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Pro12Ala Polymorphism of the PPARG2 Gene Is Associated with Type 2 Diabetes Mellitus and Peripheral Insulin Sensitivity in a Population with a High Intake of Oleic Acid[1]

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Abstract

Activation of the PPAR gamma 2 gene (PPARG2) improves the action of insulin and its lipid metabolism. We examined the association between Pro12Ala polymorphism of PPARG2, type 2 diabetes mellitus (DM2), and peripheral insulin sensitivity in a population with a high intake of oleic acid. A cross-sectional, population-based study was undertaken in Pizarra, a small town in the province of Malaga in southern Spain. A total of 538 subjects, aged 18–65 y, were selected randomly from the municipal census. All subjects underwent a clinical, anthropometrical, and biochemical evaluation, including an oral glucose tolerance test and Pro12Ala polymorphism of PPARG2. Insulin resistance was measured by homeostasis model assessment. Those subjects with the Ala-12 allele had an odds ratio for impaired fasting glucose of 0.55, for impaired glucose tolerance of 0.59, and for DM2 of 0.30. The intake of monounsaturated fatty acids (MUFA) contributed to the variance of the homeostasis model assessment insulin resistance index (HOMA IR) ($P = 0.04$), with a 2-way interaction between the Ala-12 allele of PPARG2 and the intake of MUFA ($P = 0.005$). The results suggest the existence of an interaction between Pro12Ala polymorphism of PPARG2 and dietary MUFA, such that obese people with the Ala-12 allele have higher HOMA IR values, especially if their intake of MUFA is low. J. Nutr. 136: 2325–2330, 2006.

Introduction

The PPAR gamma 2 gene (PPARG2)[2] is a member of the nuclear receptor superfamily, which also includes PPAR-α and PPAR-β/δ (1). A point mutation in the B exon of the NH_2-terminal part of PPARG2, substituting alanine for proline at position 12, has been shown to decrease receptor activity (2,3). Several studies have found that people with this mutation have a reduced risk for type 2 diabetes mellitus (DM2) (4,5), as well as a greater insulin sensitivity, lower BMI, and a more favorable lipid profile (6,7). This observation is consistent with the finding that heterozygous-deficient mice (PPARG +/−) have increased insulin sensitivity (8). However, in most studies, this association between the substitution of alanine for proline and insulin sensitivity disappears when the data are corrected for the BMI, thus suggesting a primary effect on the increase in body fat (2). The strength of the association seems to depend on the population and ethnic groups studied (9). Some studies have even found an increase in the risk for DM2 in people with the Ala-12 variant (10,11), although no reports have yet appeared of an association between the polymorphism and greater insulin resistance (12). Other studies have failed to detect any association (13,14). These divergent results suggest the existence of gene–gene or gene–environment interactions (15,16), as well as the possible effect of the mutation on other factors, such as insulin secretion in response to free fatty acids (17) or physical exercise (18).

Heated debate surrounds the role of fats in humans in the current endemic disease of obesity in developed countries, although evidence supporting the presence of a gene–diet interaction is poor (19). Numerous synthetic and natural ligands of PPARG2 have been reported, including fatty acids and their derivatives (2,20). Some studies have suggested that the affinity of the fatty acids as natural ligands of PPARG2 may vary, depending on the length of the chain and the degree of saturation (1). However, the results of studies of the gene–diet interaction are contradictory (21), with some studies finding that BMI is greater in people who consume a diet low in polyunsaturated and saturated fats, but only in subjects with the Ala allele (16), whereas other studies have found that the amount of total fat

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[2] Abbreviations used: DM2, type 2 diabetes mellitus; HOMA IR, homeostasis model assessment insulin resistance index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MUFA, monounsaturated fatty acids; OGTT, oral glucose tolerance test; OR, odds ratio; PPARG2, PPAR gamma 2.

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and saturated fat in the diet is associated with the components of the metabolic syndrome only in homozygous Pro12Pro subjects (22,23). An interaction between the intake of monounsaturated fatty acids (MUFA), the BMI, and Pro12Ala polymorphism of the PPARG2 gene has recently been reported (23).

