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ORIGINAL ARTICLE

# Influence of Bcl-1 Gene Polymorphism of Glucocorticoid Receptor Gene (NR3C1, rs41423247) on Blood Pressure, Glucose in Northern Indians

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**Abstract** Glucocorticoids and its receptor are known to be involved in the dysregulation of hormone and lipid levels. Therefore, we evaluated the association of Bcl1 gene polymorphism of glucocorticoids receptor (*GCR*) gene variant with hormone and lipid levels in Northern Indians obese. A total of 435 obese and non-obese age matched subjects were included in the case–control study. Lipid and hormonal levels were estimated using standard protocols. Analysis of +646 C>G *NR3C1* gene polymorphism was done using PCR–RFLP. The frequencies of *GR* Bcl1, C>G genotypes and alleles did not differ significantly ($P > 0.05$) between obese and non-obese. The +646 G allele carriers had higher waist to hip ratio, blood pressure, insulin and glucose levels than non-carriers in obese subjects while diastolic blood pressure and glucose in non-obese. The *NR3C1*, +646 C>G polymorphism did not associate with obesity. However, the GG genotype may modulate blood pressure, blood glucose and hormonal levels in northern Indians.

**Keywords** Abdominal obesity · Glucocorticoid receptors · Polymorphism · Risk

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## Introduction

Overweight and obesity are common health problem in developed and developing countries [1]. Obesity increases dramatically in major ethnic and racial groups including both sexes [2]. Wide variation in the distribution of excess body fat affects the risks associated with obesity. Abnormalities in glucose, insulin, lipid metabolism and hypertension are associated with abdominal obesity [3].

Although body mass index (BMI) is the most frequently used index, it does not reflect fatness uniformly in all populations, and interethnic extrapolations are not justified [4]. For a given age, sex and fat level, Caucasians have higher BMI than the Chinese, Ethiopians and Polynesians.

According to the new Asian BMI criteria, a lower cut off of 23.0 kg/m$^2$ are considered as overweight and at 25·0 kg/m$^2$ or higher are considered as obese, because Asians have more fat content at a particular BMI than Europeans [5].

Most of the physiological functions of the body regulated by glucocorticoid (GC) hormones and its appropriate plasma levels are maintained by homeostatic mechanisms. Lipogenesis and gluconeogenesis are regulated by the GC hormone [6]. Glucocorticoids also modulate the expression of several hypothalamic neuropeptides which further regulates appetite control [7]. Adrenal cortex is stimulated by the pituitary to produce and release cortisol, which in turn exerts a negative endocrine feedback regulation, mediated via centrally localized GCR. Some obese individuals have hormonal, metabolic, and circulatory changes, referred to as the metabolic syndrome, that are also common to patients with GC excess [8].

Obesity is a multifactorial disease with a significant genetic component. Animal models of genetic and

experimentally induced obesity suggest that glucocorticoid receptors (GCR) play role in the etiology and maintenance of the obese state. Human glucocorticoid receptor locus is present on chromosome 5q31–32. A biallelic polymorphism (Bcl1, C>G) was identified at downstream of the exon 2–intron 2 junction of *GCR* (*NR3C1*) gene. The polymorphism might affect processing of GCR primary transcripts and also cause increased GC sensitivity [9, 10]. This polymorphism was found to be associated with abdominal obesity and insulin resistance. In contrast, Van-Rossum et al. observed that Bcl1, C>G polymorphism was associated with the lower BMI. The polymorphism has also been linked to a cluster of cardiovascular risk factors, such as hypertension, visceral obesity and steroid sensitivity [11–15]. However, some studies did not observe significant differences in the frequencies of Bcl1, C>G genotypes between obese and non-obese individuals [11].

Obesity is a common health problem of India. Both environmental and genetic factors may have contribution towards susceptibility of obesity. Earlier, we found that *APO E4* allele showed significant association with obesity [16]. Therefore, in the present study we aimed to investigate association of *GCR* Bcl1 (*NR3C1*, +646 C>G) variation with obesity. We also evaluated the association of the polymorphism with lipid and hormonal levels in subjects from northern India.

