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Impact of interleukin 6 −174G>C polymorphism on obesity-related metabolic disorders in people with excess in body weight

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Abstract

Low-grade inflammation has been related to obesity, insulin resistance, and related metabolic disorders. In this context, the −174G>C gene polymorphism of the proinflammatory interleukin 6 (IL-6) cytokine has also been associated with these diseases. Based on this, the aim of the current study was to evaluate the role of IL-6 −174G>C polymorphism in the risk of developing metabolic alterations in people with excessive body weight. One hundred six Caucasian volunteers (body mass index, 33.2 ± 5.3 kg/m^2) were recruited to assess the potential relationship between carrying the −174G>C polymorphism and the risk of developing obesity-related metabolic disorders, such as hypertension, atherogenic dyslipidemia, and insulin resistance evaluated by the homeostasis model assessment of insulin resistance index. Subjects carrying the C allele showed higher plasma insulin concentrations and systolic blood pressure than homozygotes for the G allele. A multiple regression analysis showed that the presence of the C allele induced an increase in the homeostasis model assessment of insulin resistance index as compared with GG subjects (adjusted R^2 = .26, P < .001). Analyzing the mentioned obesity-related diseases, an enhanced prevalence of presenting high risk of developing these complications was found for the GC and CC genotypes relative to GG, with an adjusted odds ratio of 5.2 (P = .003). This association remained significant after controlling for multiple comparisons by the 10 000-permutation test (P = .004838). These data demonstrate that the occurrence of C allele of IL-6 −174 G>C gene polymorphism in people with excessive body weight is accompanying a higher risk of developing obesity-related metabolic disorders, especially insulin resistance.

1. Introduction

Obesity is a major health problem associated with multiple morbidities [1]. The risk of developing these metabolic complications partially depends on the genetic makeup, acquired characteristics of individuals, and the interaction between genetic and environmental factors [2,3].

Furthermore, low-grade inflammation has been related to obesity, insulin resistance, and related metabolic disorders [4,5]. Hence, most circulating cytokines are elevated in these metabolic complications; and their role in the pathogenesis of these diseases has been repeatedly reported [4,6].

Interleukin 6 (IL-6) is a mediator of the inflammatory and immune responses that is also involved in glucose and lipid metabolism [7]. Indeed, IL-6 plays pleiotropic effects on a variety of metabolic processes as an autocrine and paracrine regulator of the adipocyte function [8]. Adipose tissue contributes up to one third of the circulating IL-6 in healthy humans, and this is closely related to the pattern and degree of adiposity [8]. Thus, higher circulating IL-6 levels have been demonstrated in obesity [9] and type 2 diabetes mellitus [10,11], particularly in subjects presenting metabolic disturbances related to excess in body fat mass [12].

Genetic studies in different populations have suggested that the common −174G>C polymorphism in the promoter of the human IL-6 gene influences transcriptional regulation and plasma cytokine levels [13]. However, data on the effects of this polymorphism have led to conflicting results [14-17]. Indeed, some studies have shown that the G allele was associated with obesity comorbidities [18,19], whereas others reported the C allele as a factor increasing the risk of developing type 2 diabetes mellitus [20], hypertension, and cardiovascular disease [21].

Therefore, the available evidence suggests that variations in the IL-6 gene results in metabolic modulation and may consequently play an important role in the etiology of metabolic disorders linked to obesity. Based on this, the aim

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of the current study was to evaluate whether the single nucleotide polymorphism −174G>C polymorphism of the IL-6 gene promoter was related to the risk of developing metabolic alterations in people with excessive body weight.

2. Research design and methods

2.1. Subjects

One hundred six (52 women and 54 men) Caucasian subjects (body mass index [BMI], 33.2 ± 5.3 kg/m^2) were recruited to participate in the study (20-40 years old). Initial screening evaluations included a medical history, physical examination, and fasting blood profile to exclude subjects with diabetes; hypertension; liver, renal, or hematologic disease; or other clinical disorders. Other exclusion criteria were weight change ±3 kg within the 3 months before the start of the study, participation in another scientific study up to 90 days before, drug treatment, pregnancy, surgically or drug-treated obesity, and alcohol or drug abuse.

