RESEARCH ARTICLE

The insulin sensitivity response is determined by the interaction between the G972R polymorphism of the insulin receptor substrate 1 gene and dietary fat

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Scope: Insulin resistance, a condition associated with type 2 diabetes mellitus, results from the interaction of environmental and genetic factors. The aim of this study was to explore the influence of the G972R polymorphism at the insulin receptor substrate 1 gene on insulin sensitivity in a healthy young population. Furthermore, we examined whether the presence of this single nucleotide polymorphism (SNP; GR or GG) interacts with dietary fat to modulate insulin sensitivity.
Methods and results: Fifty-nine healthy volunteers consumed three diets during 4 wk each following a randomized crossover design: a saturated fatty acid diet, a low-fat and high carbohydrate (CHO) diet or a MUFA diet. For each diet, we investigated peripheral insulin sensitivity with the insulin suppression test. Steady-state plasma glucose and plasma-free fatty acids concentrations were significantly lower in GR subjects after the intake of a CHO diet, than did homozygous GG subjects ($p<0.05$). However, no differences were observed after consuming the two other diets.
Conclusions: Insulin sensitivity increased in GR subjects for the G972R polymorphism at the insulin receptor substrate 1 gene locus, after intake of a CHO diet. Increased knowledge of how these and other genes influence insulin sensitivity should increase the understanding of personalized nutrition.

Keywords:
Carbohydrates / Dietary fat / Insulin receptor substrate 1 G972R polymorphism/ Insulin sensitivity / Intervention study

1 Introduction

In the pathogenesis of common disorders, such as type 2 diabetes mellitus (T2DM), hypertension and atherosclerosis, a central role is played by insulin resistance (IR) [1]. IR clusters in families is determined by genetic and environmental factors [2–4]. In most cases, the clinical expression of the disease can be prevented by dietary and lifestyle modifications [5]. Observational evidence and intervention studies indicate that the quantity and the quality of dietary fats influence IR [6]; in particular saturated fat worsens, while monounsaturated and polyunsaturated fats improve insulin sensitivity [7]. Substituting saturated fat with unsaturated fat seems to have beneficial effects on insulin sensitivity, although the clinical significance of modifying fat quality alone is still unclear [6].

Storlien *et al.* [8] proposed a scheme linking genetic and environmental factors to the IR syndrome by changes in the

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Abbreviations: Apo, apolipoprotein; **CAD,** cardiovascular disease; **CHO,** low fat and high carbohydrate; **IR,** insulin resistance; **IRS-1,** insulin receptor substrate 1; **NEFA,** non-esterified fatty acid; **PI-3K,** phosphoinositide 3-kinase; **SFA,** saturated fatty acid; **SNP,** single nucleotide polymorphism; **SSPG,** steady-state plasma glucose; **TAG,** triacyglycerol; **T2DM,** type 2 diabetes mellitus

membrane fatty acid composition and lipid supply. A change in the quality of dietary fat may affect the capacity for insulin secretion. Elevated fatty acids in circulation are associated with impaired insulin function and are commonly linked with obesity and T2DM [9]. IR usually precedes the diagnosis of T2DM by decades and, in most cases, the clinical expression of the disease could be prevented by dietary and lifestyle modification. In the last decade there has been much debate over the relationship between dietary carbohydrates intake and IR, as the quantity and source of carbohydrates in food influence glucose levels. Thus, it has been suggested that increased consumption of refined and simple carbohydrates may promote the development of diabetes. In addition, a carbohydrates-restricted diet is postulated to improve IR and metabolic syndrome, potentially preventing the development to T2DM [10].

On the other hand, the genetic base of T2DM is very heterogeneous, and the disease has been related to various mutations in different genes that codify proteins linked to glucose and insulin metabolism, of which the insulin receptor [11], the insulin receptor substrate 1 (IRS-1) [12], the Rad protein, glycogen synthase and the 3-adrenergic receptor are the best known. However, the genetic background of IR and T2DM is more complex and can also involve other genes that seemingly are unrelated to carbohydrate metabolism [13].

