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Association of salivary cortisol levels with cardiovascular diseases

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Cardiovascular diseases continue to be the leading cause of mortality in developed countries, while traditional risk factors do not fully explain the variability in the development and progression of atherosclerosis. In recent decades, significant attention has been paid to the role of chronic psychosocial stress and hypercortisolemia as independent cardiovascular risk factors.

Aim. To evaluate the relationship between morning salivary cortisol concentration and dyslipidemia parameters, anthropometric measurements, and the severity of atherosclerotic lesions of the carotid and coronary arteries in patients with cardiovascular risk factors.

Material and methods. The study included 50 patients with cardiovascular risk factors. All participants underwent salivary cortisol level measurement, lipid profile assessment, and anthropometry. The severity of atherosclerosis was assessed by carotid intima-media thickness (IMT) and by the SYNTAX Score on coronary angiography.

Results. The mean salivary cortisol level was 8.4±3.2 nmol/L. Statistically significant correlations were found between cortisol level and triglyceride levels, total cholesterol, low-density lipoprotein cholesterol, body mass index, and waist circumference. The strongest associations were observed with markers of atherosclerosis: intima-media thickness and SYNTAX Score. Patients with cortisol levels above the median (>8.1 nmol/L) had significantly higher intima-media thickness values (1.14± 0.18 mm vs. 0.92±0.14 mm, p=0.003) and SYNTAX Score (22.5±8.4 vs. 11.3±6.7, p<0.001).

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Conclusion. Elevated salivary cortisol level, as a marker of chronic hypercortisolemia, is associated with more pronounced manifestations of dyslipidemia (hypertriglyceridemia, impaired lipoprotein ratio), abdominal obesity, and a greater extent of atherosclerotic lesions in major arteries. Salivary cortisol measurement may become a useful tool for cardiometabolic risk stratification.

Keywords: salivary cortisol, dyslipidemia, abdominal obesity, intima-media thickness, SYNTAX Score, atherosclerosis.

Conflict of Interest: none declared.

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Introduction

Cardiovascular diseases (CVD) associated with atherosclerosis continue to be the leading cause of mortality in developed countries. Traditional risk factors (RF) (dyslipidemia, arterial hypertension (AH), smoking, diabetes mellitus) do not fully explain the variability in the development and progression of atherosclerosis. In recent decades, considerable attention has been paid to the role of chronic psychosocial stress as an independent cardiovascular risk factor [1].

A key mediator of the adaptive response to stress is cortisol, the primary glucocorticoid hormone in humans. Prolonged or excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to chronic hypercortisolemia, exerts a systemic negative impact on metabolism. Cortisol stimulates lipolysis in the extremities and lipogenesis in the abdominal region, contributing to the development of visceral obesity, induces insulin resistance, impairs endothelial function, enhances pro-inflammatory processes and oxidative stress, collectively creating a pro-atherogenic environment [2].

Traditionally, cortisol is measured in serum or 24-hour urine; however, these methods have limitations (invasiveness of collection, influence of circadian rhythm, stress from venipuncture). Determination of free (biologically active) cortisol in saliva is a non-invasive, convenient, and valid method, correlating well with the level of free cortisol in plasma. Salivary cortisol reflects the short-term activity of the HPA axis and is widely used in studies linking stress and somatic pathology [3].

Despite the existence of theoretical premises, there are insufficient comprehensive studies examining the relationship between salivary cortisol levels and objective markers of atherosclerosis in different vascular beds (carotid and coronary arteries) within the same group of patients. Most studies focus either on the lipid profile or on individual ultrasound parameters.

Aim of the study. To evaluate the relationship between morning salivary cortisol concentration and dyslipidemia parameters, anthropometric measurements, and the severity of atherosclerotic involvement of the carotid and coronary arteries in patients with cardiovascular risk factors.

Material and methods

A single-center, cross-sectional, observational study was conducted. The study included 50 patients (32 men and 18 women) aged 42 to 77 years (mean age—58.3±8.7 years), who were undergoing examination and treatment in the cardiology departments of the Zakharin Clinical Hospital No. 6 in Penza with suspected coronary artery disease (CAD) or for cardiovascular risk assessment. Inclusion criteria: age from 40 to 80 years; presence of at least two classic CVD risk factors (AH, dyslipidemia, smoking, positive family history, obesity); written informed consent to participate. Exclusion criteria: acute coronary syndrome or stroke within the preceding 3 months; severe endocrine diseases (Cushing's syndrome, Addison's disease); oncological pathology; severe hepatic or renal failure; acute infectious diseases; use of systemic glucocorticoids or drugs significantly affecting lipid metabolism (statins could be discontinued by agreement with the attending physician for 2 weeks before blood sampling at the start of the study).

