

Patients with the metabolic syndrome and a disturbed cortisol balance display more microalbuminuria

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Abstract

The objective of this study was to investigate whether patients with the metabolic syndrome (MetS) and an imbalance in cortisol metabolism express increased urinary albumin excretion compared to those patients with metabolic syndrome alone.

Seventy-four patients with MetS were evaluated using a low-dose dexamethasone suppression test (LDDST) to identify disturbed cortisol balance (cortisol levels > 50 nmol/L after LDDST). The level of albumin in the urine was also evaluated.

Disturbed cortisol balance was found in 8% of all evaluated patients with MetS. Microalbuminuria was present significantly more often ($p < 0.01$) in those patients with MetS and an imbalance in cortisol metabolism compared with patients suffering MetS alone (urine albumin: 210 mg/L vs. 26 mg/L, respectively, $p < 0.01$).

A substantial percentage of patients with MetS had inappropriate cortisol homeostasis. Of importance, excretion of urinary albumin was increased in these patients. This observation may indicate that this subgroup within the MetS population has a higher cardiovascular risk and possible increased endothelial dysfunction, with a subsequent need for stricter control to prevent cardiovascular morbidity and mortality.

Diabetes Vasc Dis Res 2008;5:54–8
doi:10.3132/dvdr.2008.010

Key words: disturbed cortisol balance, metabolic syndrome, microalbuminuria

Introduction

The metabolic syndrome (MetS) is a cluster of well known cardiovascular risk factors which results in an additional risk for cardiovascular morbidity and mortality. Patients with the MetS form a heterogeneous group, ranging from mild to severe metabolic expression of the MetS. Coexistence of disturbed cortisol metabolism has been described in several previous reports.^{1–4} Both a neuroendocrine dysfunction of the hypothalamus-pituitary-adrenal (HPA)-axis^{1,2} and disturbed peripheral cortisol metabolism^{3,4} have been suggested to explain this observation of imbalance in cortisol metabolism in the MetS.

Interestingly, an increase in premature cardiovascular disease (such as hypertension and insulin resistance),⁵ atherosclerotic disease (increased intima-media thickness and increased presence of atherosclerotic plaques)⁶ and cardiovascular mortality^{5,6} are related to persistently high levels of cortisol, such as incomplete remission of Cushing's disease.

In line with these observations, we aimed to determine whether, in a cohort of patients with MetS who presented to the cardiovascular prevention clinic, disturbed cortisol balance is expressed and whether microalbuminuria is displayed in this MetS subgroup to a greater extent.

Patients and methods

Study subjects

Seventy-four adult patients with MetS (similar numbers of men and women) were included in our analysis. These subjects had all been previously referred to the Outpatient Cardiovascular Prevention Clinic (Hôpital la Pitié-Salpêtrière, Service d'Endocrinologie-Métabolisme, Paris, France) for evaluation and treatment of MetS. Subjects had no clinical signs of hypercortisolism or other significant diseases such as renal, thyroid or liver disease. No subjects were taking oestrogen or anticonvulsants. Forty-eight subjects (65%) were being treated with statins and/or fibrates. In addition, forty-seven subjects (64%) were on antihypertensive medication. One patient had a major depressive disorder (diagnosed according to DSM-V) and another had an alcohol use disorder and a major depressive disorder (diagnosed according to DSM-V). These two subjects were excluded from the cohort. Insulin resistance and diabetes

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Table 1. Criteria for glucometabolic classification according to the World Health Organization (WHO), based on venous plasma glucose measurements

Glucometabolic category	Classification criteria according to WHO definitions
Impaired fasting glucose	FPG \geq 6.1 and $<$ 7.0 and 2-h PG $<$ 7.8
Impaired glucose tolerance	FPG $<$ 7.0 and 2-h PG \geq 7.8 and $<$ 11.1
Impaired glucose regulation	IFG or IGT
Diabetes mellitus	FPG \geq 7.0 or 2-h PG \geq 11.1

All measurements are given in mmol/L

Key: FPG = fasting plasma glucose; PG = plasma glucose; h = hour

Adapted from Bartnik et al.⁷

were diagnosed in accordance with current World Health Organization (WHO) criteria and were partly based on results obtained after an oral glucose tolerance test, with measurements of fasting glucose and glucose two hours after glucose load.⁷ Table 1 shows the different categories of glucose dysregulation and their cut-off values, as defined by WHO criteria. In this cohort, the MetS was diagnosed according to WHO criteria.⁸

