*Bcl*I Glucocorticoid Receptor Polymorphism Is Associated With Greater Body Fatness: The Hoorn and CODAM Studies

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Context: The *Bcl*I polymorphism in the glucocorticoid receptor (GR) gene is associated with enhanced glucocorticoid (GC) sensitivity.

Objective: Our objective was to investigate the association of the *Bcl*I polymorphism with body fatness and insulin resistance.

Design and Setting: We conducted an observational cohort study, combining data from 2 cohort studies enriched with individuals with impaired glucose metabolism and/or diabetes mellitus type 2 (DM2).

Patients and Methods: We examined 1228 participants (mean age 64.7 years, 45% women) from the Cohort Study on Diabetes and Atherosclerosis Maastricht (CODAM, n = 543) and the Hoorn Study (n = 685). Body mass index (BMI), waist and hip circumferences, and waist-to-hip ratio (WHR) were obtained; insulin resistance was estimated using the homeostasis model assessment for insulin resistance (HOMA2-IR).

Results: We identified 519 noncarriers (CC), 540 heterozygous (CG) carriers, and 169 homozygous (GG) carriers of the G-allele of the *Bcl*I polymorphism. Homozygous carriers had a higher BMI (28.9 vs 27.9 kg/m^2) and waist (99.6 vs 97.2 cm) and hip (105.5 vs 103.2 cm) circumference compared with noncarriers, also after adjustment for age, sex, cohort, glucose tolerance, and lifestyle risk factors: β = 0.94 kg/m^2 (95% confidence interval, 0.24–1.63), β = 2.84 cm (0.95;4.73) and β = 2.38 cm (0.88–3.87), respectively. Similar results were obtained when comparing homozygous carriers with heterozygous carriers: β = 1.03 kg/m^2 (0.34–1.72), β = 2.20 cm (0.31–4.08) and β = 1.99 cm (0.51–3.48), respectively. There were no differences in WHR. Ln-HOMA2-IR was higher in GG carriers compared with CG carriers; 0.29 vs 0.17 [β = 0.09 (0.01–0.17)], but this effect was attenuated after adjustment for BMI [β = 0.04 (−0.04 to 0.11)].

Conclusion: Homozygous carriers of the *Bcl*I polymorphism of the GR gene have significantly greater total body fatness, contributing to higher HOMA2-IR, compared with heterozygous carriers and noncarriers. **(*J Clin Endocrinol Metab* 98: E595–E599, 2013)**

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Abbreviations: BMI, body mass index; CI, confidence interval; CODAM, Cohort on Diabetes and Atherosclerosis Maastricht; CVD, cardiovascular disease; DM2, diabetes mellitus type 2; GC, glucocorticoid; GR, glucocorticoid receptor; HOMA2-IR, homeostasis model assessment of insulin resistance; WHR, waist-to-hip ratio.

Glucocorticoids (GCs) exert their effects through the glucocorticoid receptor (GR), which makes the GR an essential factor in mediating cortisol effects. Although GC concentrations can be measured in plasma, their functional effects on target tissues remain difficult to predict (1).

The efficacy of GCs and the prevalence and severity of related side effects are highly variable between individuals, whereas sensitivity to GCs on an individual level seems to be rather stable, suggesting genetic factors to play a role in GR sensitivity (1). Previous studies have identified polymorphisms in the GR gene that have been associated with altered GC sensitivity and changes in body composition and metabolic variables (2), either through up- or down-regulation of the effect of GCs on target tissues. An example of a potentially up-regulating GR polymorphism is the *Bcl*I (rs41423247) polymorphism (3, 4). Although several studies have analyzed effects of the *Bcl*I polymorphism on body composition and metabolic variables, somewhat inconsistent results have been reported (3–14).

In view of these considerations, this study was performed in a large sample combining data from 2 Dutch cohort studies, which were both enriched with participants with disturbed glucose metabolism/diabetes mellitus type 2 (DM2). We hypothesized that the G-allele of the *Bcl*I polymorphism is associated with greater body fatness and higher insulin resistance compared with noncarriers.

Patients and Methods

Study populations

For the present study, we used data from the 2000 Hoorn Study follow-up examination (15) and the baseline examination of the Cohort on Diabetes and Atherosclerosis Maastricht (CODAM) Study (16, 17). Both followed a similar data collection research protocol and have been used as a combined cohort before (18). Briefly, the Hoorn Study is a population-based cohort study of glucose metabolism and related cardiovascular disease (CVD) risk factors and complications that started in 1989 in Hoorn, The Netherlands (n = 2484). In 2000 or 2001, a follow-up examination was performed among 822 participants, comprising 648 surviving participants of the baseline cohort and a group of 174 participants with DM2 from the Hoorn Screening Study (15, 19). The CODAM Study started in 1999 and is an ongoing cohort study designed to investigate the effects of glucose metabolism, obesity, blood lipids, lifestyle, and genetic factors on CVD and mortality (16, 17). It consists of 574 individuals selected on the basis of an elevated risk for DM2 and CVD from a large population-based cohort who had undergone a glucose metabolism screening test, as described elsewhere (16).