All patients underwent the following examinations:

Medical history and anthropometry: Age, sex, and diagnoses were recorded. Height, weight, and waist circumference (WC) were measured. Body mass index (BMI) was calculated using the formula:

$$\text{weight (kg)} / \text{height}^2 \text{ (m}^2\text{)}.$$

Abdominal obesity (AO) was diagnosed with WC ⩾ 94 cm for men and ⩾80 cm for women.

Determination of salivary cortisol: Saliva samples were collected in the morning (from 8:00 to 9:00 AM) on an empty stomach, at rest, at least 1 hour after waking. Patients refrained from smoking, eating, and brushing teeth for 1 hour before collection. Sterile saliva collection tubes were used. Samples were centrifuged and stored at –80 °C until analysis. Cortisol concentration was determined by enzyme-linked immunosorbent assay using a reagent kit for cortisol determination (JSC "BioKhimMak", Russia). Sensitivity of the method—0.5 nmol/L. Intra- and inter-assay coefficients of variation did not exceed 8%.

Biochemical blood test: Venous blood was drawn in the morning on an empty stomach. The following were determined: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) (calculated by the Friedewald formula), and triglycerides (TG) using an enzymatic colorimetric method. The atherogenic index (LDL-C/HDL-C) was calculated.

Assessment of carotid atherosclerosis: Ultrasound examination of the carotid arteries was performed using a Vivid S6 diagnostic ultrasound system (General Electric, Israel). Intima-media thickness (IMT) was measured in the distal segments of the common carotid arteries, bifurcations, and proximal segments of the internal carotid arteries according to standard methodology. The averaged IMT value (mean value across 12 segments) was used for analysis. The presence of atherosclerotic plaques (localized wall thickening >1.5 mm or 0.5 mm greater than adjacent segments) was recorded.

Assessment of coronary atherosclerosis: All patients underwent coronary angiography based on clinical indications (stable angina class III-IV, positive stress tests). The presence of hemodynamically significant stenoses (>50% diameter) in the major epicardial arteries was assessed. A dichotomous variable was used for analysis: presence/absence of ⩾1 significant stenosis. The anatomical complexity of coronary atherosclerosis in all patients was quantitatively assessed using the angiographic SYNTAX Score (SS). The score was calculated based on selective coronary angiography data according to the official algorithm. All hemodynamically significant lesions (stenosis ⩾50% in vessels with diameter ⩾1.5 mm) were assessed, taking into account their location, morphological complexity (occlusion, bifurcation/trifurcation, length, calcification, thrombus, etc.), and the type of coronary circulation. The final score represents the sum of the scores for all lesions. Depending on the SS value, patients were stratified into groups of low (SS⩽22), intermediate (SS 23–32), and high (SS⩾33) risk.

Ethical review

The study was conducted in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of Penza State University (Protocol No. 9 dated May 31, 2024). All participants signed informed consent.

Statistical analysis

Statistical processing was performed using the Statistica 10.0 (Stat Soft Inc., USA) and SPSS Statistics 23.0 (IBM, USA) software packages. The normality of the distribution of quantitative variables was checked using the Shapiro-Wilk test. Normally distributed data are presented as M±SD, non-normally distributed as Me [Q1; Q3]. Student's t-test or the non-parametric Mann-Whitney U-test was used to compare two independent groups. Qualitative variables were described using absolute values and percentages. Qualitative variables were compared using the Pearson chi-square (χ^2) test. Pearson's (r) or Spearman's (rs) correlation coefficients were used to assess correlations. Sensitivity and specificity analysis of the predictive role of cortisol was performed using receiver operating characteristic (ROC) curves. The overall accuracy of the method is presented as the area under the ROC curve (AUC). Differences were considered statistically significant at $p < 0.05$.

