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Corticosteroid-binding globulin affects the relationship between circulating adiponectin and cortisol in men and women

José-Manuel Fernandez-Real[a,*], Michel Pugeat[b], Abel López-Bermejo[a], Hubert Bornet[c], Wifredo Ricart[a]

[a]*Unitat de Diabetologia, Endocrinologia i Nutricio, University Hospital of Girona, "Dr Josep Trueta", 17007 Girona, Spain*
[b]*Department of Endocrinology and ERITM 322 Hôpital Neurologique Cardiologique, 69437 Lyon Cedex 08, France*
[c]*Department of Biochemistry, Fédération de Biochimie de l'Hôpital Edouard Herriot, 69437 Lyon Cedex 08, France*

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Abstract

Inflammatory pathways are increasingly recognized to be tightly associated with insulin resistance in humans. The promoter region of the adiponectin gene—*Apm1*—encompasses consensus sequences for glucocorticosteroid receptor responsive element. Dexamethasone induced downregulation of adiponectin secretion in vitro, whereas prednisolone administration increased circulating adiponectin concentrations. As previous studies have demonstrated an inverse relationship between corticosteroid-binding globulin (CBG), body mass index, and insulin resistance, we studied whether CBG could explain cortisol-to-adiponectin relationship.

One hundred twenty-two healthy subjects were enrolled in a cross-sectional study. Plasma CBG and serum cortisol concentration were measured by radioimmunoassay. The cortisol-to-CBG ratio was used to calculate free cortisol. An RIA kit (Linco Research, St Louis, Mo) was used to measure adiponectin levels. Insulin resistance was calculated using the homeostatis model of assessment (HOMA) value.

Circulating adiponectin was associated with serum CBG ($r = 0.38$, $P < .00001$), both in men ($r = 0.26$, $P = .03$, n = 79) and women ($r = 0.48$, $P = .003$, n = 43), and with insulin resistance (HOMA index) ($r = -0.30$, $P < .0001$) in both. Free cortisol correlated negatively with adiponectin only in women ($r = -0.32$, $P = .04$), but not in men ($r = 0.01$, $P = .89$).

Serum CBG concentration was significantly lower among men in the lowest quartile of adiponectin when compared with the remaining subjects (37.3 ± 5.7 vs 40.6 ± 5.1, $P = .016$), whereas men in the highest quartile of adiponectin showed significantly increased free cortisol index (14.2 ± 3.3 vs 12.2 ± 3.1, $P = .039$). Women in the lowest quartile of adiponectin also displayed significantly lower CBG concentration than that present in the remaining subjects (38.6 ± 6.9 vs 44.4 ± 5.5, $P = .016$), whereas free cortisol index was not significantly different across adiponectin quartiles ($P = .1$).

In a stepwise regression analysis, body mass index ($P = .0011$), CBG ($P = .0047$), and sex ($P = .04$) contributed to 15%, 8%, and 3%, respectively, of adiponectin variance. Using CBG as dependent variable, both adiponectin ($P = .0002$) and fasting cortisol ($P = .019$) contributed to 14% and 4%, respectively, of CBG variance.

In summary, circulating adiponectin, CBG concentration, and fasting cortisol were significantly interrelated in healthy subjects. A significant sexual dimorphism exists in this association.

1. Introduction

Adiponectin (also called Acrp30 or adipoQ in mice) is a 244–amino acid protein synthesized and secreted exclusively by the adipose tissue [1,2]. Adiponectin has been shown to modulate a wide array of biological functions. The carboxiterminal globular structure of adiponectin suggests a transductional pathway through recently identified receptors likely to be involved in the biology of complex

* Corresponding author. Diabetes, Endocrinology and Nutrition Research Unit, University Hospital of Girona "Dr Josep Trueta", Carretera de Francia s/n, 17007 Girona, Spain. Tel.: +34 972 94 02 00x2594; fax: +34 972 94 02 70.

E-mail address: uden.jmfernandezreal@htrueta.scs.es (J.-M. Fernandez-Real).

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disorders [3,4]. Adiponectin levels are under complex hormonal control, at least in rodents. The promoter region of *Apm1* contains consensus sequences for glucocorticosteroid receptor binding [5].

