

Gender-related differences in carotid atherosclerosis and flow-mediated dilation in patients with Cushing's disease

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Aim. Patients with Cushing's syndrome have a cardiovascular mortality rate four times higher than the general population. The purpose of this study was to establish any significant difference in cardiovascular morbidity evaluated by Intima-media Thickness (IMT) and endothelial dysfunction (FMD) among a group of patients with Cushing's syndrome and a control group matched for gender, age and classic risk factors for atherosclerosis.

Methods. We retrospectively studied 63 patients (45 females and 18 males) with ACTH-dependent Cushing's syndrome. This group was matched and compared with a control group selected by their anthropometric and metabolic characteristics. All subjects underwent ultrasound of carotid arteries determining the related IMT and of brachial artery for FMD.

Results. Cases presented greater IMT and lower FMD% compared with controls, particularly the women. When the two genders within the group of Cushing's patients were compared, we could find no significant differences in IMT or FMD between males and females. When these results were correlated with atherosclerotic risk factors, FMD was strongly reduced in female Cushing's patients by comparison with the female controls and it correlated closely with dyslipidemia and BMI. Among the males with Cushing's syndrome, the IMT and FMD findings correlated strongly with diabetes.

Conclusion. Our retrospective case-control study indicates that Cushing's patients have a lower FMD and a higher carotid IMT, which

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correlate with their metabolic syndrome and are uninfluenced by gender. For this reason, it is important the control of their endothelial function to prevent atherosclerosis.

KEY WORDS: Cushing's syndrome - Carotid intima-media thickness - Gender.

Cushing's syndrome (CS) is an endocrine disorder characterized by hypercortisolism, possibly caused by exogenous intake or endogenous hypersecretion of cortisol, a situation that may or may not be the result of hypersecretion of ACTH.¹

Hypercortisolism consequences are cardiovascular complications and a four time higher mortality rate than in normal population.² This is related to visceral obesity, systemic arterial hypertension, impaired glucose tolerance, hyperlipidemia and thrombotic diathesis, typical of hypercortisolism.³

Some studies have revealed the prevalence of atherosclerotic lesions only in the acute phase of CS,⁴ others also in the sub-clinical state.⁵ The atherogenic role of cortisol has been clarified in animal models treated with steroids⁶ for long periods, and

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humans chronically on steroid therapy that developed early atherosclerotic lesions.⁷⁻¹¹

Most CS patients have a metabolic syndrome, which is responsible for the progression of their atherosclerosis and for endothelial damage.¹² Color Doppler ultrasound of the carotid district reveals a greater prevalence of plaques in CS patients than in controls^{13, 14} and the cardiovascular risk in CS persists even after 5 years in remission.¹⁵

The syndrome affects females more than males (F:M=8:1) and has certain gender-related differences. Males develop the syndrome in younger age, for instance, while urinary cortisol and ACTH levels are higher in females.

As for clinical symptoms, females have no prevailing symptoms, while males have a catabolic state, osteoporosis, myopathy and *striae rubrae*.

Cardiovascular complications are seen in older age in females, but they tend to develop more quickly than in males and represent the primary cause of death among female Cushing's patients. It is important to remember that aging has also a role.¹⁶

Furthermore, atherosclerotic risk factors differ by gender. Isolated systolic hypertension is more common in females over 45 years of age than in males of the same age, due to menopause.¹⁷ Hyperglycemia and obesity are also more common in middle-aged women than in men of the same age.

Another consideration concerns protective cholesterol levels (C-HDL), which increase with age in women up until menopause, then they drop back. High C-HDL levels have protective effects against cardiovascular disease.¹⁷

LDL cholesterol also increases after menopause. Smoking increases risk for coronary disease in males and females, but has a multiple effect in women taking oral contraceptives.¹⁷ Diabetes mellitus seems to have a stronger effect on cardiovascular risk in women than in men.¹⁷

Based on these observations, we attempted to determine whether cardiovascular risk increases in patients with Cushing's syndrome by comparison with healthy

controls, by assessing their carotid intima-media thickness IMT and measuring their flow-mediated dilation (FMD) in the brachial artery.

We also tried to establish whether there was any gender-related difference in these early signs of atherosclerosis in cases and controls. This last assessment was based on the association among FMD and classic cardiovascular risk factors.