Study design

In all patients a low-dose dexamethasone suppression test (LDDST) was performed, in order to screen for an imbalance in cortisol metabolism. Patients took 10 mg dexamethasone at 23.00 hours and had an assessment of fasting cortisol levels the next morning at 08.00 hours. Levels of serum cortisol that reached 50 nmol/L or more after LDDST were considered to be indicative of disturbed cortisol balance and these patients were described as having abnormal cortisol metabolism.^{9,10} All patients with disturbed cortisol balance and those patients with normal suppression of cortisol after LDDST were classified as group A and group B, respectively.

In both groups, a number of clinical and biochemical cardiovascular variables were assessed. These parameters were used to compare the cardiovascular risk factors between the groups. The parameters were assessed by clinical examination (body weight, waist circumference, height, body mass index, fat mass and free fat mass (measured by Bio Impedance Measurement; BIA), blood pressure, presence of insulin resistance or diabetes) and biochemical parameters (glycosylated haemoglobin [HbA_{1c}], fasting glucose, fasting lipid profile (cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides), high sensitive C-reactive protein (hsCRP), fibrinogen, gamma glutamyl transferase [γ -GT], aspartate aminotransferase [AST], alanine aminotransferase [ALT], thyroid stimulating hormone (TSH) and plasminogen activator inhibitor-1 [PAI-1]). All standard blood analyses were determined by routine clinical laboratory methods. Albumin levels were measured in a 24-hour

collection of urine. Albumin levels between 30–300 mg/24 hour were considered as microalbuminuria.^{11–13}

Statistical analysis

For statistical analysis, the SPSS 9.0 SP4 M software program was used. Descriptive statistics with one-way ANOVA analysis were performed to test significant differences within and between groups. SPSS (9.0 SP4 M) simple bar charts were used to create a histogram of the amount of albumin in the urine in both groups. Significance is presumed if the p value was 0.05 or lower on two-sided testing.

Results

Presence of disturbed cortisol balance

In all, six patients displayed a disturbed LDDST by having a decreased suppression of fasting early morning cortisol. From this observation, it was calculated that 8% of patients had an imbalance of cortisol metabolism combined with MetS.

Patient characteristics

In table 2, characteristics of patients in group A are compared with those in group B. Mean age was 56 years. There were 41 men and 33 women included in the study. Their mean weight was 88 kg, mean waist circumference 106 cm and mean body mass index (BMI) 32 kg/m².

A statistically significant difference was found for fibrinogen (group A vs. group B: 5.4 g/L vs. 4.1 g/L respectively, p value 0.01). A trend was found for hsCRP (group A vs. group B: 10.7 mg/L vs. 5.3 mg/L respectively, p value 0.08).

Statistically significant associations were found between cortisol after LDDST and LDL-cholesterol ($r=-0.24$; $p=0.05$), hsCRP ($r=0.51$; $p=0.000$) and gamma glutamyl transferase (GGT) ($r=0.24$; $p=0.04$).

Microalbuminuria

The level of albumin in the 24-hour urine sample was significantly higher in group A compared to group B (277 mg/L vs. 26 mg/L respectively, $p<0.01$) (figure 1). The presence of microalbuminuria was considerably higher in group A than in group B (5/6 vs. 11/58 respectively, $p<0.01$). Moreover, the cortisol level after LDDST was associated with the presence of microalbuminuria in a statistically significant manner ($r=0.29$; $p=0.02$). The association between cortisol after LDDST and the amount of albumin in the urine was not statistically significant.

