Cortisol Effects on Body Mass, Blood Pressure, and Cholesterol in the General Population

Robert Fraser, Mary C. Ingram, Niall H. Anderson, Caroline Morrison, Eleanor Davies, John M.C. Connell

Abstract—The effects of excess cortisol secretion on blood pressure and fat deposition are well documented, but the importance of this glucocorticoid in controlling these processes in normal individuals is less clear. We studied the relationship between cortisol excretion rate (tetrahydrocortisol [THF]+allo-THF+tetrahydrocortisone [THE]) and a range of important cardiovascular risk factors in 439 normal subjects (238 male) sampled from the North of Glasgow (Scotland) population. There were marked gender differences: female subjects were lighter and had lower blood pressures and cortisol levels, whereas HDL cholesterol was higher. The pattern of cortisol metabolism was also different; the index of 11β-hydroxysteroid dehydrogenase activity (THF+allo-THF/THE) was lower and that of 5α-reductase (allo-THF/THF) was higher. There was a strong correlation of blood pressure (positive), cholesterol (positive), and HDL cholesterol (negative in women, positive in men) with age. Cortisol excretion rate did not correlate with blood pressure but correlated strongly with parameters of body habitus (body mass index and waist and hip measurements [positive]) and HDL cholesterol (negative). With multiple regression analysis, there remained a significant association of cortisol excretion rate with HDL cholesterol in men and women and with body mass index in men. These results suggest that glucocorticoids regulate key components of cardiovascular risk. **(*Hypertension*. 1999;33:1364-1368.)**

Key Words: glucocorticoids ■ blood pressure ■ body mass index ■ cholesterol

Clinical[1] and experimental[2] cortisol excesses are associated with increases in blood pressure and profound alteration of intermediary metabolism, resulting in characteristic obesity, insulin resistance, and changes in lipid metabolism. In groups of subjects with essential hypertension, plasma[3] or urinary[4] cortisol levels may be mildly but significantly higher than those of matched normal subjects, and the efficiency of cortisol metabolism by 11β-hydroxysteroid dehydrogenase (11β-HSD) or 5α-reductase may be abnormal.[5,6] Moreover, similar alterations in cortisol metabolism may contribute to obesity and to increased abdominal fat deposition in polycystic ovary disease.[7] However, in the general population, the contribution of cortisol to blood pressure and to relative obesity is less well established despite the fact that these are important predisposing factors to cardiovascular disease. A recent study of a small group of subjects concluded that differences in the level of cortisol and its metabolic disposal may be a contributory cause of obesity.[8] In the present study, we examined the association between cortisol and cardiovascular risk factors in a large sample of the middle-aged population of an area with a high prevalence of cardiovascular disease.

Methods

Population

A random sample of the North Glasgow, Scotland, population was selected as a stratified random sample of the patient lists of 30 general practitioners, randomly selected from all those practicing in North Glasgow. The subjects were those participating in the fourth Glasgow MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) coronary risk examination, which included the recording of the mean of 2 seated blood pressure measurements made by random-zero sphygmomanometer after a 10-minute rest. Approval was obtained from the appropriate ethics committees. Of the original sample of 597 subjects in whom full urinary corticosteroid data were available, 158 were excluded from the study on the grounds that they were receiving medication likely to alter cardiovascular risk parameters (eg, cardioactive drugs or hormone replacement therapy) or adrenal function (eg, inhaled or topical steroids). There remained 238 male and 201 female subjects; their demographic details are summarized in Table 1.

Biochemical Analyses

Blood samples were drawn from the antecubital vein for measurement of cholesterol and HDL cholesterol by standard laboratory methods. The subjects were not fasting. A 24-hour urine sample was collected with thymol used as preservative, and aliquots were stored frozen until analysis. Excretion rates of the cortisol metabolites tetrahydrocortisol (THF), allo-THF, and tetrahydrocortisone (THE) were measured by the method of Shackleton[9] with minor modifications. The total (ie, THF+allo-THF+THE) was used as an index of cortisol excretion rate, the ratio THF+allo-THF/THE as an index of 11β-HSD activity, and the ratio THF/allo-THF as an index of 5α-reductase activity.