In the search for susceptibility loci predisposing to IR, previous studies have identified a glycine to arginine substitution at codon 972 (G972R) (rs1801278) in the IRS-1 gene as being associated with impaired insulin action, particularly in obese patients [14–16]. The IRS-1 gene, which plays a pivotal role in the signalling cascade activated by insulin, is therefore a strong candidate for the genetic susceptibility to IR.

This mutation has been reported to significantly impair insulin action in experimental models and clinical studies have shown that the genetic variant is associated with reduced insulin sensitivity [17, 18]. Normal glucose-tolerant subjects carrying the G972R change have also been shown to have decreased insulin secretion. In addition, this polymorphism has been associated with an increased risk of cardiovascular disease (CAD) and two studies have also demonstrated an association between this polymorphism and T2DM [19, 20]. Clausen *et al.* [14] suggested that IRS-1 codon 972 variant may interact with obesity to induce greater IR than would occur with either the mutation or obesity on its own. However, to date, there were no studies analysing the interaction of this polymorphism with diet in order to determine the insulin sensitivity. Based on this previous evidence, we explored the influence of the G972R polymorphism at the IRS-1 gene on insulin sensitivity in a healthy Caucasian population. Furthermore, we examined whether the presence of this single nucleotide polymorphism (SNP) interact with dietary fat to modulate insulin sensitivity.

2 Materials and methods

2.1 Subjects and diets

Fifty-nine healthy normolipemic (total plasma cholesterol values were lower than 5.2 mmol/L) subjects (30 men and 29 women) were recruited from among 250 students at the University of Cordoba. Of these, 53 were homozygous for the most common allele G (26 men and 27 women), six were heterozygous for the allele R (five men and one woman). Subjects were younger than 30 years of age (mean age 23.1 (SD 1.8)) with no evidence of any chronic illness (such as hepatic, renal, thyroid or cardiac dysfunction) or unusually high values of physical activity. Mean initial BMIs were 21.34 (SD 2.9) and 23.80 (SD 4.28) for GG homozygotes and GR heterozygotes, respectively. Mean basal weight was 67.0 (SD 11.5). This measure remained constant at the end of each dietary period.

Dietary information, including alcohol consumption, was collected over seven consecutive days. Individual energy requirements were calculated by taking into consideration each participant's weight and physical activity. The participants were encouraged to maintain their regular physical activity and life-style and were asked to record in a diary any event that could affect the outcome of the study, such as stress, change in smoking habits and alcohol consumption or foods not included in the experimental design.

The study design included an initial 28 day period during which all the subjects consumed a saturated fatty acid (SFA)-enriched diet with 15% of energy as protein, 47% as carbohydrates (CHO, low fat and high carbohydrate) and 38% as fat (20% SFA, 12% MUFAs and 6% PUFAs (Fig. 1). All participants were then randomized, following a simple block randomization non-stratified in a crossover design and exposed to two new dietary periods: a CHO diet and a high-MUFA diet, with a typical ''Mediterranean diet'' enriched with olive oil. We randomly assigned participants consecutively to one of two sequences of dietary treatment. We prepared random allocation to each sequence, taken from a Latin square by blocks of 72 participants (36 persons in each sequence). The two groups of subjects were assigned one of two dietary regimes for 28 days each. Group 1(29 subjects) was placed on a MUFA diet followed by a CHO diet. For group 2 (30 subjects) the order was reversed. Assignment of volunteers to the sequence of diets was carried out at random. The CHO diet [21] contained 15% of energy as protein, 57% as CHO and 28% as fat (<10% SFA, 12% MUFA and 6% PUFA). The MUFA diet contained 15% of energy as protein, 47% as CHO and 38% as fat (<10% SFA, 22% MUFA and 6% PUFA). Virgin olive oil provided 75% of total MUFA consumed during this last dietary period. Each dietary period lasted 28 days. Dietary cholesterol was maintained constant in our experimental design and the mean cholesterol intake was 115 mg/1000 kcal during the three periods.