The present study included 1228 individuals (543 from CODAM and 685 from the Hoorn Study) who could be genotyped for the *Bcl*I polymorphism. These subjects did not differ in their baseline characteristics from the excluded 168 subjects in whom genetic determination was impossible (mainly due to missing DNA samples, data not shown). Informed consent was obtained from all subjects, and all were eligible to have their DNA tested under current Medical Ethics Committee permissions from the VU University Medical Center (Hoorn Study) or the Maastricht University Medical Centre (CODAM Study).

Key dependent variables and covariates

Total body fat and body fat distribution were estimated by means of body mass index (BMI) (kilograms per square meter), waist and hip circumferences (centimeters), and the computed waist-to-hip ratio (WHR) (15). The degree of insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA2-IR) calculator (www.dtu.ox.ac.uk), using fasting plasma glucose (millimoles per liter) and fasting serum insulin levels (picomoles per liter) (20). Patients on insulin treatment (n = 25) were excluded from these estimations. Study covariates included the individuals' glucose metabolism status (World Health Organization 1999 criteria) (21), the use of lipid-, glucose-, and/or blood-pressure–lowering medication and lifestyle risk factors such as smoking status and physical activity (at least 30 min/d at least 5 d/wk, yes/no) (15, 16, 19).

Single-nucleotide polymorphism analysis

The *Bcl*I restriction fragment length polymorphism (rs41423247) is a C/G (2.3 and 4.5 kilobases) single-nucleotide polymorphism located in intron 2 of the GR gene (NR3C1), 646 nucleotides downstream from exon 2 (3). Determination of the *Bcl*I GR polymorphism was performed using TaqMan single-nucleotide polymorphism genotyping assays (Laboratory of the Department of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands). DNA was genotyped by allelic discrimination using TaqMan Genotyping Master Mix (Applied Biosystems, Branchburg, New Jersey) using previously published probes (3).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences for Windows, version 18.0 (SPSS Inc, Chicago, Illinois). Hardy-Weinberg equilibrium was determined using a χ^2 test. Linear regression analyses adjusted for the study covariates were used to compare the mean levels of BMI, waist and hip circumferences, and HOMA2-IR across the three genotypes of the *Bcl*I polymorphism (GG vs CG, GG vs CC, and CG vs CC). The analyses with HOMA2-IR as dependent variables were further adjusted for BMI to investigate whether such associations were independent or mediated by these. Because HOMA2-IR data were positively skewed, natural logarithmic transformation was applied before these analyses. A two-sided P value $<.05$ was considered statistically significant.

Results

General characteristics of the Hoorn and CODAM study populations are shown in Table 1. Genetic determination of the *Bcl*I polymorphism in the combined study populations identified 519 (42%) noncarriers (CC) of the G-allele, 540 (44%) heterozygous carriers (CG), and 169 (14%) homozygous carriers (GG). These frequencies did not differ between the 2 cohorts. Genotypes were consistent with Hardy-Weinberg equilibrium ($P > .05$).

Table 1. General Characteristics of Participants of the CODAM and Hoorn Studies

Variable	CODAM (n = 543)		Hoorn (n = 685)	
	Males (n = 334)	Females (n = 209)	Males (n = 339)	Females (n = 346)
CC/CG/GG, %	44/41/15	38/49/13	44/45/11	42/42/16
NGM/IGM/DM2, %	52/21/27	55/24/21	38/23/39	37/23/40
Age, y	59.4 ± 6.9	59.7 ± 7.0	68.1 ± 7.6	69.5 ± 6.7
BMI, kg/m^2	28.4 ± 3.8	28.7 ± 5.0	27.4 ± 3.5	27.9 ± 4.6
Obesity, %	29	34	20	29
Waist, cm	101.9 ± 10.9	94.8 ± 12.2	100.4 ± 10.3	92.7 ± 12.5
Hip, cm	102.8 ± 8.0	106.0 ± 9.9	101.5 ± 6.6	105.3 ± 10.2
WHR	0.99 ± 0.06	0.89 ± 0.07	0.99 ± 0.07	0.88 ± 0.08
HOMA2-IR	1.22 (0.86–1.72)	1.06 (0.83–1.56)	1.20 (0.80–1.70)	1.20 (0.80–1.80)
FPG, mmol/L	5.8 (5.3–6.6)	5.4 (5.0–6.0)	6.0 (5.5–7.0)	6.1 (5.5–7.0)
Fasting insulin, pmol/L	62 (45–90)	56 (44–82)	60 (43–85)	62 (44–93)
HbA1c, %	5.97 ± 0.84	5.94 ± 0.73	6.09 ± 0.81	6.12 ± 0.74
Current smoking, %	18	23	19	13
Physical activity, %	66	57	74	66
Prior CVD, %	31	21	20	19
Use of BP-lowering medication, %	40	37	37	43
Use of glucose-lowering medication, %	14	12	8	8
Use of lipid-lowering medication, %	20	16	18	15

