Effect of the interaction between the fatty acid–binding protein 2 gene Ala54Thr polymorphism and dietary fatty acids on peripheral insulin sensitivity: a cross-sectional study[1–3]

Sonsoles Morcillo, Gemma Rojo-Martínez, Fernando Cardona, María de la Cruz Almaraz, María de la Soledad Ruiz de Adana, Isabel Esteva, Isabel Cardona, and Federico Soriguer

ABSTRACT

Background: The intestinal fatty acid–binding protein (FABP2) is involved in the intracellular transport and metabolism of fatty acids and may affect insulin sensitivity and glucose metabolism.

Objective: The objective was to study the effect of interaction between the Ala54Thr polymorphism of the FABP2 gene (*FABP2*) and the type of dietary cooking oil used on peripheral insulin sensitivity in a population from southern Spain.

Design: The study was cross-sectional. Anthropometric measurements were obtained for 1226 persons aged 18–65 y selected randomly from the municipal census of Pizarra, Spain. An oral-glucose-tolerance test was given to 1020 of these persons. Insulin resistance was measured by homeostasis model assessment. Samples of the cooking oil being used were taken from the kitchens of a random subset of 538 persons.

Results: Persons who consumed sunflower oil and who also had the Thr54 variant had higher insulin resistance than did those who consumed olive oil ($P = 0.01$). We detected an interaction between the Ala54Thr polymorphism and the type of oil consumed that accounted for the variance in insulin resistance ($P = 0.02$).

Conclusions: The effect of dietary fatty acids on the populational pattern of insulin resistance is not independent of the Ala54Thr polymorphism of *FABP2*. An interaction existed between this polymorphism and the intake of dietary fats in a population with a high intake of monounsaturated fatty acids. *Am J Clin Nutr* 2007;86:1232–7.

KEY WORDS Cross-sectional study, general population, dietary fatty acid, insulin resistance, FABP2, Ala54Thr polymorphism

INTRODUCTION

The intestinal fatty acid–binding protein 2 (FABP2) belongs to the family of cytoplasmatic proteins involved in the intracellular transport and metabolism of long-chain fatty acids (1). The association between fatty acid metabolism and insulin resistance is well known (2, 3), and the FABP2 gene (*FABP2*) has been suggested as a possible candidate gene in the development of insulin resistance. The expression of *FABP2* is limited to the small intestine, and it presents just one single ligand binding site with a high affinity for long-chain saturated and polyunsaturated fatty acids (4, 5). One of the best-studied polymorphisms of *FABP2* is the amino acid substitution in codon 54 of alanine (Ala) for threonine (Thr; 4). In vitro studies have shown that the Thr54 variant for long-chain fatty acids is 2-fold that of the native form Ala54. This polymorphism, first studied in Pima Indians, is associated with greater insulin resistance, increased insulin concentrations, and fasting oxidation of fatty acids (4). In other populations, the Thr54 allele has also been associated with increased insulin concentrations and insulin resistance in some studies (6, 7), but not in others (8–13).

Insulin resistance is a risk factor for the development of type 2 diabetes mellitus (DM2), obesity, and cardiovascular disease. Its manifestation depends on the interaction of certain environmental factors, including diet. Expression of *FABP2* is controlled by diet, and studies have shown an interaction between the Ala54Thr polymorphism and the content of dietary fiber (14). This association could explain the variation between individuals in the metabolic response to diet (5, 14). Other studies (15) have suggested that the Thr54 form of intestinal FABP2 is associated with a greater and more prolonged response of the free fatty acids to dietary fat in vivo, contributing to greater insulin resistance and hyperinsulinemia in persons with this allele. Dworatzek et al (16), in a group of 22 healthy, nonobese persons submitted to 3 different fat overloads (butter, sunflower oil, and olive oil), found that carriers of the Thr54 allele increased their concentrations of chylomicron cholesterol only after the olive oil test. Another study of 59 healthy persons who completed 3 diets [diet rich in saturated fatty acids, diet low in fat and high in carbohydrates, and diet rich in monounsaturated fatty acids (MUFAs)] showed that persons with the Thr54 allele experienced improved insulin sensitivity when the saturated diet was replaced by either of the other 2 diets (17). The aim of this study was to examine the association between the Ala54Thr polymorphism of *FABP2* and

[1] From the Servicio de Endocrinología y Nutrición, Hospital Universitario Carlos Haya (Red de Diabetes y Metabolismo of the Instituto de Salud Carlos III, Madrid), Málaga, Spain (SM, GR-M, MCA, MSRdA, IE, IC, and FS), and the Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario Virgen de la Victoria, Málaga, and Centro de Investigación Biomédica En Red de Fisiopatología de la Obesidad y Nutrición CB06/03 of the Instituto de Salud Carlos III, Madrid (FC).

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[3] Address reprint requests to S Morcillo, Servicio de Endocrinología y Nutrición, Hospital Civil, Plaza del Hospital Civil s/n, 29009 Málaga, Spain. E-mail: sonsoles.morcillo.exts@juntadeandalucia.es.

