Endocrine Practice 32 (2026) 329–336

Endocrine Practice™
www.endocrinepractice.org

Original Article

Prevalence of Hypercortisolism in Hypertension and Its Link to Carotid Atherosclerosis Markers

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ARTICLE INFO

Article history:
Received 14 September 2025
Received in revised form
20 October 2025
Accepted 22 October 2025
Available online 28 October 2025

Key words:
hypertension
carotid intima-media thickness
carotid stenosis
mild autonomous cortisol secretion
cortisol
blood pressure dipping pattern

ABSTRACT

Objective: The prevalence of hypercortisolism in hypertension and its association with cardiometabolic risk in hypertensive patients remains unknown. This study investigates the prevalence of hypercortisolism and the relationship between cortisol secretion and cardiometabolic parameters in hypertensive patients.
Methods: In 106 nondiabetic and nonobese hypertensive patients (age 37-70 years; 53 females), cortisol levels after a 1 mg dexamethasone suppression test (F-1mgDST), carotid intima-media thickness (cIMT), blood pressure dipping pattern, carotid stenosis, fasting glucose (FG), and glycated hemoglobin were evaluated. Hypercortisolism was defined as F-1mgDST >1.8 μg/dL (50 nmol/L).
Results: Hypercortisolism was identified in 8 patients (7.5%). Compared with those without, patients with hypercortisolism were older (56.9 vs 63.0 years, $P = .04$), had higher FG (95.3 vs 103.8 mg/dL, $P = .03$), glycated hemoglobin (5.4% vs 5.6%, $P = .001$), more frequently altered blood pressure dipping pattern (22.0% vs 62.5%, $P = .026$), pathologic cIMT (>1 mm; 7% vs 66.7%, $P = .001$), and frequently required ≥2 antihypertensive drugs (14.3% vs 50.0%, $P = .027$). Pathologic cIMT levels were associated with F-1mgDST levels (odds ratio 14.00, 95% CI 2.70-72.48, $P < .002$) after adjusting for age, sex, body mass index, smoking status, and presence of impaired FG/impaired glucose tolerance. The optimal F-1mgDST cut-off for predicting increased cIMT was identified as 1.14 μg/dL (31.4 nmol/L). This F-1mgDST threshold predicted the risk of cIMT >1 mm (odds ratio 15.57, 95% CI 2.88-84.29, $P = .001$), after adjustment for age, sex, body mass index, smoking, and presence of impaired glucose metabolism.
Conclusion: Hypercortisolism was detected in 7.5% of nondiabetic and nonobese hypertensive patients and was associated with early vascular damage. Hypercortisolism may worsen the cardiometabolic risk in hypertension.

Abbreviations: ACTH, adrenocorticotropic hormone; BMI, body mass index; BP, blood pressure; cIMT, carotid intima-media thickness; CS, carotid stenosis; DP, dipping pattern; FG, fasting glucose; F-1mgDST, cortisol levels after a 1 mg dexamethasone suppression test; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HPA, hypothalamic-pituitary-adrenal; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LVH, left ventricular hypertrophy; MACS, mild autonomous cortisol secretion; UFC, urinary free cortisol.

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https://doi.org/10.1016/j.eprac.2025.10.013

Introduction

It is known that mild autonomous cortisol secretion (MACS), present in about 50% of patients with incidentally discovered adrenal masses, is associated with an increased prevalence of chronic complications related to cortisol excess, such as hypertension, diabetes, bone fragility, and even increased all-cause mortality.[1-5] This condition is characterized by biochemical hypercortisolism, defined as cortisol levels after the 1 mg overnight dexamethasone suppression test (F-1mgDST) above 1.8 μg/dL (50 nmol/L) in the absence of the classical signs and symptoms typical of clinically overt cortisol excess, such as those seen in Cushing syndrome.[5] Unlike the rare condition of Cushing syndrome, the prevalence of MACS is not negligible. Indeed, MACS is estimated to be present in up to 50% of patients with adrenal incidentalomas, which, in turn, are described in up 7% of adults over 60 years of age. Therefore, the prevalence of MACS is estimated to be up to 3% in the general population.[6]

However, it has been reported that many patients with overt carotid stenosis (CS) exhibit few clinical signs and that there is an important overlap in symptoms between CS and MACS.[7] In addition, the prevalence and incidence of comorbidities are comparable between CS and MACS patients, including increased risks of osteoporosis, metabolic disturbances, hypertension, cardiovascular risk, and mortality.[3,8] The importance of diagnosing MACS is further reinforced by the fact that the cure of hypercortisolism in these patients is of benefits in terms of bone fragility, diabetes, and hypertension.[9-12]

Since hypercortisolism in patients with MACS may lead to complications such as diabetes, bone fragility, and hypertension, some studies have investigated the frequency of undiagnosed hypercortisolism in specific populations with an increased pretest probability of hypercortisolism, such as diabetic and osteoporotic patients. These studies found that more than 24% of patients with diabetes and up to 17% of patients with bone fragility could be affected by hypercortisolism.[13-16]

The few studies conducted so far to assess the prevalence of hypercortisolism in hypertensive patients have focused on younger individuals and/or used less sensitive criteria for diagnosing hypercortisolism than the F-1mgDST threshold of 1.8 μg/dL (50 nmol/L), and/or included patients with diabetes.[17-20] Therefore, the prevalence of hypercortisolism in hypertensive patients remains unknown.