After a detailed explanation of the protocol, all subjects gave written informed consent to participate in the study, which was previously approved by the Ethics Committee of the University of Navarra (54/2006), in agreement with the Helsinki Declaration.

Anthropometric measurements were performed following standard procedures [22]. Body weight was measured using a digital balance accurate to 0.1 kg (Seca 767, Vogel & Halke, Hamburg, Germany), and height was measured using a wall-mounted stadiometer (Seca 220, Vogel & Halke). Measurements were carried out in underwear after an overnight fast. The waist circumference was measured at the site of the smallest circumference between the rib cage and the iliac crest.

Blood pressure was measured with a standard mercury sphygmomanometer after at least 5 minutes of rest in a sitting position (Minimus II, Riester, Junginger, Germany) according to the World Health Organization criteria. The mean of 3 measurements of systolic (SBP) and diastolic (DBP) blood pressures was calculated and used in the analysis.

2.2. Genotyping

Volunteers were genotyped for the IL-6 −174 G>C gene promoter polymorphism. Genomic DNA was extracted from white blood cells using a commercial kit (MasterPure, Epicentre, Madison, WI). The −174G>C gene polymorphism in the promoter of human IL-6 gene was determined as we previously described [23]. The CC and the GC genotypes were grouped and indicated as *C carriers* (*C*+), and GG genotype was named as *C no carriers* (*C*−).

2.3. Blood measurements

Venous blood samples were drawn after an overnight fast of 12 hours. General biochemical determinations, which included plasma levels of glucose and lipid profile, were measured by specific colorimetric assays (Horiba ABX Diagnostics, Montpellier, France) using an automatized system (COBAS MIRA, Roche, Basel, Switzerland). The reported plasma low-density lipoprotein cholesterol data were calculated by the Friedewald equation [24]. Serum levels of cortisol, insulin, leptin, and adiponectin were assessed in duplicate by using commercially available radioimmunoassays (DPC, Los Angeles, CA). Insulin resistance was indirectly determined by the homeostatic model assessment of insulin resistance (HOMA-IR) index, which was calculated as follows: [fasting plasma glucose (millimoles per liter) × fasting plasma insulin (microunits per milliliter)/22.5] [25].

Fasting serum levels of IL-6 were determined by Quantikine High-Sensitivity Human IL-6 Enzymatic Immunoassay (R&D Systems, Minneapolis, MN) by using a spectrophotometer (Multiskan Spectrum, Thermo Electron, Vantaa, Finland).

2.4. Metabolic risk factors related to obesity

To analyze the risk of developing obesity-related disorders, different variables were taken as predictors, based on the National Cholesterol Education Program–Adult Treatment Panel III criteria [26]: waist circumference for abdominal obesity, SBP and DBP for hypertension, plasma concentrations of high-density lipoprotein cholesterol (HDL-C) and triacylglycerides (TG) for atherogenic dyslipidemia, and HOMA-IR index for insulin resistance.

The median value of these markers was considered as the cutoff [27] to explore the relationship between the −174G>C polymorphism and the risk of developing obesity-related diseases. Thus, volunteers with a minimum of 3 marker values above the cutoff were included in the high-risk group [26].

2.5. Statistical analysis

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the variable distribution. Unpaired *t* tests and analysis of variance (ANOVA) for parametric data and the Kruskal-Wallis and Mann-Whitney *U* tests for nonparametric data were performed to identify differences concerning each genotype in relation to phenotypical markers. The application of the Bonferroni correction for multiple comparisons involves that findings concerning markers of the metabolic syndrome are suggestive but not statistically significant.

