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*Full Length Research Paper*

# Corticosteroid binding globulin and glucocorticoid receptor genotypes influence body composition in a male population

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**Glucocorticoid Receptor (GR) polymorphisms have been repeatedly associated with obesity and metabolic parameters in man. We have previously shown the genetic influence of a polymorphism in the gene encoding CBG on some obesity parameters in a small female population. In this study we have explored possible genetic associations between obesity and metabolic measures and CBG or GR polymorphisms in a new male population. Two hundred and ninety-five men with body mass index (BMI) ranging from 19 to 55 kg/m$^2$ were studied. Serum CBG levels, CBG and GR gene polymorphisms in relation with anthropometric and biochemical parameters were analysed. GR BclI polymorphism was found to influence weight, BMI, waist circumference and glucose levels. CBG polymorphism showed a significant effect for BMI and waist circumference. The frequency of CBG allele 90 was markedly increased among men with morbid obesity compared to the rest of the population (30 versus 18%, p=0.02). The influence of GR BclI polymorphism is replicated in an additional population and CBG polymorphism has a small but significant influence on obesity in men. Further studies are needed to understand the mechanism by which these polymorphisms impact on cortisol and obesity.**

**Key words:** Obesity, genetics, cortisol, transcortin, glucocorticoids.

## INTRODUCTION

The metabolic syndrome which includes insulin resistance, glucose intolerance, dyslipidemia, hypertension and type II diabetes arises from disproportionate accumulation of visceral fat mass. Chronic excessive cortisol secretion such as in Cushing's syndrome leads to abdominal obesity and metabolic syndrome (Bjorntorp and Rosmond, 2000; Rosmond et al., 1998). As cortisol is known to regulate adipose tissue differentiation, function and distribution in the presence of high insulin levels, a rise in cortisol concentration or bioavailability may result into fat mass deposits in hyperinsulinemic patients (Bjorntorp and Rosmond, 2000). However, no clear relationship between visceral obesity and the hypothalamo-pituitary adrenal (HPA) axis activity has been reported so far. Indeed, most patients with visceral obesity and metabolic syndrome have normal or even low circulating cortisol levels. These findings have suggested that an altered peripheral metabolism of cortisol, increased clearance, differences in cortisol feedback sensitivity or variation in glucocorticoid target tissue sensitivity may contribute to the development of obesity (Walker, 2001).

As glucocorticoids exert most of their effects by binding to the glucocorticoid receptor (GR), a high number of studies have examined polymorphisms in the gene encoding the GR in relation to obesity and metabolic parameters to explain individual vulnerability. Indeed, several polymorphisms within the GR gene that influence glucocorticoid sensitivity have been described and associated with body composition and metabolic parameters (Van Rossum and Lamberts, 2004). However, many other genes are susceptible to play a role in cortisol

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driven obesity. Corticosteroid Binding Globulin (CBG) is of particular interest because of its physiological role and the recent reports highlighting its putative role in obesity. CBG is a glycoprotein synthesized mainly in liver and secreted in blood where it forms a high affinity complex with glucocorticoids (Breuner and Orchinik, 2002). Serum CBG levels have been shown to be negatively correlated with body mass index (BMI), waist-to-hip ratio, blood pressure and HOMA (homeostasis model assessment) in a human healthy Spanish population (Fernandez-Real et al., 2002) with metabolic syndrome markers such as plasma triacylglycerol concentrations and fasting blood glucose in a population of French obese women (Duclos et al., 2005). Additionally, patients with a null mutation in the CBG gene tend to be obese (Torpy et al., 2001) and it is hypothesized that absence of CBG induces locally, in adipose tissue, increased cortisol levels. Finally, by genetic mapping analysis on a pig intercross, we recently reported that CBG gene is a strong candidate for a quantitative trait locus associated with cortisol level and fat deposits (Ousova et al., 2004). CBG genetic polymerphisms have been tested in human obesity only in one small women population. In that report, we had examined the influence of CBG genotype in a female obese population extensively phenotyped for the HPA axis activity. We had shown that a strong correlation between obesity parameters (waist-to-hip ratio, waist circumference) and cortisol level was observed only for patients harbouring CBG allele 90 suggesting that this polymorphism influences cortisol driven fat distribution (Barat et al., 2005). To dissect further the putative role of CBG in obesity, we studied the influence of CBG polymorphism on a large male population phenotyped for obesity, visceral fat mass and metabolic parameters. We analysed also the role of the BclI polymorphism within the intron 2 of the GR gene, as the importance of this polymorphism in obesity and insulin resistance has been replicated in several population studies (Van Rossum and Lamberts, 2004).