Importantly, some studies have shown that in patients with adrenal incidentalomas, the risk of comorbidities exists on a continuum, increasing with higher F-1mgDST levels.[21] Indeed, some patients with nonfunctioning adrenal incidentalomas may be at higher risk of cortisol-related consequences than individuals without adrenal lesions.[21,22] Moreover, it has been suggested that in diabetic patients, cortisol secretion levels, even when within the normal range, are associated with diabetes-related chronic complications and vertebral fractures.[23,24] No data are currently available on the possible association between different cortisol secretion levels and the preclinical markers of cardiometabolic risk in hypertensive patients.

Therefore, the aims of the present study were to evaluate in hypertensive nondiabetic and nonobese patients (1) the prevalence of hypercortisolism and (2) the possible association between the degree of cortisol secretion and the preclinical markers of cardiometabolic risk.

Highlights

- Mild autonomous cortisol secretion (diagnosed by a cortisol level >1.8 μg/dL after the 1 mg dexamethasone suppression test) is present in 7.5% of nonobese, nondiabetic hypertensive patients without specific signs of cortisol excess
- In hypertensive patients, mild autonomous cortisol secretion is significantly associated with impaired glucose metabolism, vascular damage (as indicated by pathologic carotid intima-media thickness), and the need for intensified antihypertensive therapy
- A lower threshold for cortisol levels after the 1 mg dexamethasone suppression test (ie, >1.14 μg/dL) than the currently used cut-off (>1.8 μg/dL) may better predict early vascular changes

Clinical Relevance

Screening for hypercortisolism and monitoring for cardiovascular complications is advisable in hypertensive patients requiring at least 2 antihypertensive medications, and/or presenting with impaired fasting glucose, impaired glucose tolerance, pathologic carotid intima-media thickness, or an altered blood pressure dipping pattern, particularly when cortisol levels after the 1 mg dexamethasone suppression test exceed 1.14 μg/dL.

Methods

Study Design and Patients

In this cross-sectional prospective study, all patients aged 30 to 70 years with hypertension consecutively referred to our hypertension clinics between January 2022 and December 2023 were evaluated for inclusion. Exclusion criteria were (1) body mass index (BMI) ≥35 kg/m^2 (ie, severe obesity), active smoking (>10 cigarettes/d), pregnancy or lactation, hypertension associated with a family history of early-onset cerebrovascular events (<40 years), sleep apnea, prepubertal onset of hypertension, hypokalemia, hypertension in the context of adrenal insufficiency, or classic signs of hypercortisolism (lunar facies, striae rubrae, hypertrichosis, skin atrophy, buffalo hump); (2) confirmed endocrine hypertension (pheochromocytoma, primary aldosteronism, hyperparathyroidism, acromegaly, hyperthyroidism); (3) resistant hypertension, renovascular hypertension or conditions associated with increased hypothalamic-pituitary-adrenal (HPA) axis activity, including alcoholism, depressive syndrome, or chronic renal failure (glomerular filtration rate <45 mL/min); (4) use of medications affecting HPA axis function (eg, glucocorticoids, antidepressants); (5) diabetes mellitus; (6) refusal to sign informed consent.

In all patients evaluated for the study inclusion, primary aldosteronism and pheochromocytoma were excluded by measuring aldosterone-to-renin ratio and urinary fractionated metanephrines, respectively.

A total of 106 hypertensive patients (53 females) met the inclusion criteria and were enrolled. The study protocol was approved by our ethical committee.

Methods

The same cardiologist assessed the determination of blood pressure (BP) by (1) conventional measurements using a validated automatic office BP monitor (mathematical mean of 3 readings in seated position) and (2) 24-hour ambulatory BP monitoring with a validated oscillometric device in order to assess the presence of a normal blood pressure dipping pattern (DP).[25,26] Hypertension was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg, or the use of any antihypertensive treatment.[27]

A dedicated cardiologist evaluated the cardiac geometry by echocardiography; left ventricular hypertrophy (LVH) was determined according to current clinical practice recommendations.[28]

Carotid ultrasound and duplex scans were performed by a single physician to assess common intima-media thickness (cIMT) and to detect atherosclerotic plaques and CS.[29] In details, cIMT was measured using a standard clinical procedure. B-mode ultrasonography was performed on the far wall of the common carotid artery, approximately 1 cm proximal to the carotid bifurcation, in end-diastolic frames. For each side (right and left), longitudinal views were obtained, and whenever possible, thickness was assessed using the manufacturer's semiautomated edge-detection software. If the software was not available, 3 measurements were taken at 3 equidistant points, and the average of these values was calculated for each side. The primary value used for analysis was the mean of the right and left common carotid artery cIMT. Focal atherosclerotic plaques were identified as focal thickening ≥1.5 mm or a focal increase of ≥50% compared with the adjacent wall. Areas with focal atherosclerosis were excluded from cIMT calculations. A cIMT above 1 mm was considered abnormal, as it is associated with an increased risk of cardiovascular events.[30]