In in vitro studies, dexamethasone induced downregulation of adiponectin secretion [6-8]. This is in contrast to in vivo observations in which adiponectin was significantly upregulated by prednisolone [9]. In humans, we found a *positive* association between total serum cortisol and adiponectin [10]. Either lower fasting cortisol or loss of rhythmicity in cortisol production, as observed in complicated obesity [11], was hypothesized to lead to decreased adiponectin secretion [10]. However, it is also possible that the association between adiponectin and fasting serum cortisol is dependent on its carrier, corticosteroid-binding globulin (CBG).

Corticosteroid-binding globulin is the major blood transport protein for cortisol in humans [12,13]. Corticosteroid-binding globulin production and secretion are known to be regulated by cytokines and insulin [14-16]. In fact, both CBG and adiponectin have been demonstrated to circulate in inverse proportion to the degree of insulin resistance [17-20]. The mechanisms underlying these associations are unknown. However, it has long been recognized that there exist mutual influences between obesity, the hypothalamo-pituitary-adrenal axis, and insulin resistance [20]. Glucocorticoids have been postulated to contribute to the development of insulin resistance, and cortisol levels increase with the severity of obesity [21]. Adiponectin has been recently incorporated to this scheme. In addition, adiponectin has putative anti-inflammatory effects [22]. Adiponectin antagonized tumor necrosis factor-α in in vitro studies, and adiponectin knockout animals showed upregulated TNF-α expression [23]. In humans, there exists an inverse association between adiponectin and TNF-α action [10], and reciprocal associations with C-reactive protein in bloodstream and adipose tissue have also been described [24].

Table 1
Anthropometric and biochemical variables of the study subjects (significant *P* values are reported in the text)

	Men	Women
Number	79	43
Age (y)	43.1 ± 12.4	37 ± 10.2
Weight (kg)	76.4 ± 12.2	64.1 ± 12.8
Body mass index (kg/m^2)	25.9 ± 4	24.9 ± 5.4
Waist-to-hip ratio	0.96 ± 0.05	0.85 ± 0.05
Systolic blood pressure (mm Hg)	124.9 ± 14	121 ± 12
Diastolic blood pressure (mm Hg)	73.8 ± 10	70.1 ± 13
Fasting glucose (mmol/L)	5.2 ± 0.82	4.78 ± 0.59
Fasting insulin (mU/L)	7.5 ± 3.6	7.6 ± 3.3
HOMA value	1.56 ± 0.9	1.42 ± 0.74
Cholesterol (mmol/L)	5.74 ± 1.21	5.34 ± 1.14
Triglycerides (mmol/L)	1.32 ± 0.95	0.84 ± 0.32
Cortisol (nmol/L)	519.2 ± 154	427.9 ± 85
CBG (mg/dL)	40.8 ± 6.3	43.8 ± 7.5
Free cortisol index	12.9 ± 3.5	10.1 ± 2.0
Adiponectin (mg/L)	12.06 ± 6.9	16.0 ± 6.6

