

# Impact of weight loss on cortisol secretion in obese men with and without metabolic syndrome features

M. Dolores Parra

Tuesday, January 12, 2021 10:30 AM

## Introduction

This study investigates the differences in cortisol between overweight and lean individuals, as well as the impact weight loss has on cortisol levels.

## Conclusions

Lean individuals have much higher cortisol levels compared to overweight.

Cortisol plummets after consuming food.

Cortisol increases with weight loss in overweight individuals to near lean levels.

## Amendments

## Study Design & Additional Information

12 obese participants were recruited, 6 of the 12 had metabolic syndrome and the other 6 did not have metabolic syndrome (but were still obese). The researchers also recruited 6 healthy, non-obese men for the study as a comparison.

Participants went to the lab in the morning in a fasted state, and sat through the experiment that lasted 3 hours. Blood measurements were taken every 30 minutes after consuming a 100 calorie breakfast. The obese individuals (metabolic syndrome and non-syndrome) repeated the experiment 10 weeks later, after being put on a moderate calorie deficit to lose weight. They also increased their physical activity during the weight loss period.

Nutrition, Metabolism & Cardiovascular Diseases (2006) 16, 28–34



Nutrition,  
Metabolism &  
Cardiovascular Diseases

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## Impact of weight loss on cortisol secretion in obese men with and without metabolic syndrome features

M<sup>a</sup>. Dolores Parra, Blanca E. Martínez de Morentin,  
J. Alfredo Martínez\*

Department of Physiology and Nutrition, University of Navarra, C/Irurrunlarrea s/n,  
31008 Pamplona, Spain

Received 20 July 2004; received in revised form 14 October 2004; accepted 9 November 2004

### KEYWORDS

Obese;  
Cortisol;  
Metabolic syndrome;  
Weight loss;  
Calorie restriction

**Abstract** *Background and aim:* Disturbances in cortisol metabolism have been associated with obesity and metabolic syndrome development. The aim of this study was to evaluate the effect of weight loss induced by an energy-restricted diet on postprandial cortisol secretion in obese men with and without metabolic syndrome features.

*Methods and results:* Twelve obese men (BMI: 32.5–36.2 kg/m<sup>2</sup>), six without and six with at least three markers of metabolic syndrome, and six lean men (BMI: 22.2–24.9 kg/m<sup>2</sup>) participated. Plasma cortisol was measured at fasting and at 30 min intervals for 3 h after standard breakfast intake. Obese volunteers repeated those measurements after weight loss induced by a 10-week hypocaloric balanced diet. Fasting ( $p = 0.002$ ) and postprandial ( $p = 0.014$ ) cortisol secretions in obese men were statistically lower than in lean subjects. The slimming program produced a  $-0.9$  kg per week mean weight reduction with no differences between both groups ( $p = 0.297$ ). After weight loss, postprandial cortisol secretion increased in volunteers with ( $p = 0.028$ ) and without metabolic syndrome manifestations ( $p = 0.043$ ), as compared to baseline, achieving values near to those of controls. Cortisol levels negatively correlated with body weight ( $r = -0.61$ ;  $p < 0.001$ ).

*Conclusions:* Therefore, the effect of weight loss on cortisol metabolism appeared to be mediated by changes in body weight, which were apparently not affected by the occurrence of metabolic syndrome features.

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\* Corresponding author. Tel.: +34 948 425600; fax: +34 948 425642.  
E-mail address: [jalfmzt@unav.es](mailto:jalfmzt@unav.es) (J. Alfredo Martínez).

## Introduction

An interaction between disturbances in cortisol metabolism and the pathogenesis of obesity has been previously stated [1], based on some common features of Cushing's syndrome [2] and the metabolic syndrome manifestations [3], like central adiposity, insulin resistance, or type 2 diabetes mellitus [4,5]. Indeed, there is evidence that environmental stress can produce a progressive dysfunction of the hypothalamic–pituitary–adrenal axis, increasing cortisol levels [6], and this chronic status has been related to the development of central obesity and insulin resistance in subjects with genetic susceptibility [7].