## MATERIAL AND METHODOLOGY

### Inclusion and exclusion criteria

This is a retrospective study on a total of 295 men consisting of two populations. First, 253 consecutive, unselected (except for inclusion criteria, see below) Caucasian subjects, participants in an ongoing epidemiological study that began on 2003 of risk factors for cardiovascular disease in Northern Spain, were included in the study. Subjects were randomly localized from a census and they were invited to participate. The participation rate was 71%. None of the subjects was taking any medication or had any evidence of metabolic disease other than obesity. All subjects reported that their body weight had been stable for at least three months before the study. All subjects underwent a 75 g oral glucose tolerance test to define glycemic status. Inclusion criteria were:

1) Absence of any systemic disease.
2) Absence of clinical symptoms and signs of infection in the previous month by structured questionnaire to the patient.
3) Hepatitis C virus antibody sero-negative.

Cushing's syndrome was routinely excluded by using normal 24 h urinary free cortisol as exclusion criteria. Second, we also studied an additional series of 42 consecutive men with morbid obesity from the outpatients' clinic. These obese patients are all Caucasians and come from the same geographical area as the first population. Informed consent was obtained from all subjects. Local Ethics Committee approved the study.

### Measurements

Fat mass and percent fat mass were calculated using bioelectric impedance (Holtain BC Analyzer, UK). Blood pressure was measured in the supine position on the right arm after a 10 min rest; a standard sphygmomanometer of appropriate cuff size was used and the first and fifth phases were recorded. Values used in the analysis are the average of three readings taken at 5 min intervals. Patients were requested to withhold alcohol and caffeine during at least 12 h prior to the different tests.

### Assays

Blood samples were drawn from each subject after an overnight fasting period. Serum glucose concentrations were measured in duplicate by the glucose oxidase method with the use of a Beckman Glucose Analyser II (Beckman Instruments, Brea, CA). The coefficient of variation was 1.9%. Glycated hemoglobin (HbA1c) was measured by high performance liquid chromatography by means of a fully automated glycated hemoglobin analyser system (Hitachi L-9100, USA). Normal range among 774 subjects with normal glucose tolerance was 4.71 ± 0.46%. Total serum cholesterol was measured through the reaction of cholesterol esterase /cholesterol oxidase/peroxidase. Total serum triacylglycerol was measured through the reaction of glycerol-phosphate-oxidase and peroxidase. The plasma CBG concentration was measured by radio-immunoassay (Radim, KP31, Angleur, Liege, Belgium). Intra- and inter-assays coefficients of variation were 3.6 and 7.5%, respectively.

### Genetic analysis

Genomic DNA was isolated from peripheral blood samples using the commercially available extraction kit QIAamp DNA blood (Qiagen, France). CBG and GR polymorphisms were analysed by PCR as described in reference (Barat et al., 2005).

### Statistical analysis

Data are expressed as the mean ± SEM. Statistica v.6 software was used. ANOVA or non parametric Kruskal-Wallis tests were performed to compare variables between groups. Correlations between variables were performed using Spearman's correlation test. Fisher's exact test was used to compare allele frequencies among groups. The level of statistical significance used was a p value less than 0.05. The statistical power for the difference in BMI between carriers and non carriers of the polymorphism was 99% for both polymorphisms (considering a mean difference between groups of 3 points of BMI and an overall SD of 0.7).

## RESULTS

The frequency of CBG genotypes was in Hardy-Weinberg equilibrium in the whole population and did not differ from previous report [21], 86/86: 63%, 86/90: 34% and 90/90: 2.7%. First, patients of the whole cohort were grouped according to their CBG or GR genotype and compared for