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insulin resistance in a population from southern Spain with a diet rich in MUFAs and the possible interaction between the polymorphism and dietary fatty acids.

SUBJECTS AND METHODS

The study was undertaken in Pizarra, a town in the province of Malaga, in southern Spain. The details of the study design and sampling were reported previously (18–20). The overall number of persons included in the study was 1226. Selection was random and was based on the municipal census. The inclusion age was 18–65 y, and persons were excluded from the study if they were institutionalized for whatever reason, were pregnant, or had a serious clinical or psychological disorder. The subjects were requested by mail 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 participation index was 70.3%, and the final sample distribution by age and sex was not significantly different from the population distribution (21).

All subjects were informed of the nature of the study and gave their written consent to participate. The study was approved by the Ethics and Clinical Investigation Committee of Carlos Haya Hospital.

Procedures

All participants were interviewed and underwent a physical examination according to standard procedures. They also received several home visits to undertake dietary evaluation studies. All the examinations were performed by the same investigators and dietitians. All the participants were measured for height and weight, and the body mass index (BMI; in kg/m^2) was calculated. Persons with baseline blood glucose concentrations lower than 7.8 mmol/L underwent an oral-glucose-tolerance test (OGTT). Of the 206 persons who failed to do the OGTT, 73 were excluded in accordance with the protocol, and 133 refused to do the OGTT for various reasons. A blood sample was taken from each participant at baseline and at 120 min after the OGTT. The serum was stored at −70 °C, and the blood was stored at −20 °C for later analysis.

During the course of interviews about dietary habits conducted in the homes of a random subset of 538 persons, a sample was taken of the cooking oil being used. To avoid the oil being swapped 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 investigator. All the participants authorized the collection of their cooking oil.

Composition and quality of the cooking oil

Fatty acids were analyzed by use of gas chromatography after derivatization to fatty acid methyl esters with 2N KOH in methanol and triheptadecanoin as the internal standard, according to the International Union of Pure and Applied Chemistry Standard Method (22). An HP 6890 chromatograph on an HP Innowax capillary column (polyethylene glycol, 30 m × 0.25 mm internal diameter; film thickness 0.25 m; Hewlett-Packard, Palo Alto, CA) 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 250 °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 their fatty acid composition. Because only olive and sunflower oils are generally commercialized 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

Capillary glucose was measured at baseline and 2 h after the OGTT with the use of a glucose oxidase method (Glucometer-Elite; Bayer, Elkhart, IN). Serum insulin at baseline and 2 h after the load was measured by use of radioimmunoassay (Coat A Count Insulin; DPC, Los Angeles, CA; assay precision: CV < 10% at 16 μIU/mL concentration; cross-reactivity with proinsulin = 20%). The formula for the homeostasis model assessment insulin resistance index (HOMA-IR) is as follows (23):

$$\text{Insulin resistance (HOMA-IR)} = [\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)}/22.5] \quad (1)$$

The fatty acid composition of the serum phospholipids was determined by extraction of the serum fat with chloroform:methanol 2:1 and butylated hydroxytoluene at 0.025% (22) and phospholipid separation by TLC. Fatty acid methyl esters were formed by heating the extracted fat for 30 min with 0.61 mol H_2SO_4/L in anhydrous methanol. After extraction with hexane, the fatty acid methyl esters were analyzed in a Hewlett-Packard chromatograph equipped with a flame ionization detector and using a BPX75 fused-silica capillary column (SGE, Villebon, France).

Classification criteria

Classification of persons with diabetes and with different degrees of glucose tolerance was done according to the 1998 World Health Organization criteria (24). Persons were considered to be obese if their BMI was ≥ 30 (25).

Genetic analysis

DNA was isolated from whole blood by the salting-out method of Miller modified by Queipo-Ortuño et al (26). The Ala54Thr polymorphism was detected by the polymerase chain reaction–restriction fragment length polymorphism method. The polymerase chain reaction conditions and primers used were those indicated by Baier et al (4). The recommendations of Xu et al (27) were followed for quality control of genotype identification.

Statistical analysis

The results are presented as means ± SDs and proportions. Contrast hypothesis of the qualitative variables was done with the chi-square test, and analysis of variance was used to calculate the difference between means of continuous variables (post hoc comparisons were corrected by Bonferroni). In all cases, the rejection level for a null hypothesis was $\alpha = 0.05$ for 2 tails.

