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Stress-Related Cortisol Secretion in Men: Relationships with Abdominal Obesity and Endocrine, Metabolic and Hemodynamic Abnormalities*

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ABSTRACT

Abdominal obesity has been suggested to be associated with perturbations of the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. In a population of 51-yr-old men (n = 284) salivary cortisol concentrations were determined on repeated (n = 7) occasions over a random working day, and perceived stress was reported in parallel. Cortisol values were then related to reported stress (stress-related cortisol). A standardized lunch was used as a physiological challenge. A low dose (0.5 mg) dexamethasone suppression test was also performed as well as determinations of testosterone and insulin-like growth factor I (IGF-I). Body mass index [weight (kilograms)/height (meters)^2]; waist/hip circumference ratio (WHR); sagittal trunk recumbent diameter (D); fasting insulin; blood glucose; triglycerides; and total, low density (LDL), and high density (HDL) lipoprotein cholesterol were also determined.

Cortisol concentrations were highest in the morning, and lunch was followed by a peak ($P = 0.044$). Two types of diurnal cortisol curves were identified, one characterized by a high variability with high morning values, and another with low variability and low morning values. Both correlated strongly with suppression of salivary cortisol by dexamethasone ($P < 0.001$).

Stress-related cortisol secretion was associated with D ($P = 0.051$), low IGF-I ($P = 0.006$), and diastolic blood pressure ($P = 0.078$). When the type of diurnal cortisol curve was taken into consideration by statistical weighting, stress-related cortisol secretion in subjects with high variability showed associations with testosterone ($P < 0.001$), D, total and LDL cholesterol, diastolic blood pressure ($P < 0.001$), fasting insulin ($P = 0.039$), and glucose ($P = 0.030$) as well as, negatively, triglycerides ($P < 0.001$).

When weighted for a low variability of diurnal cortisol secretion, stress-related cortisol secretion showed strong negative relationships with IGF-I, testosterone, and HDL. Furthermore, strong, consistent relationships (all $P < 0.001$) were found with obesity factors (body mass index, WHR, and D), and with metabolic (insulin, glucose, triglycerides, and total and LDL cholesterol) as well as hemodynamic variables (systolic and diastolic blood pressure and heart rate).

These results clearly show interactions between diurnal cortisol secretion related to perceived stress and anthropometric, endocrine, metabolic, and hemodynamic variables. This seems to occur with apparently normal regulation of the HPA axis (high morning peaks and variability as well as dexamethasone suppression of cortisol), where other endocrine variables are not affected. With a low diurnal cortisol variation and blunted dexamethasone suppression, indicating abnormal regulation of the HPA axis, perceived stress-dependent cortisol values were strongly related to perturbations of other endocrine axes as well as abdominal obesity with metabolic and hemodynamic abnormalities. Perturbations of the regulation of the HPA axis such as those described in combination with low dexamethasone suppressibility are known to follow long term overactivation of the axis by factors such as environmental stress. (*J Clin Endocrinol Metab* **83:** 1853–1859, 1998)

REACTIONS to an environment that is perceived to threaten homeostatic conditions (stress) have been suggested to be of several types (1). One is the fight-flight response with activation of the sympathetic nervous system. This response has been much discussed in the pathogenesis of hypertension (2–4). Another type of reaction has been characterized as depressive or uncontrollable, with feelings of defeat or helplessness as consequences. The endocrine counterpart seems to be activation of the hypothalamic-pituitary-adrenal (HPA) axis with subsequent inhibition of gonadal and GH axes (5, 6).

The results of recent studies have suggested that the HPA axis is hypersensitive and sex steroid and GH secretion are inhibited in obesity with predominance of central, visceral adipose tissue depots (6, 7). The consequences of this will be a frequent overstimulation of the HPA axis, with elevated secretion of cortisol as well as low sex steroid and GH concentrations (5). This is the typical endocrine reaction following stress that is perceived as leading to an uncontrollable situation with defeat and helplessness as consequences (3). Consistent findings of psychosocial and socio-economic handicaps in subjects with centralization of body fat suggest an environment in which such stress reactions might be expected (8–12).

As the individual perception of certain environmental challenges varies, it is of importance to take this factor (coping) into consideration when examining the status of the HPA axis. Single measurements of total or free active cortisol in serum are not informative, because cortisol is secreted in a highly irregular manner, and invasive sampling by itself might be a source of bias. This might be overcome by measurements of urinary output of free cortisol. However, the perception of a stressful environment probably varies over

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different periods of the day and across days, making the consequences of psychological reactions, with activation of the HPA axis, difficult to follow. Furthermore, the difficulty of collecting complete urinary samples throughout the day are considerable. Therefore, new methods to examine these problems need to be developed.

