Endocrine and Metabolic Aberrations in Men With Abdominal Obesity in Relation to Anxio-depressive Infirmity

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Abdominal obesity, anxiety, and depression have been found to cluster in several studies. To further characterize these associations, the following study was performed. In a population of 51-year-old men (N = 284), measurements of obesity (body mass index [BMI]) and body fat distribution (waist to hip ratio [WHR] and sagittal trunk recumbent diameter [D]) were analyzed in relation to dexamethasone (0.5 mg) inhibition of cortisol secretion, measured as salivary cortisol. Symptoms of anxiety and depression were defined by a validated questionnaire. Furthermore, testosterone, insulin-like growth factor-I (IGF-I), insulin, glucose, and serum lipid levels were measured. Twenty-five men (8.8%) had symptoms of anxiety and depression. BMI, WHR, and D correlated negatively with testosterone, except for BMI in the anxio-depressive (ADP) group. IGF-I showed no significant relationship. Furthermore, fasting insulin and the insulin to glucose ratio correlated positively and high-density lipoprotein (HDL) cholesterol correlated negatively with BMI, WHR, and D in the total study population and in the subgroups. Total and low-density lipoprotein (LDL) cholesterol showed no significant relationships. Correlation coefficients tended to be higher in ADP men. Dexamethasone inhibition showed a negative significant relationship with BMI ($\rho = -.47$, $P = .025$), WHR (borderline, $\rho = -.37$, $P = .086$), and D ($\rho = -.43$, $P = .046$) only in the ADP group. Comparing the ADP group versus the group without anxio-depression (ADO) and high or low BMI ($P = .008$), WHR ($P = .026$), and D ($P = .012$) showed blunted dexamethasone inhibition only in ADP men with high anthropometric measurements. These findings suggest there is a subgroup with elevated BMI, WHR, and D in whom a blunted dexamethasone response is found associated with traits of anxiety and depression, conditions characterized by such an abnormality. The reason for the association might be insufficient control of cortisol secretion, followed by visceral fat accumulation.

ABDOMINAL OBESITY is associated with cardiovascular disease, non–insulin-dependent diabetes mellitus (NIDDM), stroke, and premature mortality in both men and women.[1] The causes of abdominal distribution of body fat are most likely both genetic and environmental. Among the latter factors, a hypersensitive hypothalamic-pituitary-adrenal (HPA) axis has been suggested via elevated cortisol secretion following this condition, storage fat may be disproportionally directed toward visceral depots,[2] as observed clearly in Cushing's syndrome.[3]

Several background factors for increased activity of the HPA axis have been suggested.[2] Among these are traits of anxiety and depression, which are both known to activate the axis.[4-8] Such traits have been described consistently in both men and women with abdominal obesity.[9-12]

Elevated cortisol secretion is frequently associated with blunted inhibition of cortisol secretion by dexamethasone, which is also found in anxiety disorders and depression.[4-8] We have recently found that men with abdominal obesity show a decreased response to dexamethasone inhibition at less than conventional (1-mg) doses.[13] In the present study, the aim was to examine how abdominal obesity, anxiety, and depression may interact in their associations with a deficient inhibition of cortisol secretion after administration of dexamethasone. More specifically, we wanted to examine the putative role of anxiety and depression in the blunted dexamethasone suppression found in abdominal obesity. The results suggest that the relative dexamethasone insensitivity in abdominal obesity follows the traits of anxiety and depression rather than abdominal obesity itself.

SUBJECTS AND METHODS

Study Population

In 1992, a cohort of men (N = 1,302) were 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 1,040 men (79.9%) responded to the questionnaire. Based on the self-reported waist to hip ratio (WHR), three subgroups were selected and defined as follows: 150 men with the lowest WHR (≤0.885), 150 with the highest WHR (≥1.01), and 150 with approximately the arithmetic mean value (0.94 to 0.96) for the WHR. They were then invited to a health examination during 1995. A total of 284 (63.1%) volunteered to participate: 94 men (62.7%) with the lowest WHR, 94 with the highest, and 96 (64.0%) with approximately the mean value for WHR. 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. The dexamethasone suppression test was performed several days after blood sampling. The examinations for each man were performed by the same research nurses and technicians.