At enrolment, data were collected on BMI, gender, smoking habit (1-9 cigarettes/d), fasting glucose (FG), glycated hemoglobin (HbA1C), adrenocorticotropic hormone (ACTH), serum cortisol at 8:00 AM, urinary free cortisol (UFC), and the presence of dyslipidemia. Dyslipidemia was defined as serum triglyceride levels ≥150 mg/dL, total cholesterol >200 mg/dL, or high-density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women, or the use of lipid-lowering therapy.[31]

On a separate day, the cortisol levels after the 1 mg suppression test (F-1mgDST) were determined by measuring serum cortisol at 9:00 AM following oral administration of 1 mg dexamethasone at 11:00 PM the previous evening. Hypercortisolism was defined as F-1mgDST >1.8 μg/dL (50 nmol/L) on 2 separate tests. Only patients who tested positive to both tests have been considered affected by hypercortisolism.

Blood and urine samples were stored at −80 °C until analysis. ACTH and cortisol levels were measured using electro-chemiluminescence immunoassay (Elecsys II, Roche Diagnostics). The intra- and interassay coefficients of variation for all assays were <5 and 10%, respectively.

Statistical Analysis

The primary end point of the study was to assess the prevalence of hypercortisolism in unselected adult patients with hypertension. Secondary end points were to evaluate the differences in terms of cIMT, LVH, CS, and DP between patients with hypercortisolism and those without, and if the degree of cortisol secretion was associated with the parameters of early cardiometabolic risk.

In a previous study, patients with hypertension had an 8% prevalence of subclinical hypercortisolism.[18] Based on these data, the sample of 106 subjects provides a reasonable estimate, with a 95% CI and an approximate margin of error of ±5% to 6%.

Statistical analyses were performed using SPSS version 28.0 (IBM Corporation) and GraphPad Prism version 9 (GraphPad). Data are presented as mean ± SD unless otherwise specified. Normality of distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were compared using *t* test or the Mann-Whitney *U* test, as appropriate, and differences among groups were analyzed by one-way ANOVA. Categorical variables were compared using the χ^2 test or Fisher exact test.

Pearson or Spearman correlations were used to assess the associations between the parameters of HPA axis activity (ie, F-1mgDST, ACTH, and UFC) and FG, HbA1C, and cIMT.

The receiver operating characteristic (ROC) curve was used to evaluate the association between the HPA axis parameters and the variables that were found to be different between patients with hypercortisolism and those without hypercortisolism.

Then, for the statistically significant associations, the ROC curve identified the F-1mgDST and/or ACTH and/or UFC cut-offs and their areas under the curve with its 95% CI with the best diagnostic accuracy in individuating the presence of these outcomes.

Logistic regression analyses were performed to determine whether significant associations and their odds ratio (OR) and 95% CI were independent of potential confounders.

Clinical characteristics were then compared according to the F-1mgDST cut-off identified by ROC analysis.

A *P* value <.05 was considered statistically significant.

Results

Eight patients (7.5%) were diagnosed with hypercortisolism. In all cases, hypercortisolism was confirmed by repeat testing performed within 3 months of the initial diagnosis. Among these patients, 3 had adrenal lesions demonstrated at computed tomography (1 patient with a 1.5 cm right adrenal mass, 1 patient with a 2 cm left adrenal mass, and 1 patient with bilateral 2 cm adrenal masses), 2 were diagnosed with pituitary-dependent hypercortisolism (both with a 0.6 mm pituitary lesion at nuclear magnetic resonance), and 3 remain under follow-up without a definitive diagnosis.

Table 1 presents the comparison of clinical and biochemical characteristics between patients diagnosed with hypercortisolism and those without. Hypertensive patients with hypercortisolism were significantly older than patients without hypercortisolism and had higher prevalence of altered DP. They also exhibited higher FG levels, HbA1C, and cIMT, had a higher prevalence of pathologic cIMT, and were more frequently treated with 2 or more antihypertensive medications compared with those without hypercortisolism, even after adjusting for age (data not shown). At variance, BMI, ACTH, UFC, and LVH levels and prevalence of female gender, impaired fasting glucose (IFG)/impaired glucose tolerance (IGT), dyslipidemia, renal function, use of antidyslipidemic drugs, smoking habit, and CS were not different between subjects with and without hypercortisolism. No patient had albuminuria >30 mg/24h.