The concentration of free active cortisol in serum is closely mirrored by its concentration in saliva (13). Collection of saliva is noninvasive and can be performed by the proband in his/her everyday life during exposure to perceived stressful events. In addition, such collection can be performed repeatedly in parallel with reports of perceived stress. Such a method was developed and used in the present study.

The time points selected for the collection of salivary cortisol were in the morning, when the HPA axis shows a lively activity, during a physiological stimulus (a standardized lunch), as well as in the evening, when the HPA axis is more quiescent. Perceived stress was reported in association with each cortisol measurement, and stress-related cortisol secretion was calculated. These measurements were then set in relation to body fat mass and distribution as well as the steady state hormonal, metabolic, and hemodynamic abnormalities associated with centralization of body fat stores (6).

Previous findings have suggested a hypersensitive HPA axis in central obesity, a condition with a high risk to develop cardiovascular disease and noninsulin-dependent diabetes mellitus and their risk factors (6, 7). We hypothesized that the HPA axis perturbations are associated with these diseases and their predictors. Therefore, this study was performed in which newly developed techniques for measurements of the status of the HPA axis were developed and used. The results show close connections between the cortisol levels of perceived stress and abdominal obesity and its endocrine, metabolic, and hemodynamic complications.

Subjects and Methods

Study population

In 1992, a cohort of men (n = 1302) was recruited from the National Population Register (Göteborg, Sweden). The target population comprised all men born during the first 6 months of 1944 and living in Göteborg. Between January and June 1992, they were mailed a self-administered questionnaire (11, 12). A total of 1040 men (79.9%) responded to the questionnaire. Based on the self-reported anthropometric measurements, 3 subgroups (each n = 150) of men with the lowest (≤0.885), median (0.94–0.96), and highest (≥1.01) waist/hip circumference ratio (WHR) were selected. They were then invited to a health examination during 1995; 284 (63.1%) volunteered to participate. No man was excluded from the study due to somatic or psychiatric disease. The study was approved by the ethical committee of the medical faculty of the University of Göteborg and by the Swedish Data Inspection Board.

Examinations

All examinations were performed in the morning after an overnight fast, and all examinations were accomplished by the same research nurses and technicians.

Anthropometry. Body weight was measured to the nearest 0.1 kg with participants in underwear, and height was measured to the nearest centimeter. The body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The waist circumference was measured midway between the lowest rib and iliac crest, and the hip circumference was measured at the level of the great trochanters (14). The WHR was calculated as the ratio between the waist and the hip circumferences. The sagittal trunk diameter (D; centimeters) was determined as the distance between the examination table and the highest point of the abdomen in a recumbent position (15).

Diurnal cortisol measurements and self-reported stress. A sampling device called Salivette (Sarstedt, Rommelsdorf, Germany) was used to collect saliva. The Salivette consists of a small cotton swab inside a standard centrifugation tube (13). On a random working day the participants delivered repeated salivary cortisol samples. A sample was obtained in the morning (0800–0900 h), then at 1145 h, and 30, 45, and 60 min after a standardized lunch at 1200 h, 1700 h, and finally just before bedtime. Salivary cortisol was determined by RIA (Orion Diagnostica, Turku, Finland). The lunch was provided by the laboratory and contained 266–277 Cal (protein, 18.2–21.0 g; carbohydrate, 33.6–36.4 g; fat, 5.6–6.5 g). The participants were asked to answer a question about self-perceived stress each hour from 0600–2300 h. This question was formulated: Did you feel any stress during this hour? The perception of stress was registered on a yes-no nominal scale. Such reports during the hours preceding the salivary collections and at the time of collection were used for comparisons with the results of salivary cortisol measurements to obtain a measurement of stress-related cortisol secretion. Careful oral and written instructions were provided to avoid misunderstanding, and the feasibility of the procedures was tested before the study in about 40 men, who were not included in the results.

Dexamethasone suppression test. This test was performed on the next day after the diurnal cortisol measurements. The participants were given two Salivettes and one tablet of dexamethasone (Decadron, MSD, Sweden) of 0.5 mg. They were asked to chew the cotton swab in the morning (0800–0900 h) for 45–60 s. At 2200 h on the second day, the dexamethasone tablet was taken, and the following morning the salivary sampling was repeated. The decrease in salivary cortisol level after dexamethasone administration was calculated as the mean of the two noninhibited morning cortisol levels (before diurnal curve and before dexamethasone test) minus the cortisol level after dexamethasone intake. The dose of 0.5 mg was chosen because we have previously shown (16) that this dose reveals differences that cannot be discovered with the conventionally used dose of 1 mg (17).