We studied the associations among Pro12Ala polymorphism of the PPARG2 receptor and the prevalence of DM2, the pattern of insulin resistance, and the possible interaction between dietary MUFA and PPARG2 polymorphism in a population from southern Spain with a high intake of olive oil and consuming a Mediterranean-type diet.

Subjects and Methods

The study was undertaken in Pizarra, a town in the province of Malaga, Andalusia, in southern Spain. Details of the study design and sample have been reported previously (24,25). A total of 538 subjects, aged 18–65 y, were selected randomly from the municipal census. All institutionalized people, for whatever reason, were excluded from the study, as were pregnant women and those with a severe clinical problem or psychological disorder. The subjects were mailed requests to attend their local health center for a medical examination. Those who failed to attend their first appointment were sent a second letter giving them another appointment, and all those still not attending were visited at home to ascertain the reason. The final sample distribution by age and sex was not significantly different from the population distribution (26).

The project was authorized by the Ethics and Clinical Investigation Committee of Carlos Haya Regional University Hospital, Malaga, Spain. All the subjects gave written, informed consent.

Procedures

All participants were interviewed and underwent a physical examination based on standard procedures. They also received several home visits to undertake dietary evaluation studies. All the examinations were performed by the same investigators and dieticians. All subjects completed a survey about their usual physical activity and provided information about the intensity of daily physical activity, which was classified as slight, moderate, or intense (27). Standardized anthropometrical measurements were made (28). Subjects with baseline blood glucose levels $<$7.8 mmol/L were given an oral glucose tolerance test (OGTT). Blood samples were taken at baseline and 120 min after the OGTT, and the serum was stored at -70°C until further study.

Classification criteria

Classification of people with diabetes and carbohydrate metabolism disorders was made according to the American Diabetes Associatio 1998 criteria (29). Subjects were considered obese if their BMI was $\geq$30 (30).

Evaluation of dietary intake

A prospective 7-d quantitative questionnaire as well as a survey on the frequency of consumption of usual foods was administered to all participants at 2 different times during the year. The questionnaires were given by experienced dieticians with special training for this project. Appointments were made by telephone for the dieticians to explain and hand over the questionnaire. Seven days later, the questionnaires were collected after resolving any queries. Transformation to energy or macronutrients was done with a computer program that included the composition of local foods, based on previous studies of food composition by some of the authors of this study (31).

During the course of dietary habit interviews conducted in the homes at various times of the year, samples were taken of the subjects' cooking oil. To avoid old oil being exchanged for newer oil, the family was unaware of the intention to request a sample of their oil until the time of the visit by the researcher.

The composition of plasma phospholipid fatty acids was studied in all subjects (32). This was used as a biological marker of the intake of vegetable oil and as an instrument to validate the surveys (25).

Composition and quality of frying oil

Fatty acids were analyzed by gas chromatography after derivatization to fatty acid methyl esters with KOH 2 mol/L in methanol and triheptadecanoin as an internal standard, according to the International Union of Pure and Applied Chemistry Standard Method (33). A Hewlett Packard 6890 chromatograph on a HP Innowax capillary column (polyethylene glycol, 30 m $\times$ 0.25 mm i.d., film thickness 0.25μm) was used under the following temperature program: 180°C (4 min), 4°C/min to 230°C (15 min). Samples were introduced into the column via a split injector (split ratio 1:40) at 25°C and the flow rate of hydrogen, used as carrier gas, was 1 mL/min. The temperature of both the split injector and the flame ionization detector was 250°C.

After analysis, samples were classified according to fatty acid composition. Knowing that only olive and sunflower oils are generally sold for domestic use in Spain, 3 groups of oils were defined as follows: oils having a proportion of linoleic acid $>$50% were classified as sunflower oils; oils having $<$25% linoleic acid were classified as olive oil; and those containing between 25% and 50% linoleic acid were classified as mixtures.

Laboratory measurements

Serum insulin at baseline and 2 h after the OGTT was measured by radioimmunoassay (Coat A Count Insulin, DPC) (assay precision: CV $<$10% at 16 μIU/mL concentration, cross reactivity with proinsulin = 20%).