## Material and Methods

### Subjects

A total of 934 subjects were enrolled initially from the out patients department of Chatrapati Shahuji Maharaj Medical University (CSMMU) and volunteers from general population of Lucknow, Uttar Pradesh (India). All subjects were asked for detailed clinical history and required measurements were done for height, weight, BMI and waist-to-hip ratio (WHR). BMI was calculated as the weight in kilogram (kg) divided by height in meter square. The blood pressure was measured twice on the right arm with the participants sitting, with a 5 min rest. Only non smoker, non diabetic, normotensive subjects who did not have history of coronary artery disease, neoplasia, congenital and mental disorders, and endocrine disorders like Myxoedema and Cushing syndrome among them were selected for the present study. Based on the BMI, two subgroups were defined which are as follows: 237 individuals with BMI $< 25$ considered as non-obese, 198 individuals with BMI $\geq 25$ considered as obese. The non-obese subjects were age and sex matched with obese. The study was approved from the ethical committee of the C. S. M. Medical University, UP, Lucknow.

### Hormones, Leptin, Glucose, and Serum Lipids

Serum leptin concentrations were determined in serum/plasma by radio-immunoassay using RIA kit (Linco Research, USA). Insulin hormone was assayed using RIA Kit [BARC, India]. Blood sugar was assayed by glucose oxidase–peroxidase (GOD-POD) method [17]. Lipid profile was done by enzymatic method using commercially available kit (Anamol, India). LDL cholesterol was calculated using the following formula: LDL cholesterol = total cholesterol − [(triglycerides/5) − HDL cholesterol].

### Genetic Analysis

The genomic DNA was extracted from peripheral blood leucocytes pellet using the standard salting out method [18]. PCR–RFLP and sequence analysis showed that the second site (+646 bp downstream of exon 2) was indeed polymorphic for the BclI polymorphism. Genotyping of Bcl1 (rs41423247) GCR gene has been described in detail previously [9]. The PCR products were subjected to restriction digestion with 4 U of the restriction endonuclease *Bcl*1 at 37°C for 3 h. Digestion of the PCR product gave the following predicted fragment sizes: 86 and 43 bp in the case of heterozygotes, a band of 86 bp for C allele in homozygous individuals, and a single band of 43 bp for G allele homozygotes.

### Statistical Analysis

Statistical analysis was performed by SPSS (version 11.5) software. Direct gene counting method was used to determine the frequency of genotypes and alleles. The chi-square test or Fisher's exact test was used to determine differences in frequencies. All continuous variables were expressed as mean ± SD and tested by one-way ANOVA test. Odds ratio was calculated using logistic regression. $P$-value $< 0.05$ was considered as significant.

## Results

### Association of Anthropometric Parameter, Blood Pressure, Lipid profile and Hormonal Levels with Obesity

A total of 198 obese (BMI = 30.40 ± 4.49) and 237 non-obese (BMI = 21.00 ± 2.45), were evaluated for differences in anthropometric, lipid and hormonal profiles (Table 1). We observed higher systolic blood pressure ($P = 0.014$), diastolic blood pressure ($P = 0.030$), WHR ($P = 0.002$), LDL-cholesterol ($P = 0.0001$), HDL-cholesterol ($P = 0.003$), VLDL-cholesterol ($P = 0.001$), total