However, low circulating levels of cortisol have also been reported in obesity [8]. These findings have prompted the occurrence of different mechanisms to explain the role of cortisol in obesity comorbidities, such as alterations in hypothalamic–pituitary–adrenal axis in response to feeding [9], glucocorticoid receptor dysfunctions [10], or an increment in cortisol turnover [11].

In order to elucidate the processes involved in these potential obesity-related disturbances, different dynamic probes have been developed to test the ACTH and the cortisol response against a challenge, such as intramuscular administration of glucagon [12], insulin administration [10], or the oral glucose tolerance test [13]. The food intake has also been reported to modify cortisol secretion [9,14]. In fact, nutrient intake has been applied to explore differences in hypothalamus–pituitary–

adrenocortical modulation between obese and lean subjects [15].

In this context, the aim of the present work was to evaluate the cortisol response using a non-aggressive protocol in which the macronutrient intake was controlled, in obese subjects with and without metabolic syndrome, as well as the effect of weight loss in this process.

## Methods

### Subjects

The volunteers enrolled were 12 obese individuals (body mass index between 32.5 and 36.2 kg/m<sup>2</sup>), who were recruited by a physician of the Department of Physiology and Nutrition of the University of Navarra. Six of these were considered as obese with metabolic syndrome, based on the presence of three or more of the following characteristics according to the National Cholesterol Education Program [16]: waist circumference greater than 102 cm; blood pressure of at least 130/85 mmHg; serum glucose level of at least 110 mg/dl (6.1 mmol/l); serum triacylglycerol level of at least 150 mg/dl (1.69 mmol/l); and high-density lipoprotein (HDL) cholesterol level of less than 40 mg/dl (1.04 mmol/l). Also, six healthy men (body mass index between 22.2 and 24.9 kg/m<sup>2</sup>) acted as control group (Table 1). The inclusion procedure required that all volunteers (24–42 years old) give their written informed consent,

1. Low levels of cortisol are associated with obesity.

2. 12 obese participants were recruited, 6 of the 12 had metabolic syndrome and the other 6 did not have metabolic syndrome (but were still obese). The researchers also recruited 6 healthy, non-obese men for the study as a comparison.

**Table 1** Demographic and metabolic syndrome markers of volunteers at baseline

Demographic and metabolic syndrome markers	Lean healthy controls	Obese without metabolic syndrome features	Obese with metabolic syndrome features	Differences between groups (ANOVA <i>p</i> -value)
Body mass index (kg/m <sup>2</sup> )	23.8 ± 1.5	34.8 ± 1.8*	34.1 ± 2.0*	0.000
Waist/hip ratio	0.86 ± 0.02	0.96 ± 0.07*	1.00 ± 0.07* <sup>#</sup>	0.001
Systolic blood pressure (mmHg)	122 ± 12	130 ± 12	133 ± 11	0.250
Diastolic blood pressure (mmHg)	78 ± 9	83 ± 4	88 ± 7	0.087
Plasma triacylglycerol (mg/dl)	67.8 ± 54.3	93.2 ± 31.3	203.5 ± 121.0* <sup>#</sup>	0.017
Plasma HDL-cholesterol (mg/dl)	43.5 ± 9.1	46.2 ± 5.4	41.1 ± 4.3	0.363
Homeostatic model assessment for insulin resistance (HOMA-IR)	0.88 ± 0.33	2.80 ± 1.73	4.72 ± 2.69* <sup>#</sup>	0.008

Data are expressed by the mean ± standard deviation. Differences between groups are expressed by the ANOVA *p*-value. Statistical differences (*p* < 0.05) estimated by the Bonferroni post hoc test are expressed as \* (with respect to lean group) and # (with respect to both obese groups).

which had previously been approved by the Ethics Committee of the University of Navarra, in agreement with the Helsinki Declaration.