Data Analyses

Data have been expressed as medians with interquartile ranges. They were tested for normality of distribution (Anderson-Darling test[10])

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TABLE 1. Demographic Variables of Population Studied

Variable	Men (n=238)	Women (n=201)	P
Age, y	48 (39–56)	46 (36–57)	0.42
Systolic blood pressure, mm Hg	130 (121–142)	120 (109–133)	<0.0005
Diastolic blood pressure, mm Hg	82 (76–90)	74 (66–88)	<0.0005
Hip measurement, cm	100 (96–105)	99 (94–105)	0.21
Waist measurement, cm	91 (84–100)	77 (71–86)	<0.0005
Weight, kg	78 (70–87)	65 (59–72)	<0.0005
BMI	26.4 (24–29)	25.3 (23–28)	0.47
Total cholesterol, mmol/L	5.95 (5.15–6.53)	5.89 (5.14–6.84)	0.49
HDL cholesterol,* mmol/L	1.15 (0.98–1.37)	1.38 (1.1–1.64)	<0.0005

*Log transformed before testing.

and, where necessary, they were logarithmically transformed before statistical evaluation. Comparison of data from male and female subjects was performed by ANOVA and simple regression analysis by calculation of Pearson correlation coefficients, and multivariate models were fitted by a combination of stepwise and best subsets regression methods.

Results

There were marked gender differences both in demographic variables (Table 1) and in cortisol metabolite excretion rates (Table 2). Although not significantly different in age or body mass index (BMI), female subjects had lower blood pressures and weighed less. Total cholesterol concentration was similar in the 2 groups, but female subjects had higher HDL cholesterol levels. Male subjects had higher cortisol excretion rates than female subjects, and there were gender differences in the pattern of metabolism. Thus, the index of 11β-HSD activity was higher in male subjects; the reverse was true of the index of 5α-reductase activity. Blood pressure and cholesterol correlated positively with age in both men and women; HDL cholesterol and age correlated positively in men but not in women (Table 3).

BMI as well as waist and hip measurements correlated significantly with systolic and diastolic blood pressures (Table 4). However, there was no relationship between corticosteroid variables and blood pressure. Plasma total cholesterol concentration correlated with systolic and diastolic blood pressures (except in female subjects), but HDL cholesterol levels did not correlate with blood pressure.

Cortisol excretion rate was positively correlated with BMI in both gender groups, as was waist measurement. There was a significant correlation with hip measurement only in male subjects (Table 5). In both groups, HDL cholesterol concentration was negatively correlated with cortisol excretion, but there was no relationship with total cholesterol concentration.

Table 6 summarizes the multiple regression analysis of these data. From the equations, the cortisol-related variables, particularly cortisol excretion rate, contributed significantly with body habitus to the determination of HDL cholesterol levels. Age was also a factor in men. Cortisol levels also appear to contribute to BMI in men but not in women. Cortisol-related variables did not appear to make an important contribution to blood pressure in this population. The relationship between cortisol excretion, HDL cholesterol levels, and BMI for the 2 gender groups is illustrated in the Figure.

TABLE 2. Corticosteroid Excretion Rates and Ratios

Variable	Men (n=238)	Women (n=201)	P
Cortisol metabolites,* μmol/24 h	12.24	8.27	<0.0005
THF+allo-THF+THE	8.05–19.13	5.33–12.30	
11β-HSD activity*	1.16	1.00	<0.0005
THF+allo-THF/THE	0.86–1.5	0.76–1.28	
5α-Reductase activity*	1.58	1.96	<0.0005
THF/allo-THF	0.99–2.53	1.20–3.60	

*Log transformed before testing.

Discussion

Gender and Age Differences

The finding of higher cortisol excretion rates in men than in women is in general agreement with previous studies (eg, References 8, 11, and 12), although Weaver et al[13] found no gender differences. Because plasma cortisol concentration is not influenced by gender, this suggests a difference in metabolism or tissue binding (see Reference 14). Apparent 11β-HSD activity was higher in men, but 5α-reductase activity, in agreement with Andrew et al,[8] was higher in women. The higher HDL cholesterol level in women may reflect the negative correlation with cortisol excretion rate and is likely to be influenced by estrogens.

Cortisol and Blood Pressure

Several studies have reported clear differences in the level of plasma or urinary cortisol and the pattern of its metabolism between normal subjects and groups of frankly hypertensive but otherwise matched subjects. For example, Filipovsky et al[15] found morning plasma cortisol concentration to be higher in hypertensive than in normotensive subjects, particularly in lean hypertensive subjects. Similarly, Litchfield et al[4] reported higher urinary free cortisol excretion rates in hypertensive patients; rates were higher in men than women and higher with high salt intake. Young adults with a predisposition to hypertension have mildly but significantly higher plasma cortisol concentrations[3] or secretion rates[16] than those without this trait. The study by Walker et al[16] also noted differences in cortisol metabolism between these groups. Differences in cortisol metabolite excretion rates between

TABLE 3. Correlations With Age

Subjects	Systolic Blood Pressure	Diastolic Blood Pressure	Cholesterol	HDL Cholesterol
Men (n=238)	0.268 (0.0005)	0.181 (0.005)	0.331 (0.0005)	0.159 (0.018)
Women (n=201)	0.473 (0.0005)	0.333 (0.0005)	0.460 (0.0005)	−0.08 (0.276)