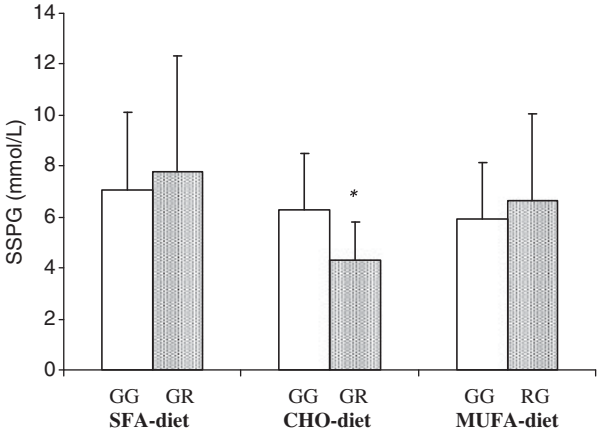

Figure 1. SSPG concentrations during the insulin suppression test according to the G972R polymorphism in the IRS-1 gene after SFA-rich diet, CHO or MUFA-rich diet, in the total population (53 GG and six GR). Values are means, with SD represented by vertical bars. The effect of diet was significant ($p<0.029$); the effect of genotype was not significant ($p<0.604$); the diet–genotype interaction was significant ($p<0.001$) (ANOVA). $^{*}p<0.05$ when comparing GG *versus* GR. There is no difference between two groups after the consumption of MUFA diet and SFA diet.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Human Investigation Review Committee, which approved this study at the Reina Sofia University Hospital. Informed consent was obtained from all participants.

The composition of the experimental diets was calculated using the United States Department of Agriculture (USDA) food tables or the Spanish food composition tables for local foodstuffs. Fourteen menus, prepared with regular solid foods, were rotated during the experimental period. We used virgin olive oil for cooking and salad dressing during the MUFA diet and palm oil and butter for the high-SFA diet. During the CHO-diet period, biscuits, bread and jam replaced some olive oil or palm oil. Lunch and dinner were consumed in the hospital dining room, whereas breakfast and an afternoon coffee break were eaten in the medical school cafeteria. A dietician supervised all meals. Duplicate samples from each menu were collected, homogenized and stored at −80°C. Protein, fat and carbohydrates content of the diet was analysed using standard methods [22]. Evaluation of dietary compliance was also performed by examining the food diaries and by analysing the fatty acid content of the cholesterol ester fraction in LDL [23].

2.2 Blood sampling and biochemical determinations

Venous blood for analysis of insulin, glucose, lipid and lipoprotein was collected from the subjects in tubes containing EDTA after a 12 h overnight fast at the end of each dietary period. Each analysis was performed in triplicate. Total cholesterol, HDL-cholesterol, LDL-cholesterol and triacyglycerol (TAG) were assayed by procedures described previously [24–27]. Unesterified free fatty acid concentrations were determined by an enzymatic colorimetric assay (Boehringer Mannheim) as described by Shimizu *et al.* [28]. To reduce interassay variation, plasma for biochemical determinations was stored at −80°C and analysed at the end of the study in triplicate.

2.3 Insulin suppression test

At the end of each dietary period all subjects underwent a modified insulin suppression test [29, 30]. The study began at 08:00 h, after 12 h of fasting. A continuous infusion of somatostatin (214 nmol/h), insulin (180 pmol/m^2/min) and glucose (13.2 mol/m^2/min) was infused in the same vein. Somatostatin was used to inhibit endogenous insulin secretion. Blood was sampled every 30 min for the first two and half hours, by which time steady-state plasma glucose (SSPG) concentrations were achieved. Blood was then sampled at 10-min intervals for the last 30 min (at 150, 160, 170 and 180 min) to measure plasma glucose concentrations. These four values determined the SSPG concentrations. SSPG concentrations provided a measure of the ability of insulin to promote disposal of infused glucose.