Results of the study

The mean age of patients was 58.3±8.7 years. The sex distribution was as follows: 64% men (n=32) and 36% women (n=18). The mean values of the main studied parameters are presented in Table 1. AO was diagnosed in 36 patients (72%). Elevated TG levels (>1.7 mmol/L) were observed in 29 patients (58%), and low HDL-C levels (<1.0 mmol/L for men, < 1.2 mmol/L for women) were observed in 21 patients (42%). The mean salivary cortisol level was 8.4±3.2 nmol/L (range 3.1 to 16.8 nmol/L), with a median value of 8.1 nmol/L. Increased IMT (⩾0.9 mm)

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Table 1. **General characteristics of the examined patients**

Parameter	All patients, (n=50)	Men, (n=32)	Women, (n=18)	p 2-3
	1	2	3	
Age, years	58.3 ± 8.7	56.9 ± 9.1	60.8 ± 7.5	0.121
BMI, kg/m²	30.1 ± 4.5	29.5 ± 4.0	31.2 ± 5.1	0.185
WC, cm	101.8 ± 11.3	102.5 ± 10.8	100.5 ± 12.4	0.543
Salivary cortisol, nmol/L	8.4 ± 3.2	8.6 ± 3.4	8.0 ± 2.8	0.512
TC, mmol/L	5.6 ± 1.1	5.4 ± 1.0	5.9 ± 1.2	0.098
LDL-C, mmol/L	3.5 ± 0.9	3.4 ± 0.8	3.7 ± 1.1	0.245
HDL-C, mmol/L	1.2 ± 0.3	1.1 ± 0.3	1.3 ± 0.3	0.019
TG, mmol/L	2.0 [1.5; 2.7]	2.1 [1.6; 2.8]	1.8 [1.4; 2.4]	0.210
Atherogenic index (LDL-C/HDL-C)	3.0 [2.4; 3.8]	3.1 [2.6; 3.9]	2.8 [2.1; 3.3]	0.087
Mean IMT, mm	1.03 ± 0.20	1.05 ± 0.21	0.99 ± 0.18	0.308
Presence of atherosclerotic plaques, n (%)	34 (68%)	23 (72%)	11 (61%)	0.430
SYNTAX Score	16.4 [8.0; 25.0]	17.6 [9.0; 26.0]	15.6 [6.0;23.0]	0.045

Note. Data are presented as M±SD or Me [Q1; Q3], p—significance level of differences between men and women (t-test or Mann-Whitney U-test). The χ^2 test was used to compare categorical variables (presence of plaques). Statistically significant differences were obtained for HDL-C and the degree of coronary artery involvement (SYNTAX Score).

and/or presence of plaques in the carotid arteries were detected in 33 patients (66%). The SYNTAX Score was 16.4 [8.0; 25.0].

Subsequently, a correlation analysis was performed, the results of which demonstrated the presence of statistically significant positive relationships between salivary cortisol levels (a marker of chronic stress and HPA axis activity) and most of the studied cardiometabolic parameters (Table 2).

When analyzing salivary cortisol levels and the lipid spectrum, statistically significant moderate positive correlations were found with TC, LDL-C, and TG. The correlation with HDL-C was negative but did not reach statistical significance. Significant moderate positive correlations were identified. This confirms the known role of cortisol in the pathogenesis of abdominal (visceral) obesity—the most metabolically dangerous type of obesity. Among all parameters, the most significant moderate positive correlation was with carotid artery IMT. IMT is an ultrasound marker of early atherosclerosis and subclinical vascular damage. Such a close relationship indicates a direct association between the level of chronic stress (cortisol) and structural changes in the arteries. A strong positive correlation was also found with the SYNTAX Score, which quantitatively assesses the anatomical complexity and extent of coronary artery involvement. The moderate correlation with cortisol suggests that chronic stress may be associated not only with early but also with pronounced, clinically significant forms of CAD.

A comparative analysis of patient groups with low and high salivary cortisol levels was also conducted. When the sample was divided by the median cortisol value (8.1 nmol/L), significant differences were identified (Table 3). The high cortisol group (>8.1 nmol/L, n=29) had significantly higher values of WC, TG, atherogenic index, IMT, and coronary atherosclerosis compared to the low cortisol group (≤8.1 nmol/L,

Table 2. **Correlation of salivary cortisol levels with the studied parameters**

Parameter	Correlation coefficient (r/rs)	p
TC	0.45	0.007
TC LDL-C	0.51	<0.001
TC HDL-C	0.22	0.127
TG	0.39	0.009
BMI	0.32	0.004
WC	0.41	0.008
Carotid artery IMT	0.61	<0.001
SYNTAX Score	0.58	<0.001

Note. r/r_s—Pearson's or Spearman's correlation coefficient; p—level of statistical significance. Statistically significant correlations ($p < 0.05$) are highlighted.