#### Study design

The experimental protocol started at 8:30 a.m. and was performed after an overnight fast, at rest with the subjects seated throughout a 3-h period. A catheter was inserted into an antecubital vein for blood extraction. Blood was taken every 30 min for 3 h, after ingestion of a normalized breakfast (test meal) with a controlled macronutrient distribution of 57.9% energy from carbohydrates, 37.2% from proteins, and 4.9% from lipids, and a total energy content of 107 kcal (Meritene, Novartis, Switzerland). Obese volunteers repeated this experimental protocol after the nutritional intervention trial devised to lose weight (day 70).

#### Weight loss program

One day after the hormone secretion test, the obese volunteers began a weight-reduction program by applying a calorie-restricted otherwise balanced diet (carbohydrates: 55%; lipids: 30%; proteins: 15%) during 10 weeks. The calorie restriction was 500 kcal less than the resting energy expenditure measured by indirect calorimetry (Deltatrac, Datex-Ohmeda, Finland), based on a previously described procedure [17], in every participant.

The physical activity pattern was not increased during the slimming period, which was assessed and controlled by a dietitian of the Department of Physiology and Nutrition at the University of Navarra.

#### Blood measurements

General biochemical determinations, which included plasma levels of glucose and lipid profile, were assayed on an LX-20 autoanalyser (Beckman, USA). Plasma levels of ACTH were measured by an automated immunoassay on an IMMULITE analyser (DPC, USA, intra-assay variability:  $5.6 \pm 2.3\%$ ; inter-assay variability:  $7.8 \pm 1.8\%$ ), and plasma levels of cortisol (intra-assay variability:  $4.7 \pm 0.7\%$ ; inter-assay variability:  $5.2 \pm 1.2\%$ ), and insulin (intra-assay variability:  $5.2 \pm 2.5\%$ ; inter-assay variability:  $7.3 \pm 2.1\%$ ) were assessed by using commercially available radioimmunoassays (DPC, USA). Insulin resistance was indirectly determined by the homeostatic model assessment index (HOMA-IR), as the multiplication of fasting

insulinemia ( $\mu\text{U/ml}$ ) and glycemia (mM) and divided by 22.5 corrected factor [18].

According to the established values from the Laboratory of Biochemistry of the University Clinic of Navarra, the normal range for fasting plasma ACTH was between 10 and 55 pg/ml, for cortisol it was between 5 and 25  $\mu\text{g/dl}$ , and for insulin  $< 25 \mu\text{U/ml}$ .

#### Statistical analysis and other calculations

The Kolmogorov–Smirnov and the Shapiro–Wilk tests were used to determine variable distribution. The Kruskal–Wallis, the Wilcoxon for matched pairs and the Mann–Whitney *U*-tests were performed to analyse non-parametric data between groups, and the Pearson correlation coefficient was used to identify related variables. Weight loss was analysed using the paired Student *t*-test. Hormone secretion was calculated as the area under the plasma level curve, using the trapezoidal rule [18]. Analyses of variance (ANOVA) together with the Bonferroni post hoc test were applied for the general comparison of data between groups (analysis of differences between lean control and both obese groups). Results are reported as mean  $\pm$  SE, and statistical significance was set at  $p < 0.05$ . Statistical analysis was performed using the SPSS 11.0 program for Windows 98 (Microsoft, USA).

### Results

#### Basal metabolic markers

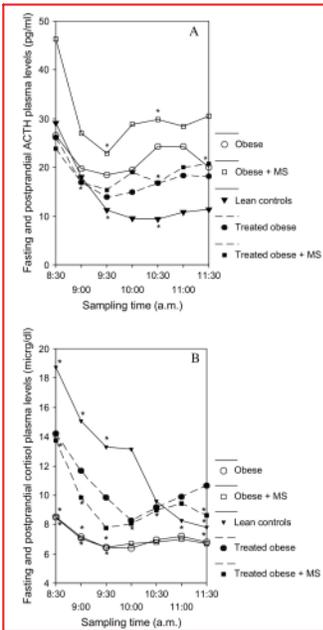
Obese subjects showed higher values for triacylglycerol, glucose and insulin, as well as for homeostasis model assessment, than lean individuals (Table 1). As designed, there were predicted differences and trends between both groups of obese subjects concerning metabolic syndrome features (Table 1).