2.4 Genotyping of IRS-1 gene polymorphism

A PCR-restriction fragment length polymorphismassay was developed for genotyping. Genomic DNA was isolated from white blood cells and DNA extraction was performed by standard procedures. The genomic DNA fragment flanking the G972R polymorphism (rs1801278) was amplified using two primers. PCR was carried out with 250 ng of genomic DNA and 0.2 μmol of each oligonucleotide primer (P1; 5′-CTGGAGCCCAGCCTTCCACATC-3′ and P2, 5′-CCCTGGGCAGGCTCACCTCCTC-3′) in 50 μL. DNA was denatured at 94°C for 5 min, followed by 30 cycles of denaturation at 95°C for 35 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s and concluded with a final extension at 72°C for 10 min. The PCR product (10 μL) was digested with 5 units of restriction enzyme Xma I at 37°C (New England Biolabs, Beverly MA, USA) in a total volume of 35 μL. The predicted digestion product sizes are 435 bp, 174 pb for Gly972 homozygotes; 600 pb for Arg972 homozygotes; and 600 bp, 435 bp, 134 bp for Gly972Arg heterozygotes [31].

2.5 Statistical analysis

Statistical analyses were carried out using SPSS statistical package version 17.0 (SPSS, Chicago). ANOVA for repeated measures was used to analyse the effect of differences in

plasma lipid, glucose and SSPG concentrations between dietary phases. The general linear model for repeated measures procedure was used to test the main effects of genes and diet, after adjustment for the covariate of BMI. In the present analysis, we studied the effect of the interaction of both factors (genotype and time), which is indicative of the magnitude of the postprandial response in each group of subjects. When statistically significant effects were observed, Bonferroni's *post hoc* test was used to identify between-group differences. Correlation was done with Pearson's correlation coefficient. IRS-1 genotypes were dichotomized for these analyses. We have determined the power of our study according to the sample size. The observed power in the ANOVA for repeated measures for the analysis of the interaction between diet and genotype adjusted by BMI and age was 92.3%. A p value of less than 0.05 was considered statistically significant. All data are given in the text and tables as means and SDs.

3 Results

Dietary composition was analysed in duplicate meal portions and the results were in good agreement with values obtained from the food composition tables (Table 1). Analysis of the cholesterol ester fraction of plasma LDL showed good adherence to the different diets. During consumption of the SFA diet, there was a significant higher concentration in palmitic acid (16:0) (27.2 (SD 1.4)) compared with that recorded during the high-CHO and MUFA dietary periods (18.9 (SD 3.9) and 15.1 (SD 0.4), respectively, $p<0.004$ in both cases). We also observed a higher concentration in oleic acid (18:1) when subjects switched from CHO diet to MUFA diet (38.5 (SD 9) and 49.7 (SD 4.7), respectively, $p<0.004$), and from SFA diet to CHO diet (20.2 (SD 3.6) and 33.6 (SD 16), respectively, $p<0.05$)

The baseline characteristics of the subjects according to the G972R polymorphism at the IRS-1 gene are shown in Table 2. Subjects carrying the GG allele showed higher levels of apolipoprotein (Apo) A1 ($p<0.05$) compared with heterozygous for the R allele. However, no significant differences were found between the two groups for the rest of the lipid parameters. Genotype distributions did not deviate from Hardy–Weinberg expectations for the G972R SNP.

Plasma lipid and Apo levels are shown in Table 3 as a function of the G972R genotype for polymorphism in the IRS-1 gene after 4 wk on the three diets described. We further examined the genotype effect on plasma LDL-C and Apo B levels, such that subjects carrying the GR genotype showed higher levels of LDL-C and Apo B than did homozygotes for the G allele, regardless of the type of diet consumed ($p = 0.029$ and $p = 0.043$, respectively).

The SSPG, a measure of insulin sensitivity, value was significantly lower during both the Mediterranean (6.2 (SD 3.1)) and CHO (6.6 (SD 3.1)) diets compared with the high-SFA diet (8.1 (SD 4.1)) (data not shown). The SSPG was greater after consuming the diet rich in SFA than for the other two diets administered in the study, independently of the genotype. We also observed a genotype interaction with the type of diet on peripheral sensitivity to