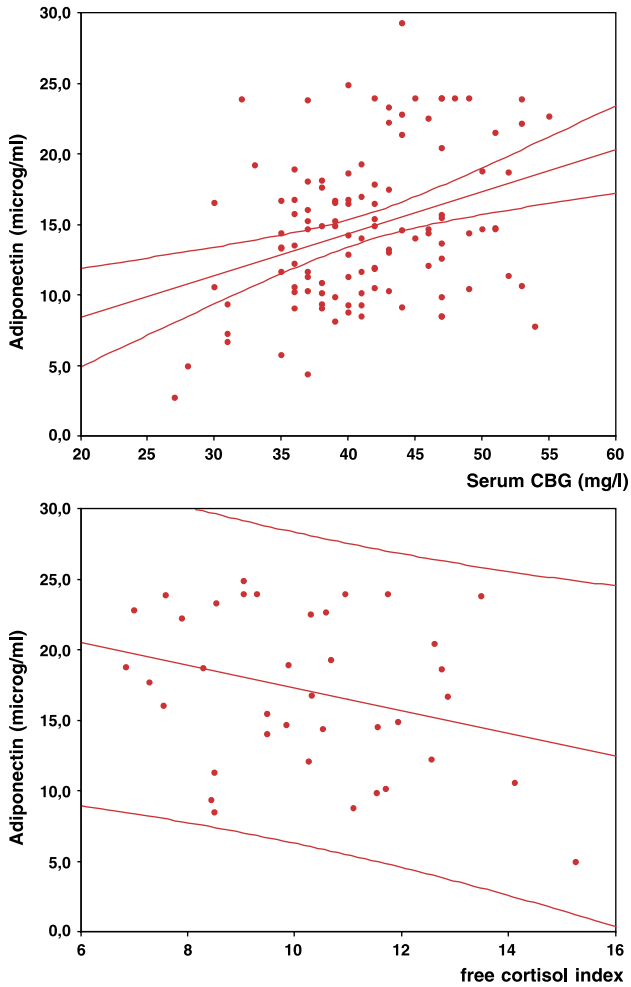

Fig. 1. Linear association between circulating CBG and adiponectin in all subjects (upper panel) and between adiponectin and free cortisol in women (lower panel).

No information is available regarding the possible influence of adiponectin on CBG, although both proteins are negatively regulated by IL-6 [8,15]. We therefore aimed to study the relationships among adiponectin, CBG concentration, fasting cortisol, and insulin resistance in apparently healthy subjects.

2. Research design and methods

2.1. Subjects

One hundred seventy-six white subjects (79 men and 43 women) were evaluated as part of an ongoing epidemiological study in Catalonia (Spain) aimed at evaluating inflammatory parameters in the prediction of cardiovascular risk. None of the subjects were taking any medication or had any evidence of metabolic disease, although some were obese. Their body weight was stable for at least 3 months before the study and they were normotensive. Once the subjects were seated, serum cortisol was evaluated in fasting samples obtained from an indwelling catheter, at −10 and

0 minutes, 20 and 30 minutes after venepuncture. The mean arithmetic value of the 2 measurements was considered as basal cortisol. Serum samples were obtained and frozen at −80°C until assay.

2.2. Anthropometric measurements

All subjects were evaluated through the body mass index (BMI), calculated as weight (in kilograms) divided by height (in meters) squared, and the waist-to-hip ratio. The subjects' waist was measured with a soft tape midway between the lowest rib and the iliac crest. The hip circumference was measured at the widest part of the gluteal region. Inclusion criteria were (1) BMI, <40 kg/m^2; (2) absence of any systemic disease; (3) absence of any infections in the previous month; (4) serum glucose lower than 6.6 mmol/L. Resting blood pressure was measured after the subjects had been in a sitting position for a minimum of 15 minutes. Using a mercury sphygmomanometer, the same investigator measured blood pressure 3 times in the right arm. The mean of 3 measurements was used for this study. None of the subjects were taking any medication (including glucocorticoids or estrogens) or had any evidence of metabolic disease other than obesity. Liver disease and thyroid dysfunction were specifically excluded by biochemical workup. All women had regular menstrual cycles and serum was obtained at the follicular phase. The protocol was approved by the Hospital Ethics Committee, and informed consent was obtained from each subject.

2.3. Analytical methods

The serum glucose concentration was measured in duplicate by the glucose oxidase method. The serum insulin level was measured in duplicate by monoclonal immunoradiometric assay (Medgenix Diagnostics, Fleunes, Belgium). The lowest limit of detection was 4.0 mU/L. The intra-assay coefficient of variation was 5.2% at a concentration of 10 mU/L. The interassay coefficient of variation was 6.9% at 14 mU/L. The fasting insulin resistance index (HOMA) was calculated through the formula: HOMA = fasting glucose (mmol/L) * fasting insulin (mU/L) / 22.5. In our experience, HOMA correlates with the S_I calculated using the minimal model approach ($r = 0.79$, $P < .0001$) [25]. Total serum cholesterol was measured through the reaction of cholesterol esterase/cholesterol oxidase/peroxidase. Total serum triglycerides were measured through the reaction of glycerol-phosphate-oxidase and peroxidase.