Anxio-depressive Infirmity

The participants completed a questionnaire, the Göteborg Quality of Life Instrument,[14] which contains 48 items about social, mental, and physical well-being. We defined anxio-depressive infirmity using the following symptoms perceived during the prior 3 months: (1) general fatigue, (2) sleeping disturbance, (3) nervousness, (4) irritability, (5)

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exhaustion, (6) impaired concentration, (7) restlessness, (8) depression, (9) crying easily, and (10) difficulty relaxing. Each symptom is scored by a "yes-no" nominal scale. If the subjects indicated "yes" on at least three of these symptoms, they were classified as anxio-depressive. This instrument has been thoroughly validated previously.[14]

Physical Health Status and Current Medication

The participants were asked to report a history of the following diseases if diagnosed by a physician: (1) angina pectoris, (2) cerebral infarction and/or hemorrhage (stroke), (3) endocrine disorder, (4) hyperlipidemia, (5) hypertension, (6) insulin-dependent diabetes mellitus (IDDM), (7) myocardial infarction, and (8) NIDDM. In addition, information about the current use of medication (drug name and dosage) was obtained.

Anthropometry

Body weight was measured to the nearest 0.1 kg with participants dressed in underwear, and height was measured to the nearest 1 cm. 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 lower rib and iliac crest, and the hip circumference at the level of the greater trochanter.[15] The WHR was calculated as the ratio of the waist and hip circumferences. The sagittal trunk diameter ([D] in centimeters) was determined as the distance between the examination table and the highest point of the abdomen in a recumbent position.[16]

Hormones, Glucose, and Serum Lipids

Salivary cortisol was determined by radioimmunoassay ([RIA] Orion Diagnostica, Turku, Finland). A sampling device (Salivette; Sarstedt, Rommelsdorf, Germany) was used to measure salivary cortisol levels. The Salivette consists of a small cotton swab inside of a standard centrifugation tube.[17] The participants were given three Salivettes and one tablet of dexamethasone (Decadron; MSD, Sollentuna, Sweden) 0.5 mg. They were asked to chew the cotton swab in the morning (8:00 to 9:00 AM) for 45 to 60 seconds for 2 consecutive days. At 10:00 PM on the second day, the dexamethasone tablet was swallowed, and the following morning the salivary sampling was repeated. The participants were given careful oral and written instructions. The decrease in salivary cortisol after dexamethasone administration was calculated as the mean level of noninhibited cortisol minus the cortisol level after dexamethasone.

Serum total testosterone was determined by a nonextraction method in which testosterone bound to bovine serum albumin (BSA) at C-19 (testosterone-19-carboxymethylether-BSA) was used as the antigen (Testosterone ^{125}I RIA; ICN Biomedicals, Costa Mesa, CA). Insulin-like growth factor-I (IGF-I) was determined by hydrochloric acid-ethanol (12.5% 2N HCl/87.5% ETOH)–extraction RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA). The insulin level 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 assayed as described by Wiklund et al.[19]

Statistical Analysis

Standard methods were used to calculate the descriptive statistics. Before entering the variables into the analyses, a distribution fitting test was completed. The Shapiro-Wilk W test[20] showed that the variables were not compatible with a gaussian (normal) distribution. To evaluate the accuracy of classification of the subjects as either ADP or ADO, the differences in the proportion of response to each symptom between the two groups were examined by Fisher's exact permutation test.[21] Tests of associations between anthropometric, endocrine, and metabolic measurements were accomplished with Spearman's rho (ρ).[22] BMI, WHR, and D were then arranged into three equal ordered strata of each frequency distribution. Based on this stratification, a two-group model was assigned by designating individuals within the highest strata as one group and all others as another group for each anthropometric measurement (ie, BMI $\geq$ 27.35 v BMI $<$ 27.35, WHR $\geq$ 0.967 v WHR $<$ 0.967, and D $\geq$ 24.0 v D $<$ 24.0). Hypothesis testing on differences in the mean Wilcoxon score for the decrease of salivary cortisol after dexamethasone administration in the two-group model in relation to anxio-depressive infirmity was performed by the Wilcoxon rank-sum test.[23]

Nonparticipation analyses were performed using tests appropriate to the scale of measurement of each variable.[11,12] The statistical significance was relaxed to an α level of .10 to increase the sensitivity to detect potential selection (nonparticipant) bias.