**Table 1** Anthropometric parameter, blood pressure, lipid profile and hormonal levels in obese and non-obese subjects

| Clinical features | Obese ($n = 198$) | Non-obese ($n = 237$) | $P$-value |
|---|---|---|---|
| Waist to hip ratio and blood pressure | | | |
| WHR | 0.94 ± 0.06 | 0.84 ± .054 | 0.002 |
| SBP (mmHg) | 121.78 ± 9.20 | 119.58 ± 12.30 | 0.014 |
| DBP (mmHg) | 86.78 ± 4.57 | 79.15 ± 5.13 | 0.030 |
| Lipid profile | | | |
| LDL-cholesterol (mg/dl) | 155.02 ± 7.94 | 114.52 ± 10.67 | 0.0001 |
| VLDL-cholesterol (mg/dl) | 26.04 ± 6.71 | 24.03 ± 7.48 | 0.001 |
| HDL-cholesterol (mg/dl) | 34.12 ± 4.33 | 48.57 ± 7.13 | 0.003 |
| Triglyceride (mg/dl) | 134.26 ± 11.30 | 121.16 ± 17.42 | 0.0001 |
| T-cholesterol (mg/dl) | 218.19 ± 11.42 | 188.66 ± 11.56 | 0.0001 |
| Hormonal profile | | | |
| Leptin (mg/ml) | 20.45 ± 5.37 | 7.44 ± 2.18 | 0.002 |
| Insulin (μU/ml) | 20.56 ± 6.20 | 16.63 ± 10.21 | 0.001 |
| Blood glucose (mg/dl) | 117.92 ± 6.45 | 84.06 ± 17.55 | 0.015 |

Values are expressed in Mean ± SD

*SBP* systolic blood pressure (mmHg), *DBP* diastolic blood pressure (mmHg), *WHR* waist to hip ratio, *LDL* low density lipid (mg/dl), *VLDL* very low density lipid (mg/dl), *HDL* high density lipid (mg/dl), *TG* triglyceride (mg/dl), *TC* total cholesterol (mg/dl), Blood glucose (mg/dl), Leptin (mg/ml), Insulin (μU/ml)

cholesterol ($P = 0.0001$), triglyceride ($P = 0.0001$), Leptin ($P = 0.002$), Insulin ($P = 0.001$) and blood glucose ($P = 0.015$) in obese as compared with non-obese group.

### Association of *GCR* (Bcl1, C>G) Gene Polymorphism with Obesity

The frequencies of genotypes and alleles followed Hardy–Weinberg equilibrium in non-obese individuals. The frequencies of *GCR (Bcl1C>G)* +646 genotype and +646 G allele did not differ significantly between obese and non-obese subjects (Table 2).

### Association of *GCR* (Bcl1, C>G) Gene Polymorphism with Clinical Parameters

The +646 G allele carriers had higher waist to hip ratio ($P = 0.004$), systolic ($P = 0.002$) and diastolic ($P = 0.007$) blood pressure, insulin ($P = 0.046$) and blood glucose ($P = 0.044$) levels than non-carriers in obese subjects. However, in non-obese, +646 G allele carriers had higher diastolic blood pressure ($P = 0.004$) and blood glucose ($P = 0.008$) (Tables 3, 4).

## Discussion

In the present study, the frequencies of *GCR Bcl1* genotypes and alleles did not differ significantly between obese and non-obese. However, G allele carriers had significantly higher diastolic blood pressure and blood glucose in obese and non-obese groups.

Glucocorticoid activity appears to be essential for the development of hyper-insulinaemia and subsequent fat deposition. In humans, glucocorticoid excess is associated with central fat distribution. Studies have reported that cortisol production was enhanced in obesity [19]. In monozygotic twins cortisol show almost identical secretary patterns [20]. Abdominal obesity and its associated metabolic disturbances are under genetic control also [21]. There is thus reason to believe that susceptibility to abnormal HPA axis activity might be genetically determined.

