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Carotid Intima–Media Thickness May Be a Useful Biomarker in Determining Early Cardiovascular Risk in Mild Autonomic Cortisol Hypersecretion

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Abstract

Objective: This study aimed to assess the cardiovascular risk in patients with mild autonomous cortisol hypersecretion (MACS). To this end, the suitability of carotid intima–media thickness (cIMT) as a surrogate biomarker was evaluated.

Methods: This cross-sectional study was conducted with patients presenting to the endocrinology outpatient clinic of a tertiary care hospital. Patients with adrenal Cushing's syndrome (CS), MACS and nonfunctional adrenal adenoma (NFA) were consecutively included. Patients with known cardiovascular disease were excluded. Biochemical data and sonographically determined cIMT values were collected. Data were compared between the three groups.

Results: A total of 20 CS patients with a mean age of 49.3 ± 6.9 years, 19 MACS patients with a mean age of 48.1 ± 11.1 years, and 19 NFA patients with a mean age of 41.7 ± 13.3 years were included in this study ($P = .158$). Cushing's syndrome and MACS patients had significantly higher mean cIMT values compared to NFA patients ($P < .001$ and $P = .0048$, respectively). However, when patients with diabetes and obesity were excluded, cIMT did not differ between MACS and NFA patients ($P = .861$). Nevertheless, it was still significantly higher in CS patients compared to MACS and NFA patients ($P = .005$ and $P = .002$, respectively).

Conclusion: This study confirms the presence of vascular damage and increased cardiovascular risk in patients with CS. We also found vascular damage in patients with MACS. Carotid intima–media thickness could be a useful biomarker for early assessment of cardiovascular risk in patients with MACS.

Keywords: Carotid intima–media thickness, Cushing's syndrome, cardiovascular risk, mild autonomous cortisol hypersecretion

Introduction

Cushing's syndrome (CS) is characterized by increased morbidity and mortality rates and carries risks such as obesity, diabetes, hypertension, muscle weakness, severe osteoporosis, and immunosuppression.[1] Cardiovascular mortality is significantly increased, with untreated CS patients having a 5 times higher risk than the general population and a persistently high cardiovascular risk even after remission.[2,3] Regardless of endogenous or exogenous glucocorticoid excess, CS is associated with increased cardiovascular risk due to the direct and indirect effects of cortisol.[4]

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Mild autonomous cortisol hypersecretion (MACS), which accounts for 5%-20% of adrenal incidentalomas, manifests as mild activation of the hypothalamic–pituitary–adrenal (HPA) axis without recognizable clinical manifestations.[5,6] The relationship between mild chronic hypercortisolism in patients with MACS and associated diseases remains unclear, but chronic cortisol hypersecretion in CS is primarily associated with risk factors for cardiovascular disease.[7,8]

There are several methods for predicting subclinical atherosclerosis; the use of carotid intima–media thickness (cIMT) for this purpose is also the subject of research.[9] Studies have reported accelerated atherosclerosis and impaired endothelial function in CS patients using various methods to assess cardiovascular risk.[10-12] A meta-analysis found increased cIMT, a greater prevalence of carotid plaques, and reduced flow-mediated dilation in CS patients compared to controls.[13] However, the use of cIMT measurement as a standard for risk assessment was not recommended due to concerns regarding the lack of methodological standardization and the lack of added value in predicting future cardiovascular events.[14]

The fact that hypercortisolemia is associated with increased mortality related to cardiovascular disease emphasizes the need for early detection of both overt CS and MACS. However, diagnosis is often delayed, especially in cases where the clinical manifestations of hypercortisolism, referred to as cushingoid features, are minor or absent, particularly when cortisol excess is subtle.

This study aims to investigate the relationship between cortisol and cIMT. The suitability of cIMT as a surrogate biomarker for early atherosclerosis in patients with MACS will be investigated.