Indices of insulin resistance. The formula for the homeostasis model assessment is as follows (34):

$$\text{Homeostasis model assessment insulin resistance (HOMA IR)} = [\text{Fasting insulin } (\mu\text{U/mL}) \times \text{Fasting glucose (mmol/L)}]/22.5.$$

Genetic analysis

DNA was isolated from whole blood by the salting-out method of Miller modified by Queipo-Ortuño (35). The Pro12Ala polymorphism was detected by the PCR restriction fragment length polymorphism method. The PCR conditions and primers used were those indicated by Hara et al. (36). The recommendations of Xu et al. (37) were followed for quality control of genotype identification.

Statistical analysis

The results are presented as the mean, standard deviation, and proportions. Contrast hypothesis of the qualitative variables was done with the χ^2 test and ANOVA was used to calculate the difference between means of continuous variables (post hoc comparisons were made by the Bonferroni and Duncan tests, respectively). The strength of the association between 1 variable (dependent) and other potentially explanatory variables was measured by calculating the odds ratio (OR) from the coefficients of a logistic regression model.

The interaction between dietary MUFA (as a categorical variable) and the PPARG2 Pro12Ala polymorphism was tested in a multivariate interaction model, controlling for other confounding factors such as sex, carbohydrate metabolism disorders, obesity, and the intake of MUFA, expressed as the proportional contribution to the daily energy intake. These analyses were undertaken for the whole population and for the population without DM2. To facilitate interpretation of the results, a stratified analysis was done for the obese and the nonobese subjects. This analysis was done using a logistic regression model, with the dependent variable being HOMA 75 (HOMA IR above or below the 75th percentile of the distribution of HOMA IR in OGTT normal subjects).

The carbohydrate metabolism disorders were coded as follows: *1*) OGTT-N (oral glucose tolerance test normal), *2*) IFG (impaired fasting glucose), *3*) IGT (impaired glucose tolerance) and *4*) DM (diabetes mellitus), with the reference criteria being the OGTT-N group. The intake of MUFA, expressed as the proportional contribution of MUFA to the daily energy, was categorized as follows: $\leq$25th percentile (p25); $>$p25 and $<$75th percentile (p75); and $\geq$75th percentile ($\geq$p75). The 95% CIs were calculated. In all cases the rejection level for a null

hypothesis was an $\alpha = 0.05$ for 2 tails. The statistical analyses were done with SPSS, version 11.5.

Results

The prevalence of the Pro12Ala polymorphism of the PPARG2 gene was 85.8% for Pro12Pro, 13.4% for Pro12Ala, and 0.8% for Ala12Ala. Because of the low frequency of the Ala12Ala genotype, all analyses were done comparing the people who were homozygous for the Pro-12 allele with those who had the Ala-12 allele (14.2%). The genotype distribution adjusted to the Hardy-Weinberg equilibrium. The age, sex, prevalence of obesity, insulinemia 120 min after the OGTT, and the pattern of insulin resistance (measured by HOMA IR) were all significantly different in subjects with OGTT-N, IFG, IGT, and DM2. The distribution of the Pro12Ala polymorphism of PPARG2 was not significantly different, depending on the presence or absence of carbohydrate metabolism disorders (**Table 1**). The prevalence of IFG, IGT, and DM2 was lower in the subjects with the Ala-12 allele. Logistic regression analysis showed that the OR of having IFG, IGT, and DM2 was less in subjects with the Ala-12 allele, after adjusting for age, sex, HOMA IR, and obesity, although it was only significantly different in people with DM2 (Table 1).

The HOMA IR values were greater in obese subjects with the Ala-12 variant who consumed fewer MUFA, suggesting an interaction between the polymorphism and obesity according to the diet (**Fig. 1**).

An ANOVA model including the entire study population except subjects with DM2 (**Table 2**, **Model 1**) showed a contribution of the Ala-12 allele of PPARG2 to the variance of the HOMA IR ($P = 0.04$) in the presence of other variables, which were also associated with the HOMA IR, including obesity ($P < 0.0001$) and the presence of a carbohydrate metabolism disorder ($P < 0.0001$). This model showed an interaction between the Ala-12 allele of PPARG2 and obesity ($P = 0.01$).