F-1mgDST levels were directly associated with both cIMT and HbA1C (R = 0.230, *P* = .018; and R = 0.312, *P* = .002, respectively). No other significant associations were observed between HPA axis indexes and cardiometabolic risk parameters (ie, fasting glucose, HbA1C, and cIMT). Logistic regression analysis revealed that F-1mgDST levels were independently associated with increased cIMT after adjusting for age, sex, BMI, smoking status, and the presence of IFG/IGT (Table 2). No significant associations were found between F-1mgDST levels and the presence of CS or LVH, nor between ACTH or UFC levels and cIMT, DP, CS, or LVH.

F-1mgDST levels were predictive of increased cIMT (area under the curve = 0.766 ± 0.09, *P* = .003) as shown by ROC curve (Fig.). The optimal F-1mgDST cut-off value for predicting increased cIMT was identified as 1.14 μg/dL (31.4 nmol/L). Table 3 presents the clinical and biochemical characteristics of hypertensive patients stratified by F-1mgDST levels, comparing those with values ≥1.14 μg/dL (31.4 nmol/L) to those with values <1.14 μg/dL (31.4 nmol/L). Patients with F-1mgDST levels ≥1.14 μg/dL were older and had a lower BMI, a higher frequency of using ≥2 antihypertensive drugs, increased cIMT, and a higher prevalence of pathologic cIMT and

Table 1
Characteristics of Hypertensive Patients Diagnosed With Hypercortisolism and of Patients Without Hypercortisolism

Variables	All (n = 106)	Nonhypercortisolism (n = 98)	Hypercortisolism (n = 8)	P
Age (y)	57.4 ± 8.2 (37-70)	56.9 ± 8.2 (37-70)	63.0 ± 4.7 (57-69)	**.040**
BMI (kg/m^2)	25.4 ± 3.4 (17.5-34.9)	25.5 ± 3.4 (17.5-34.9)	24.4 ± 3.1 (20.0-29.7)	.386
GFR (mL/min)	88.5 ± 13.8 (60-116)	89.1 ± 13.3 (60-116)	80.1 ± 17.0 (63-105)	.08
F-1mgDST (μg/dL)	0.96 ± 0.44 (0.05-2.49)	0.86 ± 0.28 (0.05-1.44)	2.14 ± 0.22 (1.86-2.49)	**<.001**
ACTH (pg/mL)	28.4 ± 15.1 (5.4-63.8)	28.4 ± 14.7 (7.9-63.8)	28.0 ± 19.8 (5.4-63.8)	.932
UFC (μg/24hr)	56.2 ± 23.7 (12.4-132.0)	57.1 ± 23.7 (12.4-132.0)	45.9 ± 22.4 (18.4-76.0)	.386
Smoking habit (n)	13 (12.3)	12 (12.2)	1 (12.5)	.662
Women (n)	53 (50.0)	49 (50.0)	4 (50.0)	.642
Fasting glucose (mg/dL)	95.9 ± 10.7 (73.0-126.0)	95.2 ± 10.1 (73.0-126.0)	104.5 ± 15.4 (86-123.0)	**.018**
HbA1C (%)	5.4 ± 0.3 (4.7-6.5)	5.4 ± 0.3 (4.7-6.5)	5.6 ± 0.5 (5.1-6.4)	**.032**
IFG/IGT (n)	30 (37.5)	27 (27.6)	3 (37.5)	.405
Antihypertensive drugs (0/1/2/3/4)	9/28/51/13 (8.5/26.4/48.1/12.3/4.7)	9/26/49/11/3 (9.2/26.5/50.0/11.2/3.1)	0/2/2/2/2 (0.0/25.0/25.0/25.0/25.0)	**.024**
≥2 Antihypertensive drugs (n)	18 (17.0)	14 (14.3)	4 (50.0)	**.027**
Dyslipidemia (n)	70 (66.0)	63 (64.3)	7 (87.5)	.174
Antidyslipidemic drugs (0/1/2)	81/20/5 (76.4/18.9/4.7)	77/16/5 (78.6/16.3/5.1)	4/4/0 (50.0/50.0/0.0)	.244
cIMT (mm)	0.80 ± 0.18 (0.50-1.50)	0.79 ± 0.18 (0.50-1.50)	0.94 ± 0.17 (0.60-1.10)	**.031**
cIMT >1 mm (n)	11 (11.3)	7 (7.8)	4 (57.1)	**.003**
Carotid stenosis (n)	40 (40.4)	37 (40.2)	3 (42.9)	.594
Altered DP (n)	21 (26.3)	16 (22.2)	5 (62.5)	**.026**
LVH (n)	22 (25.3)	2 (40.0)	20 (24.4)	.372

Abbreviations: ACTH = adrenocorticotropic hormone (n.v.: 5-55 pg/mL); BMI = body mass index; cIMT = carotid intima-media thickness (assessed in 97 patients, 7 with hypercortisolism, 90 without hypercortisolism); DP = blood pressure dipping pattern (assessed in 80 patients, 8 with hypercortisolism, 72 without hypercortisolism); F-1mgDST = cortisol levels after the 1 mg dexamethasone suppression test; GFR = glomerular filtration rate; HbA1C = glycated hemoglobin; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; LVH = left ventricular hypertrophy (assessed in 87 patients, 5 with hypercortisolism, 82 without hypercortisolism); UFC = urinary free cortisol (n.v. 10-130 μg/24hr).
Carotid stenosis was assessed in 99 patients (7 with hypercortisolism, 92 without hypercortisolism).
Categorical variables are reported as absolute number with percentage in parentheses. Continuous variables are reported as mean ± SD with range in parentheses. Boldface values indicate statistically significant differences.