Plasma CBG concentration was measured by RIA (Radim, KP31, Angleur, Liège, Belgium) as previously described [26]. Serum cortisol was analyzed by RIA. The cortisol-

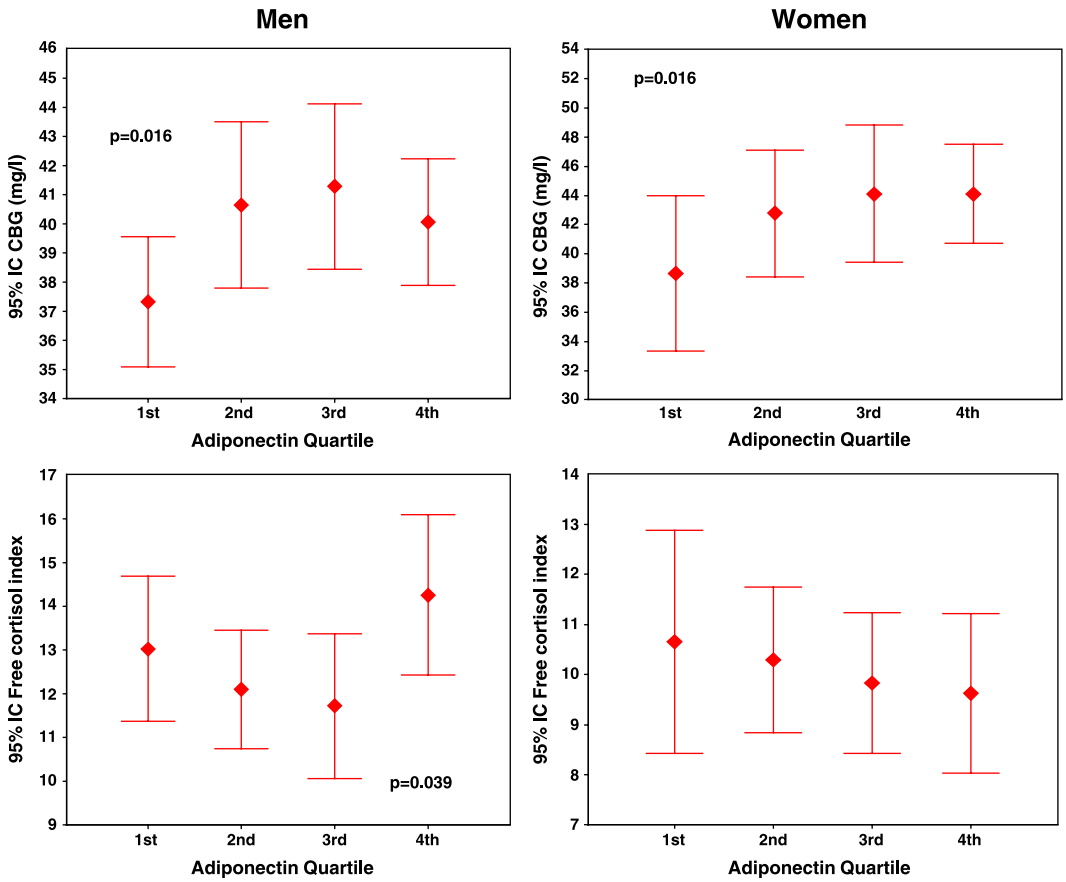

Fig. 2. Ninety-five percent confidence interval (IC) of serum CBG (upper panels) and free cortisol index (lower panels) in men and women according to adiponectin quartiles.

Table 2
Comparison among quartiles of serum adiponectin in men

Characteristic	Quartile adiponectin (95% CI for mean μg/L)				
	1 (7.39-9.33), n = 20	2 (11.4-12.4), n = 20	3 (14.8-15.5), n = 20	4 (18.3-24.0), n = 19	*P*
Adiponectin (mg/L)	8.36	11.9	15.2	21.1	.00001
Age (y)	38 ± 10.2	43.1 ± 10.7	38.5 ± 10.3	43.6 ± 15	NS
BMI (kg/m^2)	26.8 ± 4.7*	24.9 ± 3.2	24.6 ± 2.8	23.6 ± 4.1	.022*
Waist-to-hip ratio	0.98 ± 0.04	0.97 ± 0.04	0.95 ± 0.05	0.97 ± 0.05	NS
Fasting glucose (mmol/L)	5.06 ± 0.6	4.9 ± 0.55	4.68 ± 0.65	4.98 ± 0.93	NS
Fasting insulin (mU/L)	8.21 ± 4.3	6.6 ± 2.5	7.3 ± 2.46	6.68 ± 2.7	NS
HOMA index	1.92 ± 1.2**	1.37 ± 0.61	1.37 ± 0.55	1.36 ± 1.1	.08**
Fasting cortisol (mmol/L)	491.9 ± 136	525.8 ± 160	504.0 ± 172	564.2 ± 144	NS
CBG (mg/dL)	37.3 ± 4.4†	42.8 ± 8	41.4 ± 5.4	41.2 ± 5.3	.016†
Free cortisol index	13.02 ± 3.4	12.4 ± 3.3	12.2 ± 3.8	14.2 ± 3.3‡	.039‡