The amount of energy consumed by the men was 11.009 ± 3000 kJ/d and by the women 8204.7 ± 2393.2 kJ/d ($P < 0.0001$). Women consumed a greater proportion of fat than men (41.92 ± 5.76% of total daily energy vs. 39.69 ± 5.86% of total daily energy; $P < 0.0001$). Saturated fats accounted for 9.82 ± 2.61% of total energy, (n-6) fatty acids for 5.06 ± 1.81%, and (n-3) fatty acids for 0.45 ± 0.18%, with no significant differences between the men and women. The proportion of energy from the dietary MUFA was lower in men than women (17.28 ± 4.27 vs. 18.68 ± 4.04; $P = 0.0001$). Olive oil alone was used for cooking by 54.3% of the subjects, with this being the most important source of MUFA, sunflower oil alone was used by 24.8%, and a mixture of both oils was used by the remaining 20.9%. The ratio of dietary polyunsaturated to saturated fatty acids was 0.54 ± 0.24 and the ratio of MUFA to PUFA was 3.31 ± 1.03. In terms of physical activity, 76.2% of the subjects undertook light activity, 9.3% moderate activity, and just 0.5% engaged in intense activity. The sexes differed from one another (19.4% of the men undertook moderate or intense activity compared with 6.2% of the women; $P < 0.0001$).

The intake of MUFA, expressed as a proportion of total energy consumed, contributed to the variance in the HOMA-IR ($P = 0.04$), with a 2-way interaction between the Ala-12 allele of PPARG2 and the intake of MUFA ($P = 0.005$) (**Table 2**, **Model 2**). Neither (n-3) or (n-6) intake nor physical activity contributed significantly to the variance in HOMA IR (data not shown).

Logistic regression analysis showed that the OR of having a high HOMA IR (≥p75 of the distribution frequency of the HOMA IR in subjects with OGTT-N) was significantly associated with obesity (OR = 3.2, CI = 2.3–4.6), IFG (OR = 3.5, CI = 2.2–5.6), IGT (OR = 2.4, CI = 1.4–3.9), and DM2 (OR = 10.5, CI = 6.3–17.4), after adjusting for age and sex.

A logistic regression analysis with the dependent variable HOMA-75 and the independent variables Pro12Ala polymorphism, obesity, and carbohydrate metabolism disorders (data not shown) showed that the Ala-12 allele was not associated with the risk of insulin resistance (OR = 0.87, P = NS). Nevertheless, when obese and nonobese subjects were analyzed separately, the association between the Ala-12 allele and high HOMA IR was positive in the obese subjects (OR = 2.5: CI = 1.1–5.6) (**Table 3**). The MUFA variable in the logistic regression model of Table 3 was not statistically significant, but it increased the strength of the association between the Ala-12 allele and HOMA-IR (OR = 4.8; CI = 1.3–18.2).

In the subjects who were OGTT-N, those who consumed olive oil had lower levels of HOMA IR than those who consumed a mixture of olive oil and sunflower oil, they in turn had lower levels than those who consumed sunflower oil alone (1.86 ± 1.12 vs. 2.00 ± 1.38 vs. 2.51 ± 1.60; $P = 0.03$) after adjusting for age, sex, and BMI.

TABLE 1 Characteristics of the study population and the odds ratio of having IFG, IGT, or DM2, according to the Pro12Ala polymorphism of the PPARG2 gene