Hormones, glucose, and serum lipids. Total serum testosterone was determined by a nonextraction method, where testosterone bound to BSA at C-19 (testosterone-19-carboxymethylether-BSA) was used as the antigen (Testosterone ^{125}I RIA, ICN Biomedicals, Costa Measa, CA). Insulin-like growth factor I (IGF-I) was determined by hydrochloric acid-ethanol (12.5% 2 N HCl-87.5% ethanol) extraction RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA). Insulin was measured by RIA (Pharmacia Insulin RIA 100, Kabi Pharmacia Diagnostics, Uppsala, Sweden). Glucose was determined by a commercially available enzymatic method (18), and serum lipids were determined as described by Wiklund *et al.* (19).

Blood pressure. Two blood pressure measurements were taken, on the right arm with the participants sitting, with a random-zero mercury sphygmomanometer (20). Blood pressure was measured after 5 min of rest and with a 5-min interval and before blood samples were taken. Heart rate was recorded simultaneously. The individual mean systolic and diastolic blood pressures were calculated as the mean of the two measurements.

Physical health status and current medication. The participants were asked to report history of the following diseases, if diagnosed by a physician: 1) angina pectoris, 2) cerebral infarction and/or hemorrhage (stroke), 3) endocrine disorders, 4) hyperlipidemias, 5) hypertension, 6) insulin-dependent diabetes mellitus, 7) myocardial infarction, and 8) noninsulin-dependent diabetes mellitus. In addition, information about their current use of medication (names and doses) was obtained.

Statistical analysis

Standard methods were used to calculate the descriptive statistics. To estimate the covariability between self-reported stress and salivary cortisol levels, we calculated a coefficient (δ) for each individual using the Pearson's product-moment [$\mathrm{Covar}(x, y)/\mathrm{SD}_x \times \mathrm{SD}_y$]. This coefficient ($\delta_i$) is thus an expression of the stress-related cortisol secretion for each individual. Sixty-eight (23.9%) participants indicated no self-perceived

stress, and four (1.4%) reported continuous stress during the registered hours. In such cases the stress variable becomes a constant, and the coefficient (δ) of covariability is not possible to calculate.

Based on the repeated measurements of salivary cortisol (n = 7) for each individual, the within-individual cortisol variance (ν_i) was estimated. As the variance in cortisol secretion is a measurement of the functional status of the HPA axis (21), the greatest weight in the analysis was given to the within-individual cortisol variance (ν_i). In addition, we performed analyses with greater weight given to the inverse within-individual cortisol variance ($\omega_i = 1/\nu_i$). The inversion (reciprocal) of the variance was performed to give the smallest variance a greater weight in the analyses.

Before entering the variables into the analyses, a distribution fitting test was completed. The Kolmogorov-Smirnov goodness of fit test (22) showed that the variables were not compatible with a Gaussian (normal) distribution. Test of possible associations between stress-related cortisol secretion (δ_i) and anthropometric, endocrine, metabolic, and blood pressure measurements were performed with the Spearman's ρ (23). Spearman's ρ can be thought of as the regular Pearson's product-moment correlation coefficient in terms of proportion of variability accounted for, except that Spearman's ρ is computed from ranks (23). Hypothesis testing on the differences in mean rank was performed using the Wilcoxon matched paired, signed rank test (24).

Nonparticipation analyses were performed using tests appropriate to the scale of measurement of each variable (11, 12). The statistical significance was relaxed ($\alpha = 0.10$) to increase the sensitivity to detect potential selection (nonparticipant) bias.

Throughout this report, all confidence intervals and P values are two sided. The level of statistical significance was considered to be the conventional $\alpha = 0.05$. The data analyses were accomplished with SPSS software (SPSS for Windows, release 7.5, SPSS, Chicago, IL).

Results

The men examined in this report were recruited as subgroups of men (n = 1040), who had been examined previously (11, 12). Information from questionnaires was available from all of these men. There were no statistically significant differences in the characteristics of participants (n = 284) and nonparticipants in the subgroups examined here, evaluated from previously obtained information (11, 12), concerning use of anxiolytics, hypnotics, and antidepressant drugs; sleeping disturbances; educational level; and degree of life satisfaction as well as depressive symptoms.

Fifty-five (19.4%) of the participants did not perform the stress-related salivary cortisol measurements for various reasons. However, these subjects did not differ statistically in regard to the anthropometric, endocrine, metabolic, and hemodynamic measurements presented here.

Table 1 presents the physical health status and current use of medication in the total population. Six (2.1%) subjects reported the use of lipid-lowering drugs, and 44 (15.5%) had hypertension. Antidepressant drugs were used by 6 (2.1%) of the men.

Figure 1 shows the average (arithmetic mean) of the cortisol values during the day. The values were highest in the morning, and lunch was associated with an elevation of about 1-h duration. The average of the elevated cortisol concentrations at 30, 45, and 60 min after lunch (mean rank = 117.4) was significantly increased ($z = -2.0$; $P = 0.044$) compared to the cortisol concentration at 1145 h (mean rank = 106.4).