Throughout this report, all confidence intervals and P values are two-sided. Statistical significance was accepted for an α value of .05. All data analyses were performed using the Statistical Analysis System (SAS for Windows, release 6.12; SAS Institute, Cary, NC).

RESULTS

There were no statistically significant differences in the characteristics of participants and nonparticipants, evaluated from previously obtained information[11,12] and by means of the Wilcoxon rank-sum test and Fisher's exact permutation test, concerning the use of anxiolytics, hypnotics, and antidepressants, sleeping disturbances, educational level, and degree of life satisfaction, as well as melancholy.

Table 1 presents the physical health status and current medication use in the total study population. Sixty-eight subjects (23.9%) had hyperlipidemia and 44 (15.5%) had hypertension. Antidepressants were used by six (2.1%) of the participants. Hyperlipidemia and hypertension were significantly positively associated with BMI, WHR, and D. There were no relationships between reported disease history or medication use and dexamethasone inhibition.

Table 1. Physical Health Status and Current Medication Use in the Total Study Population (N = 284)

Physical Health Status	No. of Subjects	%	CI*	Medication Used	No. of Subjects	%	CI*
Angina pectoris	6	2.1	0.8-4.5	Antidepressant drugs	6	2.1	0.8-4.5
Endocrine disorders	2	0.7	0.1-2.5	Angiotensin-converting enzyme inhibitors	8	2.8	1.2-5.5
Hyperlipidemia	68	23.9	19.1-29.3	β-Adrenergic antagonists and Ca^{2+} channel blockers	25	8.8	5.8-12.7
Hypertension	44	15.5	11.5-20.2	Hypnotics, sedatives, and neuroleptic drugs	14	4.9	2.7-8.1
IDDM	2	0.7	0.1-2.5	Insulin	2	0.7	0.1-2.5
Myocardial infarction	4	1.4	0.4-3.6	Lipid-lowering drugs	6	2.1	0.8-4.5
NIDDM	6	2.1	0.8-4.5	Oral hypoglycemic agents	6	2.1	0.8-4.5
Stroke	3	1.1	0.2-3.1	Thyroid drugs	2	0.7	0.1-2.5

Abbreviation: CI, confidence interval.

*Exact (Fisher's) 95% CI.

Table 2 shows the mean ± SD values for anthropometric, endocrine, and metabolic measurements in the total study population and in ADO and ADP subjects. ADP subjects had higher mean values for BMI, WHR, and D, as well as a lower mean value for the decrease in salivary cortisol after dexamethasone inhibition, compared with the total population and ADO subjects.

The difference in the decrease of salivary cortisol after dexamethasone inhibition between ADO subjects (mean Wilcoxon score, 112.1) and ADP subjects (mean Wilcoxon score, 91.4) was not statistically significant ($P = .147$).

Table 3 shows the difference in the proportion of response to each symptom between ADO subjects and ADP subjects. Within the ADP group, the proportion of subjects who responded "yes" for each symptom was significantly increased, with the exception of crying easily ($P = .178$) and difficulty relaxing ($P = .066$). The fraction of the total study population classified as ADP was 8.8%.

The association between the BMI and endocrine and metabolic variables in relation to anxio-depression is presented in Table 4. Results are given for the total population and ADO and ADP subjects. The decrease of salivary cortisol after dexamethasone was significantly negatively related in the ADP group only. A negative significant relationship was found between the BMI and testosterone in the total study population and the ADO group. Fasting insulin values were highly related to BMI in all groups, as was the fasting glucose concentration, except in the ADP group. The fasting insulin to glucose ratio and triglycerides were also highly significantly positively related in all three groups. Total and low-density lipoprotein (LDL) cholesterol showed no relationship and high-density lipoprotein (HDL) cholesterol showed a negative significant correlation with BMI in all groups.

The association between the WHR and endocrine and metabolic variables in relation to anxio-depression is shown in Table 5. Testosterone was significantly negatively related to the WHR in all groups, and dexamethasone inhibition (borderline, $P = .086$) and IGF-I were significantly negatively related to the WHR only in the ADP group. Positive significant relationships were found in all groups with fasting insulin, fasting glucose (except ADP), the insulin to glucose ratio, and triglycerides. Total and LDL cholesterol showed no significant relationships and HDL cholesterol showed negative significant relationships in the total study population and subgroups.