Methods

Overview of the Study

This cross-sectional study was conducted at a tertiary care university hospital. Ethical approval for the study was obtained from the Medical Research Ethics Committee of İstanbul University-Cerrahpaşa (Approval no: 264558, Date: December 3, 2014).

Participants and Clinical Decision

Participants included individuals diagnosed with adrenal incidentalomas at the Department of Endocrinology and Metabolism Clinic at İstanbul University-Cerrahpaşa. Of these incidentalomas, 20 consecutive patients were diagnosed with CS, and 19 were diagnosed with MACS. Mild autonomous cortisol hypersecretion was defined as mild autonomous cortisol hyperproduction devoid of specific clinical signs but detectable biochemically through anomalies in the HPA axis function. Diagnostic criteria recommended by the National Italian Group on Adrenal Tumors were applied, requiring the absence of clinical signs of hormone excess and at least 2 abnormalities in HPA axis function.[15-17] Additionally, 19 individuals with NFA, matched for age and sex, were included as healthy controls. Individuals with known cardiovascular disease were excluded from the study.

Data Collection

Demographic and clinical data were collected from all participants, including smoking habits, physical inactivity, family history of coronary heart disease, hypertension, diabetes, and osteoporosis. Body mass index (BMI) was calculated, and participants with a BMI between 25 and 30 kg/m^2 were categorized as overweight, while participants with a BMI greater than 30 kg/m^2 were categorized as obese.[18] Waist circumference (WC) was measured according to a standard procedure.[19]

Biochemical data, including glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, insulin, C-reactive protein (CRP), 25-OH vitamin D, dehydroepiandrosterone sulfate (DHEA-S), and fibrinogen levels, were obtained from the medical records of participants' most recent outpatient clinic visits. In addition, participants were asked about current CS-related symptoms.

Measurement of Carotid Intima–Media Thickness

The intima–media thickness of the carotid artery was examined using echo color Doppler ultrasound (US) on both the right and left common carotid artery (R-CC and L-CC). The examination was performed in the supine position, and multiple measurements were taken on the vessel wall, away from the US guide probe, with the mean of the 3 highest values recorded for statistical analysis.[20] All sonographic examinations and measurements were performed by a 5-year experienced endocrinologist (O.H.), who was blinded to the participants' clinical information.

Laboratory Assays

Plasma adrenocorticotropic hormone (ACTH), serum cortisol, DEHA-S, and 24-hour urinary free cortisol (UFC) were analyzed using the ECLIA method with Roche cobas e systems. Glucose, insulin, 25-OH-vitamin D, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, fibrinogen, and CRP were measured by enzymatic colorimetric or immunoturbidimetric methods on Roche/Hitachi cobas c systems.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA). Demographic and clinical variables were presented as counts and percentages (%). Categorical variables were analyzed using the chi-square test and Fisher's exact test. Differences among groups were examined using the Mann–Whitney *U* or Kruskal–Wallis tests, with Bonferroni correction applied in cases involving comparisons of three or more groups. Data were reported as mean and standard deviation, and correlation between variables was assessed using Pearson and Spearman correlation tests. A significance level of $P < .05$ was considered statistically significant.

Results

Participants Characteristics

Demographic data and clinical characteristics of 20 patients with CS, with a mean age of 49.3 ± 6.9 years, 19 patients with MACS aged 48.1 ± 11.1 years, and 19 patients with NFA with a mean age of 41.7 ± 13.3 years are presented in Table 1. The age and BMI of the patients with CS, MACS, and NFA were similar ($P = .158$ and .236, respectively). Among CS and MACS patients, 18 out of 20 CS patients were obese (BMI over 30 kg/m^2), while 7 out of 19 MACS patients were obese ($P = .001$). There were no statistically significant differences in the frequency of cigarette smoking, family history of CVD, hypertension, hyperlipidemia, or osteoporosis between the groups ($P > .05$ for all). However, the frequency of diabetes mellitus was higher in patients with CS and MACS. Eight (40%) of CS patients and 8 (42.1%) of MACS patients had diabetes mellitus, while only 1 (5.3%) of the 19 patients with NFA had diabetes mellitus ($P = .012$).