The mean values and SDs (with 95% confidence intervals) of the anthropometric, endocrine, metabolic, and blood pressure measurements are presented in Table 2. The mean salivary cortisol level (n = 7) was 7.41, with a SD of 3.64. Nevertheless, as indicated by the relatively small confidence interval (95% confidence interval, 6.92–7.90), this sample mean can be considered a sufficient estimator of the unknown (true) population means (μ_i).

The unweighted correlations between the stress-related cortisol secretion and anthropometry, endocrine and metabolic measurements, and blood pressure are given in Table 3 in terms of Spearman's ρ. Sagittal recumbent trunk diameter and diastolic blood pressure were positively connected to stress-related cortisol secretion (borderline significance). There was a negative correlation between stress-related cortisol secretion and IGF-I ($\rho = -0.244$; $P = 0.006$).

Table 4 shows the results of the correlations, weighted by the within-individual cortisol variance (ν_i), between stress-related cortisol secretion and anthropometric, endocrine, metabolic, and blood pressure measurements. The within-individual cortisol variance (ν_i) was strongly positively correlated to the dexamethasone suppression test ($\rho = 0.695$; $P < 0.001$; not shown in Table 4). A positive, significant relationship was found between stress-related cortisol secretion and sagittal recumbent trunk diameter, testosterone, fasting insulin and glucose, cholesterol, LDL cholesterol, as well as diastolic blood pressure. Triglycerides were negatively related to stress-related cortisol secretion ($\rho = -0.197$; $P < 0.001$). Furthermore, the cortisol peak after lunch was negatively related to BMI ($\rho = -0.237$; $P < 0.001$), WHR ($\rho = -0.363$; $P < 0.001$), and D ($\rho = -0.304$; $P < 0.001$).

In addition, we performed a similar analysis, with a greater weight given to the inverse within-individual cortisol

TABLE 1. The physical health status and current use of medication in the total study population (n = 284)

Physical health status	No. of subjects/total no. (%)	Medication used	No. of subjects/total no. (%)
Angina pectoris	6/(2.1; 0.8–4.5)	Antidepressant drugs	6/(2.1; 0.8–4.5)
Cerebral infarction and/or hemorrhage (stroke)	3/(1.1; 0.2–3.1)	Angiotensin-converting enzyme inhibitors	8/(2.8; 1.2–5.5)
Endocrine disorders	2/(0.7; 0.1–2.5)	β-Adrenergic antagonists and Ca^{2+} channel blockers	25/(8.8; 5.8–12.7)
Hyperlipidemias	68/(23.9; 19.1–29.3)	Hypnotics, sedatives and neuroleptic drugs	14/(4.9; 2.7–8.1)
Hypertension	44/(15.5; 11.5–20.2)	Insulin	2/(0.7; 0.1–2.5)
Insulin-dependent diabetes mellitus (IDDM)	2/((0.7; 0.1–2.5)	Lipid-lowering drugs	6/(2.1; 0.8–4.5)
Myocardial infarction	4/(1.4; 0.4–3.6)	Oral hypoglycaemic agents	6/(2.1; 0.8–2.5)
Noninsulin-dependent diabetes mellitus (NIDDM)	6/(2.1; 0.8–4.5)	Thyroid drugs	2/(0.7; 0.1–2.5)

Figures within *parentheses* are percentages of the total number of subjects with exact (Fisher's) 95% confidence intervals for the proportions.

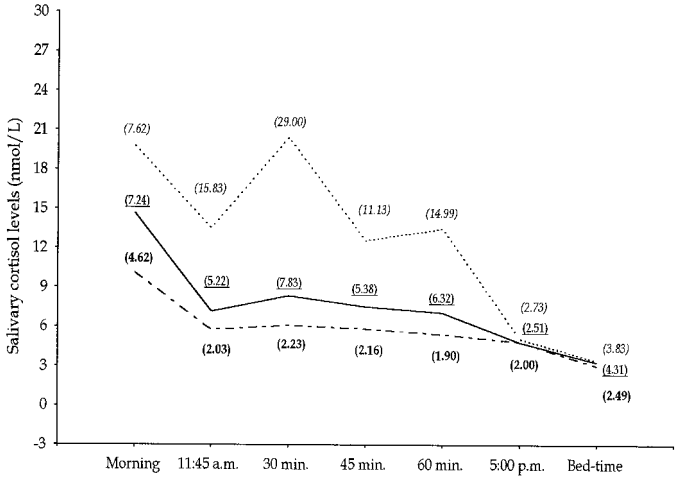

FIG. 1. Salivary cortisol levels (nanomoles per L) over a day (*continuous line*). Lunch was given at 1200 h. Results are given as arithmetic means and SDs (in *parentheses*). The *dashed line* illustrates diurnal cortisol secretion weighted by the inverse within-individual cortisol variance ($\omega_i = 1/\nu_i$; smallest variation), and the *dotted line* illustrates diurnal cortisol secretion weighted by the within-individual cortisol variance (ν_i; largest variation).