**Table 1.** Influence of genotype on patient's obesity.

| | Weight (kg) | BMI (kg/m2) | Waist (cm) | Glucose (mM) | TG (mM) | CBG (nM) |
|---|---|---|---|---|---|---|
| CBG 86/86 (n) | 87.7±1.6 (186) | 29.7± 0.5 (186) | 97.7±1.3 (181) | 5.7±2.2 (185) | 1.3±0.1 (178) | 744±11 (169) |
| CBG 90/-(n) | 95.1± 2.8 (109) | 32.1±0.9 (107) | 102.9± 2.0 (106) | 5.7±0.1 (108) | 1.3±0.1 (103) | 714 ±12 (101) |
| p | ns | 0.039 | 0.049 | ns | ns | 0.09 |
| GR C/C(n) | 87.3±2.2 (122) | 29.6±0.7 (122) | 96.6±1.6 (118) | 5.4±0.1(121) | 1.2±0.1 (118) | 731±11 (120) |
| GR G/- (n) | 94.6±2.2 (144) | 31.9±0.7 (144) | 103.0±1.7 (140) | 5.9±0.1(143) | 1.4±0.1(134) | 744±12 (105) |
| p | 0.014 | 0.017 | 0.009 | 0.004 | 0.064 | ns |
| 86/C | 83.7±2.9 (77) | 28.5±0.7 (77) | 94.3±1.8 (76) | 5.3±0.1(77) | 1.2±0.1 (75) | 744.4±15 (75) |
| 86/G | 92.2±3.0 (73) | 31.1±0.9 (73) | 100.8±2.3 (69) | 5.9±0.2 (72) | 1.3±0.1 (68) | 738.8±16 (66) |
| 90/C | 93.4±3.8 (45) | 31.4±1.3 (45) | 100.9±3.1 (42) | 5.5±0.1 (44) | 1.2±0.1 (43) | 729.4±15 (42) |
| 90/G | 97.1±3.0 (71) | 32.8±1.1 (71) | 105.2±2.5 (71) | 5.9±0.2(71) | 1.5±1.1 (66) | 714.4±18 (64) |
| p | 0.046 | 0.025 | 0.01 | 0.016 | ns | ns |
| p(86C vs 90G) | 0.049 | 0.017 | 0.006 | 0.015 | NA | NA |

Data are presented as means ± SEM. **BMI**; body mass index, **TG**; triacylglycerols, **n**; number of subjects, **p**; p value of non parametric Kruskal-Wallis analysis of variance test, p (86C vs90G) and p value for bilateral comparison between groups 86C and 90G. ns= non significant; NA= not applicable.

for every phenotype measured. Subjects with 86/90 and 90/90 CBG genotypes, named "90/-"were combined in statistical analysis because of the small number of 90/90 patients. Non parametric Kruskal-Wallis test was used to compare the groups as the variances of groups were often not homogenous. The main results are summarized in Table 1. CBG genotype was found to influence signify-cantly BMI and waist circumference. A trend toward lower serum CBG levels was found in 90/- patients compared to 86/86 ones (CBG (nM): 714 ± 12, n=101 vs. 744 ± 11, n=169 respectively, p=0.07 by ANOVA, p=0.09 by Kruskal-Wallis test). This trend became significant when subjects with morbid obesity were excluded from the analysis (701.0 ± 11.4, n=83 vs. 741.8 ± 11.2, n=159 respectively, p=0.012). No difference was found for blood pressure, plasma glucose, cholesterol, HDL and fasting triacylglycerols between CBG genotypes. The frequency of GR genotypes was also found in Hardy-Weinberg equilibrium in the whole population C/C: 45.9%, C/G: 44.3%, G/G: 9.8%, that is, 68.9% allele C and 31.1% allele G which is comparable to previous reports [24]. Subjects with G/C and G/G GR genotypes, named "G/-"were combined in statistical analysis because of the small number of G/G patients (Table 1). Weight, BMI, waist circumference, and plasma glucose were found significantly increased in G/- compared to C/C patients and they also show a trend towards higher fasting triacyl-glycerols. No difference was found for blood pressure between GR genotypes. Finally, subjects were stratified in four groups according to their genotype at both CBG and GR loci. Overall the same results (p value) were found as for GR analysis but the groups means are more contrasted between 86/C and 90/G suggesting an addi-tive effect of genotypes at CBG and GR loci.

In a second step, patients were divided in different groups according to Garrow's classification: lean (BMI below 25), overweight (BMI between 25 and 30), obese (BMI between 30 and 40) and morbidly obese patients (BMI greater than 40). Anthropometrical and biochemical data are summarized in Table 2. Fifty-six percent of mor-bidly obese subjects had three or more components of the metabolic syndrome according to ATP III criteria. We compared allelic distribution between these patients gro-ups. Although no difference was found between lean, overweight and obese subjects, the frequency of CBG allele 90 rose from 18 to 30% in morbidly obese patients (Table 3). Among these morbidly obese subjects, serum CBG concentration was negatively associated with BMI (n=28, r =-0.4133, p = 0.029) and waist circumference (n= 27, r =-0.4163, p = 0.031). These correlations were not found when the total population is considered. A trend towards increased frequency of GR G allele was obser-ved in obese subjects (p = 0.07) that became significant in morbidly obese subjects (Table 3).