Table 6 shows similar examinations in relation to D, and dexamethasone inhibition was negatively related to D only in the ADP group. Testosterone was significantly negatively related in all groups. Fasting insulin and glucose and their ratio, as well as triglycerides, showed statistically significant relationships in all groups, except fasting glucose in the ADP group. Total and LDL cholesterol showed no significant relationship and HDL cholesterol showed a significant negative relationship in all groups.

Table 7 shows the difference in mean Wilcoxon scores for the decrease in salivary cortisol after dexamethasone administration in relation to anxio-depressive infirmity in subgroups of the anthropometric measurements. In groups with the highest BMI (≥27.35), WHR (≥0.967), and D (≥24), subjects with ADP showed a significantly smaller decrease of salivary cortisol

Table 2. Anthropometric, Endocrine, and Metabolic Measurements (mean ± SD)

Parameter	Total Study Population (n = 284)	ADO Subjects (n = 259)	ADP Subjects (n = 25)
BMI (kg/m²)	26.3 ± 4.1	26.1 ± 3.9	27.8 ± 5.2
WHR	0.94 ± 0.07	0.93 ± 0.07	0.96 ± 0.07
Sagittal trunk recumbent diameter (cm)	22.7 ± 3.8	22.7 ± 3.6	23.1 ± 4.7
Salivary cortisol inhibition by dexamethasone (nmol/L)	12.0 ± 5.3	12.1 ± 5.2	10.7 ± 5.3
Testosterone (nmol/L)	19.7 ± 5.5	19.8 ± 5.4	19.3 ± 6.5
IGF-I (μg/L)	204.6 ± 64.6	205.4 ± 64.1	196.6 ± 69.3
Fasting insulin (mU/L)	12.7 ± 10.9	12.6 ± 11.0	14.2 ± 10.1
Fasting glucose (mmol/L)	4.6 ± 1.0	4.6 ± 1.1	4.3 ± 0.4
Insulin/glucose ratio	2.8 ± 2.7	2.7 ± 2.7	3.3 ± 2.3
Triglycerides (mmol/L)	1.8 ± 1.1	1.8 ± 1.1	2.0 ± 0.9
Cholesterol (mmol/L)	6.2 ± 1.1	6.2 ± 1.1	6.1 ± 1.2
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.4
LDL cholesterol (mmol/L)	4.1 ± 1.0	4.1 ± 1.0	4.0 ± 1.2

Table 3. Differences in the Proportion of Response to Each Symptom Between ADO Subjects and ADP Subjects

	ADO Subjects (n = 259)				ADP Subjects (n = 25)				
	Yes		No		Yes		No		
Symptom	No.	%	No.	%	No.	%	No.	%	P*
General fatigue	118	45.6	141	54.4	25	100	0	0	<.001
Sleeping disturbance	64	24.7	194	74.9	24	96.0	1	4.0	<.001
Nervousness	16	6.2	242	93.4	16	64.0	9	36.0	<.001
Irritability	74	28.6	181	69.9	23	92.0	2	8.0	<.001
Exhaustion	59	22.8	199	76.8	18	72.0	7	28.0	<.001
Impaired concentration	61	23.6	196	75.7	16	64.0	9	36.0	<.001
Restlessness	75	29.0	183	70.7	18	72.0	7	28.0	<.001
Depression	84	32.4	173	66.8	15	60.0	10	40.0	.008
Crying easily	27	10.4	231	89.2	5	20.0	20	80.0	.178
Difficulty relaxing	73	28.2	182	70.3	12	48.0	13	52.0	.066

*Fisher's exact permutation test.

Table 4. Spearman's ρ and *P* Value for Correlations Between BMI and Endocrine and Metabolic Variables

	BMI					
	Total Study Population (n = 284)		ADO Subjects (n = 259)		ADP Subjects (n = 25)	
Variable	ρ	P	ρ	P	ρ	P
Salivary cortisol inhibition by dexamethasone (nmol/L)	−.02	>.200	.06	>.200	−.48	.025
Testosterone (nmol/L)	−.38	<.001	−.38	<.001	−.28	.183
IGF-I (μg/L)	−.03	>.200	−.01	>.200	−.17	>.200
Fasting insulin (mU/L)	.57	<.001	.55	<.001	.70	<.001
Fasting glucose (mmol/L)	.28	<.001	.29	<.001	.29	.164
Insulin/glucose ratio	.54	<.001	.51	<.001	.69	<.001
Triglycerides (mmol/L)	.42	<.001	.40	<.001	.64	<.001
Cholesterol (mmol/L)	.04	>.200	.03	>.200	.24	>.200
HDL cholesterol (mmol/L)	−.40	<.001	−.37	<.001	−.64	<.001
LDL cholesterol (mmol/L)	.03	>.200	.03	>.200	.18	>.200