	OGTT-N	IFG	IGT	DM2	*P*
	n = 324	*n = 67*	*n = 67*	*n = 80*	
Population prevalence, %	60.3	12.4	12.4	14.9	
Men/Women, %	33.2/66.8[a1]	53.5/46.5[b]	31/69[a]	47.4/52.6[b]	<0.0001[2]
Obesity, %	19.2[c]	38.2[b]	36.5[b]	55.7[a]	<0.0001[2]
Age, *y*	35.04 ± 12.1[d]	43.17 ± 12.5[c]	46.32 ± 13.1[b]	52.83 ± 10.7[a]	<0.0001[3]
HOMA IR	2.09 ± 1.4[c]	3.23 ± 2.0[b]	2.80 ± 1.8[b]	6.19 ± 5.4[a]	<0.0001[3]
INS-120,[4] *pmol/L*	240.8 ± 94.3[c]	254.2 ± 223.8[c]	589.1 ± 437.9[a]	432.7 ± 291.6[b]	<0.0001[3]
OR[5]	1	0.55*	0.59**	0.30***	
CI[6]		(0.28–1.11)	(0.31–1.17)	(0.13–0.74)	

[1] Values are means ± SD or %. Values in a row with superscripts without a common letter differ, $P < 0.05$.
[2] Chi-square test.
[3] ANOVA adjusted for age and sex.
[4] INS-120: Insulin 120 min after OGTT.
[5] OR for IFG, IGT, or DM if a carrier of the Ala allele, adjusted for sex, age, HOMA-IR, and obesity. *$P = 0.08$; **$P = 0.12$; ***$P = 0.007$.
[6] CI = confidence intervals.

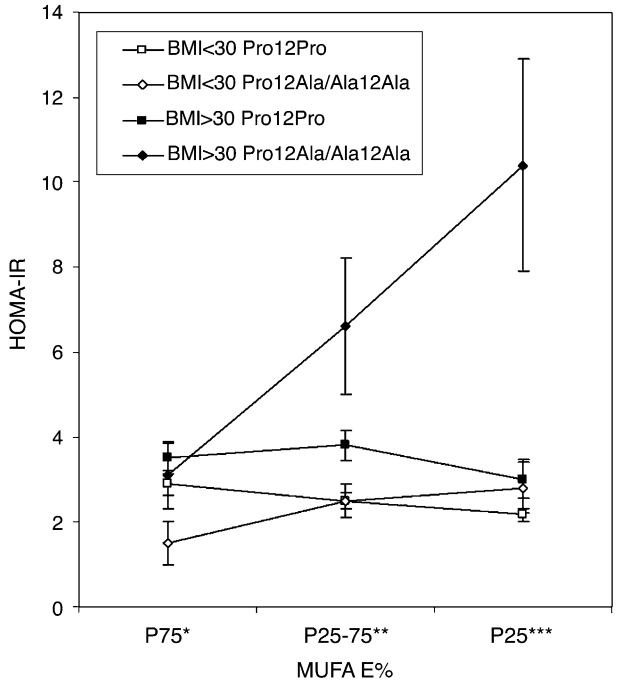

Figure 1 HOMA-IR according to the total amount of MUFA in the diet, the presence of obesity, and the Pro12Ala polymorphism of PPARG2. Values are means ± SEM, $n = 538$. *$P \geq 0.05$ (NS); ** $P = 0.01$; *** $P = <0.0001$ [** and *** indicate significant differences in HOMA IR values according to the polymorphism and obesity for each of the percentiles of MUFA intake (ANOVA)]. MUFA %E (contribution of MUFA to the daily energy): ≤25th percentile (p25), >p25th and <75th percentile (p75) and ≥p75.

Discussion

The most notable results of this study were that the subjects with the Ala-12 allele of PPARG had a lower risk for DM2 and that there was an interaction between the intake of MUFA and the Pro12Ala polymorphism of PPARG2, such that obese people with the Ala-12 allele who consumed fewer MUFA had a higher HOMA IR.