Lean and obese volunteers had plasma levels of ACTH in the normal range at baseline (from 10 to 55 pg/ml), and no statistical differences ( $p = 0.555$ ) were found between groups (Fig. 1A). Also, basal plasma levels of cortisol were in the normal range (from 5 to 25  $\mu\text{g/dl}$ ), but the obese volunteers showed the lowest ( $p = 0.002$ ) hormone levels (Fig. 1B).

#### Weight-reduction effect on metabolic markers

After the dietary intervention devised to lose weight, body weight reduction (Table 2) was

- Participants went to the lab in the morning in a fasted state, and sat through the experiment that lasted 3 hours. Blood measurements were taken every 30 minutes after consuming a 100 calorie breakfast. The obese individuals (metabolic syndrome and non-syndrome) repeated the experiment 10 weeks later, after being put on a moderate calorie deficit to lose weight. They also increased their physical activity during the weight loss period.



**Figure 1** Time-course curves concerning plasma levels of adrenocorticotrophic hormone and cortisol in lean controls and obese with and without metabolic syndrome, before and after weight loss induced by a 10-week caloric restriction program. The statistical significance ( $p < 0.05$ ) estimated by the Bonferroni post hoc test comparing each obese group and the lean volunteers and the intra-group differences in obese volunteers, before and after the weight loss, are expressed as \*.

statistically significant for obese volunteers with metabolic syndrome features, mean and 95% C.I.:  $-9.7\%$  [ $-13.9\%$  to  $-5.5\%$ ], and for the control obese subjects, mean and 95% C.I.:  $-7.8\%$  [ $-8.9\%$  to  $-6.7\%$ ], and no differences were detected between both groups regarding the percentage weight loss outcome ( $p = 0.297$ ). The intervention

globally improved the measured metabolic and hormonal biomarkers, although no differences in this beneficial effect were detected between both diet-treated obese groups (Table 2).

After the slimming process (Table 2), the ACTH tended to be lower than at baseline, but no statistical differences were detected. In contrast, raising levels of circulating cortisol accompanied the weight loss, both in obese with ( $p = 0.028$ ) and without ( $p = 0.043$ ) metabolic syndrome manifestations (Table 2).

#### Weight-reduction effect on circulating cortisol and adrenocorticotrophic changes

Before weight loss, ACTH plasma levels fell during the first exploration in which the challenge load was administered, being statistically different ( $p = 0.002$ ) in obese volunteers with respect to the control group (Fig. 1A). In fact, lean men had the area under the time-course curve lower than obese with ( $p = 0.011$ ) and without ( $p = 0.002$ ) metabolic syndrome (Fig. 2A).

Cortisol plasma levels clearly decreased in lean men under the experimental challenge period, while this secretion only had a soft slope in the obese groups (Fig. 1B). Controls showed the highest area under the cortisol curve, with statistical significance ( $p = 0.039$ ) with respect to the metabolic syndrome group, and with marginal significance ( $p = 0.055$ ) in comparison with otherwise healthy obese (Fig. 2B).

When the obese individual lost body weight, the plasma levels of both hormones tended to reproduce the profile registered in lean men (Fig. 1A and B). Thus, the circulating ACTH levels decreased ( $p = 0.003$ ) in the treated metabolic syndrome group (Fig. 2A), as well as in the obese without the syndrome ( $p = 0.014$ ). Likewise, cortisol plasma levels increased after the weight loss in both obese groups, with ( $p = 0.028$ ) and without ( $p = 0.043$ ) metabolic syndrome manifestations (Fig. 2B). Accordingly, the association analyses showed that fasting plasma levels of cortisol were inversely correlated with postprandial ACTH secretion ( $r = -0.51$ ;  $p = 0.003$ ) as well as with body weight ( $r = -0.61$ ;  $p < 0.001$ ).