The glucocorticoid receptor gene is polymorphic and two of its sensitizing variants (Asn363Ser and Bcl1, C>G) are associated with the increased glucocorticoid sensitivity and higher cortisol levels. *GCR* (Bcl1, C>G) polymorphism associated with regulation of the HPA axis activity [22]. In the present study, we did not observe significant association of Bcl1, C>G polymorphism with obesity which is also corroborated with other studies [11, 15]. Our findings regarding the high WHR in obese subjects are found similar to study by Rosmond et al. [3] who reported that the G-allele was associated with increased abdominal sagittal diameter, BMI and WHR. Other studies also showed an association between the G-allele and increased abdominal fat mass [13, 23]. However, G allele carriers in non-obese group did not show higher fat deposition which influences WHR. Therefore, contrary to Van-Rossum et al. [9] *GCR* (Bcl1, C>G) polymorphism may not have any direct effect on abdominal obesity. Several genetic evidences suggest influence of glucocorticoid receptor on hypertension [14, 24]. Kenyon et al. [25] reported the involvement of glucocorticoid receptor gene in regulation of blood pressure in hypertensive rat as compared with normotensive rats. Lin et al. [26] showed a weak gender specific association of *GCR* variation (intron 4) with hypertension. Glucocorticoids with its mild activity increases retention of $Na^+$ and excretion of $K^+$ and synthesis of angiotensinogen which increase secretion of

**Table 2** Association of *GR* gene polymorphism (Bcl1, C>G) with obesity: distribution of genotype and allele frequencies in obese and non-obese

| Genotype | Obese[a] *n* (%) | Non-Obese *n* (%) | *P*-value | OR (95% CI) |
|---|---|---|---|---|
| CC | 88 (44.45) | 114 (48.1) | – | Reference |
| CG | 74 (37.37) | 90 (38.0) | 0.806 | 1.05 (0.70–1.59) |
| GG | 36 (18.18) | 33 (13.9) | 0.131 | 1.41 (0.87–2.58) |
| G allele carriers[b] | 110 (55.56) | 123 (51.9) | 0.256 | 1.19 (0.82–1.65) |
| Allele[c] | | | | |
| C | 250 (63.13) | 318 (67.1) | – | Reference |
| G | 146 (36.87) | 156 (32.9) | 0.134 | 1.21 (0.88–1.56) |

[a] Total number of obese (198) and non-obese subjects (237) for genotypes

[b] Subjects with CG or GG genotype (CG + GG)

[c] Total number of chromosomes in obese (396) and non-obese (474) for alleles

**Table 3** Association of *GR* gene polymorphism (Bcl1, C>G) with clinical parameters in obese subjects ($n = 198$)

| Clinical features | *GR* gene polymorphism (Bcl1, C>G) | | *P*-value |
|---|---|---|---|
| | G allele carrier ($n = 110$) | G allele non-carrier ($n = 88$) | |
| Waist to hip ratio and blood pressure | | | |
| WHR | 0.95 ± 0.06 | 0.93 ± 0.07 | 0.004 |
| SBP (mmHg) | 126.97 ± 7.33 | 114.16 ± 5.46 | 0.002 |
| DBP (mmHg) | 89.97 ± 8.12 | 82.36 ± 5.52 | 0.007 |
| Lipid profile | | | |
| LDL-cholesterol (mg/dl) | 153.40 ± 8.04 | 154.40 ± 6.14 | 0.876 |
| VLDL-cholesterol (mg/dl) | 26.44 ± 5.40 | 25.53 ± 7.82 | 0.677 |
| HDL-cholesterol (mg/dl) | 34.34 ± 5.08 | 35.45 ± 3.43 | 0.123 |
| Triglyceride (mg/dl) | 134.23 ± 12.50 | 133.76 ± 14.09 | 0.758 |
| Total-cholesterol (mg/dl) | 216.33 ± 13.45 | 215.51 ± 14.22 | 0.324 |
| Hormonal profile | | | |
| Leptin (mg/ml) | 21.11 ± 5.65 | 20.34 ± 6.45 | 0.231 |
| Insulin (μU/ml) | 23.94 ± 5.05 | 19.11 ± 4.31 | 0.046 |
| Blood glucose (mg/dl) | 123.23 ± 7.12 | 115.12 ± 8.75 | 0.044 |

aldosterone that causes excessive retention of $Na^+$ and water leading to hypertension. In the present study, we also report the contribution of *GCR* (Bcl1, C>G) variation with increase in blood pressure both in obese and non-obese subjects. Earlier, Whitworth et al. [27] studied the physiological mechanisms by which cortisol raises blood pressure in short term studies of cortisol administration in normal men. Here, we postulate that cortisol sensitivity due to *GCR* (Bcl1, C>G) variation may be attributed to high blood pressure in non obese subjects. As the frequency of G allele is high (>30%), thus one may expect high blood pressure in the control population. The study by Kelly et al. [28] showed the role of nitric oxide and cortisol mediated pathways in hypertension.