Comparison of Clinical Findings

The frequency of clinical symptoms related to CS, such as striae, plethora, buffalo hump, fatigue, and purplish discoloration, is summarized in Table 2. These symptoms were most common among patients with CS, with frequencies ranging from 65% to 95%. In MACS patients, the frequencies of these symptoms varied from 15.85% to 63%. All symptoms related to hypercortisolemia were significantly more common among CS patients compared to MACS patients ($P < .001$ for striae, plethora, buffalo hump, and fatigue between CS and MACS patients). These symptoms were rare in patients with NFA, ranging from 0% to 21.1%. Additionally, osteoporosis was more common in CS patients compared to both MACS, with a frequency of 65% ($P = .003$).

Comparison of Biochemical Findings

Regarding biochemical levels of 8:00 AM basal cortisol, basal ACTH, 1 mg overnight DST, 24-hour UFC, and DHEA-S, all these 5 parameters were found to be elevated in patients with CS and MACS, with the highest levels observed in CS patients ($P < .001$ for all, Table 3). Other biochemical results obtained from parameters

Table 1. Comparison of General Characteristics of the Study Population According to Disease Groups

General characteristics	CS (n = 20)	MACS (n = 19)	NFA (n = 19)	*P*
Age, year, mean ± SD	49.3 ± 6.9	48.1 ± 11.1	41.7 ± 13.3	.158
Sex, female, n (%)	16 (80.0)	17 (89.5)	17 (89.5)	.497
BMI, kg/m^2, mean ± SD	33.5 ± 9.3	30.2 ± 9.5	28.8 ± 5.6	.236
Waist circumference, cm, mean ± SD	103.1 ± 12.6	99.3 ± 10.7	85.2 ± 9.2	.010*
Systolic blood pressure, mm Hg, mean ± SD	128.5 ± 20.2	119.3 ± 10.6	121.6 ± 13.8	.307
Diastolic blood pressure, mm Hg, mean ± SD	83.0 ± 14.1	75.9 ± 9.1	77.7 ± 8.0	.296
Cigarette smoking, n (%)	4 (20)	12 (63.2)	7 (36.8)	.154
Family history of cardiovascular disease, n (%)	4 (21.1)	7 (36.8)	4 (21.1)	.281
Diabetes mellitus, n (%)	8 (40)	8 (42.1)	1 (5.3)	.012**
Hyperlipidemia, n (%)	9 (45)	9 (47.4)	8 (42.1)	.711
Hypertension, n (%)	11 (55)	8 (42.1)	8 (42.1)	.903
Sedentary lifestyle, n (%)	17 (78.9)	17 (89.5)	15 (78.9)	.328

BMI, body mass index; CS, Cushing syndrome; MACS, mild autonomous cortisol hypersecretion; NFA, nonfunctional adrenal incidentalomas.
*P = .042 between patients with CS and MACS, P = .010 between patients with CS and NFA, P = .027 between patients with MACS and NFA.
**P = .282 between patients with CS and MACS, P = .012 between patients with CS and NFA, P = .009 between patients with MACS and NFA.

such as glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, CRP, fibrinogen, and insulin did not show significant differences between patients. While LDL cholesterol levels were higher in patients with NFA, the difference between groups was not statistically significant (P = .516). Fibrinogen, considered a risk factor for CVD, was significantly higher with mean values of 425.8 ± 123.3 mg/dL in CS and 409.2 ± 144.3 mg/dL in MACS patients compared to patients with NFA (P = .024). Vitamin D levels were lower in patients with CS and MACS than in patients with NFA, showing a statistically significant difference between the groups (P = .012). The lowest level of 25-OH vitamin D, with a mean value of 13.3 ± 11.1 ng/mL, was observed among patients with CS.