#### Discussion

It is widely recognized that secondary obesity to Cushing's syndrome is related to high levels of circulating cortisol, as well as the role that this

#### Figure 1

This data shows the differences in adrenocorticotrophic hormone (ACTH, stimulates cortisol release) [1A] and cortisol levels [1B] in healthy individuals, obese individuals without metabolic syndrome, obese individuals with metabolic syndrome, and then again with "treatment" (the weight loss over 10 weeks). The 8:30am time point is a fasting condition, and all the others are after eating the same breakfast.

#### Primary Results:

- Obese with metabolic syndrome and without metabolic syndrome have lower cortisol compared to healthy participants.
- Both obese conditions after weight loss have increased cortisol compared to their pre-weight loss selves.
- Healthy participants have the greatest levels of fasting cortisol.

#### Take Away:

There is cortisol dysregulation in obese individuals, regardless of metabolic syndrome. Healthy individuals have elevated cortisol levels when fasting that sinks when eating.

**Table 2** Metabolic changes reflected by biomarkers after the weight-reduction intervention

Biomarkers	Obese without metabolic syndrome features		Obese with metabolic syndrome features		Inter-group difference (95% C.I.)
	Baseline	After weight loss	Baseline	After weight loss	
Body weight (kg)	110.1 ± 8.9	99.4 ± 4*	101.7 ± 9.5	93.7 ± 8.7*	[-6.1 to 2.3], NS
Plasma cholesterol (mg/dl)	211 ± 53	177 ± 30	198 ± 14	176 ± 38	[-19.9 to 15.2], NS
Plasma glucose (mg/dl)	91 ± 10	86 ± 11	90 ± 8	87 ± 4	[-14.7 to 9.3], NS
Plasma insulin (μU/ml)	12.3 ± 7.1	8.9 ± 3.9	20.0 ± 11.3	11.3 ± 5.8*	[-13.9 to 72.5], NS
Plasma ACTH (pg/ml)	25.6 ± 8.3	26.1 ± 13.9	43.8 ± 25.8	29.6 ± 16.8	[-50.3 to 118.9], NS
Plasma cortisol (μg/dl)	8.7 ± 0.9	14.2 ± 2.8*	8.6 ± 2.5	14.7 ± 3.1*	[-77.5 to 39.7], NS

Statistical differences ( $p < 0.05$ ) with respect to baseline are expressed as \*. The comparison between both obese groups concerning the changes occurring after the weight loss is expressed by means of the 95% confidence intervals ( $p > 0.05$  is expressed as NS).

hormone plays in body fat distribution [19]. Based on the common features accompanying Cushing and metabolic syndromes [20], a relationship between the disruption of hypothalamus–pituitary–adrenocortical axis and the development of obesity and co-morbidities has been suggested [21,22]. However, idiopathic obesity usually shows normal or decreased basal cortisol levels [10].

In the current research, no differences in basal adrenocorticotrophic hormone levels were found between obese and lean volunteers, as other authors have reported [23]. However, obese individuals had statistically lower plasma cortisol levels than lean subjects. Despite that no pathological levels were found, the low circulating cortisol could indicate a subclinical disturbance in the hypothalamus–pituitary–adrenocortical axis.

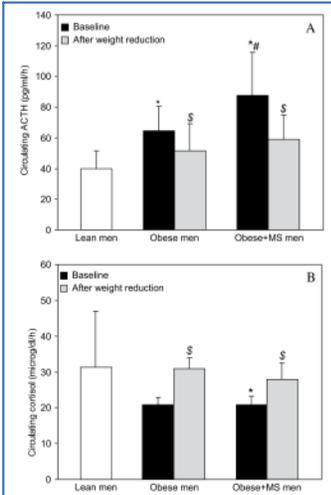
In this context, basal plasma cortisol levels could not evidence abnormalities on obesity, while the cortisol profile could be impaired under some circumstances [10]. Based on this assumption, we performed a dynamic probe, with time control and test meal intake, and involving the analysis of blood samples taken during 3 h in the morning, having in mind the circadian rhythm of cortisol. The protocol included the acute ingestion of a test breakfast, in which carbohydrate and protein were the main macronutrients, since food intake could modify cortisol secretion [9,14]. Thus, higher ACTH and lower cortisol levels were detected in both obese groups as compared to lean volunteers, but within the laboratory reference range. These results point to the lack of a major disturbance in the hypothalamus–pituitary–adrenocortical axis in primary obesity [10,11,13]. In fact, the

circulating cortisol and the adrenocorticotrophic hormone were inversely correlated, supporting this statement.