Abbreviations: BP, blood-pressure; FPG, fasting plasma glucose; IGM, impaired glucose metabolism; HbA1c, glycated hemoglobin; NGM, normal glucose metabolism. Data are frequencies (in percent), means ± SD, or median (interquartile range) as appropriate. Obesity is defined as BMI ≥ 30 kg/m^2. Physical activity indicates whether the subject met the Dutch Physical Activity Guidelines (30 min/d at least 5 d/wk, yes/no).

Associations between *Bcl*I polymorphism and measures of body fatness and fat distribution

Mean levels of BMI, waist and hip circumferences, and WHR across the 3 genotypes of the *Bcl*I polymorphism are displayed in Table 2. Homozygous carriers (GG) had a higher BMI (28.9 vs 27.9 kg/m^2), waist (99.6 vs 97.2 cm) and hip circumferences (105.5 vs 103.2 cm) compared with noncarriers (CC) (unadjusted data). These differences were also statistically significant after adjustments for age, sex, glucose metabolism status, and lifestyle risk factors: β = 0.94 (95% confidence interval [CI], 0.24–1.63) kg/m^2 ($P < .01$); β = 2.84 (0.95–4.73) cm ($P < .01$); and β = 2.38 (0.88–3.87) cm ($P < .01$), respectively (Table 2, model 1).

A similar association was seen when comparing homozygous carriers (GG) with heterozygous carriers (CG); BMI 28.9 vs 27.9 kg/m^2, waist 99.6 vs 97.6 cm, and hip circumference 105.5 vs 103.7 cm, respectively (Table 2, model 1). This was also statistically significant in the adjusted analyses: β = 1.03 (0.34–1.72) kg/m^2 ($P < .01$); β = 2.20 (0.31–4.08) cm ($P < .05$); and β = 1.99 (0.51–3.48) cm ($P < .01$), respectively (Table 2, model 1). There were no differences in WHR.

Associations between *Bcl*I polymorphism and insulin resistance

Mean levels of the logarithmically transformed HOMA2-IR (Ln-HOMA2-IR) are given in Table 2. Ln-

Table 2. Associations of *Bcl*I Polymorphism With Measures of Body Fatness/Fat Distribution and Insulin Resistance

Dependent Variable	Mean Values			Model	GG vs CG		GG vs CC		CG vs CC	
	GG	CG	CC		β	95% CI	β	95% CI	β	95% CI
BMI, kg/m^2	28.9 ± 4.5	27.9 ± 4.1	27.9 ± 4.2	1	1.03	0.34–1.72[a]	0.94	0.24–1.63[a]	−0.09	−0.57 to 0.39
Waist, cm	99.6 ± 12.2	97.6 ± 12.0	97.2 ± 12.1	1	2.20	0.31–4.08[b]	2.84	0.95–4.73[a]	0.64	−0.67 to 1.95
Hip, cm	105.5 ± 9.8	103.7 ± 8.6	103.2 ± 8.8	1	1.99	0.51–3.48[a]	2.38	0.88–3.87[a]	0.38	−0.65 to 1.42
WHR	0.94 ± 0.1	0.94 ± 0.1	0.94 ± 0.1	1	0.00	−0.01 to 0.02	0.01	0.00–0.02	0.00	0.00–0.01
Ln-HOMA2-IR	0.29 ± 0.55	0.17 ± 0.50	0.19 ± 0.52	1	0.09	0.01–0.17[b]	0.06	−0.02 to 0.14	−0.03	−0.08 to 0.03
				2	0.04	−0.04 to 0.11	0.01	−0.06 to 0.09	−0.02	−0.07 to 0.03

Data are shown as means ± SD. The unstandardized regression coefficient (β) indicates the difference in dependent variable (in its units) between groups being compared; note that for HOMA2-IR, differences were calculated on the basis of log-transformed data (Ln-HOMA2-IR); back transformation to original scale can be obtained by e^{β}, and values obtained thus indicate the ratio of the geometric means between the groups being compared. Model 1 was adjusted for cohort, age, sex, glucose metabolism status, lifestyle risk factors, and use of medication. Model 2 was adjusted as model 1 plus adjustment for BMI.