Table 5. Spearman's ρ and *P* Value for Correlations Between WHR and Endocrine and Metabolic Variables

	WHR					
	Total Study Population (n = 284)		ADO Subjects (n = 259)		ADP Subjects (n = 25)	
Variable	ρ	*P*	ρ	*P*	ρ	*P*
Salivary cortisol inhibition by dexamethasone (nmol/L)	.01	>.200	.07	>.200	−.37	.086
Testosterone (nmol/L)	−.33	<.001	−.30	<.001	−.46	.019
IGF-I (μg/L)	−.08	.188	−.05	>.200	−.36	.076
Fasting insulin (mU/L)	.53	<.001	.52	<.001	.56	.004
Fasting glucose (mmol/L)	.31	<.001	.34	<.001	.21	>.200
Insulin/glucose ratio	.48	<.001	.47	<.001	.58	.003
Triglycerides (mmol/L)	.37	<.001	.34	<.001	.65	<.001
Cholesterol (mmol/L)	7×10^{-4}	>.200	.01	>.200	.02	>.200
HDL cholesterol (mmol/L)	−.30	<.001	−.26	<.001	−.50	.011
LDL cholesterol (mmol/L)	−.05	>.200	−.03	>.200	−.10	>.200

levels after dexamethasone, whereas this was not the case in men with a lower BMI, WHR, and D.

Finally, the dexamethasone-inhibited salivary cortisol level was correlated with the BMI, WHR, and D within the ADP group. Negative relationships were found in relation to BMI ($\rho = -.47$, $P = .025$; Fig 1) and WHR ($\rho = -.37$, $P = .086$; Fig 2), as well as D ($\rho = -.43$, $P = .046$; Fig 3).

DISCUSSION

Subjects with abdominal, visceral obesity have previously been found to consistently show traits of anxiety and depression in both men and women in several studies.[9-12] Anxiety and depression are known to be associated with blunted dexamethasone inhibition,[5,24] and men with abdominal obesity have recently been found to show a defect in such inhibition with 0.5 mg dexamethasone.[13] We therefore hypothesized that anxiety and depression might be factors mediating dexamethasone insensitivity in abdominal obesity.

This assumption was confirmed by the nonsignificant relationships between the decrease in cortisol after dexamethasone and

Table 6. Spearman's ρ and *P* Value for Correlations Between Sagittal Trunk Recumbent Diameter and Endocrine and Metabolic Variables

	Sagittal Trunk Recumbent Diameter					
	Total Study Population (n = 284)		ADO Subjects (n = 259)		ADP Subjects (n = 25)	
Variable	ρ	*P*	ρ	*P*	ρ	*P*
Salivary cortisol inhibition by dexamethasone (nmol/L)	.01	>.200	.07	>.200	−.43	.046
Testosterone (nmol/L)	−.37	<.001	−.34	<.001	−.47	.018
IGF-I (μg/L)	.02	>.200	.06	>.200	−.32	.119
Fasting insulin (mU/L)	.61	<.001	.59	<.001	.65	<.001
Fasting glucose (mmol/L)	.36	<.001	.38	<.001	.29	.162
Insulin/glucose ratio	.54	<.001	.53	<.001	.65	<.001
Triglycerides (mmol/L)	.46	<.001	.43	<.001	.69	<.001
Cholesterol (mmol/L)	.05	>.200	.03	>.200	.22	>.200
HDL cholesterol (mmol/L)	−.40	<.001	−.37	<.001	−.62	<.001
LDL cholesterol (mmol/L)	7×10^{-3}	>.200	−.01	>.200	.15	>.200

Table 7. Mean Wilcoxon Score for Differences in the Decrease of Salivary Cortisol (nmol/L) After Dexamethasone Administration in Relation to Anxio-depressive Infirmity in Subgroups of Anthropometric Measurements