Materials and methods

We studied 63 patients (45 females, 18 males) with ACTH-dependent Cushing's syndrome (61 from pituitary adenoma), only 2 of whom (one male and one female) had ectopic ACTH secretion, during the active phase of disease. Our data were collected from medical records of all the patients attending the Endocrinology Clinic at Padova University between 2000 and 2010. All the subjects had active Cushing's syndrome. For all patients, we recorded the classic atherosclerotic risk factors, such as hypertension, BMI, diabetes or glucose intolerance, hyperlipidemia, and smoking habit. The diagnosis of Cushing's syndrome was based on the following criteria: 1. an increased daily urinary cortisol excretion with inappropriately high plasma ACTH concentrations; 2. a raise in basal serum cortisol concentrations with a loss of the physiological circadian rhythm; and 3. failure of low-dose dexamethasone to induce urinary and serum cortisol, while more than 50% decrease was recorded with high-dose dexamethasone test. All of the Cushing's patients had undergone pituitary NMRI or CT.

To assess the subjects' cardiovascular risk, we examined all the results of color Doppler ultrasound of the carotid (to study IMT) and the brachial artery (for the FMD study). All the vascular tests were conducted at the same center and by the same team.

The control group was composed of subjects matched by age, BMI and cardiovascular risk factors, taking no steroid therapy and referring to the II Medical Clinic at Padova University. We ruled out subjects with

cardiovascular, immunological or endocrinological diseases, or pregnancy.

The experimental protocol was designed and performed according to the principles of the Helsinki Declaration and was approved by the Ethical Committee of the Padua University Central Hospital.

Table I shows the similar characteristics of cases and controls.

Clinical assessments

BMI was calculated as the person's weight divided by their height squared. We considered obesity as a BMI of 30 kg/m² or more, overweight in the range of 25-30 kg/m², and normal weight between 20 and 24 kg/m². Hypertension was diagnosed if the individual's blood pressure was higher than 140/90 mmHg or they were taking antihypertensive therapy.

Laboratory assessments

We considered glycemia, total cholesterol (TC), triglycerides (TG), urinary free cortisol, ACTH and plasmatic cortisol after the dexamethasone test (1 mg).

We classified cases and controls according to whether or not they were: smokers (if they smoked 10 or more cigarettes a day at the time of the assessment or quit less than a month earlier); hypertensive (systolic values >140 mmHg and/or diastolic values >90 mmHg on at least two occasions when measured in a supine position after a 20 minute rest, or the use of antihypertensive medication); obese (BMI >26); diabetic (plasma glucose >126 mg/dL after fasting

on at least two occasions, or >200 mg/dL 2 hours after 75 g oral glucose challenge, and/or the use of anti-diabetic drugs). Insulin resistance was assessed by the homeostasis index (HOMA), calculated by fasting plasma glucose levels (FPG) in mmol/L and fasting plasma insulin levels (FIRI) in μ U/mL (HOMA IR = FPGx μ FIRI/22.5). Their lipid profile was obtained by measuring total HDL and LDL cholesterol, and triglyceride concentrations: hyperlipidemia was classified as fasting venous concentrations of cholesterol >240 mg/dl and or triglycerides >250 mg/dL on at least two occasions, and/or the use of lipid-lowering drugs.

Ultrasound assessment

All subjects underwent color Doppler ultrasound of the carotid artery with an Esaote Technos MP high-definition instrument using a 7.5 MHz annular phased array transducer. All carotid artery districts were divided into three segments (inferior, medial and superior) with a 60° angle of incidence. Two technicians completed the exams and a third operator reviewed the images acquired.

Two parameters were considered for each arterial district, *i.e.*, IMT (in mm) and the extent of atherosclerotic lesions, expressed as the percentage of stenosis in the vascular lumen. IMT was measured using the method described by Pignoli *et al.*¹⁸

FLOW-MEDIATED BRACHIAL ARTERY DILATION

FMD measurements are widely accepted as a valid indicator of endothelial function

TABLE I.—Characteristics of examined subjects.

	Females		Males	
	Cases (45)	Controls (45)	Cases (18)	Controls (18)
Mean age	42.1±13.9	41.6±13.8	43.2±13.7	42.7±14.6
BMI	27.5±5.1	25.6±4.0	28.4±5.1	27.4±4.7
Hypertension% (>140/90 mmHg)	51	50	61	61
Dyslipidemia% (CT and/or TG)	38	38	56	50
Smokers %	22	22	67	65
IGT or diabetes %	42	38	39	33

BMI: body mass index, IGT: impaired glucose tolerance; CT: total cholesterol; TG: triglycerides.

and FMD is considered one of the earliest signs of atherosclerosis.¹⁹ The procedures adopted were those described in the Guidelines of the International Brachial Artery Reactivity Task Force.²⁰ We did not perform FMD endothelium-dependent vasodilatation with nitroglycerin because insulin-resistance limits it, and it is impaired in diabetics subjects.^{21, 22}

Statistical analysis

IMT and FMD findings were compared using Student's two-tailed t-test for matched data. Data are given as mean \pm SD. Statistical significance was assumed where $p < 0.05$.

Results

Cases and controls had a similar cardiovascular risk profile.