Table 2. Comparison Of Clinical Findings of the Study Population According to Disease Groups

Findings	CS (n = 20)	MACS (n = 19)	NFA (n = 19)	*P**
Obesity, n (%)	18 (90)	7 (36.8)	8 (42.1)	.001
Purple striae, n (%)	13 (65)	3 (15.8)	1 (5.3)	<.001
Pleatorrhea, n (%)	17 (85)	3 (15.8)	0	<.001
Buffalo hump, n (%)	17 (85)	5 (26.3)	1 (5.3)	<.001
Easy fatigue, n (%)	19 (95)	12 (63.2)	4 (21.1)	.009
Easy bruising, n (%)	16 (80)	8 (42.1)	2 (10.5)	<.001
Osteoporosis, n (%)	13 (65)	5 (26.3)	2 (11.1)	.003

CS, Cushing syndrome; MACS, mild autonomous cortisol hypersecretion; NFA, nonfunctional adrenal incidentalomas.
**P* values were obtained by comparing the findings of patients with Cushing syndrome and patients with mild autonomic cortisol hypersecretion.

Comparison of Carotid Intima–media Thickness

The comparison of cIMT values of all patients included in the study is presented in Figure 1. In the vascular ultrasound assessment, patients with CS and MACS showed significantly higher average cIMT values compared to patients with NFA (P < .001 and P = .0048, respectively). The mean cIMT value of CS patients (0.0902 ± 0.0036 cm) was also significantly higher than that of MACS patients (0.0532 ± 0.0097 cm) (P = .001). No significant correlation was found between cIMT levels and the other analyzed parameters.

Since diabetes and obesity are the most important risk factors for CVD, we compared the groups in terms of cIMT after excluding these 2 risk factors to observe the effects of hypercortisolism alone. Figure 2 depicts the comparison of cIMT among 3 CS patients, 8 MACS patients, and 11 NFA patients. Cushing's syndrome patients had significantly higher cIMT thickness compared to both MACS and NFA patients (P = .005 and P = .002, respectively). However, when diabetes and obesity were excluded, the difference in cIMT thickness between MACS patients and NFA patients was not significant (P = .861).

Discussion

This study confirms the significant vascular damage and increased cardiovascular risk associated with CS. It also sheds light on a previously unexplained but crucial finding: vascular damage in MACS begins at an early stage. It is observed that cardiovascular damage begins to develop when nonspecific clinical conditions associated with CS, such as diabetes and obesity, occur. The results show that cIMT is significantly increased in patients with MACS compared to control subjects, even in the presence of well-controlled and/or new-onset diabetes and obesity.

Cushing's syndrome, characterized by chronic cortisol excess, is closely associated with an increased risk of cardiovascular morbidity, with vascular events being one of the leading causes of death in untreated individuals with this syndrome.[10,21,22] The primary vascular abnormality associated with CS is arterial

Table 3. Comparison of Biochemical Test Results According to Disease Groups of the Study Population