Table 3. **Comparison of groups with low and high salivary cortisol levels**

Parameter	Group 1: cortisol ≤ 8.1 nmol/L (n=29)	Group 2: cortisol > 8.1 nmol/L (n=21)	p
Cortisol, nmol/l	5.9 ± 1.6	11.0 ± 2.1	<0.001
WC, cm	95.2 ± 9.1	108.4 ± 10.0	<0.001
TG, mmol/l	1.6 [1.3; 2.0]	2.5 [1.9; 3.2]	<0.001
LDL-C/HDL-C	2.6 [2.1; 3.2]	3.5 [2.9; 4.2]	0.001
Mean IMT, mm	0.92 ± 0.14	1.14 ± 0.18	0.003
Hemodynamically significant coronary artery stenoses	9.8 ± 3.0	6.9 ± 2.8	0.011

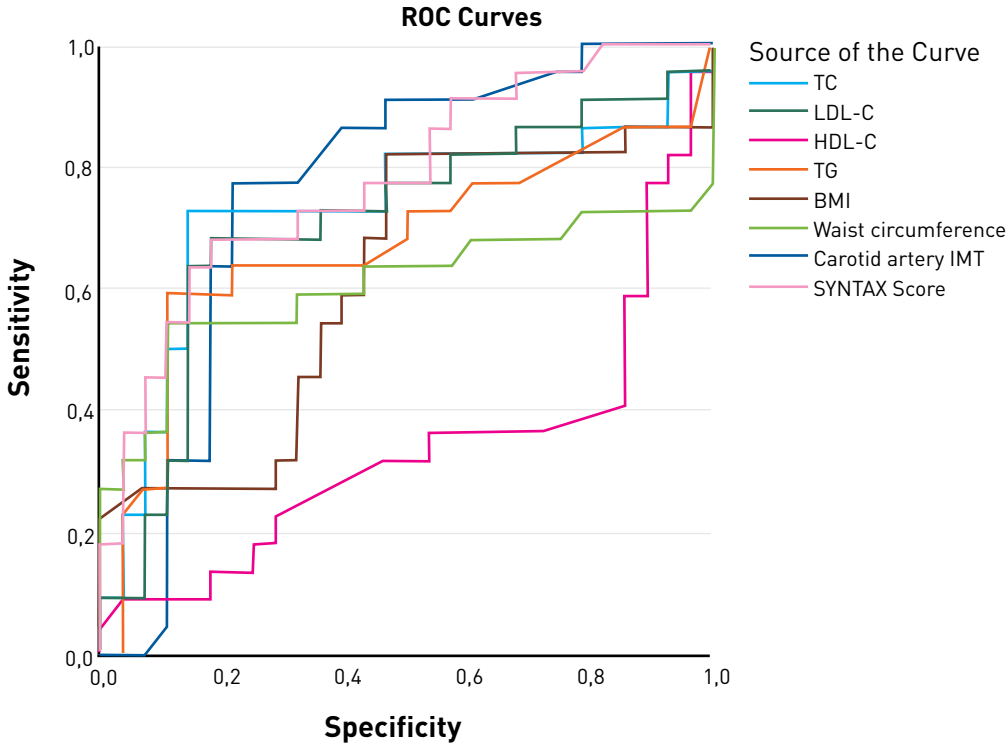

Fig. 1. ROC curve of the predictive role of salivary cortisol in the assessment of the studied parameters
*__Note.__ Area under the ROC curve (AUC): TC = 0.729; LDL-C = 0.705; HDL-C = 0.335; TG = 0.671; BMI = 0.614; WC = 0.608; carotid artery IMT = 0.761; SYNTAX Score = 0.780.

n=21). No differences in age, sex, BMI, or TC were observed between the groups.

Among the 50 patients who underwent coronary angiography, hemodynamically significant stenoses were detected in 29 individuals (57%). All patients with high salivary cortisol levels had plaques in the carotid arteries upon ultrasound examination.

At the final stage, an ROC analysis of the predictive role of salivary cortisol in assessing the studied parameters (TC, LDL-C, HDL-C, TG, BMI, WC, carotid artery IMT, SYNTAX Score) was performed (Fig. 1).

Discussion

The conducted study allowed us to identify a significant prevalence of cardiovascular risk factors and subclinical atherosclerosis among the examined middle-aged patients with CAD. The main result of the study is the demonstration of significant associations between salivary cortisol levels, which is an integrative marker of HPA axis activity and chronic psychosocial stress, and key parameters of lipid metabolism, AO, as well as the severity of atherosclerotic involvement of the carotid and coronary arteries.