In obese, homozygous G allele carriers had higher insulin and blood glucose (0.044) levels and were more insulin resistant (0.046), when compared to a group consisting of G allele non-carriers. Weaver et al. [11] also showed that unrelated, non-diabetic, premenopausal white women homozygous for the 4.5 kb fragment had higher fasting insulin, as compared to age-matched, normal-weight controls. This observation suggests that *GCR* (Bcl1, C>G) polymorphism is associated with a sensitivity of the feedback regulation of the HPA axis. This relative sensitivity also results in an effect of cortisol on glucose metabolism, causing slightly higher glucose concentrations, as well as higher insulin levels. However, association of *GCR* (Bcl1, C>G) variation with glucose levels may contribute towards risk for diabetes. In addition, increased glucose levels in Bcl1 G allele carriers may also have influence on blood pressure.

The mechanism for *GCR* (Bcl1, C>G) polymorphism to increase the sensitivity of negative feedback mechanism of GCs may involve direct effect of the SNP on *NR3C1* gene

**Table 4** Association of *GR* gene polymorphism (Bcl1, C>G) with clinical parameters in non-obese subjects ($n = 237$)

| Clinical features | *GR* gene polymorphism (Bcl1, C>G) | | *P*-value |
|---|---|---|---|
| | G allele carrier ($n = 123$) | G allele non-carrier ($n = 114$) | |
| Waist to hip ratio and blood pressure | | | |
| WHR | 0.83 ± 0.05 | 0.85 ± 0.05 | 0.088 |
| SBP (mmHg) | 121.14 ± 11.15 | 118.13 ± 13.17 | 0.060 |
| DBP (mmHg) | 80.89 ± 9.22 | 77.50 ± 8.81 | 0.004 |
| Lipid profile | | | |
| LDL-cholesterol (mg/dl) | 115.21 ± 11.61 | 114.17 ± 17.09 | 0.788 |
| VLDL-cholesterol (mg/dl) | 25.31 ± 8.56 | 23.44 ± 6.96 | 0.066 |
| HDL-cholesterol (mg/dl) | 48.42 ± 7.69 | 49.61 ± 4.76 | 0.161 |
| Triglyceride (mg/dl) | 126.54 ± 12.80 | 117.22 ± 14.80 | 0.066 |
| Total-cholesterol (mg/dl) | 187.82 ± 11.63 | 189.09 ± 10.89 | 0.756 |
| Hormonal profile | | | |
| Leptin (mg/ml) | 7.39 ± 2.56 | 7.37 ± 2.88 | 0.972 |
| Insulin (μU/ml) | 17.89 ± 4.61 | 15.30 ± 4.75 | 0.052 |
| Blood glucose (mg/dl) | 89.50 ± 7.41 | 78.133 ± 6.64 | 0.008 |

expression. It is also possible that the polymorphism is in linkage disequilibrium which can alter the transcriptional activity of target genes concerned in glucose and insulin homeostasis. As several other polymorphisms in coding and splicing region of *GCR* are known, studies are also required to look for association of these polymorphisms in obesity to understand the exact role of *GCR* in the pathogenesis of obesity. In conclusion, although *GCR* Bcl1, C>G polymorphism did not associate significantly with obesity but the *GCR* Bcl1, G allele carriers had significantly higher BP and blood glucose levels than non-carriers, thus contributing to obesity phenotype. However, obesity is a multifactorial phenotype where large number of low penetrance genes along with environmental factors is also involved. Therefore, more studies are required to look the association of polymorphic variants in other genes involved in lipid and hormone metabolism.

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