Biochemical tests	CS (n = 20)	MACS (n = 19)	NFA (n = 19)	*P*
Basal cortisol, µg/dL, mean ± SD	24.2 ± 8.5	20.1 ± 7.3	13.3 ± 6.3	<.01*
ACTH, pg/mL, mean ± SD	5.7 ± 2.9	8.7 ± 3.6	21.5 ± 6.5	<.01*
1 mg-DST, µg/dL, mean ± SD	13.1 ± 9.6	5.3 ± 5.7	1.2 ± 0.64	<.01*
24-h UFC, µg/24 h, mean ± SD	437.0 ± 279.4	86.2 ± 29.3	61.1 ± 15.6	<.01*
DHEA-S, µg/dL, mean ± SD	21.4 ± 11.5	81.7 ± 12.9	152.4 ± 115.0	<.01*
Glucose, mg/dL, mean ± SD	121.4 ± 71.3	107.2 ± 40.3	92.5 ± 11.5	.071
T. cholesterol, mg/dL, mean ± SD	207.7 ± 42.6	204.2 ± 33.9	211.1 ± 37.1	.719
LDL cholesterol, mg/dL, mean ± SD	132.1 ± 26.3	134.1 ± 31.4	141.7 ± 30.4	.516
HDL cholesterol, mg/dL, mean ± SD	57.9 ± 28.0	49.5 ± 10.2	54.5 ± 13.0	.563
Triglyceride, mg/dL, mean ± SD	144.8 ± 65.8	149.4 ± 83.6	142.5 ± 63.6	.991
CRP, mg/dL, mean ± SD	9.05 ± 4.9	3.5 ± 1.1	5.3 ± 1.6	.187
Fibrinogen, mg/dL, mean ± SD	425.8 ± 123.3	409.2 ± 144.3	318.8 ± 94.0	.024**
Insulin, uIU/ml, mean ± SD	14.8 ± 10.6	10.4 ± 6.5	15.4 ± 7.7	.078
25-OH vitamin-D, ng/mL, mean ± SD	19.1 ± 12.9	13.3 ± 11.1	22.4 ± 14.4	.012***

BMI, body mass index; CS, Cushing syndrome; MACS, mild autonomous cortisol hypersecretion; NFA, nonfunctional adrenal incidentalomas.
**P*-values were obtained comparing patients with both CS and MACS to patients with NFA.
***P* = .216 between patients with CS and MACS, *P* = .024 between patients with CS and NFA, and *P* = .032 between patients with MACS and NFA.
****P* = .048 between patients with CS and MACS, *P* = .116 between patients with CS and NFA, and *P* = .012 between patients with MACS and NFA.

atherosclerosis. Carotid ultrasound, which measures cIMT and carotid plaque, is a valuable tool for determining the extent of subclinical atherosclerosis.[23] Both cIMT and the presence of carotid plaque are reliable markers for predicting subclinical atherosclerosis, which indicates potential coronary and cerebrovascular events.[13] In addition, individuals with CS often have higher levels of early atherosclerosis.

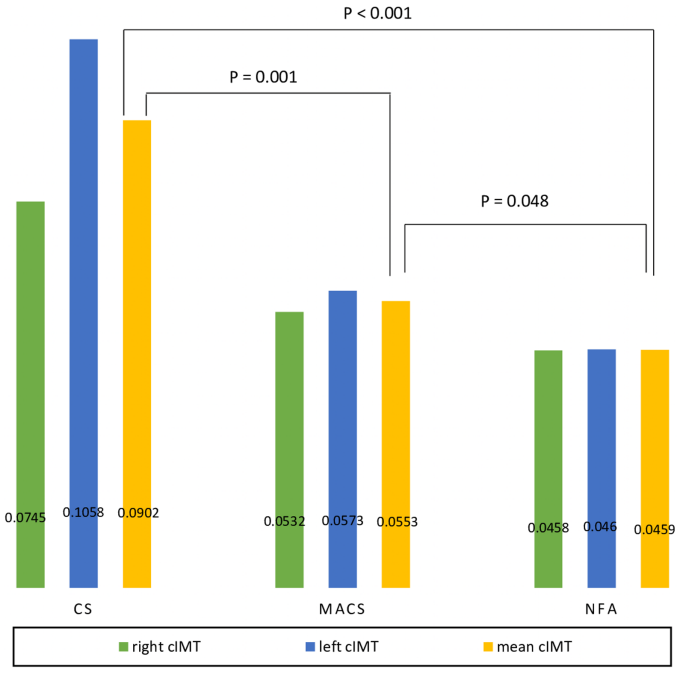

Figure 1. Comparison of carotid intima–media thicknesses (cIMT) of patients with Cushing syndrome (CS) and mild autonomic cortisol hypersecretion (MACS) and nonfunctional adrenal incidentalomas (NFA).