[a] $P < .01$.

[b] $P < .05$.

HOMA2-IR was higher in homozygous carriers (GG) compared with heterozygous carriers (CG), 0.29 vs 0.17, also after adjustments for the study covariates: $\beta = 0.09$ (95% CI, 0.01–0.17) ($P < .05$) (Table 2, model 1). There were no differences between noncarriers (CC) and heterozygous or homozygous carriers (CG, GG). To investigate whether the increased HOMA2-IR is mediated by the increase in body weight, BMI was added to the statistical model. As illustrated, the effect was attenuated: $\beta = 0.04$ (95% CI, −0.04 to 0.11) ($P > .05$) (Table 2, model 2).

Discussion

In this relatively large study containing data from 2 Dutch cohort studies, we demonstrated that homozygous carriers of the G-allele (GG) of the *Bcl*I polymorphism have greater total body fatness. Also, we observed increased insulin resistance in homozygous carriers, which might largely be attributed to the increase in body fatness. Our findings suggest that increased sensitivity of the GR can lead to adverse effects of endogenous GCs.

We found a higher BMI and waist and hip circumference in homozygous carriers (GG) compared with heterozygous carriers (CG) and noncarriers (CC). Previous studies have reported inconsistent results regarding the association between the *Bcl*I polymorphism and body fat and/or BMI (2). An association with an increased BMI and visceral fat has been reported (8, 9, 22, 23), whereas 2 studies described an association with increased visceral fat but not with general obesity (5, 24). A study performed in the elderly showed a decreased BMI, which was attributed to loss of lean body mass due to GC hypersensitivity (3). One study found an association of the *Bcl*I polymorphism with increased WHR in obese subjects only (11). Other studies in obese subjects reported no association with body fat or BMI (4, 6, 10, 25). To our knowledge, our study is the first to investigate metabolic effects of the *Bcl*I polymorphism in a large and metabolically well-characterized sample.

No differences in WHR were found among the 3 genotypes, indicating an increase in overall body fat mass rather than an increase in fat deposition in the abdomen and trunk, as was previously suggested (22). A recent study in children using dual-energy x-ray absorptiometry also showed that homozygous carriers had an increased whole-body fat mass (26).

GCs are also known for their ability to induce insulin resistance. In the present study, HOMA2-IR was higher in homozygous carriers (GG) compared with heterozygous carriers (CG). Previous studies have reported different results regarding insulin resistance; some studies have found higher fasting insulin concentrations and/or increased insulin resistance in homozygous carriers (4, 8, 9), although another study found no association of insulin resistance with the *Bcl*I polymorphism (27). Also no association was found in a recent study calculating insulin sensitivity from data obtained in 2-hour hyperglycemic clamps (28).

In our study, the observed increased insulin resistance in homozygous carriers of the *Bcl*I polymorphism might largely be attributed to the increase in total body fatness, because after adjustment for BMI, an important attenuation of the effect was observed. It should be noted that in our analysis, exclusion of patients on insulin treatment may have led to an underestimation of the actual effects on insulin resistance.

At present, the exact mechanism through which the *Bcl*I polymorphism leads to hypersensitivity of the GR and its subsequent metabolic and body compositional effects is not known. There is no evidence that the *Bcl*I polymorphism has an effect on processing of GR pre-mRNA or alternative splicing. It might be linked to variations in the promoter region (increased expression) or 3′-UTR (increased stability) of the GR gene (3). No genetic linkage has been found between the *Bcl*I polymorphism and other previously described GR gene polymorphisms that were associated with altered GC sensitivity (14).

A limitation of our study was that the used anthropometric measures do not differentiate between fat and lean body masses, nor between subcutaneous and visceral fat, with the latter two potentially carrying different risks for the development of CVD. Studies using dual-energy x-ray absorptiometry, MRI and/or slice CT scans would allow for more precise investigations into the effects of the *Bcl*I polymorphism on specific fat depots and on the distribution of body fat.

In conclusion, this large study demonstrated that homozygous carriers of the *Bcl*I polymorphism of the GR gene have significantly greater total body fatness, contributing to increased insulin resistance, supporting the hypothesis that even small genetic variations in the GR, which are known to alter GC sensitivity, can have metabolic implications.

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