Table 2
Association Between Altered cIMT Levels With F-1mgDST Levels After Adjusting for Age, Sex, BMI, Smoking Status, and the Presence of IFG/IGT

Variables	OR	95% CI	P
F-1mgDST (1 μg/dL increase)	14.00	2.70-72.48	**<.002**
Age (1-y increase)	1.00	0.94-1.00	.936
Gender (women)	2.19	0.46-10.45	.327
BMI (1 kg/m^2 increase)	1.18	0.92-1.52	.204
Smoking status (presence)	1.95	0.29-13,23	.496
IFG/IGT (absence)	0.26	0.03-2.00	.197

Abbreviations: Altered cIMT = carotid intima-media thickness ≥1 mm; BMI = body mass index; F-1mgDST = cortisol levels after the 1 mg dexamethasone suppression test; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OR = odds ratio.
Boldface values indicate statistically significant differences.

altered DP, compared to those with F-1mgDST <1.14 μg/dL. Smoking habits, gender distribution, fasting glucose and HbA1C levels, prevalence of dyslipidemia, use of lipid-lowering drugs, and the presence of CS and LVH did not differ between the 2 groups.

The logistic regression analysis showed that F-1mgDST levels ≥1.14 μg/dL (31.4 nmol/L) were independently associated with increased cIMT (Table 4) but not with CS (OR 2.08, 95% CI 0.78-5.55, P = .142), altered DP (OR 2.20, 95% CI 0.73-7.28, P = .157), or LVH (OR 1.53, 95% CI 0.41-5.70, P = .524), after adjusting for age, sex, BMI, smoking status, and the presence of IFG/IGT.

Discussion

This study aimed to evaluate the prevalence of hypercortisolism in hypertensive patients and to investigate the possible association between the degree of cortisol secretion and early cardiometabolic risk parameters. We found that 7.5% of hypertensive patients referred to our hypertension clinics were affected by hypercortisolism. Patients with hypercortisolism were more frequently treated with at least 2 antihypertensive drugs and more often presented with IFG and/or IGT, as well as altered cIMT and DP. Moreover, F-1mgDST levels were associated with cIMT after adjusting for age, sex, BMI, smoking status, and the presence of IFG/IGT. Finally, our data suggest that the optimal F-1mgDST cut-off value for predicting increased cIMT is 1.14 μg/dL (31.4 nmol/L) and that hypertensive patients with F-1mgDST levels ≥1.14 μg/dL (31.4 nmol/L) exhibited a worse cardiometabolic profile as compared with hypertensive patients with F-1mgDST levels <1.14 μg/dL (31.4 nmol/L).

This is the first study to evaluate the prevalence of hypercortisolism in a cohort of hypertensive, nondiabetic, and nonobese patients screened by using the F-1mgDST cut-off of 1.8 μg/dL (50 nmol/L), which is currently adopted for the diagnosis of MACS.[5] Among the 4 available studies on this topic, the reported prevalence of hypercortisolism varies depending on the characteristics of the screened population and the diagnostic criteria applied. In the study by Wang et al,[19] which assessed the prevalence of secondary causes of hypertension using an F-1mgDST threshold of 5 μg/dL (138 nmol/L), the prevalence of hypercortisolism was 0.1% (4 cases of 3003 subjects) . A slightly higher prevalence (2%) was reported by Omura et al[20] in 1020 hypertensive patients, using basal morning cortisol levels >20 μg/dL (551 nmol/L) as an initial screening, followed by F-1mgDST with a cut-off of 3.0 μg/dL (83 nmol/L) in those who screened positive. Conversely, Trifanescu et al[17] found a 7.5% prevalence of hypercortisolism among 80 young hypertensive patients (<40 years), using a F-1mgDST cut-off of 1.8 μg/dL (50 nmol/L), which aligns with our findings. Additionally, in a cohort of 423 patients with treatment-resistant hypertension, screening with an F-1mgDST cut-off of 1.8 μg/dL (50 nmol/L), combined with 2 elevated late-night salivary cortisol measurements, revealed a prevalence of hypercortisolism of 8%.[18] Importantly, in all above-mentioned study diabetes was not among the exclusion criteria.