TABLE 2. The arithmetic means (SD) with asymptotic 95% confidence intervals of the anthropometric, endocrine, metabolic, and blood pressure measurements

	Mean (SD)	95% CI[a]
BMI (kg/m^2)	26.3 (4.1)	25.8–26.8
WHR	0.94 (0.07)	0.93–0.95
Sagittal trunk recumbent diameter (cm)	22.7 (3.8)	22.3–23.2
Diurnal salivary cortisol level (nmol/L)	7.4 (3.6)	6.9–7.9
Testosterone (nmol/L)	19.7 (5.5)	19.1–20.4
IGF-I (μg/L)	204.6 (64.6)	197.0–212.1
Fasting insulin (mU/L)	12.7 (10.9)	11.5–14.0
Fasting glucose (mmol/L)	4.6 (1.0)	4.5–4.7
Triglycerides (mmol/L)	1.8 (1.1)	1.7–2.0
Cholesterol (mmol/L)	6.2 (1.1)	6.1–6.3
HDL cholesterol (mmol/L)	1.2 (0.3)	1.2–1.3
LDL cholesterol (mmol/L)	4.1 (1.0)	4.0–4.2
Systolic blood pressure (mm Hg)	130.1 (18.0)	128.0–132.2
Diastolic blood pressure (mm Hg)	83.9 (10.8)	82.6–85.2
Heart rate (beats/min)	69.1 (10.6)	67.8–70.3

[a] Confidence interval ($\bar{X}_i \pm 1.96 \times S_E X_i$).

variance ($\omega_i = 1/\nu_i$). Table 5 illustrates such associations between stress-related cortisol secretion and anthropometric, endocrine, metabolic, and blood pressure measurements. The inverse within-individual cortisol variance was strongly negatively correlated to the dexamethasone suppression test ($\rho = -0.695$; $P < 0.001$; not shown in Table 5). A positive, significant relationship was found with BMI, WHR, and sagittal recumbent trunk diameter ($\rho = 0.341$, $\rho = 0.447$, and $\rho = 0.472$, respectively). Fasting insulin and glucose, triglycerides, cholesterol, and LDL cholesterol were also found to be strongly associated with stress-related cortisol secretion. Furthermore, systolic and diastolic blood pressure as well as heart rate showed positive relationships. Inverse significant correlations were found between stress-related cortisol secretion and testosterone, IGF-I, and HDL cholesterol ($\rho = -0.179$, $\rho = -0.331$, and $\rho = -0.244$, respectively). All of these relationships were highly statistically significant

TABLE 3. Spearman's rho (ρ) and P values of the correlations between stress-related cortisol secretion (δ_i) and anthropometric, endocrine, metabolic, and blood pressure measurements

	Stress-related cortisol	
	ρ	P values
BMI (kg/m^2)	0.060	>0.200
WHR	0.056	>0.200
Sagittal trunk recumbent diameter (cm)	0.174	0.051
Testosterone (nmol/L)	0.002	>0.200
IGF-I (μg/L)	−0.244	0.006
Fasting insulin (mU/L)	0.037	>0.200
Fasting glucose (mmol/L)	0.024	>0.200
Triglycerides (mmol/L)	−0.116	0.194
Cholesterol (mmol/L)	−0.028	>0.200
HDL cholesterol (mmol/L)	−0.034	>0.200
LDL cholesterol (mmol/L)	0.084	>0.200
Systolic blood pressure (mm Hg)	−0.004	>0.200
Diastolic blood pressure (mm Hg)	0.157	0.078
Heart rate (beats/min)	0.144	0.107

TABLE 4. Spearman's rho (ρ) and P values of the correlations, weighted by the within-individual cortisol variance (v_i), between stress-related cortisol secretion (δ_i) and anthropometric, endocrine, metabolic, and blood pressure measurements

	Stress-related cortisol	
	ρ	P values
BMI (kg/m^2)	0.069	>0.200
WHR	−0.005	>0.200
Sagittal trunk recumbent diameter (cm)	0.176	0.001
Testosterone (nmol/L)	0.243	<0.001
IGF-I (μg/L)	0.060	>0.200
Fasting insulin (mU/L)	0.113	0.039
Fasting glucose (mmol/L)	0.120	0.030
Triglycerides (mmol/L)	−0.197	<0.001
Cholesterol (mmol/L)	0.223	<0.001
HDL cholesterol (mmol/L)	0.042	>0.200
LDL cholesterol (mmol/L)	0.340	<0.001
Systolic blood pressure (mm Hg)	0.094	0.089
Diastolic blood pressure (mm Hg)	0.303	<0.001
Heart rate (beats/min)	0.001	>0.200

($P < 0.001$). Moreover, the cortisol peak after lunch was positively related to BMI ($\rho = 0.254$; $P < 0.001$), WHR ($\rho = 0.185$; $P < 0.001$), and D ($\rho = 0.277$; $P < 0.001$).