A multiple regression analysis was used to evaluate the role of the −174G>C gene polymorphism on insulin resistance. Hence, the model was adjusted for those variables that were predictors in the univariate analysis (waist circumference, TG, adiponectin, cortisol, and leptin concentrations). The Pearson coefficient was used to characterize relationships between the polymorphism and the variables included in the multiple regression model.

A χ^2 test was also used to evaluate the Hardy-Weinberg equilibrium, and a Fisher exact test was used to analyze the

frequency distribution of the genotypes on the risk of developing metabolic complications related to obesity. A logistic regression analysis adjusted for sex and BMI, which were independent predictors in the model, was carried out to assess the potential risk linked to the genotypes in relation to the codified disease markers. To correct the statistical significance of the obtained odds ratio (OR), a multiple testing (10 000 permutations) was performed by the UNPHASED program (3.0.6 version, MRC Biostatistics Unit, Cambridge, United Kingdom). The best *P* value from each iteration was used as an empirical null distribution to evaluate the study-wide significance.

General data are expressed with the median together with the interquartile range and by using mean ± SD when genotypes are considered. Statistical analyses were carried out using the SPSS 13.0 (Chicago, IL) program for Windows XP (Microsoft, Redmond, WA). A 2-tailed *P* value less than .05 was chosen as the level of statistical significance.

3. Results

3.1. Gene variants' effect on clinical and biochemical features

Clinical and biochemical variables were analyzed depending on the −174G>C polymorphism in all the participants (Table 1). The frequency distribution of the C allele in the participants was 37.3%. The prevalence of GG, GC, and CC genotypes was 40.6%, 44.3%, and 15.1%, respectively. Genotype distribution did not differ from that expected by the Hardy-Weinberg equation ($P > .05$). There were no differences in age, sex, and BMI among the 3 genotype groups. Body weight was apparently higher in subjects carrying the C allele, but without statistical significance (Table 1). This trend was also found in waist circumference (Table 1).

Genotype effects were not observed in fasting lipid profile or in fasting glucose concentrations (Table 1). However, subjects carrying the C allele showed higher plasma insulin concentrations, HOMA-IR index, and SBP than GG homozygotes (Table 1). Moreover, the C allele involved lower concentrations of adiponectin, circulating leptin, and leptin corrected for body weight as compared with the GG genotype (Table 1). In contrast, no effect was detected on IL-6 and cortisol concentrations (Table 1). After applying the Bonferroni correction for multiple comparisons, these results did not remain statistically significant ($P > .05$). However, these suggestive observations were helpful to perform a multiple regression analysis to evaluate factors potentially involved in insulin resistance (Table 2).

The univariate exploration showed IL-6 genetic variants, waist circumference, circulating TG, adiponectin, cortisol, and leptin as potential predictors for HOMA-IR index ($P < .050$). These variables showed no collinearity

Table 1
Clinical and biochemical characteristics according to the −174G>C polymorphism of the IL-6 gene in the 106 overweight/obese subjects