Discussion

Disturbances in cortisol homeostasis (in Cushing's syndrome, for example) are associated with a pro-atherosclerotic phenotype (such as central obesity, hypertension, insulin resistance, dyslipidaemia, a pro-thrombotic state and increased inflammation).^{5,6} Conversely, disruption of cortisol metabolism is found in patients with the MetS.^{1–4} In our study, we confirm an increased presence of disturbed cortisol balance in a French population with the MetS (six out of 74 patients, equivalent to 8%). In line with our results, previous studies, in which obese and lean subjects were compared, showed an increased cortisol state in obese individuals.^{1–4}

Table 2. Baseline characteristics of study subjects in group A (MetS and disturbed cortisol balance) and group B (MetS and normal cortisol balance)

	Group A mean n=6	Group B mean n=68	Total population mean	P value
Sex (male/female)	4/2	37/31	74	
Age (years)	62	55	56±8.5	
Weight (kg)	89	88	88.0±13	
Waist circumference (cm)	109	106	106±13	
BMI (kg/m ²)	32	32	32.0±5.2	
% fat mass	37	36	36±9.5	
Insulin resistance or diabetes (% of total population)	67	80	78	
HbA _{1c} (%)	7.1	6.7	6.7±1.8	
Fasting glucose (mmol/L)	7.6	6.6	6.7±2.2	
Systolic BP (mmHg)	145	133	134±19	
Diastolic BP (mmHg)	79	75	76±11	
Total cholesterol (mmol/L)	5.4	6.1	6.3±2.5	
HDL-cholesterol (mmol/L)	1.1	1.2	1.2±0.3	
LDL-cholesterol (mmol/L)	2.8	3.6	3.5±1.3	
Triglycerides (mmol/L)	3.4	3.5	3.5±3.3	
Cortisol after LDDST (nmol/L)	117	30	37±43	†
CEM (nmol/L)	52	443	450±152	
hsCRP (mg/L)	10.7	5.3	5.8±7.2	
Fibrinogen (g/L)	5.4	4.1	4.2±1.2	*
GGT (U/L)	84	57	59±59	
AST (U/L)	35	34	34±11	
ALT (U/L)	40	43	43±25	
TSH (UI/L)	2.4	2.4	2.4±1.5	
PAI-1 (µg/L)	69	65	66±39.6	
Urine albumin (mg/24 hour)	277	26	49±141	†
Microalbuminuria (number of subjects)	5	11 (n=58)	16	†

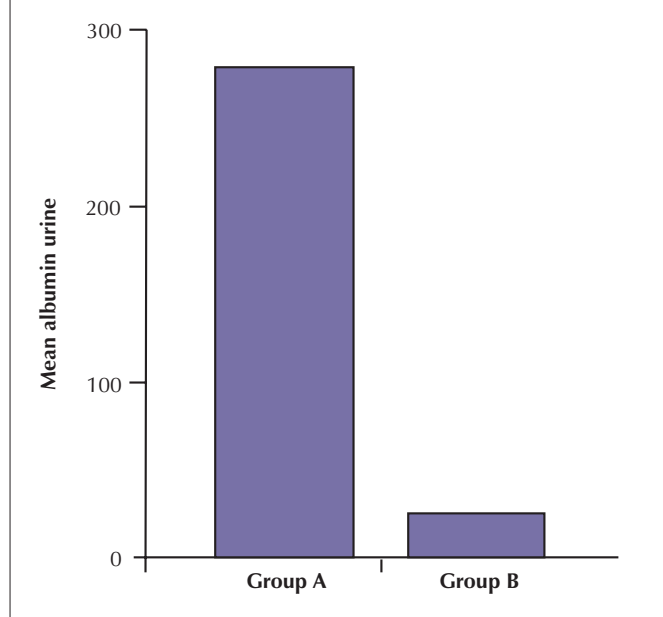
Key: HbA_{1c} = glycosylated haemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; GGT = gamma glutamyl transferase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; TSH = thyroid stimulating hormone; PAI-1 = plasminogen activator inhibitor-1; BMI = body mass index; BP = blood pressure; LDDST = low-dose dexamethasone suppression test; CEM = cortisol early morning; * p<0.05 group A vs. group B; † p<0.01 group A vs. group B

Analysis with LDDST has generally been accepted as a relative simple test which is highly accurate (sensitivity 83–100%,¹⁰ specificity 74–79%¹⁰ and positive predictive value 80%)¹⁴ in screening for disturbed cortisol balances. Since hypercortisolism has to be confirmed with additional testing, our results do no more than suggest a disturbance in cortisol homeostasis. In addition, with the use of LDDST we are not able to specify the level of origin of the inappropriate cortisol homeostasis (HPA axis or adipose tissue).