The relationship between BMI and stress-related cortisol secretion, weighted by the inverse within-individual cortisol variance ($\omega_i = 1/\nu_i$), is illustrated in Fig. 2A, and Fig. 2B and C shows similar analyses for WHR and D. As indicated by the confidence bands around the fitted (regression) line, the probability that the true fitted line (in the population) falls between the bands is 0.95.

Discussion

In this study perceived stress was reported and analyzed in relation to salivary, free, active cortisol over a working day under conditions of everyday life in a population of middle-aged men. Cortisol levels were, as expected, higher in the morning, on the average, and were elevated after a standardized lunch, confirming previous information (5). Cortisol concentrations in serum and saliva have been shown to correlate strongly (13), as also demonstrated in our labora-

TABLE 5. Spearman's rho (ρ) and P values of the correlations, weighted by the inverse within-individual cortisol variance ($\omega_i = 1/v_i$), between stress-related cortisol secretion (δ_i) and anthropometric, endocrine, metabolic, and blood pressure measurements

	Stress-related cortisol	
	ρ	P values
BMI (kg/m^2)	0.341	<0.001
WHR	0.447	<0.001
Sagittal trunk recumbent diameter (cm)	0.472	<0.001
Testosterone (nmol/L)	−0.179	<0.001
IGF-I (μg/L)	−0.331	<0.001
Fasting insulin (mU/L)	0.394	<0.001
Fasting glucose (mmol/L)	0.426	<0.001
Triglycerides (mmol/L)	0.179	<0.001
Cholesterol (mmol/L)	0.350	<0.001
HDL cholesterol (mmol/L)	−0.244	<0.001
LDL cholesterol (mmol/L)	0.374	<0.001
Systolic blood pressure (mm Hg)	0.306	<0.001
Diastolic blood pressure (mm Hg)	0.387	<0.001
Heart rate (beats/min)	0.313	<0.001

tory (not shown), verifying the usefulness of measurements of salivary cortisol. Furthermore, this sampling method made it possible to measure cortisol concentrations under the everyday conditions that the participants were experiencing without the interference of invasive procedures in the artificial surroundings of a research laboratory. Reports in parallel with the cortisol sampling allowed an evaluation of the relationship between perceived stress and cortisol concentration and was designed to follow the reactions in the natural milieu of the participants.

The variability of the cortisol values in individuals was dominated by the difference between morning and evening values, as shown in Fig. 1. A high variability is thus a sign of the typical normal diurnal curve, with peaks in the morning and low values in the evening. In contrast, a low variability with a flattened curve indicates diminished differences between morning and evening values due to lower morning and/or higher evening concentrations.

The HPA axis is regulated by feedback inhibition from central glucocorticoid receptors, which, when occupied by glucocorticoids, diminish or totally inhibit the activity of the axis. This can be tested by administration of dexamethasone and subsequent measurements of inhibition of cortisol secretion. The variability of diurnal cortisol secretion and the degree of dexamethasone suppression after a dose of 0.5 mg showed strong correlations. This means that high morning and low evening values of cortisol, indicating an intact HPA axis, were followed by effective dexamethasone suppression. In contrast, a flattened diurnal curve was associated with higher levels of cortisol after dexamethasone administration. Thus, normal or diminished plasticity of HPA axis regulation was found, using two different, independent methods. A flattened diurnal cortisol curve as well as a diminished dexamethasone suppression are both considered to be consequences of frequently repeated or chronic challenges of the HPA axis by factors such as environmental stress (21, 25).

Cortisol concentrations in saliva were measured repeatedly in relation to perceived stress. The relationship between these two variables was calculated over the day as an average