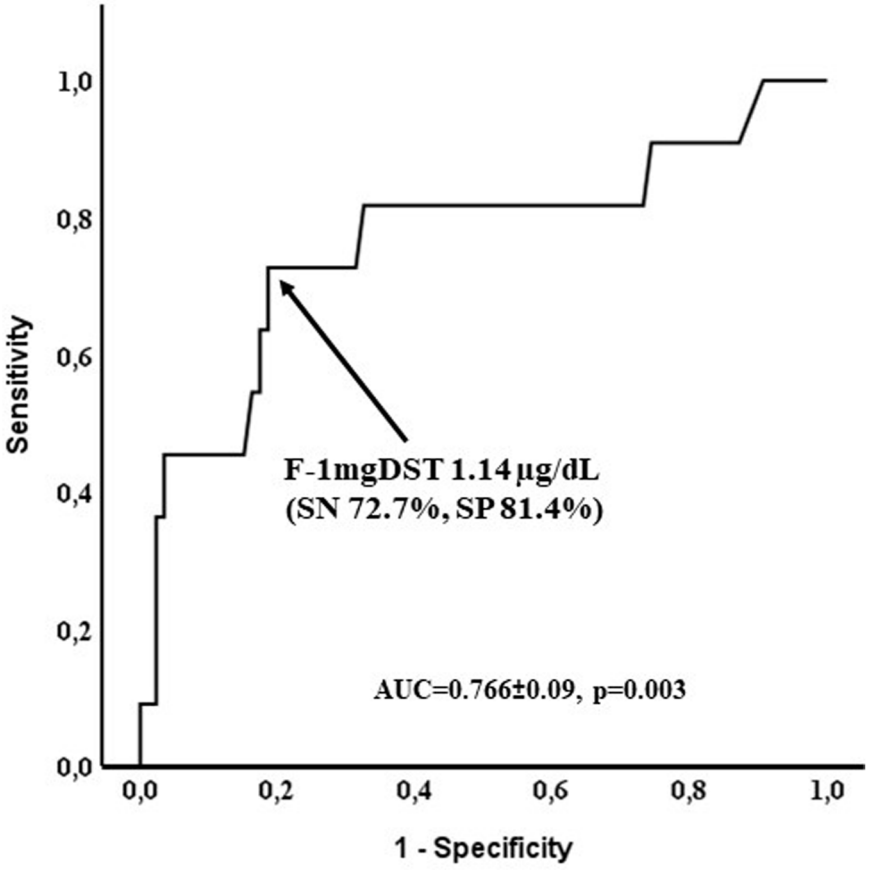

Fig. Receiver operating characteristic curve analysis showing the association between F-1mgDST levels and pathologic cIMT. Pathologic cIMT is defined as >1 mm. AUC = 0.819 ± 0.076, $P < .0001$. The optimal F-1mgDST cut-off value for predicting increased cIMT was identified as 1.14 µg/dL (31.4 nmol/L). *AUC* = area under the curve; *cIMT* = carotid intima-media thickness; *F-1mg DST* = cortisol levels after the 1 mg dexamethasone suppression test; *SN* = sensitivity; *SP* = specificity.

Table 3
Comparisons Between Hypertensive Patients With F-1mgDST <1.14 (31.4 nmol/L) and Patients With F-1mgDST ≥1.14 (31.4 nmol/L)

Variables	F-1mDST <1.14 ($n = 78$)	F-1mgDST ≥1.14 ($n = 28$)	*P*
Age (y)	56.3 ± 8.0 (37-70)	60.4 ± 7.6 (43-69)	**.018**
BMI (kg/m^2)	25.8 ± 3.5 (17.5-34.9)	24.1 ± 2.9 (18.6-29.7)	**.025**
F-1mgDST (µg/dL)	0.76 ± 0.28 (0.05-1.11)	1.52 ± 0.42 (1.14-2.49)	**<.001**
ACTH (pg/mL)	29.3 ± 14.9 (7.9-63.8)	26.1 ± 15.7 (5.4-63.8)	.331
UFC (µg/24hr)	58.6 ± 24.9 (20.4-132.0)	49.8 ± 19.1 (12.4-82.5)	.094
Smoking habit (*n*)	8 (10.3)	5 (17.9)	.293
Women (*n*)	41 (52.6)	12 (42.9)	.378
Fasting glucose (mg/dL)	96.0 ± 10.4 (73.0-126.0)	96.0 ± 11.8 (81-123.0)	.977
HbA1C (%)	5.4 ± 0.3 (4.7-6.5)	5.5 ± 0.4 (5.1-6.4)	.249
IFG/IGT (*n*)	24 (30.8)	6 (21.4)	.347
Antihypertensive drugs (0/1/2/3/4)	8/23/39/7/1 (10.3/29.5/50.0/9.0/1.3)	1/5/12/6/4 (3.6/17.9/42.9/14.3/4.7)	**.015**
≥2 Antihypertensive drugs (*n*)	8 (10.3)	10 (35.7)	**.002**
Dyslipidemia (*n*)	51 (65.4)	19 (67.9)	.813
Antidyslipidemic drugs (0/1/2)	62/13/3 (79.5/16.7/3.8)	19/7/2 (67.9/25/7.1)	.450
cIMT (mm)	0.77 ± 0.16 (0.50-1.50)	0.91 ± 0.19 (0.54-1.30)	**.001**
cIMT >1 mm (*n*)	3 (4.1)	8 (33.3)	**<.001**
Carotid stenosis (*n*)	26 (35.6)	14 (53.8)	**.104**
Altered DP (*n*)	12 (20.3)	9 (42.9)	**.044**
LVH (*n*)	16 (24.6)	6 (27.3)	.804