Among the Cushing's cases, there were more male than female smokers (67% *versus* 22% of women) and this male subgroup also contained more cases of hypercholesterolemia (56% *versus* 38% in women) and hypertension (61% *versus* 51% of the females) (Table I). HOMA index was available only in cases (3.0 \pm 1.8).

Comparison of color Doppler ultrasound

findings between women with CS *versus* women without Cushing's syndrome, and between the men with CS *versus* men without the syndrome demonstrated that FMD was significantly reduced in the Cushing's patients of both genders. IMT was significantly greater in Cushing's patients in common carotid arteries (Table II).

When the CS group was considered alone, there was no difference in the IMT or FMD between males and females (Table III), and risk factors that seemed to correlate with FMD were glucose intolerance/diabetes and HOMA index in females ($p < 0.04$, $p < 0.01$) and smoking habit in males ($p < 0.02$).

In control group, men had a higher IMT and a more severely reduced FMD than females. FMD seemed to correlate with age ($p < 0.0001$) and dyslipidemia in females ($p < 0.02$).

Comparing the changes in FMD between CS cases and controls in terms of their atherosclerotic risk factors we discovered a reduced FMD in females (both CS cases and controls) was closely connected to a higher BMI ($p < 0.0006$), dyslipidemia ($p < 0.004$) and smoking ($p < 0.02$), while for males (both cases and controls) the correlation was with glucose intolerance/diabetes ($p < 0.05$) (Table IV).

Among the subjects under 50 years old,

TABLE II.—Intima-media thickness (IMT) and flow-mediated dilation (FMD) in female and male cases and controls.

	Female			Male		
	Cases	Controls	P	Cases	Controls	P
IMT-CC mm	0.9 \pm 0.3	0.7 \pm 0.2	0.0009	0.9 \pm 0.2	0.8 \pm 0.2	0.01
IMT-B mm	0.8 \pm 0.3	0.8 \pm 0.2	ns	0.9 \pm 0.3	0.9 \pm 0.2	ns
IMT-ICA mm	0.8 \pm 0.3	0.8 \pm 0.2	ns	0.9 \pm 0.3	0.9 \pm 0.2	ns
FMD %	12.3 \pm 5.2	23.9 \pm 12.6	0.000003	10.06 \pm 3.9	15.5 \pm 6.2	0.04

CC: common carotid artery; B: bulb; ICA: internal carotid artery.

TABLE III.—Intima-media thickness (IMT) and flow mediated dilation (FMD) in female and male Cushing's patients and in female and male controls.

Cushing males/females	IMT-CC mm	IMT-B mm	IMT-ICA mm	FMD %
P	n.s.	n.s.	n.s.	n.s.
Controls males/females	IMT-CC	IMT-B	IMT-ICA	FMD
P	0.03	0.009	0.03	0.008

IMT: intima-media thickness; CC: common carotid artery; B: bulb; ICA: internal carotid artery.

TABLE IV.—Correlation between reduced flow-mediated dilation (FMD) and atherosclerotic risk factors in female and male cases and controls.

	Female	Male	
	Cases/Controls	Cases/Controls	Cases/Controls
BMI>25	P<0.0006	BMI>25	P<0.02
Dyslipidemia	P<0.004	Hyperglycemia	P<0.05
Smoking	P<0.02	Smoking	P<0.003

TABLE V.—Reduction in flow-mediated dilation (FMD) in cases and controls and age: gender-related differences.

FMD	Controls	Cases
M<50 years	17.4±6.0	14.3±5.0
F<50 years	28.1±12.8	16.6±1.6
P	<0.001	<0.01
M>50 years	12.4±5.4	11.2±3.2
F>50 years	14.7±5.3	12.2±2.2
P	ns	ns

male controls had a greater (reduction) FMD than the females controls; beyond this age, gender-related differences in FMD were less evident (Table V). Much of the same findings applied to CS cases, but the differences were less marked (Table V).

Discussion

Our study on 63 cases of Cushing's syndrome aimed to identify early cardiovascular changes and gender-related differences and to correlate them with classic atherosclerotic risk factors by comparison with a homogeneous control group.

Our study was retrospective, therefore we chose a control group with no cardiovascular diseases and with strong similarity to our CS cases. This enabled us to see if issues other than classic atherosclerotic risk factors might influence the evolution of atherosclerosis in Cushing's patients, also depending on gender.

Our results showed that CS patients have early markers of atherosclerosis, such as a reduced FMD and an increased IMT, with no gender-related differences (which were identified instead in controls). We did not make flow-mediated dilation of brachial artery in these patients because it is now accepted that this parameter can be im-

paired if subjects are diabetics like Cushings^{21, 22} even if some authors did it.²³ Risk factors relating to these findings were an increased glycemia and insulin resistance in women and smoking in men. These findings confirm the value of insulin resistance in the process of endothelial dysfunction and atherosclerotic damage.²⁴ Our data should be considered with caution, however, because our group of CS cases included fewer males (due to the fact that Cushing's syndrome has a female predilection, and that males were three times more likely to be smokers than females).

