes was 6.3%, in patients with microvascular complications it was 10.5%, and in patients without microvascular complications it was 2%. These findings are in contrast to the results reported by Catargi et al. (2003) [14]. In their study, researchers conducted a 4 mg dexamethasone test on overweight T2D individuals with unsuppressed DEX cortisol and ACTH, to confirm the presence of occult Cushing's Syndrome (CS). This confirmatory testing revealed a prevalence of occult CS in 2% of the patients. Nevertheless, our results are consistent with the metanalysis conducted by Aresta et al. (2022) [17], which employed a variety of confirmatory tests, including late night salivary cortisol, late night serum cortisol, and urinary free cortisol. The estimated prevalence of hypercortisolism in patients with T2D was 8.4–10.2% in a total of 2283 patients.

Our finding of higher median age, LDL-C, and HDL-C in a group of patients with microvascular complications is in accordance with previous studies [23, 24]. We found higher median CRP, which has been demonstrated in individuals with T2D [25]. In previous studies, a positive correlation was found between cortisol and inflammation in patients without diabetes [26], as well as an association between cortisol and hyperglycemia, which was thought to be mediated by chronic inflammation. A significant result of our study is a positive correlation of C-reactive protein, a sensitive indicator of systemic inflammation, with cortisol in patients with complications compared to patients without complications. More precisely, elevated cortisol values followed elevated CRP values.

Given the acknowledged adverse impacts of glucocorticoids on inflammation [26, 27], it is possible to

assume that greater cortisol secretion may contribute to endothelial damage, resulting in a higher prevalence of microvascular complications in T2D. However, in our sample, the marker of inflammation (i.e., fibrinogen) was comparable amongst patients with and without complications and had no association with cortisol. These findings reveal the need for further investigation into the role of other recognized inflammatory indicators in the etiology of microvascular complications.

This study has clinical and practical significance in terms of increasing awareness about the role of cortisol in the potential development of chronic microvascular complications, and its connection to inflammation. Additional investigations are necessary to ascertain the causal mechanisms that underlie this connection, with the aim of developing preventive and treatment measures.

It is crucial to diagnose this form of hypercortisolism because patients with T2D typically experience improved blood sugar control once cortisol levels normalize.

Study limitations

There are some limitations to this study that should be discussed. Firstly, this study's design prevents us from drawing causal conclusions. We cannot conclude from this data that cortisol secretion has a causal effect in the pathophysiology of microvascular complications. Secondly, because every patient who was recruited was admitted to the hospital, the results could not be generalized to all T2D patients. Thirdly, we did not perform imaging diagnostics of the adrenal glands on all patients. Instead, we excluded patients who had a known adrenal gland disorder. Furthermore, we did not conduct a confirmatory 4 mg DEX test to further rule out potential false positive DEX cortisol unsuppressed results.

Conclusions

The prevalence of hypercortisolemia with unsuppressed DEX cortisol and ACTH levels was found to be 6.3% in patients with T2D, 10.5% in patients with microvascular complications, and 2% in patients without microvascular complications. A higher cortisol level with unsuppressed ACTH is associated with microvascular complications in patients with diabetes. In patients with polyneuropathy, retinopathy, and kidney disease, cortisol is associated with inflammation. This suggests that it plays a role in the inflammatory pathway that leads to chronic complications. If future research proves the causal link between cortisol levels and chronic complications, strategies for lowering cortisol can be considered. Additionally, until we develop strategies to lower cortisol, understanding the correlation between cortisol and inflammation could aid clinicians in identifying and treating inflammation in its early stages.

Article information

Data availability

All data that support the findings of this study are available on request from the corresponding author, Selma Jusufovic.

Ethics statement

The study protocol was approved by the Ethical Committee of the University Clinical Centre Tuzla. The researcher explained to each participant the goal of the study. Furthermore, all participants were informed of their right to refuse or cease participation in accordance with the ethical norms of the 1983 Helsinki Declaration.

Authors' contributions

Selma Jusufović made a substantial contribution to the conception and design of the work and final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Alma Halilčević performed the analysis, Enes Osmanović statistical analysis, Rasim Jusufović contributed data and analysis tools, and Vedad Herenda and Amina Godinjak performed the analysis.

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Conflict of interest

The authors declare no conflict of interest.

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