Table 1. Daily intake during each experimental diet period

	SFA diet	CHO diet	MUFA diet
Protein (% of energy intake)			
Calculated	15	15	15
Analysed	18.1	17.6	17.5
Fat (% of energy intake)			
Saturated			
Calculated	20	10	10
Analysed	22.6	9.2	9.2
Monounsaturated			
Calculated	12	12	22
Analysed	10.1	13.5	24.4
Polyunsaturated			
Calculated	6	6	6
Analysed	5.0	5.2	4.8
Carbohydrates (% of energy intake)			
Calculated	47	57	47
Analysed	44.2	54.5	44.1
Cholesterol (mg/dL)			
Calculated	115	115	115
Analysed	112	113	117
Energy (MJ)			
Calculated	10.2	10.2	10.2
Analysed	10.8	10.6	10.8

Table 2. Baseline anthropometrics characteristics and plasma lipid and Apo concentrations according to IRS-1 genotype[a)]

	GG ($n=53$)	GR ($n=6$)	p^*
BMI (Kg/m^2)	21.34±2.92	23.80±4.28	0.273
Age (years)	21.18±2.31	21.20±1.30	0.984
Total cholesterol (mmol/L)	4.13±0.63	4.45±0.80	0.288
Triacylglycerol (mmol/L)	0.72±0.30	0.93±0.53	0.149
LDL-C (mmol/L)	2.43±0.60	2.78±0.92	0.235
HDL-C (mmol/L)	1.37±0.38	1.24±0.45	0.468
Apo AI (g/L)	1.5±0.16	1.31±0.10	0.013
Apo B (g/L)	0.72±0.13	0.82±0.12	0.102
Fasting glucose (mmol/L)	4.43±0.42	4.40±0.33	0.899

a) HDL-C: high-density lipoprotein cholesterol. Values are mean±SD. $^*p<0.05$ by ANOVA.

Table 3. Plasma lipid and Apo concentrations in healthy volunteers, according to G972R polymorphism at the IRS-1 gene, after they consumed the SFA-rich diet followed by the CHO- or MUFA-rich diet[a)]

	TC (mmol/L)	TAG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	Apo AI (g/L)	Apo B (g/L)
GG (53)						
SFA	4.16±0.58	0.72±0.28	1.27±0.26	2.52±0.52	1.51±0.16	0.72±0.13
CHO	3.59±0.60	0.77±0.28	1.14±0.27	2.09±0.53	1.40±0.16	0.65±0.14
MUFA	3.67±0.62	0.76±0.28	1.20±0.29	2.13±0.53	1.46±0.18	0.65±0.13
GR (6)						
SFA	4.45±0.82	0.86±0.53	1.08±0.26	2.98±0.80	1.35±0.13	0.83±0.11
CHO	4.01±0.61	0.79±0.27	1.00±0.17	2.64±0.57	1.32±0.16	0.75±0.12
MUFA	4.09±1.05	0.90±0.60	1.02±0.20	2.65±0.90	1.32±0.11	0.78±0.21
p^*						
Diet	0.001	0.731	0.002	0.001	0.005	0.001
Genotype	0.142	0.373	0.138	0.029	0.064	0.043
Interaction	0.639	0.489	0.582	0.61	0.3	0.483

a) TC: Total cholesterol; HDL-C: high-density lipoprotein cholesterol. Values are mean±SD. $^*p$ value by ANOVA for repeated measurements.

insulin. In this regard, the GG genotype subjects showed higher SSPG levels after consuming the CHO diet ($p<0.05$) in comparison with subjects who were heterozygous for the R allele (Fig. 1). However, no significant differences were observed between the two genotypes for the other two diets analysed.

Similarly, we in addition observed a dietary effect and a genotype–diet interaction in the analysis of non-esterified fatty acids (NEFAs). After consuming the CHO diet, the NEFA levels were lower in persons with the GR genotype than in GG homozygotes (Fig. 2). However, no differences in the free fatty acids were observed between the two genotypes for the two other diets studied.

4 Discussion

Our findings show that G972R polymorphism at the IRS-1 gene determines the insulin sensitivity as a function of the type of diet. Heterozygous GR individuals have greater insulin sensitivity and lower free fatty acid levels after the intake of CHO-rich diet than do homozygous GG subjects. However, no differences were observed after consuming the two other enriched fat diets.