Values are r^2 ($P \leq$).

hypertensive and normotensive subjects, indicative of differences in 11β-HSD or 5α-reductase activity, have also been described.[6]

No relationship between cortisol excretion and blood pressure was discernible, nor did the cortisol metabolite ratio indexes of 11β-HSD or 5α-reductase correlate with blood pressure. However, it should be emphasized that our study group was normotensive and had a narrow blood pressure range. Although these observations suggest that cortisol secretion rate is not a direct determinant of blood pressure in normotensive adults, it may act through differences in glucocorticoid receptor kinetics[16–18] or by in utero fetal programming.[19]

Body Habitus and Blood Pressure

The significant relationship between blood pressure and aspects of body habitus agrees with previous studies. According to Wing et al,[20] obese subjects have higher blood pressures and lower HDL levels; as in our subjects, HDL cholesterol was not related to body parameters. Fat distribution seemed to be the key determinant, because the significance of the correlation of blood pressure with waist/hip ratio (WHR), also seen in the present study, survived correction for BMI. This may reflect an underlying relationship between sensitivity to insulin and blood pressure.[21]

Cortisol and Obesity

The tendency to obesity with characteristic fat distribution in Cushing's syndrome is well established. Moreover, chronically stressed primates show a similar distribution of fat,[22] and psychosocial influences have also been identified in human subjects.[20] Glucocorticoid secretion in obese human subjects and genetically obese rats may be more sensitive to ACTH or "stress," and in rats, some of the effects are prevented by adrenalectomy.[23,24] Cortisol secretion is said not to be resistant to dexamethasone suppression in obesity,[25] but a more recent study found that levels in obese men were not as well suppressed as those of normal men.[26]

The majority of studies have found that cortisol excretion rate but not plasma concentration may correlate with parameters of body habitus. Urinary cortisol excretion rate has been reported to correlate with abdominal diameter and WHR,[25] in agreement with the present study. However, BMI and cortisol were unrelated in the previous study. Previous investigations[27] also claim that when corrected for creatinine excretion, cortisol excretion rates did not correlate with weight, nor were there gender differences. Conversely, Andrew et al[8] reported clear gender differences, also seen in the present study, but also found cortisol excretion to be unrelated to hip or waist circumference. This latter population was only mildly obese and thus more comparable with our own.

In our larger study, univariate analysis revealed a clear positive correlation between cortisol excretion rate and BMI or WHR. Such an association does not necessarily imply causality. However, it is possible that a small but chronic excess of cortisol does eventually result in a central fat deposition qualitatively similar to that in Cushing's syndrome (see Reference 28). Alternatively, changes in metabolism, perhaps as a consequence of excess central fat tissue expression of 11β-HSD, may alter secretion rate, although there was no correlation between 11β-HSD activity and either BMI or WHR. If increased exposure to cortisol favors the development of central obesity, the relationship should persist in multiple regression analysis. This was the case in men but not in women, again emphasizing gender differences. The clear relationship in

TABLE 4. Correlations With Blood Pressure

	Men (n=238)		Women (n=201)	
Variable	Systolic Blood Pressure	Diastolic Blood Pressure	Systolic Blood Pressure	Diastolic Blood Pressure
Waist	0.29 (<0.01)	0.25 (<0.01)	0.27 (<0.01)	0.31 (<0.01)
Hip	0.22 (<0.02)	0.18 (>0.05)	0.14 (>0.05)	0.20 (<0.01)
BMI	0.26 (<0.01)	0.22 (<0.02)	0.24 (<0.02)	0.26 (<0.01)
Cortisol*	0.03	−0.03	0.11	0.10
11β-HSD*	−0.09	−0.07	0.03	0.12
5α-Reductase*	0.09	0.10	0.04	0.10
Cholesterol	0.20 (<0.05)	0.25 (<0.01)	0.34 (<0.001)	0.18 (>0.05)
HDL cholesterol	0.09	0.09	−0.07	0.00

Cortisol: THF+alloTHF+THE; 11β-HSD: THF+allo-THF/THE; 5α-reductase: THF/allo-THF.
Values are r^2 (P).