Parameter	ADO Subjects	ADP Subjects	*P**
Total study population	112.1 (n = 259)	91.4 (n = 25)	.147
BMI ≥ 27.35	39.6 (n = 80)	22.5 (n = 14)	.008
BMI < 27.35	73.4 (n = 179)	83.1 (n = 11)	>.200
WHR ≥ 0.967	38.7 (n = 84)	22.8 (n = 13)	.026
WHR < 0.967	73.9 (n = 175)	74.8 (n = 12)	>.200
Sagittal trunk recumbent diameter ≥ 24.0	41.3 (n = 95)	21.3 (n = 10)	.012
Sagittal trunk recumbent diameter < 24.0	71.2 (n = 164)	74.2 (n = 15)	>.200

NOTE. *Wilcoxon rank-sum test. Figures within parentheses are the total number of subjects in each group.

the BMI, WHR, and D in the total population. The BMI provides an estimation of obesity, WHR of body fat distribution, and D of visceral fat mass.[16] Relationships to all these measurements have therefore been interpreted to indicate associations with abdominal (WHR and D) obesity (BMI). However, significantly blunted inhibition was found in the groups with elevated BMI, WHR, and D where anxio-depression was found, but this was not the case either when symptoms of depression and anxiety were absent or in subgroups with low values on obesity and body fat distribution measurements. Thus, the tentative conclusion from these data is that a decreased dexamethasone response is found only in men with abdominal obesity who have traits of anxiety and depression. This was significant despite the relatively low number of men in this subgroup (N = 25).

The men examined in this report were recruited from a previously selected population of men (N = 1,040). A response to the questionnaire was available from all men recruited for the present study. There were no significant differences between participants (N = 284) and nonparticipants in the subgroups examined here, evaluated from previously obtained information,[11,12] concerning the use of anxiolytics, hypnotics, and antidepressants, sleeping disturbances, educational level, and degree of life satisfaction or melancholy. The prevalence of reported hyperlipidemia (23.9%; Table 1) is surprisingly high, but based only on the report of the participants. Our own measurements do not support such a high prevalence (Table 2).

The index of anxio-depression was selected from defined positive responses to a previously tested life-quality instrument.[14] When this index, consisting of three or more positive answers out of 10, was tested against any of the separate 10 items, highly significant differences were found for the proportion of subjects classified as ADO and subjects classified as ADP, suggesting the validity of this index. The results suggest that 8.8% of this middle-aged Swedish population suffers from anxio-depressive symptoms.

The dexamethasone dose of 0.5 mg was used, guided by previous results.[13] Salivary cortisol was examined to allow testing at home under ordinary life conditions and to avoid venipuncture. When such measurements are performed simultaneously with serum cortisol, a strong significant correlation is found.[17] We have also confirmed these data (Ljung T, et al, unpublished results, 1995).

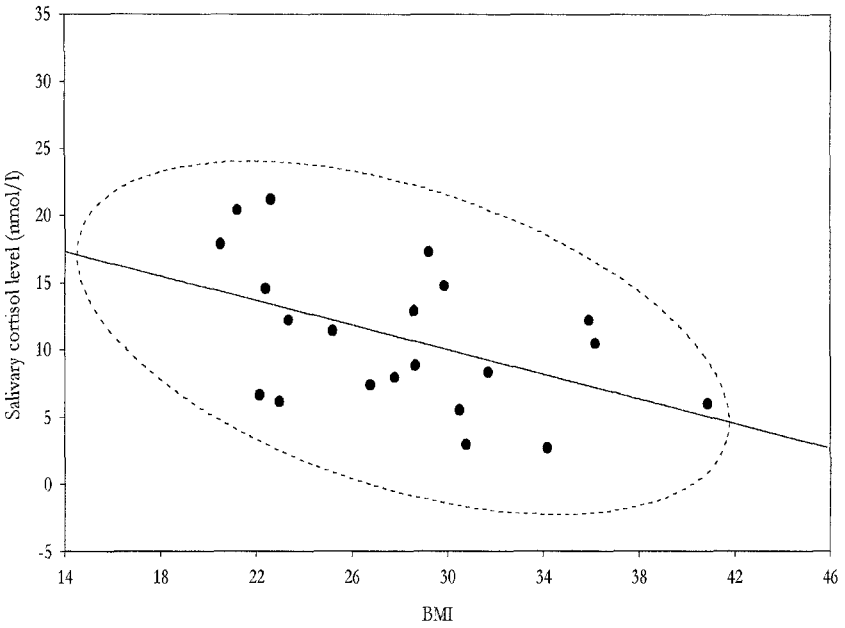

Fig 1. Association between the decrease of salivary cortisol (nmol/L) after dexamethasone administration and the BMI among subjects with anxio-depressive infirmity. The ellipse represents a 95% confidence area.