*,**,†,‡ *P* value in comparison with the rest of quartiles.

to-CBG ratio was used to calculate free cortisol. For the adiponectin assay (Linco Research), the inter- and intra-assay coefficients of variation were 4% and 7%, respectively.

2.4. Statistical analysis

Descriptive results of continuous variables are expressed as mean ± SD. Before statistical analysis, normal distribution and homogeneity of the variances were tested. Parameters that did not fulfill these tests (adiponectin, HOMA, triglycerides) were log-transformed. Comparison of proportions was made using χ^2 test. Comparison of variables between groups of subjects was performed using Student *t* test. Relationships between variables were sought by linear correlation analysis (Pearson's *r*) and by stepwise multivariate linear regression analysis. Levels of statistical significance were set at $P < .05$.

3. Results

Anthropometric and biochemical characteristics of the study subjects are shown in Table 1. Mean age ($P = .001$), BMI and waist-to-hip ratio ($P = .011$ and $P < .0001$, respectively), serum glucose ($P = .001$), and serum triglycerides ($P = .002$), but not serum insulin ($P = .73$), were significantly higher in men than in women. Women had significantly higher mean serum CBG concentration than men ($P = .01$) and significantly lower free cortisol index ($P < .0001$).

Circulating adiponectin was associated with serum CBG ($r = 0.38$, $P < .00001$), both in men ($r = 0.26$, $P = .03$) and in women ($r = 0.48$, $P = 0.003$) (Fig. 1), and with HOMA ($r = -0.30$, $P < .0001$). The measurement of cortisol was directly related to that of CBG in both men and women ($r = 0.35$, $P = .002$, and $r = 0.77$, $P < .00001$, respectively). However, although free cortisol index correlated negatively with adiponectin in women ($r = -0.32$, $P = .04$) (Fig. 1), it was not significantly associated in men ($r = 0.01$, $P = .89$) (Fig. 2).

To further characterize the link among adiponectin, CBG, and free cortisol index, we divided our population into quartiles of adiponectin (Tables 2 and 3). Men in the lowest quartile of adiponectin were more obese and tended to show increased HOMA values than the remaining subjects. In parallel with these factors, CBG was significantly lower in these subjects when compared with the remaining subjects (37.3 ± 5.7 vs 40.6 ± 5.1, $P = .016$) (Table 2 and Fig. 2). Unexpectedly, men in the highest quartile of adiponectin showed significantly increased free

Table 3
Comparison among quartiles of serum adiponectin in women

Characteristic	Quartile adiponectin (95% CI for mean μg/L)				
	1 (8.04-11.5), n = 11	2 (14.2-16.6), n = 11	3 (18.9-21.6), n = 10	4 (23.4-24.3), n = 11	*P*
Adiponectin (mg/L)	9.77	15.4	20.3	23.8	.00001
Age (y)	35.6 ± 8.6	36.5 ± 11.6	42.4 ± 11.9	35.8 ± 11.3	NS
BMI (kg/m^2)	26.1 ± 7.05*	24.4 ± 3.7	23.5 ± 3.5	21.6 ± 4.5	.1*
Waist-to-hip ratio	0.87 ± 0.05	0.85 ± 0.04	0.86 ± 0.03	0.85 ± 0.03	NS
Fasting glucose (mmol/L)	4.6 ± 0.5	4.7 ± 0.63	4.82 ± 0.52	4.59 ± 0.65	NS
Fasting insulin (mU/L)	8.09 ± 3.5	6.94 ± 2.4	5.73 ± 1.6	5.94 ± 1.87	NS (.1)
HOMA index	1.53 ± 0.53	1.50 ± 0.99	1.35 ± 0.85	1.10 ± 0.45	NS (.1)
Fasting cortisol (mmol/L)	404.3 ± 102	435.7 ± 71	442.1 ± 94	429.5 ± 75	NS
CBG (mg/dL)	38.6 ± 6.9†	42.7 ± 5.6	45.3 ± 6.4	45.1 ± 4.8	.016†
Free cortisol index	10.65 ± 2.8	10.3 ± 1.8	9.8 ± 1.8	9.62 ± 2.0	NS

*,† *P* value in comparison with the rest of quartiles.

cortisol index (14.2 ± 3.3 vs 12.2 ± 3.1, $P = .039$) (Table 2 and Fig. 2).