Finally, when serum CBG concentration was analysed as dependent variable and BMI, fasting glucose and CBG gene polymorphism as independent variables, stepwise multiple linear regression analysis showed that in non-obese subjects, only BMI (not glucose or CBG gene poly-morphism) contribute to almost 6% of the serum CBG variance ($R^2$ = 0.059, p < 0.0001). In obese subjects, both BMI (p = 0.001) and CBG gene polymerphism (p=0.023) independently contribute to 5.4 and 2.5%, res-pectively, of serum CBG variance ($r^2$ in additive models of 0.054 and 0.079).

## DISCUSSION

In this study, we have found that CBG genotype is associated with BMI and waist circumference in a male population. Furthermore, the frequency of CBG allele 90 is markedly increased in the morbid obese population.

Our data suggest that this CBG polymorphism is associated with decreased CBG levels. Indeed, in the

**Table 2.** Anthropometrical and biochemical variables of the study subjects according to BMI.

| | Normal | Overweight | Obese | Morbidly obese |
|---|---|---|---|---|
| n | 65 | 118 | 67 | 45 |
| Age (year) | 47.1 ± 1.6 | 52.8 ± 1.02 | 51.2 ± 1.8 | 42.3 ± 1.8 |
| Obesity parameters | | | | |
| Weight (kg) | 68.5 ± 0.8 | 65.3 ± 0.6 | 99.3 ± 1.8 | 137.3 ±3.0 |
| BMI (kg/m²) | 23.0 ± 0.2 | 27.3 ± 0.1 | 33.9 ± 0.4 | 45.5 ± 0.7 |
| Visceral fat mass parameters | | | | |
| Waist circumference (cm) | 82.1 ± 0.8 | 91.7 ± 0.5 | 108.2 ± 1.3 | 134.7 ± 1.6 |
| Free Fat mass (kg) | 68.6 ± 1.2 | 72.0 ± 1.0 | 75.2 ± 1.3 | 85.8 ± 3.1 |
| Fat mass (kg) | 8.0 ± 1.2 | 7.99 ± 1.0 | 38.4 ± 1.5 | 47.6 ± 3.2 |
| Metabolic parameters | | | | |
| SBP (mmHg) | 119.2 ± 1.6 | 126.2 ± 1.5 | 135.0 ± 2.1 | 137.4 ± 2.8 |
| DBP (mmHg) | 74.2 ± 1.0 | 77.9 ± 1.0 | 84.7 ± 1.4 | 85.0 ± 1.8 |
| Plasma glucose (mM) | 5.3 ± 0.1 | 5.4 ± 0.07 | 5.6 ± 0.08 | 6.9 ± 0.4 |
| Cholesterol (mM) | 5.13 ± 0.1 | 5.43 ± 0.09 | 5.46 ± 0.12 | 5.28 ± 0.20 |
| HDL (mM) | 1.41± 0.05 | 1.36 ± 0.03 | 1.27 ± 0.04 | 1.11 ± 0.04 |
| LDL (mM) | 3.23 ± 0.09 | 3.48 ± 0.09 | 3.43 ±0.11 | 3.19 ± 0.17 |
| Triacylglycerols (mM) | 1.06± 0.09 | 1.12 ± 0.05 | 1.50 ± 0.09 | 1.83 ± 0.17 |
| $HbA_{1c}$ (%) | 4.81 ± 0.1 | 4.88 ± 0.1 | 5.17 ± 0.1 | 5.91 ± 0.2 |
| Serum CBG (nM ) | 760±20<br>n = 64 | 710± 10<br>n = 115 | 720 ± 20<br>n = 63 | 780 ± 4<br>n = 28 |

Data are presented as means ± SEM. **BMI**; body mass index, **SBP**; systolic blood pressure, **DBP**; diastolic blood pressure, **HDL**; high-density lipoprotein, **LDL**; low-density lipoprotein and **$HbA_{1c}$**; glycated hemoglobin.