Other endocrine examinations were also performed, including total testosterone and IGF-I, the latter an indicator of growth hormone secretion.[25] Testosterone was decreased with BMI in the total population and in ADO subjects, but not in ADP subjects. However, with an elevation of the regional measurements WHR and D, testosterone was also low in the ADP group. IGF-I was independent of obesity, but tended to be lower with a high WHR and D, although not significantly, perhaps due to the relatively low number of subjects. It then seems that both testosterone and IGF-I are inversely associated with obesity and abdominal distribution of body fat, in accordance with previous reports.[26,27] To what extent anxio-depression might be involved additionally is uncertain from the present data with a small number of subjects.

As shown repeatedly,[2] fasting insulin and glucose and their ratio, as an approximation of insulin sensitivity, as well as triglycerides and HDL cholesterol (negative) but not total and LDL cholesterol, were related to measurements of generalized obesity and centralized body fat. An exception was glucose in the ADP group. This was the case in the total population and in the ADO and ADP groups. Of note is the observation that the correlation coefficients in all instances were higher in the ADP group versus the other groups, suggesting a more disturbed metabolism in this group.

A diminished response to subconventional (1 mg) doses of dexamethasone has been reported recently in men with abdominal obesity[13]; traits of anxiety and depression were not measured in the study. Here, we report that anxio-depressive symptoms seem essential for blunted dexamethasone inhibition, but only in men with abdominal obesity. Subjects with anxiety

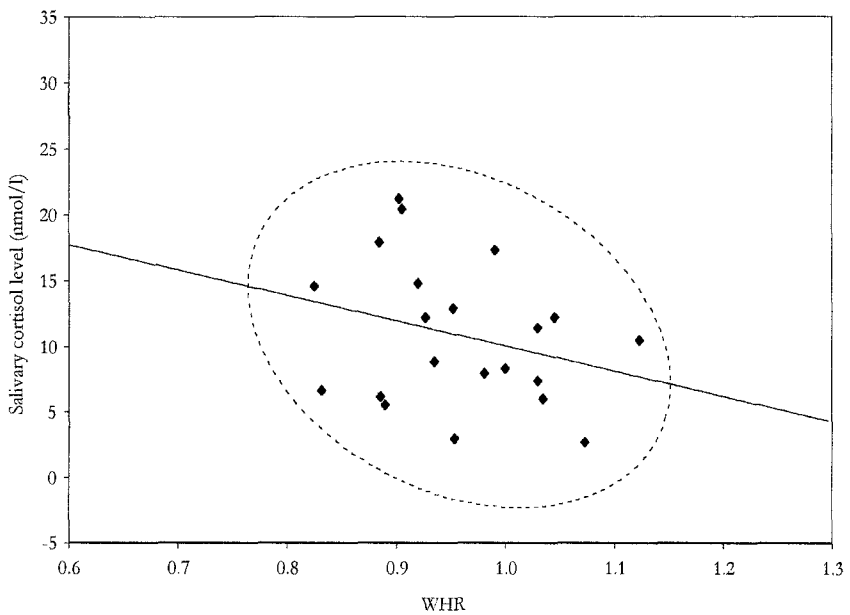

Fig 2. Association between the decrease of salivary cortisol (nmol/L) after dexamethasone administration and the WHR among subjects with anxio-depressive infirmity. The ellipse represents a 95% confidence area.