Our data on differences in blood glucose levels seems to be of greater interest because this risk factor carried the same weight in the two cases group (males and females) and the literature indicates a higher prevalence of glucose intolerance among women after menopause than men.²⁵

In our control group, there were relevant gender-related differences and the correlation between atherosclerotic risk factors was more evident in older women, with high blood lipid and glucose levels. These findings are consistent with recent reports that menopause marks the time when cardiovascular risk becomes the same in men and women.²⁶

IMT in the carotid district was greater in Cushing's patients than in controls, par-

ticularly in common carotid artery. This condition has already been reported in literature,²⁷ but it becomes more significant considering that our CS cases were a mean of 41 years old and their gender did not influence the result.

FMD is an early marker of atherosclerosis, so we attempted to establish whether it correlated with the classic atherosclerotic risk factors. Comparing FMD in CS cases *versus* controls revealed a correlation with all risk factors, but no gender-related differences. Correlation was stronger in older women, BMI and dyslipidemia than in men. These results are consistent with current literature;²⁸ a high BMI and central obesity are important triggers for metabolic syndrome and hormone changes are responsible for a greater cardiovascular risk (increasing IMT and decreasing FMD). Gender and age also influence cardiovascular risk.²⁹ We did not find a correlation with hypertension and cases, like reported in literature,³⁰ probably because all were in treatment with two or three drugs. Literature indicates a correlation between age and carotid artery IMT while females are at lower cardiovascular risk than males, but only until menopause; this risk increases in women with metabolic syndrome.³¹

Conclusions

Our retrospective case-control study demonstrates that Cushing's patients have a reduced FMD and an increased IMT in the carotid district - results that cannot be explained by the metabolic syndrome alone.

The changes in the carotid arteries were not found gender-dependent in cases of CS, in contrast with the condition of general population. This is due to their hypercortisolism *per se*. In older women, metabolic syndrome may have a stronger influence in reducing FMD than in males, thus predisposing them to cardiovascular events.

The early identification and treatment of Cushing's syndrome is mandatory. In particular, treating metabolic syndrome in meno-

pause may prevent the progression of atherosclerosis, improving these patient's prognosis *quoad vitam e quoad valetudinem*.

Riassunto

Differenze genere-correlate nell'aterosclerosi carotidea e dilatazione flusso-mediata in pazienti con malattia di Cushing

Obiettivo. I pazienti affetti da m. di Cushing presentano una mortalità cardiovascolare quattro volte maggiore rispetto la popolazione generale. Lo scopo di questo studio è stato quello di valutare l'incidenza di precoci lesioni aterosclerotiche a livello del distretto carotideo e brachiale mediante studio dell'intima-media thickness (IMT) e della flow mediated dilation (FMD) in un gruppo di soggetti affetti da m. di Cushing appaiati a controlli per sesso, età ed i comuni fattori di rischio per l'aterosclerosi.

Metodi. Abbiamo pertanto svolto uno studio retrospettivo comprendente 63 pazienti (45 femmine e 18 maschi) con una s. di Cushing ACTH dipendente. Il gruppo è stato appaiato ad un campione di controllo selezionato per caratteristiche antropometriche e metaboliche. Tutti i soggetti hanno eseguito eco-color Doppler delle arterie carotidi per lo studio dell'IMT ed ecografia dinamica dell'a. brachiale per lo studio dell'FMD.

Risultati. I casi presentavano un'IMT maggiore ed una FMD inferiore rispetto i controlli e tale risultato era particolarmente evidente nel sesso femminile. Tra i soggetti di sesso maschile e femminile con Cushing i valori di IMT e di FMD erano comparabili. Valutando poi l'influenza dei fattori di rischio per l'aterosclerosi su questi rilievi, si evidenziava come l'FMD delle femmine dei casi si correlasse con la dislipidemia e il BMI. Viceversa nei casi di sesso maschile, FMD correlava con il diabete mellito.

Conclusioni. Questo studio retrospettivo caso-controllo ha evidenziato come i malati di Cushing presentino precoci alterazioni aterosclerotiche che correlano con la loro s. metabolica e non sono influenzate dal genere. Si propone l'esecuzione precoce di eco-color Doppler nei soggetti affetti da malattia di Cushing al fine di prevenire le note complicanze cardio-vascolari.

PAROLE CHIAVE: Sindrome di Cushing - Intima-media carotidea, spessore - Genere.

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