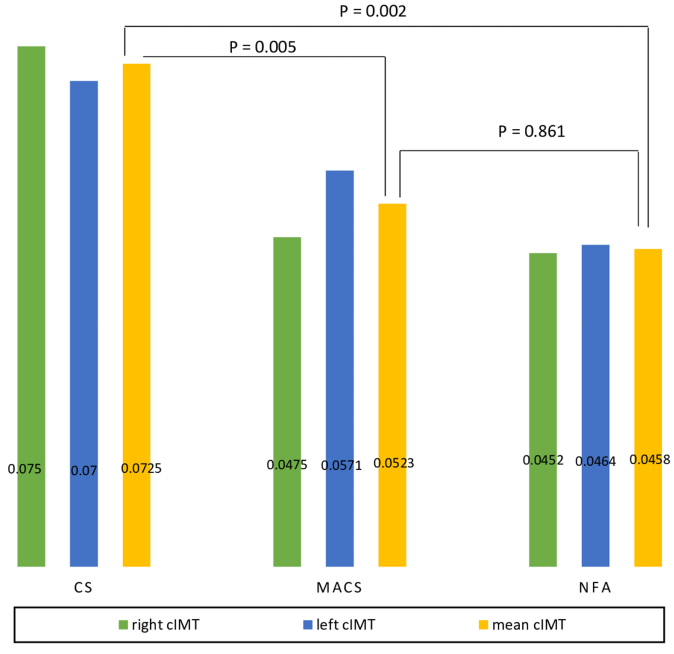

Figure 2. Comparison of carotid intima–media thickness (cIMT) of patients with Cushing syndrome (CS) and mild autonomic cortisol hypersecretion (MACS) and nonfunctional adrenal incidentaloma (NFA) after exclusion of obesity and diabetes.

The results of our current study show that cIMT is elevated not only in patients with full-blown CS but also in patients with MACS, suggesting that atherosclerosis may also be a significant problem in individuals with MACS. Considering that MACS is characterized by milder autonomic cortisol hyperproduction, which may not be manifested by specific clinical signs but can be detected biochemically by disturbances in HPA axis function, our study underscores the importance of close monitoring of patients with MACS.

Although CS has already been found to be associated with an increased risk of cardiovascular morbidity, the status of MACS, whether it serves as a predictor of CS or represents an independent state of hypercortisolemia, remains a matter of debate.[2,4,7] Little is known about whether this condition is a predictor of cardiovascular risk in early life. Our study provides a new contribution to this ongoing debate, as we found elevated cIMT levels in patients with MACS that are similar to those observed in individuals with full-blown CS. However, we were able to show that cIMT in patients with MACS without diabetes and obesity is similar to that in patients with NFA. This finding may necessitate a rethinking of treatment approaches for MACS. Currently, there is no definitive treatment approach for patients with MACS.[5,6] The traditional approach is to monitor these patients in the absence of significant clinical symptoms or signs, such as the development of overt cardiovascular disease, uncontrolled diabetes, and hypertension.[5,6] However, our study suggests that early atherosclerotic processes may begin before the onset of clinical symptoms, requiring a potentially more proactive approach to the management of patients with MACS, possibly even before clinical symptoms manifest.

Among the various factors associated with metabolic syndrome in CS, abdominal obesity and insulin resistance play a central role in the initiation and maintenance of atherosclerosis. Excessive accumulation of central obesity is associated with increased mortality and cardiovascular risk, which includes conditions such as diabetes, hyperlipidemia, hypertension, and atherosclerosis.[2] In our study, waist circumference, which is considered a reliable predictor of central obesity, was significantly greater in both CS and MACS patients compared to BMI-matched patients with NFA. Specifically, patients with CS had a mean waist circumference of 103.1 cm, while patients with MACS had a similar mean waist circumference of 99.3 cm. Despite similar BMI values in all groups, waist circumference was significantly higher in individuals with hypercortisolemia.