Women in the lowest quartile of adiponectin also displayed significantly lower CBG concentration than the remaining subjects (38.6 ± 6.9 vs 44.4 ± 5.5, $P = .016$) (Table 3 and Fig. 2). No significant differences were observed regarding free cortisol index, although a tendency toward significance was observed ($P = .1$).

In a stepwise regression analysis, using adiponectin as dependent variable, BMI ($P = .0011$), CBG ($P = .0047$), and sex ($P = .04$) contributed to 15%, 8%, and 3%, respectively, of adiponectin variance. Excluded variables in this model were fasting cortisol and HOMA. Using CBG as dependent variable, both adiponectin ($P = .0002$) and fasting cortisol ($P = .019$), but not sex ($P = .054$), BMI, or HOMA, contributed to 14% and 4%, respectively, of CBG variance.

4. Discussion

The main findings of this manuscript were as follows: (*a*) circulating adiponectin was positively associated with fasting cortisol in men. In addition, men in the highest quartile of adiponectin showed significantly increased free cortisol index; (*b*) on the contrary, adiponectin correlated negatively with free cortisol index in women; and (*c*) adiponectin was positively associated with CBG in both men and women.

Regarding the association between adiponectin and serum cortisol, the promoter region of the adiponectin gene (*Apm1*) contains consensus sequences for glucocorticosteroid receptor binding [5], and prednisolone has been described to upregulate circulating adiponectin in in vivo studies [9]. However, in vitro studies have shown that dexamethasone downregulated adiponectin secretion [6-8], and free cortisol index was negatively associated with adiponectin in women in this series. This apparent paradox has also been observed for another steroid hormone such as estrogen [9]. Estrogen suppresses adiponectin secretion, whereas basal adiponectin concentration is clearly greater in women than in men. This has been interpreted as that the inhibitory effect of elevated estrogen exposure in women cannot eliminate the sex-specific "set point" [9]. As for estrogen, it could be possible that a neonatal glucocorticoid/gonadal exposure [9], or the influence of stress, plays a major role in establishing a sexual dimorphism in the interaction between adiponectin and hypothalamo-pituitary axis.

A direct association between adiponectin and cortisol has also been reported by Gavrila et al [27] and by our group [10]. We confirm this association but specifically in men.

We also describe here an association between adiponectin and CBG. Both CBG secretion and adiponectin are negatively regulated by insulin and by several cytokines which are involved in insulin resistance [14-16,20], and specifically IL-6 [8,15]. In fact, inflammatory and anti-inflammatory pathways are increasingly recognized to be linked to human physiology [28]. The association between CBG and adiponectin could reflect these interactions. One alternative explanation is that adiponectin could directly influence CBG gene expression which would account for a link between body mass index, insulin resistance, and CBG. No information is available in the literature regarding the possible influence of adiponectin on liver protein synthesis in general or on CBG synthesis in particular. However, our observations are particularly interesting after considering recent findings that suggest that CBG deficiency modulates the response of human preadipocytes to glucocorticoids in humans, predisposing them to obesity. CBG-negative preadipocytes (from an individual with complete deficiency of CBG due to a homozygous null mutation) proliferated more rapidly and showed greater peroxisome proliferator–activated receptor-gamma–mediated differentiation than normal preadipocytes [29]. The relationships among cortisol, adiponectin, and CBG described here should be seen in this context. A low CBG could create a more favorable environment for glucocorticoid effect on preadipocytes to stimulate adipogenesis and inhibit adiponectin production [29]. These hypotheses are currently under investigation.

In summary, circulating adiponectin, CBG concentration, and cortisol covaried significantly in healthy subjects. Interestingly, a significant sexual dimorphism exists in this association.

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