TABLE 5. Correlations With Cortisol (THF+allo-THF+THE)

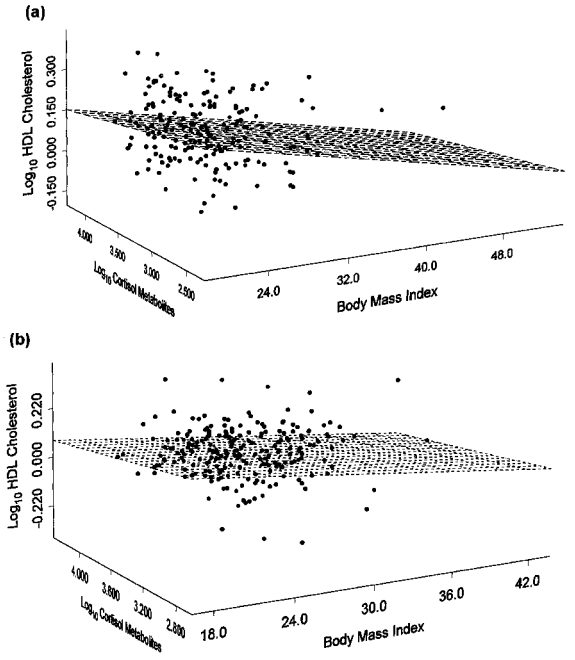
Variable	Men (n=238)	Women (n=201)
Waist	0.29 (0.01)	0.27 (0.01)
Hip	0.31 (0.01)	0.14
BMI	0.34 (0.001)	0.23 (0.02)
Cholesterol	0.05	0.12
HDL cholesterol	−0.27 (0.01)	−0.22 (0.05)

Values are r^2 ($P<$).

men suggests a role for cortisol within the normal range in modulating the amount and distribution of body fat. Central girth is a powerful index of cardiovascular risk,[29] and these data provide a possible explanation of this relationship in the general population.

The clear pathological effects of cortisol hypersecretion on body fat levels and the difficulty in identifying a similar relationship in normal or even clinically obese subjects may mean that differences in the potency of cortisol at the target tissue are important. Fat deposition may be affected by the affinity or concentration of glucocorticoid receptors. Also, the clearance rate of the hormone from the tissue might be altered with a higher proportion of 5α-reductase than 5β-reductase metabolism.[8] In the present study, the ratio of cortisol to cortisone metabolites did not correlate with body parameters, but the ratio of 5α-reductase to 5β-reductase metabolites was a contributory factor in determining HDL cholesterol levels (negative influence) and BMI (positive influence) in men.

Rosmond et al[30] weighted cortisol secretion measurements by a factor based on amplitude of individual diurnal variation of plasma cortisol concentration to control for variable stress. These values correlated positively with BMI, WHR, and total or HDL cholesterol in obese subjects. Cortisol correlated with HDL cholesterol but not total cholesterol in the present study. The inverse relationship between cortisol and HDL cholesterol was significant in both men and women and survived



Interrelationship between HDL cholesterol, cortisol excretion, and BMI in women (a) and men (b). Plane represents multiple regression surface for $\log_{10}$ HDL cholesterol in terms of BMI and $\log_{10}$ cortisol metabolites.

stepwise multiple regression analysis. Thus, cortisol may affect peripheral cholesterol metabolism to alter HDL cholesterol formation. Because lower HDL levels are strongly associated with cardiovascular risk,[31] a small long-term excess of cortisol may explain in part the risk associated with obesity. For both genders, the lowest HDL cholesterol levels are seen in subjects with the highest cortisol excretion rates and BMI (Figure).

Excess secretion of cortisol increases the risk of cardiovascular disease. Within a relatively normal population, the present study has identified a 3-way association between this steroid, BMI, and HDL cholesterol that may explain this risk.

TABLE 6. Multiple Regression Models and Proportion of Variance Explained

Dependent Variable	Model	Adjusted R^2
Men		
HDL cholesterol	0.333−0.008 BMI+0.002 Age−0.065 $\log_{10}$ Cortisol+0.045 $\log_{10}$ 5α/β+0.014 Cholesterol	18.5%
Total cholesterol	0.122+3.83 WHR+0.016 DBP+0.021 Age	19.6%
BMI	6.76+3.09 $\log_{10}$ Cortisol+0.049 SBP−3.46 HDL+0.084 Age−1.94 $\log_{10}$ 5α/β+0.465 Cholesterol	29.0%
SBP	83.9+0.358 Waist+0.339 Age	10.7%
DBP	60.8−0.050 Na+0.623 BMI+1.78 Cholesterol+4.40 $\log_{10}$ 5α/β	15.4%
Women		
HDL cholesterol	0.499−0.007 BMI−0.051 $\log_{10}$ Cortisol	12.7%
Total cholesterol	1.43+0.039 Age+2.10 WHR+0.009 SBP	24.2%
BMI	20.7−4.49 HDL+0.133 DBP+0.047 K	19.0%
SBP	66.1+0.785 Age+0.780 BMI	26.4%
DBP	43.7+0.266 Age+0.224 Waist	17.1%

5α/β indicates 5α-/reductase; DBP, diastolic blood pressure; and SBP, systolic blood pressure.
Cortisol: (THF+allo-THF+allo-THE); 5α/β: THF/allo-THF.

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