Mild autonomic cortisol hypersecretion due to moderate hormone secretion is associated with impaired insulin resistance, altered lipid profiles, increased waist circumference, and diseases such as osteoporosis.[16] In our study, glucose levels, triglycerides and waist circumference were higher in both CS and MACS patients, while insulin levels were higher in healthy controls. However, these differences did not reach statistical significance between the groups. In a study by Evran et al, plasma glucose, insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and triglyceride levels were compared between patients with NFA, patients with MACS, and a healthy control group. They found that the values of these parameters were significantly higher in NFA patients and MACS patients than in the healthy control group. However, no significant statistical difference in these parameters was found between patients with NFA and MACS patients.[24] In our study, we deliberately selected patients with NFA who had similar profiles of cardiovascular risk factors to defuse debates about the possible influence of other risk factors such as hyperlipidemia or hyperglycemia on cardiovascular damage. We specifically included patients with a high cardiovascular risk profile in our analysis.

Another important parameter is fibrinogen, a precursor of fibrin, a critical cofactor in platelet aggregation, and an important determinant of blood viscosity and atherogenesis.[25] Fibrinogen is the most abundant component of thrombi and has been repeatedly linked to coronary heart disease and cardiovascular disease in numerous studies.[26] Elevated fibrinogen levels have been detected in patients with myocardial infarction, stroke, and transient ischemic attacks, all conditions characterized by an overt thrombotic state.[27] The use of glucocorticoids in drug therapy and chronic hypercortisolism, the hallmark of CS, contribute to blood coagulation abnormalities by increasing the risk of venous thromboembolism and accelerating the progression of atherosclerosis. Przemysław Witek and colleagues demonstrated significantly higher fibrinogen levels in patients with CS compared to a sex- and age-matched control group.[28] In our study, we found that fibrinogen levels were significantly increased in patients with CS compared to controls. In addition, fibrinogen levels were elevated in patients with MACS, which is a milder form of hypercortisolemia, compared to patients with NFA. These results suggest that cardiovascular risk is also increased in patients with MACS compared to patients with NFA.

However, it is imperative to recognize several limitations of this study. First, due to its cross-sectional design, the study could only assess patients at the time of diagnosis and could not monitor their condition over time, particularly in terms of treatment status and disease progression. Secondly, the rarity of the disease resulted in a relatively small sample size, and the study could not accurately determine the exact stage at which the increased risk of cardiovascular disease observed in participants began. In addition, no echocardiographic examinations of the heart were performed. Another limitation is the assessment using the cIMT measurement, which is not recommended as a standard for risk assessment due to the lack of methodological standardization and the lack of added value in predicting future cardiovascular events. Future larger scale and prospective studies are needed to draw more definitive conclusions.

Conclusion

This study provides robust evidence of increased cardiovascular risk in patients with Cushing's syndrome using a multifaceted approach to assessment. Furthermore, it demonstrates an increased risk in individuals with mild autonomic cortisol hypersecretion, traditionally considered a less severe form of hypercortisolemia. Quantification of carotid intima–media thickness is shown to be a valuable biomarker that provides practical utility for targeting treatment strategies and facilitates monitoring of cardiovascular risk and damage in patients with mild autonomic cortisol hypersecretion. These results emphasize the need for thorough cardiovascular risk assessment and careful management in individuals with both full-blown Cushing's syndrome and the early stages of cortisol hypersecretion.

Data Availability Statement: All data obtained or analyzed as part of this study are included in this article (along with its tables). The data archive can be made available on request. Further requests can be directed to the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul University-Cerrahpaşa (Approval no: 264558, Date: December 3, 2014).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Declaration of Interests: Hande Mefkure Özkaya is serving as the Section Editor of this journal. We declare that Hande Mefkure Özkaya had no involvement in the peer review of this article and has no access to information regarding its peer review. The authors have no conflict of interest to declare.

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