Abbreviations: ACTH = adrenocorticotropic hormone (n.v.: 5-55 pg/mL); BMI = body mass index; cIMT = carotid intima-media thickness (assessed in 97 patients, 7 with hypercortisolism, 90 without hypercortisolism); DP = blood pressure dipping pattern (assessed in 80 patients, 8 with hypercortisolism, 72 without hypercortisolism); F-1mgDST = cortisol levels after the 1 mg dexamethasone suppression test; HbA1C = glycated hemoglobin; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; LVH = left ventricular hypertrophy (assessed in 87 patients, 5 with hypercortisolism, 82 without hypercortisolism); UFC = urinary free cortisol (n.v. 10-130 µg/24hr). Carotid stenosis was assessed in 99 patients (7 with hypercortisolism, 92 without hypercortisolism).
Categorical variables are reported as absolute number with percentage in parentheses. Continuous variables are reported as mean ± SD with range in parentheses. Boldface values indicate statistically significant differences.

Table 4
Association Between F-1mgDST ≥1.14 (31.4 nmol/L) and Altered cIMT Levels After Adjusting for Age, Gender, BMI, Smoking Status, and the Presence of IFG/IGT

Variables	OR	95% CI	*P*
F-1mgDST ≥1.14 (presence)	15.57	2.88-84.29	**.001**
Age (1-y increase)	1.07	0.93-1.14	.624
Gender (women)	2.76	0.53-14.44	.229
BMI (1 kg/m^2 increase)	1.17	0.90-1.53	.238
Smoking status (presence)	1.19	0.15-9.12	.870
IFG/IGT (absence)	0.49	0.08-2.95	.434

Abbreviations: Altered cIMT = carotid intima-media thickness ≥1 mm; BMI = body mass index; F-1mgDST = cortisol levels after the 1 mg dexamethasone suppression test; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OR = odds ratio. Boldface values indicate statistically significant differences.

Overall, the present and previous data suggest that, when using a F-1mgDST cut-off of 1.8 μg/dL (50 nmol/L), in hypertensive patients referred to specialized clinics hypercortisolism may be present in approximately 7% to 8% of cases.

Interestingly, our findings indicate that hypercortisolism should be particularly suspected in patients with pathologic cIMT, altered DP, the need for more than 2 antihypertensive drugs, and the presence of IFG and/or IGT. The results on cIMT and DP are particularly interesting, considering that these parameters were included as secondary end points, whereas the sample size was calculated based on the expected prevalence of hypercortisolism (the primary end point). These observations confirm and expand upon the recommendations of the Position Statement and Consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension, which advises screening for hypercortisolism in hypertensive patients presenting with the following features: age under 40 years, sudden worsening of hypertension, resistant hypertension, altered diastolic function, and significant hypertension-mediated organ damage.[32]

An additional interesting finding of the present study is the correlation between F-1mgDST levels and cIMT values, with an F-1mgDST threshold of 1.14 μg/dL (31.4 nmol/L) being the most accurate cut-off for predicting the presence of pathologic cIMT. Furthermore, F-1mgDST levels ≥1.14 μg/dL (31.4 nmol/L) were independently associated with increased cIMT regardless of age, sex, BMI, smoking status, and the presence of IFG/IGT. This finding is not entirely unexpected, as previous data suggest that an F-1mgDST cut-off of 1.2 μg/dL (33.1 nmol/L) is the most sensitive threshold for predicting cardiovascular risk in patients with adrenal incidentalomas.[33-35] Although somewhat anticipated, the observation that a similar F-1mgDST cut-off (ie, around 1.2 μg/dL or 33.1 nmol/L) is associated with a worse cardiovascular profile in hypertensive patients screened for hypercortisolism reinforces the idea that the currently used F-1mgDST cut-off of 1.8 μg/dL (50 nmol/L) may need to be reconsidered.[35]

The idea that cortisol excess, even if mild, could be associated with hypertension derives from several evidences. The mechanisms involved in the pathogenesis of hypertension in hypercortisolism include alternations in the renin-angiotensin and vasoregulatory systems, as well as mineralocorticoid activity. Indeed, excess cortisol activates the renin-angiotensin system leading to angiotensin receptor signaling dysregulation. It is known that cortisol can bind the mineralocorticoid receptor with relatively similar affinity to aldosterone. However, as plasma cortisol levels are 1000-fold greater than those of aldosterone, in hypercortisolism, excess cortisol can saturate the 11β-hydroxysteroid dehydrogenase enzyme activity, leading to functional mineralocorticoid excess due to cortisol binding and activation of the mineralocorticoid receptors, which, in turn, can affect plasma volume and contribute to increases in BP. In addition, excess cortisol modulates the balance between vasoconstrictors and vasodilators, leading to vascular damage and subsequent increases in BP. Finally, reductions in natriuretic peptides have also been reported, which can lead to salt retention and increased BP.[36]