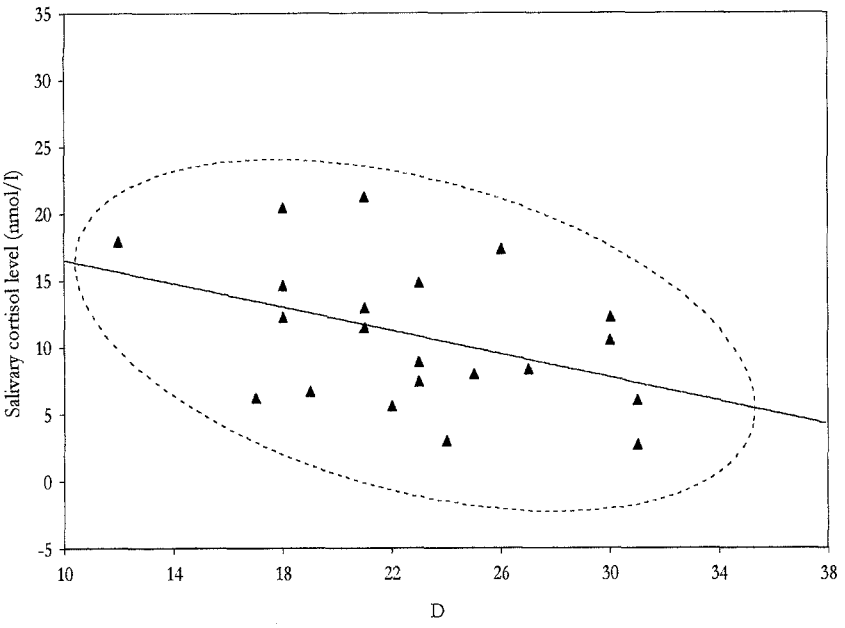

Fig 3. Association between the decrease of salivary cortisol (nmol/L) after dexamethasone administration and the sagittal trunk recumbent diameter (D) among subjects with anxio-depressive infirmity. The ellipse represents a 95% confidence area.

and depression show abnormalities in regulation of the HPA axis.[4-8,24,28] The basis for a diminished dexamethasone response has been considered to be hyperactivity of the HPA axis, perhaps mediated via downregulation of central glucocorticoid receptors.[29] We have previously shown that cortisol secretion is positively related to the sagittal trunk recumbent diameter (D).[30] Furthermore, the response to corticotropin and to laboratory stress tests is elevated in terms of cortisol secretion,[30-32] and this seems to be the case also with the response to both corticotropin-releasing hormone and arginine vasopressin.[32,33] These observations suggest a hyperactive HPA axis in subjects with abdominal obesity, with at least periodically elevated cortisol secretion, which then may provide an explanation for the relative insensitivity to dexamethasone inhibition.[29]

The reason that a blunted dexamethasone inhibition was found only in relation to abdominal obesity is not known, but can be a matter of speculation. Abdominal obesity might cause anxiety and depression. This seems unlikely, because the majority of men with abdominal obesity did not show symptoms of anxiety and depression. Another possibility to consider is that both anxiety and depression, and obesity are symptoms of central serotonin deficiency and both are improved or cured by serotonin agonistic effects.[34] These effects are most likely mediated via 5-hydroxytryptophan receptors. This may mean that effects on several receptors are responsible for the combined phenomena of anxiety-depression symptoms and abdominal obesity. Some support for this contention is found in observations that patients with depression may have either associated hyperphagia or anorexia.[35]

A tentative conclusion from this study might be that the syndrome of abdominal obesity may show subgroups with different characteristics. Subjects with dexamethasone insensitivity in relation to anxiety and depression may be one such subgroup. There might be other parts of the syndrome depending on, for example, alcohol, stress, and smoking tobacco, found to be associated with abdominal obesity. These factors are all known to activate the HPA axis and show blunted dexamethasone inhibition.[2] The results reported here remained unchanged after taking smoking into account (not shown). Since the alcohol reports collected may be considered unreliable, we did not analyze this factor separately, and a potential influence therefore cannot be ruled out. It seems likely that these various environmental pressures on the HPA axis are highly interwoven. The results presented here also suggest there may be subjects with abdominal obesity without HPA axis involvement. This is currently the subject of further analyses.

Very recently, it has been shown that cynomolgus monkeys subjected to mild stress by social subordination develop behavioral depression and a diminished response to the inhibition of cortisol secretion with a small dose of dexamethasone.[36] This is in excellent agreement with the data presented here in humans, particularly since psychosocial handicaps clearly are also involved in the human syndrome.[11]

We would like to hypothesize that the syndrome of abdominal obesity may be expressed with more or less environmental pressure of different origin with genetic background factors involved.[37]

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