	Median (IQR)	IL-6 promoter genotypes			GG, GC, and CC comparisons *P* value [a]	C carriers (GC, CC) vs GG comparisons *P* value [b]
		GG (n = 43)	GC (n = 47)	CC (n = 16)		
Sex (male/female)	54/52	19/24	24/23	11/5		
Age (y)	34 (25-43)	33 ± 6	34 ± 5	32 ± 5	.388	.728
Body weight (kg)	88.5 (71.9-105.1)	86.8 ± 10.2	88.5 ± 10.9	92.4 ± 12.7	.209	.200
BMI (kg/m^2)	30.5 (28.3-32.7)	30.5 ± 1.4	30.3 ± 1.5	30.5 ± 1.2	.839	.668
Waist circumference (cm)	94.4 (82.3-106.5)	93.1 ± 8.1	94.9 ± 6.3	96.0 ± 8.6	.315	.071
Total cholesterol (mmol/L)	5.29 (4.04-6.53)	5.18 ± 0.88	5.27 ± 0.96	5.62 ± 1.12	.310	.374
LDL-C (mmol/L)	3.40 (2.29-4.51)	3.23 ± 0.66	3.35 ± 0.82	3.62 ± 1.16	.291	.273
HDL-C (mmol/L)	1.34 (0.93-1.74)	1.41 ± 0.37	1.36 ± 0.33	1.40 ± 0.45	.859	.662
TG (mmol/L)	1.05 (0.37-1.73)	1.20 ± 0.70	1.24 ± 0.79	1.24 ± 0.52	.729	.460
SBP (mm Hg)	124 (107-141)	124 ± 14	130 ± 15	129 ± 10	.106	.038
DBP (mm Hg)	71 (61-81)	70 ± 7	73 ± 9	72 ± 11	.277	.135
Glucose (mmol/L)	4.91 (4.45-5.36)	4.91 ± 0.34	5.05 ± 0.45	4.97 ± 0.34	.291	.152
Insulin (μU/mL)	8.8 (4.5-13.1)	8.8 ± 2.8	10.2 ± 4.5	11.0 ± 5.4	.134	.036
HOMA-IR	2.00 (0.84-3.16)	1.94 ± 0.68	2.29 ± 1.15	2.43 ± 1.23	.087	.013
Adiponectin (μg/mL)	10.9 (2.3-19.5)	14.0 ± 6.4	11.4 ± 6.4	9.5 ± 4.8	.029	.013
Leptin (ng/mL)	18.4 (1.7-35.1)	24.7 ± 14.2	20.6 ± 12.0	15.9 ± 9.05	.069	.045
Leptin corrected for weight (ng/mL × kg)	0.23 (0.01-0.45)	0.30 ± 0.19	0.24 ± 0.15	0.17 ± 0.12	.040	.034
Cortisol (mmol/L)	358.7 (173.8-543.5)	372.5 ± 121.4	402.8 ± 151.7	344.9 ± 149.0	.306	.597
IL-6 (pg/mL) [c]	1.38 (0.44-2.23)	1.75 ± 1.55	1.85 ± 1.38	1.54 ± 0.93	.649	.463

Data are shown as the median and the interquartile range and the mean ± SD. IQR indicates interquartile range; LDL-C, low-density lipoprotein cholesterol; TG, triacylglycerides.

[a] *P* value for comparison among the 3 genotypes using ANOVA.

[b] *P* value for comparisons of differences between grouped genotypes (GG vs GC + CC) using the Student *t* test.

[c] Nonparametric variables: the *P* value was calculated using the Kruskal-Wallis or the Mann-Whitney *U* tests. The *P* values were not corrected for multiple comparisons.

Table 2
Independent predictors of insulin resistance (HOMA-IR as dependent variable) in a multiple linear regression analysis

	B (95% CI)	*P* value
−174 G>C polymorphism [a]	0.27 (−0.13;0.67)	.185
Waist circumference (cm)	0.05 (0.02;0.08)	.003
TG (mmol/L)	0.02 (−0.01;0.01)	.171
Adiponectin (μg/mL)	−0.04 (−0.07;−0.01)	.044
Cortisol (mmol/L)	0.05 (0.01;0.09)	.012
Leptin (ng/mL)	0.03 (0.01;0.04)	.003
Adjusted R^2 = 0.26		<.001

All the variables included in the model appeared as potential predictors in the univariate analysis ($P < .05$).

[a] −174G>C polymorphism genotypes were encoded as 0 = C− and 1 = C+.

(tolerance >.2) despite the genetic variants and the circulating adiponectin being statistically correlated (r = .24, P = .013). Afterward, all these variables accounted for 26% of the variation ($P < .001$) in insulin resistance when included in the fitted multiple regression model (Table 2), showing an increase in HOMA index of 0.27 attributed to the C allele of the −174 G>C gene polymorphism (Table 2).