Furthermore, similar circulating ACTH and cortisol profiles were found in both obese groups. According to this, the reduced plasma levels of cortisol could be mainly linked to adiposity instead of metabolic syndrome features. Indeed, circulating cortisol and ACTH tended to approach control values after the calorie restriction period, showing the reversibility of obesity-related abnormalities in cortisol metabolism [24,25,26]. However, a role for the change in dietary constituents instead of weight loss could not be ruled out, in the light of some recent findings concerning different macronutrient distribution intake [9,13,25].

Curiously, obesity has been related to an increased tissue cortisol production [13,23,26], despite the low circulating cortisol levels. This apparent controversy could be explained in terms of a high hormone clearance rate [27,28], which involves changes in enzyme activities and receptor functions [26,29]. These processes could be adaptive mechanisms, different to hypothalamic–pituitary–adrenocortical axis, to modulate the obesity-related cortisol excess [10,25,27,30]. Therefore, body fat accumulation could be one of the required signals to increase cortisol turnover in obese subjects [28,31]. Supporting this, cortisol levels changed after the body fat loss related to the slimming, both with and without metabolic syndrome volunteers. On the other hand, this nutritional intervention was less aggressive than previous works in which very low calorie diet were applied to reduce body weight [26,32]. Therefore,

4. Other studies have shown different results with different macronutrient intakes. Also, adrenal glands have been implicated in increasing their production of cortisol in obesity, which might imply that low cortisol in obese individuals could be explained by high hormonal clearance.



**Figure 2** Circulating adrenocorticotrophic hormone and cortisol calculated as the area under the concentration time-course curves. Statistical differences ( $p < 0.05$ ) with respect to lean controls are expressed as \*, between obese with and without metabolic syndrome by # and differences with respect to baseline levels by §.

the potentially confounding effect of calorie restriction on stress could be considered as negligible in our work.

In conclusion, obese men had lower cortisol but not adrenocorticotrophic hormone levels than lean volunteers under our experimental conditions. This decrease in plasma cortisol profile seems to be the outcome of a higher cortisol clearance when the hypothalamus–pituitary–adrenocortical axis is not impaired in idiopathic obesity. Our results confirm this observation, since the weight loss process is able to improve plasma cortisol levels. The beneficial effect of slimming was not apparently related to the metabolic syndrome status, seeming to be mainly mediated by changes in body weight.

Although the trial involved a relatively small number of volunteers, these findings suggest the involvement of cortisol on body weight homeostasis, which could be a target to develop new therapeutic strategies for obesity treatment based on conjoint dietary and pharmacological approaches.

#### Acknowledgements

Thanks are given to the Government of Navarra (Public Health and Education Departments) that has supported this work included in the *Linea Especial* of the University of Navarra. We also thank our nurse Salomé Pérez and our technicians Ana Lorente and Verónica Ciaurritz, as well as the Laboratory of Biochemistry of the University Clinic of Navarra, for the excellent technical assistance.

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#### Figure 2

This data shows the differences in adrenocorticotrophic hormone (ACTH, stimulates cortisol release) [2A] and cortisol levels [2B] in healthy individuals (white bars), obese individuals without metabolic syndrome (black bars), obese individuals with metabolic syndrome (black bars), and then again with 'treatment' (gray bars, the weight loss over 10 weeks).

#### Primary Results

- Cortisol is lower in obese individuals (with and without metabolic syndrome).
- Cortisol rises after weight loss.

**Take Away:** Cortisol is dampened in obese individuals, but that effect is reversed with weight loss.

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