There are several modifiable factors such as weight loss, physical activity and diet (mainly its fat content), which have an important effect on the development of T2DM, CAD and IR. Studies done *in vitro* suggest that the amount and type of fatty acid ingested in the diet affects IR [32]. In fact, there is evidence to suggest that a reduction in SFA fat intake improves insulin sensitivity in patients with T2DM [33]. However, the data obtained in studies by our group on healthy individuals have shown than both a CHO-rich diet and the Mediterranean diet induced an increase in peripheral insulin sensitivity, in comparison with an SFA diet, when the overall population is studied [9]. However, in this study, we demonstrated for the first time that, unlike the rest of the population, subjects with the GR genotype of the G972R polymorphism in the IRS-1 gene showed greater improvement in their peripheral insulin sensitivity when they consumed a nutritional model rich in CHO diet compared with a MUFA diet.

IR plays an important role in the pathogenesis of common diseases like T2DM, high blood pressure and

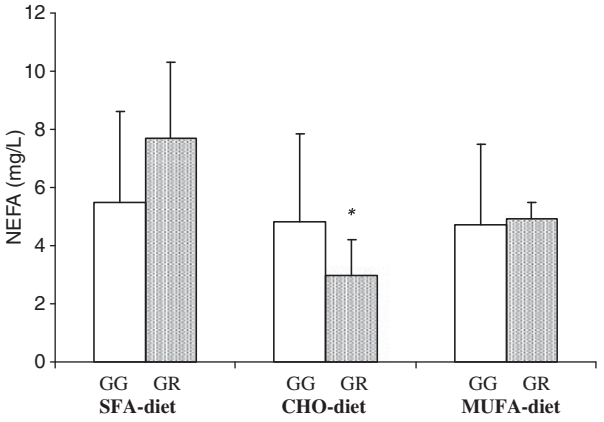

Figure 2. NEFA concentrations in young subjects, according the G972R polymorphism in the IRS-1 gene after SFA-rich diet followed by the CHO- or MUFA-rich diet, in the total population (53 GG and 6 GR). Values are means, with SD represented by vertical bars. The effect of diet was significant ($P<0.001$); the effect of genotype was not significant ($p<0.878$); the diet–genotype interaction was significant ($p<0.05$) (ANOVA). $^{*}p<0.05$ when comparing GG *versus* GR. There is no difference between two groups after the consumption of MUFA diet and SFA diet.

atherosclerosis. The IRS-1 gene has been considered to be a candidate for metabolic diseases like T2DM and obesity. The presence of genetic variations in the IRS-1 gene may potentially contribute to developing IR. In previous studies, substituting arginine for glycine at codon 972, a common variant in the IRS-1 gene, has been associated with lower insulin sensitivity [34]. Baroni *et al.* [15] studied the frequency of this mutation in patients with angiographic evidence of coronary atherosclerosis and observed that it was twice as common in these patients as in the controls. When adjusted for other risk factors, the relative risk of CAD attributable to polymorphism was three times as great and increased to seven times in obese patients and to 23 times in patients with IR syndrome. The allele frequency analysed in our population was 5%, similar to that observed in other groups [15]. Several studies have demonstrated that the presence of the G972R SNP at the IRS-1 gene is associated with dyslipemia [13, 19] and may predispose to proaterogenic alterations in plasma lipid. These findings are consistent with the higher levels of LDL-C and Apo B and lower levels of Apo A1 observed in subjects carrying the minor R allele in comparison with GG subjects. A multivariate analysis clearly demonstrated that the association of the G972R mutation with increased risk of CAD was independent of diabetes, indicating that additional factors may play a role [13]. Previous studies [12, 13] described significantly higher triglyceride levels in heterozygous carries of the G972R mutation, suggesting a direct role of the IRS-1 gene in modulating triglyceride levels. In our study we did not observe significantly differences in plasma triglycerides according to the G972R SNP. However, in subjects carrying the GR genotype the CHO diet improved peripheral insulin sensitivity compared with GG subjects. Although speculative, the fact that the high-CHO diet did not result in detrimental changes in TAG could be explained because in our study volunteers consumed a high complex CHO diet.