On the other hand, the association between cortisol levels and cIMT in patients with hypertension is in line with data in patients with hypercortisolism. Indeed, it is known that the fatty streak phase of atherosclerosis begins with endothelial dysfunction and the retention of lipids such as low-density lipoprotein and very low-density lipoprotein in the vascular wall.[37] Excess cortisol, as seen in Cushing syndrome, can contribute to increased fatty acid accumulation, a key mechanism for the development of atherosclerosis.[37-39] Hypercortisolism promotes endothelial dysfunction, evidenced by elevated humoral markers of endothelial impairment in these patients.[40] Additionally, patients with hypercortisolism exhibit increased levels of vascular endothelial growth factor, a potent chemotactic and mitogenic factor for endothelial cells, which promotes neo-angiogenesis within atherosclerotic plaques, contributing to plaque development and stabilization.[40] Moreover, unbalanced adipokines levels may contribute to a low-grade inflammation state, which increases the risk of metabolic aberrations including cardiovascular complications.[41] These mechanisms explain why patients with hypercortisolism demonstrate greater cIMT levels and higher prevalence of carotid plaques compared to both healthy controls and patients with essential hypertension, highlighting the exacerbating effect of cortisol excess on atherosclerotic burden.[42] Therefore, glucocorticoids are considered active players and therapeutic targets in atherosclerotic cardiovascular disease.[38]

We acknowledge the limitations of the present study. First, its cross-sectional design does not allow for conclusions regarding causality. Second, the absence of a control group limits the strength of our findings concerning the prevalence of hypercortisolism in hypertensive patients compared with the general population. However, the fact that the prevalence observed in hypertensive patients is similar to that reported in individuals with unexplained bone fragility or type 2 diabetes[13,43] supports the reliability of our results. Third, the relatively small sample size and the limited number of patients with F-1mgDST levels >1.8 μg/dL constrained our ability to draw definitive conclusions regarding the predictors of hypercortisolism in hypertensive patients. Nonetheless, patients with hypercortisolism more frequently required at least 2 antihypertensive medications and more often presented with IFG and/or IGT, as well as increased cIMT and altered DP. Fourth, the lack of serum dexamethasone measurement could be considered a limitation. However, hypercortisolism was defined based on F-1mgDST >1.8 μg/dL (50 nmol/L) on 2 separate occasions, which helps reduce the risk of false-positive results. The F-1mgDST is anyway considered a test with good diagnostic accuracy even in the absence of dexamethasone determination.[44] Finally, data on the urinary free cortisone/cortisol ratio, as an index of 11β-hydroxysteroid dehydrogenase enzyme activity, and on glucocorticoid receptor gene variants, which influence peripheral cortisol sensitivity, are currently unavailable. From a pathophysiologic perspective, this should be considered a limitation of the study. Indeed, some evidence suggests that in eucortisolemic postmenopausal women, the combined assessment of cortisol secretion, cortisone-to-cortisol peripheral activation, and glucocorticoid sensitivity is associated with the presence of hypertension.[45] However, it should also be noted that the diagnosis of hypercortisolism (both mild and overt) does not require the measurement of cortisone levels or determination of glucocorticoid receptor gene variants.[5,46] Therefore, despite the absence of these data, the clinical relevance of the present findings remains unchanged.

Despite these limitations, our findings are of interest, as they suggest that up to 7.5% of nondiabetic and nonobese hypertensive patients referred to hypertension clinics may be affected by hypercortisolism, particularly those requiring at least 2 antihypertensive drugs and/or presenting with IFG and/or IGT, pathologic cIMT, and altered DP. Moreover, F-1mgDST levels were associated with cIMT with the optimal F-1mgDST cut-off value for predicting increased cIMT being 1.14 μg/dL (31.4 nmol/L).

Larger and prospective studies are warranted to confirm these results. Indeed, if future research demonstrates that cortisol levels below 1.8 μg/dL (50 nmol/L) can still be clinically harmful, treatment criteria may need to be expanded to include patients with biochemical evidence of cortisol excess and relevant comorbidities. Although awaiting robust evidence from large-scale studies, it may be appropriate to screen for hypercortisolism, and monitor for related cardiovascular complications, those hypertensive patients requiring at least 2 antihypertensive medications, with IFG and/or IGT, pathologic cIMT and DP, particularly in the presence of F-1mgDST values above 1.14 μg/dL.

Disclosure

I.C. received consulting fees from Corcept Therapeutics and Esteve. V.F. received honoraria from Corcept Therapeutics as a speaker and from Recordati Rare Diseases for scientific board activities. The other authors have no conflicts of interest to disclose.

Acknowledgment

This work has received support from Istituto Auxologico Italiano, Ricerca Corrente, PRECOR Study (CE 2019_01_29_06).

Author Contributions

A.M. and C.P. are co-first authors and contributed equally to the work.

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