**Table 3.** Allelic distribution in different groups of patients classified by BMI.

| CBG gene | Allele 86 | | Allele 90 | | Odds ratio | | |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | | 95%CI | p Fisher |
| BMI < 25 | 107 | 82.3 | 23 | 17.7 | | | |
| BMI 25 – 30 | 193 | 81.8 | 43 | 18.2 | 1.036 | 0.59-1.81 | 0.51 |
| BMI 30 – 40 | 110 | 82.1 | 24 | 17.9 | 1.015 | 0.54-1.91 | 0.54 |
| BMI > 40 | 63 | 70 | 27 | 30 | 1.994 | 1.054-3.77 | 0.02* |
| **GR gene** | **Allele C** | | **Allele G** | | **Odds ratio** | | |
| | n | % | n | % | | 95%CI | p Fisher |
| BMI < 25 | 83 | 71.6 | 33 | 28.5 | | | |
| BMI 25 – 30 | 152 | 73.8 | 54 | 26.2 | 0.89 | 0.54-1.49 | 0.38 |
| BMI 30 – 40 | 78 | 61.9 | 48 | 38.1 | 1.55 | 0.90-2.65 | 0.07 |
| BMI > 40 | 49 | 58.3 | 35 | 41.7 | 1.80 | 0.99-3.25 | 0.03* |

Allelic distribution analysis was performed with a Fisher's exact test with one group of men patients compared to normal patients (BMI<25).

morbidly obese male population, serum CBG was negatively correlated to BMI and waist circumference. These results are consistent with those obtained from other independent studies in which serum CBG concentration was also negatively correlated with several markers of obesity including BMI in individuals of both sexes from a healthy population (Fernandez-Real et al., 2002; Lapidus et al., 1986). These data also confirm our previous finding that subjects with CBG allele 90 are more associated with cortisol driven fat distribution than allele 86 patients (Barat et al., 2005). CBG protein concentration also tended to be lower among CBG 90/- subjects when the whole population was examined, a finding that became signifycant when morbidly obese patient are excluded from the analysis (p = 0.016). Thus, CBG levels appear to decreease with BMI until the patients become morbidly obese. It is well known that normal homeostatic mechanisms are lost in morbid obesity; this may explain why CBG levels are higher in this group.

Although some reports suggest that CBG may help to

capture low concentrations of cortisol and facilitate its active transfer into the cells, several studies on human patients with either variant or total deficiency of CBG strengthen the hypothesis of the cortisol sequestering effect of CBG (Torpy et al., 2001; Joyner et al., 2003; Emptoz-Bonneton et al., 2000; Roitman et al., 1984). In particular, ligand-binding experiments demonstrated that in the CBG-deficient patient peaks in cortisol secretion during the circadian cycle are accompanied by large increases in free cortisol (not yet bound to albumin) that are even higher after stress-induced naloxone stimulation (Lewis et al., 2005). To compare cortisol levels between patients, strict conditions should be applied in order to avoid variations due to the circadian cycle of cortisol secretion as well as stress levels. Unfortunately, cortisol levels could not be measured in this retrospective study but only CBG that does not vary so rapidly.

Our study further replicates the association between GR BclI polymorphism and obesity markers in middle-aged population. The molecular mechanism of the BclI polymorphism is not known but it has been associated with increased glucocorticoid sensitivity that leads to different consequences during life. Thus, BclI G-allele carriers show higher abdominal fat mass when young, whereas late in life they show lower lean mass due to muscle atrophy (Van Rossum and Lamberts, 2004). When we grouped the patients according to their genotype at both CBG and GR loci, we observed that the subjects harbouring CBG allele 90 and GR allele G are the most obese whereas patients with CBG allele 86 and GR allele C show the lowest values of obesity parameters. Interestingly, waist circumference came out as the most significant phenotype in this genetic analysis. This suggests that CBG and GR polymorphisms would influence central rather than peripheral obesity which fits with the hypothesis of the role of hypercortisolemia in central obesity. Although the contrast is apparently mostly driven by GR genotype, both loci would be interesting to consider in future studies.

In conclusion, our data suggest that polymorphisms located in intron 1 of the CBG gene and in intron 2 of the GR gene are associated with morbid obesity in a Spanish middle aged male population. Selection bias of the morbid obese group is unlikely as subjects come from the same geographical area as the rest of the population and also because the frequency of GR allele G is already increased in the obese group. However, our sample size is still too small to prove a direct effect of CBG or GR genotypes in such complex disease traits. Additional work is required to unravel the mechanism by which CBG and GR polymorphisms influence free cortisol concentrations in a larger sample size. Our data suggest that lowered plasma CBG levels may be one mechanism.

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