One of the metabolic processes in which IRS-1 is involved is the activation of phosphoinositide 3-kinase (PI-3K), which plays an important role in transporting glucose mediated by insulin in skeletal muscle and adipose tissue [35, 36]. The presence of the G972R polymorphism in the IRS-1 gene may result in less PI-3K activity, interfering with the antilipolytic effects of insulin. These effects may be modified by the type of diet consumed. Frangioudakis *et al.* [32] suggested that the total amount of fat provided in a high-fat diet, rather than the particular fatty acid subtype provided, has a major impact on insulin action *in vivo*. This group has shown a major defect in insulin signalling with chronic high-fat diet-induced IR at the level of the IRS-1. At the molecular level, the IRS protein has been suggested to be a target of free fatty acids for IR [37] and a decrease in glucose uptake is linked to reduced tyrosine phosphorylation of IRS-1 and PI-3K activation. Our results indicate that subjects carrying the G972R polymorphism show improvement in insulin sensitivity after eating a CHO diet, in comparison with the two fat-rich diets, possibly due to activation of PI-3K mediated by phosphorylation of IRS-1. As a result of this metabolic process, higher glucose uptake and insulin sensitivity may be induced in these subjects when they consume a low-fat and high-CHO diet, in comparison with homozygous GG subjects.

On the other hand, the ''flexibility'' of adipose tissue to trap dietary fatty acids and regulate lipolysis may contribute to muscle lipid accumulation. The type of fat present in the diet and even the percentage of carbohydrates ingested may influence the lipolysis index generated in adipose tissue. A recent study has shown that a high fat and low carbohydrate diet fed to mice leads to a greater rate of lipolysis *via* an increase in the number of fat cells and an insulin signalling defect in adipocytes [38]. Also, previous studies have demonstrated that an increase in free fatty acid plasma levels is associated with a reduction in PI-3K activity, associated with activation of IRS-1 by insulin, and a reduction in phosphorylation of IRS-1 tyrosine residues [39]. Our results indicate that the carriers of the G972R polymorphism showed lower levels of free fatty acids after eating a CHO diet, possibly due to an efficient storage of these fatty acids and reduced lipolysis in adipose tissue. If lipids are properly stored in adipose tissue until needed, IR will not develop.

One limitation of our study is the small sample size in GR genotype. In contrast the cohort is very well characterized in terms of their metabolic phenotyping. In addition, the power observed in the ANOVA for repeated measures for the analysis of the interaction between diet and genotype adjusted by BMI and age was 92.3%. Given that in our study the gender ratio is not comparable between GG and GR groups, it would be interesting to analyse the possible interaction between this SNP and gender in future studies.

In conclusion, our findings show that, in a healthy population, ingesting a high-CHO, low-fat diet induces greater peripheral sensitivity to insulin in subjects with the G972R polymorphism in the IRS-1 gene than do high-fat diets. These results suggest that subjects carrying this polymorphism may obtain greater benefits from CHO-rich diets than from MUFA-rich diets.

C.M., P.P.-M. and J.L.-M. carried out the studies and data analyses and drafted the manuscript. C.M., J.D.-L., P.G., E.M.Y-S., A.G.-R. and A.C. carried out the samples analyses. C.M., J.L.-M. and F.P.-J. participated in the design of the study and performed the statistical analysis. J.L.-M. and F.P.-J. conceived of the study, and participated in its design and coordination and helped to draft the manuscript. The present work was supported by grants from the Ministerio de Ciencia e Innovación (AGL 2004/07907, AGL2006-01979/ALI to J.L.-M. and SAF2003-05770, SAF2007-62005 to F.P.-J.), the Spanish Ministry of Health (FIS PI041619 to C.M., and CB06/03/0047 -CIBER Fisiopatologia de la Obesidad y Nutricion is an initiative of ISCIII to F.P.-J.), Consejeria de Innovación, Ciencia y Empresa, Proyectos de Investigación de Excelencia Junta de Andalucia (AGR 05/00922 to P.P.-M. and P06-CTS- 01425 to J.L.-M.); Consejería de Salud, Junta de Andalucía (06/128, 07/43 to J.L.-M., 06/129 to F.P.-J., 06/127 to C.M.), the Diputación Provincial de Córdoba (to F.P.-J.).

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