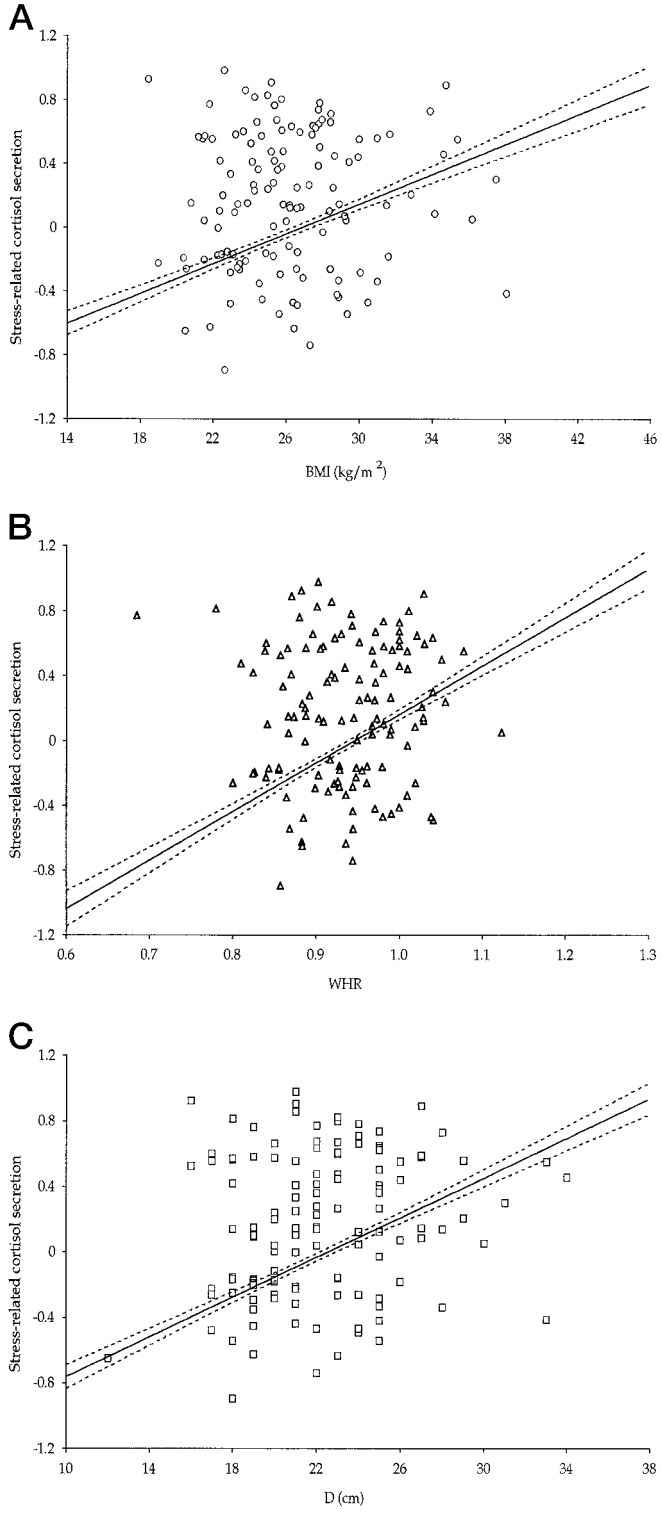

FIG. 2. The relationship between stress-related cortisol secretion (δ_i) and BMI (kilograms per meter squared; a), WHR (b), and D (centimeters; c), weighted by the inverse within-individual cortisol variance ($\omega_i = 1/v_i$). The *dashed lines* represent 95% confidence bands.

index of stress-related cortisol secretion. A high index indicates that a given degree of perceived stress is associated with an elevated cortisol response due to HPA axis activation and

vice versa. Such stress-related cortisol secretion would be expected to be different depending on the status of the HPA axis. This initial characterization of the HPA axis summarized above, showing that normal or deficient diurnal regulation correlated with normal or deficient feedback control, provided such an opportunity. Therefore, when associations were sought between stress-related cortisol secretion and anthropometric, endocrine, metabolic, and hemodynamic variables, the basic status of the HPA axis was weighted into these analyses. Significant associations were then found with signs of both a normal and a blunted activity of the HPA axis. However, the relationships were consistently stronger in men with a flattened diurnal curve and a blunted suppression by dexamethasone and comprised negative relationships with testosterone, IGF-I, and HDL and strong positive relationships to all other measured anthropometric, metabolic, and hemodynamic variables ($P < 0.001$).

These results suggest that the perceived stress-related cortisol secretion measured under ordinary living conditions during a random working day is related to various disadvantageous anthropometric, endocrine, and hemodynamic factors. It seems particularly striking that when the HPA axis has been adapted to blunted activity with poor feedback control, these associations became uniformly stronger. Provided that the day of measurements was representative, this might be interpreted to mean that perceived stress with subsequent HPA axis activation is associated with problems in the homeostasis of several somatic systems. The observation that this is more pronounced with signs of a poorly regulated HPA axis might mean that the exposure to perceived stress had been more frequent or severe during the period preceding the examination, leading to the adaptations of the HPA axis observed, which are those observed after prolonged stress. This might presumably also result in a sensitization of the axis to the perceived stress, with the consequence of pronounced stress-related cortisol secretion (21, 25). In combination with abdominal obesity, this is apparently also the case after the physiological challenge of eating.