The examined patient group was characterized by a high frequency of AO (72%) and atherogenic dyslipidemia (elevated TG—58%, low HDL-C—42%), which corresponds to current concepts of metabolic syndrome as a crucial pathogenetic link in CVD [4]. he mean salivary cortisol level (8.4±3.2 nmol/L) was within the physiological range, which is expected for patients without endocrine pathology and confirms that the observed associations are mediated by prolonged, rather than acute, glucocorticoid exposure.

The correlation analysis data are consistent with the known pathophysiological effects of cortisol. Moderate positive correlations with TC (r=0.45), LDL-C (r=0.51), and TG (r=0.39) reflect the stimulating effect of chronic hypercortisolemia on the synthesis of very low-density lipoproteins in the liver, activation of lipolysis in visceral adipose tissue with subsequent increased flow of free fatty acids into the portal circulation, and the development of insulin resistance [2, 5]. The trend towards a negative correlation with HDL-C, which did not reach statistical significance in our sample, is also described in the literature and may be related to decreased lipoprotein lipase activity [6]. The identified correlations between cortisol levels and BMI (r=0.32) and, especially, with WC (r=0.41) confirm the central role of the HPA axis in the pathogenesis of abdominal (visceral) obesity, which is a key

component of metabolic syndrome and an independent risk factor for cardiovascular events [7].

The most significant results are the moderate positive correlations between salivary cortisol levels and the ultrasound marker of subclinical atherosclerosis—carotid artery IMT (r=0.61), as well as with the quantitative indicator of coronary bed involvement—the SYNTAX Score (r=0.58). These data suggest that cortisol-mediated chronic stress is associated not only with metabolic disorders but also directly with structural and functional changes in blood vessels. The results are consistent with studies demonstrating a link between elevated cortisol levels (including salivary), arterial stiffness, and endothelial dysfunction [8]. Proposed mechanisms include the direct pro-atherogenic effect of glucocorticoids on the vascular wall, enhancement of oxidative stress, pro-inflammatory processes, and smooth muscle cell proliferation [9].

Additional confirmation of the clinical significance of the identified relationships comes from the results of the comparative analysis of groups divided by the median cortisol level. Patients with cortisol concentration >8.1 nmol/L had significantly higher values of WC, TG, atherogenic index (LDL-C/HDL-C), IMT, and more severe coronary artery involvement, despite comparable age, sex, and BMI. This fact emphasizes that even within the framework of physiological fluctuations, a relatively higher basal cortisol level can act as a marker of an unfavorable cardiometabolic and atherosclerotic profile [10, 11]. It is important to note that all patients in the high cortisol subgroup were found to have atherosclerotic plaques in the carotid arteries.

The results of the ROC analysis indicate a significant predictive role of salivary cortisol levels in assessing the risk of cardiometabolic disorders and the degree of atherosclerotic involvement [10]. The highest diagnostic accuracy, determined by AUC, was noted for indicators of coronary atherosclerosis severity and structural vascular changes: SYNTAX Score (AUC=0.780), carotid artery IMT (AUC=0.761), as well as for TC=0.729 and LDL-C=0.705, which is consistent with data on the pathogenetic link between chronic stress and dyslipidemia [6, 7].

Limitations of the conducted study: the cross-sectional and single-center nature of the study, which included a small sample size (n=50). The study included patients with already suspected or diagnosed CAD. A single measurement of salivary cortisol (morning) was performed, which has high variability and may not fully reflect chronic HPA axis activity.

Ways to overcome limitations: conducting a prospective multicenter study involving a larger number of participants to increase power and representativeness. Inclusion of not only cardiology patients but also individuals from the general population with different levels of cardiovascular risk, including healthy volunteers. Determination of cortisol in several saliva samples throughout the day to calculate its daily variability.

The obtained data allow considering salivary cortisol determination as a promising non-invasive biomarker for the integrated assessment of cardiovascular risk.

Conclusion

In patients with CVD risk factors, elevated morning salivary cortisol levels were associated with more pronounced manifestations of metabolic syndrome: abdominal obesity (by waist circumference), hypertriglyceridemia, and an increased atherogenic index.

An independent positive association was found between salivary cortisol concentration and objective markers of vascular atherosclerotic involvement: carotid artery IMT and coronary calcium index.

Patients with hemodynamically significant coronary artery stenoses according to angiography had significantly higher salivary cortisol levels compared to patients without significant stenoses.

Determination of salivary cortisol can be considered as an additional, non-invasive tool for the stratification of cardiometabolic risk, integrating the impact of chronic stress on metabolism and the vascular wall.

Conflict of Interest: none declared.

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