The association between the substitution of alanine for proline at codon 12 of PPARG and the risk for DM2 has been widely studied since Yen et al. first reported this polymorphism (3). Nevertheless, the results of these studies vary considerably. Most have found that carriers of the Ala-12 allele had a lower risk for DM2 and insulin resistance (2,4,5,7), although not all studies have found this association (13,14). Indeed, some studies have even found an increased risk for DM2 in subjects with the Ala-12 variant (10,11), but no association has so far been reported between the polymorphism and greater insulin resistance (12). Similar discrepancies have also been noted for the association between the Pro12Ala polymorphism of PPARG and BMI (9,14,38,39). Contradictory results have been reported within the same study elsewhere, as was the case of Mori et al. (40), who found that the Ala-12 variant was associated with a reduced risk for the development of diabetes in the general population, but that it may also be a risk factor for insulin deficiency and disease severity in individuals with DM2. This paradox is similar to that found in our study. Although we are unable to explain why, we do know that the mechanisms of PPARG2 are diverse and may produce the same effect through two completely opposing pathways. This occurs with insulin sensitivity, where PPARG2 acts both via activation by agonists and by reduction of its activity (6,8,9,41).

The inconsistencies among the results of the different studies may be partly explained by the presence of a gene–gene or gene–environment interaction. However, studies of this type of interaction are scarce. The first study to report the presence of a gene–diet interaction was that by Luan et al. (16), who found that the BMI was higher in people with the Ala-12 allele when they consumed a diet with a low ratio of polyunsaturated to saturated fats. More recently, however, Robitaille et al. (22) failed to detect this interaction and their results even suggested an opposite association, as they found that it was not the Ala-12 allele, but rather the Pro12Pro genotype, which was associated with the diet. Similar results have also been reported by Memisoglu (23). Two other studies, however, examined the efficacy of a low-fat diet, with 1 study (11) showing that subjects with IGT and the Ala12Ala genotype lost more weight, and the other study (42) finding that subjects with the Ala-12 allele had greater carbohydrate oxidability, lower fat oxidability, and increased insulin sensitivity than Pro12Pro subjects. These discrepancies may be due to problems inherent to the nature of both studies and to the difficulty in evaluating precisely the amount of a specific type of dietary fat. Both the study by Luan et al. (16) and that of Robitaille (22) were prospective, but they

TABLE 2 ANOVA with HOMA IR as a dependent variable

	Model 1 Whole population (not including intake of MUFA)		Model 2 Whole population (including intake of MUFA)	
	Mean square	***P***	**Mean square**	***P***
Covariates				
Age, *y*	1.3	NS	0.67	NS
Main effects				
Ala-12 PPARG (Yes/No)	10.0	0.04	4.2	NS
Sex	12.4	0.02	1.4	NS
Carbohydrate metabolism disorder[1]	31.1	<0.0001	20.5	<0.0001
Obesity (BMI≥30)	90.7	<0.0001	31.5	<0.0001
MUFA (%E)[2]	—	—	6.9	0.04
2-Way Interactions				
Ala-12 PPARG × Obesity	13.6	0.016	15.7	0.01
Ala-12 PPARG × MUFA Quartiles (%E)	—	—	12.4	0.005

[1] Carbohydrate metabolism disorder includes OGTT-N, IFG, and IGT. The subjects with DM2 have been excluded.
[2] MUFA %E (contribution of MUFA to the daily energy: ≤25th percentile (p25), > p25th and <75th percentile (p75) and ≥p75.

TABLE 3 Logistic regression model[1]

Model	Dependent variable: HOMA75		
	Beta	OR (95% CI)	*P*
Non obese (BMI <30)			
Allele Ala-12 *vs* Pro-12[2]			
BMI	−0.52 (0.46)	0.6 (0.24–1.5)	NS
CMD[3]	0.15 (0.05)	1.20 (1.05–1.28)	0.004
IFG	1.43 (0.33)	4.2 (2.2–8.1)	<0.0001
IGT	1.02 (0.34)	2.70 (1.4–5.5)	0.003
Obese (BMI ≥30)			
Allele Ala-12 vs Pro-12[2]			
BMI	0.93 (0.4)	2.5 (1.1–5.6)	0.02
CMD	0.12 (0.04)	1.13 (1.04–1.2)	0.007
IFG	1.25 (0.4)	3.5 (1.6–7.7)	0.002
IGT	0.58 (0.42)	1.8 (0.7–4.1)	NS