3.2. Gene variants' effect on the risk of developing obesity-related metabolic disorders

To assess the contribution of the IL-6 −174G>C promoter polymorphism on the risk of developing obesity comorbidities, the allelic frequency was explored using the χ^2 test and taking as the cutoff the median value of the previously selected metabolic markers (Table 1). Based on the definition of the metabolic syndrome [26,28], the median values for waist circumference (men, 100.5 cm [94.1-106.9 cm]; women, 88.6 cm [81.8-95.4 cm]) and HDL-C (men, 1.16 mmol/L [0.80-1.52 mmol/L]; women, 1.47 mmol/L [1.03-1.92 mmol/L]) were considered depending on sex.

The analysis of the frequency distribution of the alleles was individually explored for each metabolic syndrome marker. Thus, no statistical significance was observed when blood pressure, HDL-C, and TG were analyzed. However, the C allele was more frequent in volunteers showing waist circumference (χ^2 = 5.81, P = .019) and HOMA-IR (χ^2 = 11.38, P = .010) values higher than the median cutoff.

Taking into account such dysfunction markers, 48 volunteers were included in the group at low risk of developing metabolic complications, with less than 3 values above the median; and 58 were in the high-risk group, with 3 or more markers above the median value [28]. Thus, a Fisher exact test was performed, showing statistical differences (P = .010) in the frequency distribution of the alleles depending on the risk of obesity-complications development. In fact, volunteers carrying the C allele presented a 76% prevalence of developing complications (Fig. 1). To confirm this observation, a binary logistic regression was carried out to calculate the risk of developing metabolic disturbances linked to C allele and related to the GG genotype. The unadjusted model shows an OR of 4.2 (P = .001; 95% confidence interval [CI], 1.8-10.1); and when covariates (BMI and sex) were included in the model, the OR was increased to 5.2 (P = .003; 95% CI, 1.8-15.4). After permutation procedure, which was performed to correct for multiple hypothesis testing ($P < .004838$), the obtained OR (P = .003) remained statistically significant.

4. Discussion

Increasing evidences suggest that a low-grade inflammation could be one of the determinants in the pathogenesis of insulin resistance and other metabolic complications commonly related to obesity [4,5,29]. On the basis of the potential role of proinflammatory cytokines in this process [8,11,30], we evaluated the effect of the IL-6 −174G>C gene promoter polymorphism on the risk of developing metabolic disorders in healthy people with excess in body weight.

Firstly, we tested the genotype distribution of the polymorphism in the volunteers, with the frequency of the C allele being similar to previously published values in other white populations [21]. Indeed, previous Spanish data revealed a similar frequency distribution of IL-6 polymorphism, in agreement with our observations [18]. Based on these findings, we assumed the sample as representative to evaluate the involvement of the polymorphism modulating the predisposition to develop obesity-related disorders.

The present data demonstrate the C allele association to insulin resistance in subjects with excess in body weight. Thus, the linear regression analysis showed that the polymorphism in IL-6 gene partially explained the increase in insulin resistance when expressed as HOMA-IR, probably acting together with other single nucleotide polymorphisms [23] and as a surrogate for the other measures related to the metabolic syndrome as those included in the multivariate model: leptin in relation with body fat, waist circumference as marker of abdominal distribution of the fat, adiponectin for insulin modulation by adipocytes, TG in relation with exogenous lipid metabolism, and cortisol as stress-related

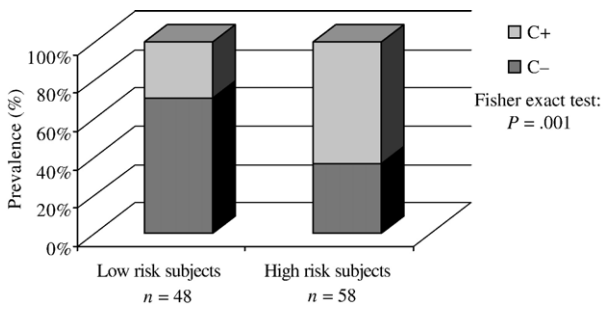

Fig. 1. Differences in the frequency distribution of the encoded genotypes (−174G>C IL-6 promoter polymorphism) depending on the risk of developing obesity-related metabolic complications. Fisher exact test showed statistical differences (P = .001) in the frequency distribution depending on the grouped genotypes.

hormone [31,32]. In fact, blood adiponectin concentration, a factor linked to carbohydrate metabolism, was decreased in subjects carrying the C allele. Recently published reports also indicate this association between the CC genotype and insulin resistance and type 2 diabetes mellitus [20,33].