Previous work has indicated that morning cortisol levels are low in obesity, in general (26), including central obesity (16, 17), and the diurnal curve is consequently more flattened. This is occurring while cortisol turnover is higher than normal (26) and seems to result in an occasionally elevated net output of cortisol in abdominal obesity, as measured by urinary free cortisol (17). The strong relationships between the measurements of HPA axis activity and measurements of abdominal (WHR and D) obesity (BMI) shown here are thus in general agreement with previous studies of the net results of HPA axis activity in abdominal obesity. Other indicators of a dysregulation of the HPA axis in abdominal obesity are high secretion of cortisol after laboratory stress tests (17, 27), elevated cortisol secretion after lunch, as reported here, ACTH levels after administration of CRH (28, 29), and cortisol concentrations after challenges with ACTH (17, 28). This might mean sensitized and/or hyperresponsive hypothalamic centers, pituitary as well as adrenal regulatory mechanisms, that result in elevated net cortisol production in individuals with abdominal obesity.

The results reported here are thus consistent with previous work suggesting a dysregulation of the HPA axis in abdominal obesity. Such dysregulation is apparent in a disturbed diurnal regulation of HPA activity and a hyperresponsiveness or hypersensitivity to various challenges of psychological, physiological, or endocrine nature, occasionally resulting in elevated total net secretion and urinary output of cortisol. As neither perceived daily stress, laboratory stress tests, nor food intake produces maximal stimulation of the HPA axis, it seems highly likely that the axis is hypersensitive, rather than hyperresponsive, in abdominal obesity.

It should be noted that the associations between stress-related cortisol and other variables were less evident without statistical weighting of the status of the HPA axis. It should also be noted that some of the correlations shifted direction in comparisons between high and low cortisol variabilities, suggesting a change of relationships. Clearly, however, low cortisol variability shows stronger associations than high variability with anthropometric, endocrine, metabolic, and hemodynamic parameters.

The endocrine associations deserve attention. Without weighting for diurnal cortisol secretion pattern, IGF-I, indicating GH secretion (30), showed a significant negative relationship, whereas associations with testosterone were not significant. With signs of normal HPA axis regulation (high variability), this shifted to a nonsignificant relationship with IGF-I. Finally, with a low variability in diurnal cortisol secretion, strong negative relationships were found with both testosterone and IGF-I. These shifts in associations with the status of the HPA axis suggest the following interpretation. With normal HPA axis status, perceived stress might be followed by elevation of testosterone values, whereas with signs of a perturbed HPA axis, regulation of both GH and testosterone secretion is severely inhibited. This has been found to follow chronic HPA axis activation (25). Statistical path-analytic models as well as subgrouping of the material according to endocrine status suggest that poor regulation of the HPA axis is followed by decreased testosterone and IGF-I values (Rosmond R., and P. Björntorp, to be published), giving support to the interpretation that HPA axis perturbations are followed by decreased testosterone and GH secretion (25).

Other statistical findings in this report might be possible to interpret mechanistically. Increased HPA axis activity is followed by visceral fat accumulation, as seen dramatically in Cushing's syndrome (31); events at the adipocyte level have been at least partly elucidated (7). This might also be a consequence of low testosterone and GH secretion, with or without HPA axis dysregulation (7). Furthermore, the endocrine perturbations might cause or amplify insulin resistance (6). There is evidence that insulin resistance might be followed by both dyslipidemia and elevated blood pressure (32). This chain of events suggests a central role of perturbations in the HPA axis in the development of a number of complications. An activation of the central sympathetic nervous system may also be involved, because the central regulation of this system and that of the HPA axis are tightly coupled (25). Such involvement is suggested by the positive relationships between HPA axis activity and blood pressure as well as heart rate.

Although we are aware that statistical associations do not give information about causality, the observations summa-

rized above strongly suggest that cortisol secretion as a response to perceived stress is a powerful factor regulating disease-generating events in the periphery. This seems to be particularly the case when the HPA axis functions with low reactivity and poor feedback control. This indicates that it is necessary to follow the acute reactions of the HPA axis following perceived stress to detect the associations reported in this work.

The condition of abdominal obesity with disturbed HPA axis described here and previously (6, 7) shows similarities with Cushing's syndrome. Both are characterized by a perturbed HPA axis status, centralization of body fat, and abnormal endocrine, metabolic, and hemodynamic features. Abdominal obesity might be considered as a functional Cushing's syndrome. The prevalence of the classical Cushing's syndrome in the population studied was extremely low, and subjects with Cushing's syndrome would have been revealed by failure to suppress endogenous cortisol secretion normally when dexamethasone was administered. It is, therefore, highly unlikely that the presence of Cushing's syndrome among the men studied (n = 284) would occur and thereby distort the results.

Socio-economic handicaps, repeatedly described in subjects with abdominal obesity (8–12), provide an environment in which stress reactions would be expected to be frequent. Via adaptations of the regulatory systems of the HPA axis, this seems then to be followed by risk factors for prevalent disease. The results presented here might elucidate the long sought mechanism by which psychological and socio-economic factors influence somatic disease, particularly since these factors are also involved in the population studied here (11, 12).

It is hoped that the new methodology developed and reported here will provide better possibilities to examine putative pathogenetic factors causing the perturbations of HPA axis regulation associated with such risk factors.

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