In our analysis, microalbuminuria was present more often among those patients with the combination of MetS and disturbed cortisol balance. Microalbuminuria may be indicative of diffuse endothelial disease, a key symptom in early atherosclerotic disease. Increased cardiovascular mor-

tality and an increased prevalence of left ventricular hypertrophy are associated with microalbuminuria.^{11–13} Koh *et al.* investigated urinary albumin excretion in patients with Cushing's syndrome.¹⁵ They found that 84.6% of these patients had increased urinary albumin excretion (UAE), which resolved after treatment. The change in UAE was not correlated with changes in blood pressure, plasma glucose and cholesterol levels or with urinary free cortisol after treatment. These findings indicated that endogenous hypercortisolism is a reversible cause of increased UAE. In our population of patients with MetS, it is not possible to be certain that hypercortisolism is present since we only performed one LDDST. However, the finding that a disturbed cortisol balances in 8% of the subjects is significantly associated with

Figure 1. Mean albumin in the urine (mg/24 hour) in group A (metabolic syndrome [MetS] and disturbed cortisol balance) and group B (MetS and normal cortisol balance)



microalbuminuria, remains striking. Disturbed cortisol balance may indicate a higher cardiovascular risk, with the suggestion of endothelial dysfunction.

Moreover, fibrinogen was significantly increased in group A compared with group B. Increased fibrinogen indicates a pro-thrombotic state, which plays a role in the pathogenesis of atherosclerosis. Cortisol might elicit this hypercoagulable state that contributes to early atherosclerosis.¹⁶ In addition, the cortisol level after LDDST was positively associated with hsCRP and GGT. Both microalbuminuria and elevated levels of hsCRP are known predictors for early endothelial damage. GGT seems to be a possible marker for oxidative stress, a critical component of many pathways linked to inflammation.¹⁷ Inflammation, in turn, is a well-known risk factor for early atherosclerosis.

In addition to the described factors that are associated with endothelial damage, one might also expect a difference in PAI-1 levels between group A and B. PAI-1 is involved in the (dys)regulation of the fibrinolytic system and its levels increase in abdominal obesity. In our study, the levels of PAI-1 between groups were very similar. PAI-1 increases with obesity; however, the relation between PAI-1 and cortisol is less clear. In cell culture, PAI-1 levels increase after adding glucocorticoids.¹⁸ *In vivo*, De Pergola *et al.*¹⁹ investigated the possible relationship between cortisol and PAI-1 in obese women. They found a highly significant linear inverse correlation between cortisol excretion rate and both PAI-1 antigen ($r=0.79$; $p<0.001$) and activity ($r=0.77$; $p<0.001$), even after stepwise regression analysis and correction for several variables. The authors even suggest a possible direct inhibitory effect of cortisol on PAI-1 production in obese women, with a possible protective role for the reduced fibrinolytic activity. Other investigations found no relation between cortisol and PAI-1.^{20,21} As the role of cortisol on PAI-1 level

remain uncertain, the factors known to influence the PAI-1 level between groups are the variables of obesity, and these were similar between both groups.

Limitations

Our cohort was limited in size, introducing an increased risk on type II errors. Therefore, additional studies will need to be performed to confirm these retrospective results. Due to the composition of our cohort, patients may have used lipid-lowering medication and anti-hypertensive drugs. However, no differences (in percentage of use of these compounds) were found between both groups and therefore our results suggest a pivotal role for cortisol balance in the development of endothelial dysfunction.

Conclusions

In conclusion, our findings suggest that an imbalance in cortisol metabolism in the presence of MetS causes increased microalbuminuria (suggesting dysfunction of the endothelial wall), increased plasma fibrinogen (suggesting a pro-thrombotic state) and has significant associations with plasma hsCRP and GGT (suggesting a pro-inflammatory state), all part of an increased cardiovascular risk profile. This defined population within the MetS may need a more aggressive approach in the prevention of cardiovascular morbidity and mortality.

Acknowledgement

Miss Sarah Janssen was supported by a European Student Bourse, the "Leonardo Da Vinci Grant", obtained from the French-Dutch Network for Higher Education and Research (<http://www.ufn-fnu.org>).

Conflicts of interest statement

None declared.

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