To split 2 groups of people depending on the predisposition to develop obesity comorbidities, the median values of waist circumference, blood pressure (SBP, DBP), HDL-C, TG, and HOMA-IR index were selected as the cutoff [28]. Based on the screening criteria, all studied volunteers were overweight or grade 1 obese without other associated morbidities; but the median values of these metabolic features appeared near the limits assumed in the metabolic syndrome description, according to the criteria from National Cholesterol Education Program–Adult Treatment Panel III [26]. Thus, we found that the frequency of the C allele was clearly higher in the high-risk group and that its participation predicted the mentioned risk. In accordance with this statement, some studies have associated the C allele with hypertension [27], insulin resistance [33], and with the risk of coronary artery disease [21]. In disagreement with these findings, the G allele has been related to obesity [34] and comorbidities [19] such as hypertension [35], diabetes [36], or dyslipidemia [37].

The comparison of these studies is hampered by the fact that study groups differed in age, degree of obesity, glucose tolerance, interethnic variation, and sex distribution. Indeed, several published articles have described a BMI-dependent response of the polymorphism to insulin resistance [27,33] and other metabolic complications due to the subclinical systemic inflammation [21]. Moreover, it can be assumed that hypertension or circulating lipid profile could also interact with the IL-6 gene polymorphism and modulate its impact on insulin function [21,37]. In this context and according to our observations, most of the published studies in overweight or moderately obese subjects have suggested a higher risk of presenting insulin resistance linked to other metabolic disorders in relation with the C allele [21,33,38,39]. However, studies on glucose intolerance or diabetic subjects have described a higher prevalence of the disease in subjects carrying the G allele [40,41]. Therefore, to analyze the potential relationship between IL-6 −174 G>C promoter polymorphism and the risk of developing metabolic alterations, interactions between genetic heterogeneity [23] and all the different environmental factors should be considered.

Similarly, the impact of the IL-6 −174G>C gene polymorphism on IL-6 levels in humans is controversial [20,37]. Once more, it might be speculated that the influence of the BMI could be the responsible for the contradictory results described in the literature. In our study, BMI was not statistically different between genotypes; and it was placed on a slight range, in agreement with the inclusion criteria. Therefore, we postulated that this could be the reason circulating IL-6 was not found to be significantly different between groups, based on previous reports [20].

One limiting aspect of the current study could be the sample size, although this is comparable with other subject-specific studies [15,42-44]. The included volunteers were healthy with excess in body weight in a strength range of BMI and confined to one single geographic area. Despite this, statistical differences were found, suggesting that the statistical error type β is not occurring [45] and allowing the statistical interpretation of the current outcomes; it might be interesting to corroborate these observations in larger populations representing more diversified ethnic groups.

Despite the findings concerning the phenotypical characterization of the 3 genotypes being in agreement with other studies [33,38,39], measurements should be considered with caution because of the possibility of a type I error (false positive) resulting from multiple comparisons. Thus, although the studied variables were not totally independent of each other, the Bonferroni correction for multiple comparisons should be considered when interpreting the metabolic syndrome markers.

In conclusion, our study demonstrates that subjects with excess in body-weight-for-height carrying the C allele of the IL-6 −174 G>C showed higher risk of developing obesity-related metabolic disorders, especially insulin resistance, than GG homozygotes. These observations contribute to providing knowledge for preventing obesity comorbidities and for describing those subjects who might profit most from weight reduction strategies in a personalized manner.

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