[1] HOMA IR above or below the 75th percentile of the distribution of HOMA IR in subjects with OGTT-N stratified to whether they were nonobese or obese. 0, HOMA IR ≤2.76; 1, HOMA IR >2.76 (p75 HOMA IR subjects with OGTT-N).
[2] Adjusted for age and sex (Age, *y*; Sex, Men/Women).
[3] CMD coded as dummy variable: 0, OGTT-N (reference criteria); 1, IFG; 2, IGT. Subjects with DM2 were excluded.

were not representative of the population, nor did they provide information about association between the Pro12Ala polymorphism of PPARG2 and carbohydrate metabolism disorders. Memisoglu (23) studied a large group of women from the control groups of 3 case-control studies during the course of the Nurses Health Study, and who completed a semiquantitative food frequency questionnaire. This study (23) was also the first, as far as we are aware, to find an interaction between Pro12Ala polymorphism of PPARG2, the intake of monounsaturated fat, and the BMI. All of these studies, however, were carried out in populations in which the vegetable oils habitually consumed are rich in PUFA but not in MUFA.

Our study was undertaken in a Mediterranean population with a high intake of MUFA. The type of vegetable oil used for frying, cooking, and condiments was evaluated by food frequency questionnaires, as well as from the chemical analysis of random samples taken from the families' kitchens at different times during the study (25). The quantification of the fat consumed was calculated from 7-d prospective quantitative surveys, also carried out at different times during the study. Finally, a biological marker of the type of dietary fat consumed was obtained by the systematic measurement of the fatty acid composition of the plasma phospholipids, thereby enabling a biological validation of the survey results (25). This multiple approach enabled us to gather more precise data about the type and amount of fat consumed. The results suggest an association between the Pro12Ala polymorphism of PPARG2 and dietary MUFA, with obese subjects who have the Ala-12 allele having higher values of HOMA IR, especially if their consumption of MUFA was low.

Numerous experimental studies support the possible association between PPARG and dietary fat. PPARG seems to play a critical role in adipocyte hypertrophy and in the development of insulin resistance, secondary to a fat-rich diet (2,6).

The presence of a gene–diet interaction is especially interesting in that it concerns fats, because diets vary widely in their fatty acid composition among different countries, and even within the same country. Different nutritional studies indicate that the quotient of polyunsaturated to saturated (P/S) fats may vary from 0.11 in Hungary to 1.2 in Portugal (43). In the north of Spain the P/S ratio is 0.36 and the ratio of MUFA to polyunsaturated fats is 3.6. In our study, the P/S ratio in the diet was 0.54, but the ratio of MUFA to polyunsaturated fats was 3.31, indicating a high consumption of MUFA, which accounted for 18.3% of the total daily energy consumed.

This interaction between dietary fatty acids and PPARG might partly explain the controversial results reported in different studies, as their results might depend on the fat composition of different populations or even fat composition within the same population group. The results of our study provide information about the interaction between dietary fatty acids and PPARG in the context of a population consuming a Mediterranean type diet. Nevertheless, the results should be taken with caution because the study was cross-sectional. Furthermore, it is very difficult in this type of study to determine whether the effect is due to an increase in a particular dietary fatty acid, in this case oleic acid, or due to a reduction in the consumption of other fats. The intake of olive oil is a marker of other health-related habits (44), such as exercise or alcohol consumption, which may also have acted as confounding variables, despite the fact that both variables were considered in the ANOVA in this study.

Our results are supported for the following reasons: *1*) the concordance in the protective role of the Ala-12 allele against DM2 in this study and others; *2*) the consistency in the correlations between the pattern of insulin resistance with the clinical phenotypes of diabetes and obesity; and *3*) the prior observation of Memisoglu about the interaction among dietary MUFA, the PPARG2 Ala-12 allele, and BMI.

As far as we are aware, this study is the first to report this association between MUFA, PPARG, and insulin resistance in the context of a population consuming a Mediterranean-type diet. The results of this study, as well as those of others, support the idea that in the future dietary recommendations should perhaps be individualized, a question that is acquiring special importance given the alarming increase in the incidence of obesity. This study also provides information about the biological value of olive oil in the prevention of insulin resistance (45), especially in genetically predisposed obese people.

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