TABLE 1
Characteristics of the study population[1]

	NGT (n = 303)	IFG (n = 69)	IGT (n = 72)	DM2 (n = 94)
Population prevalence (%)	56.4	12.8	13.4	17.4
Sex (%)[2]				
M	29.7	44.3	18.8	39.8
F	70.3	55.7	81.3	60.2
Obesity (%)[2]	18.6	42.4	44.4	53.9
Age (y)	37.6 ± 12.6[3,a]	44.9 ± 12.2[b]	48.9 ± 12.9[b]	53.3 ± 9.8[c]
BMI (kg/m^2)	26.3 ± 4.4[a]	29.5 ± 5.7[b]	30.1 ± 5.1[b]	30.8 ± 4.6[c]
HOMA-IR	2.0 ± 1.3[a]	3.4 ± 2.3[b]	2.8 ± 1.9[a,b]	6.0 ± 4.7[c]
Thr allele (%)[4]	48.1	48.3	42.6	46.6
Type of oil consumed (%)[4]				
Olive	55.0	52.5	60.9	49.4
Mixture	23.0	16.4	20.3	19.3
Sunflower	21.9	31.1	18.8	31.3

[1] Values in the same row with different superscript letters are significantly different, $P < 0.05$ (Bonferroni adjustment for comparisons). NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM2, type 2 diabetes mellitus; HOMA-IR, homeostasis model assessment insulin resistance index.
[2] The values are proportions. Chi-square test, $P < 0.0001$.
[3] $\bar{x}$ ± SD (all such values, adjusted for age and sex).
[4] The values are proportions. Chi-square test, P = NS.

RESULTS

The genotype frequencies for the Ala54Thr polymorphism of *FABP2* in the study population were 52.4% Ala54Ala, 39.6% Ala54Thr, and 7.9% Thr54Thr. The frequency of the Thr allele was 0.27. The distribution of the genotypes adjusted to Hardy-Weinberg equilibrium. No significant differences were seen in allele frequency of the polymorphism according to sex. For data analysis, the participants were grouped as homozygous for the Ala54 allele (Ala54Ala) compared with carriers of the Thr54 allele (Ala54Thr/Thr54Thr).

The characteristics of the study population (n = 538) are shown in **Table 1**. No significant differences existed between any of the study variables compared with the overall study population (n = 1026). Age, sex, the prevalence of obesity, BMI, and the pattern of insulin resistance (measured by the HOMA-IR) were significantly different according to the presence of different degrees of glucose tolerance. These differences remained after adjustment for age and sex. The frequencies of the Thr54 allele and the type of oil consumed were not significantly different according to the clinical phenotypes studied.

Olive oil alone was used for cooking by 54.3% of the participants (this was the most important source of MUFAs). Sunflower oil alone was used by 24.8%, and a mixture of the 2 oils was used by 20.9%.

The fatty acid composition of the serum phospholipids followed the expected model, depending on the fatty acid composition of the cooking oils used (**Table 2**). Persons who consumed olive oil alone had higher concentrations of oleic acid than did persons who consumed sunflower oil or a mixture ($P < 0.0001$), whereas those who consumed sunflower oil or a mixture had higher concentrations of linoleic acid in their serum phospholipids, although only the mixture group was significant ($P < 0.0001$).

The variance in the HOMA-IR in the persons without diabetes was explained by obesity ($P < 0.0001$) and by impaired fasting glucose and impaired glucose tolerance ($P < 0.0001$; **Table 3**,

TABLE 2
Fatty acid composition of the serum phospholipids according to the type of oil consumed[1]

	Type of oil		
	Olive (n = 292)	Mixture (n = 112)	Sunflower (n = 134)
Myristic acid (%)	0.39 ± 0.47[a]	0.41 ± 0.52[a]	0.50 ± 0.59[a]
Palmitic acid (%)	31.46 ± 7.07[a]	29.81 ± 5.34[a]	31.38 ± 6.79[a]
Palmitoleic acid (%)	0.52 ± 1.01[a]	0.50 ± 0.45[a]	0.51 ± 0.53[a]
Stearic acid (%)	13.94 ± 2.24[b]	14.47 ± 1.92[a,b]	14.70 ± 2.16[a]
Oleic acid (%)	12.24 ± 2.68[a]	11.20 ± 1.87[b]	10.57 ± 2.04[b]
Linoleic acid (%)	23.96 ± 4.30[b]	25.90 ± 3.83[a]	25.13 ± 4.08[a,b]
Arachidonic acid (%)	11.96 ± 3.93[a]	11.99 ± 2.89[a]	11.97 ± 2.97[a]
Eicosapentaenoic acid (%)	0.73 ± 0.63[a]	0.67 ± 0.51[a]	0.66 ± 0.55[a]
Docosahexaenoic acid (%)	4.73 ± 1.49[a]	4.71 ± 1.45[a]	4.56 ± 1.49[a]

[1] All values are $\bar{x}$ ± SD. Values in the same row with different superscript letters are significantly different, $P < 0.05$ (ANOVA and Bonferroni adjustment for comparisons).

TABLE 3
Influence of the Ala54Thr polymorphism on the variance of the homeostasis model assessment insulin resistance index[1] (HOMA-IR)

	ANOVA model 1: excluding the type of oil consumed (n = 848)		ANOVA model 2: including the type of oil consumed (n = 538)	
	Mean square	P	Mean square	P
Covariables				
Age	3.596	NS	0.5	NS
Main effects				
Thr54 allele (yes or no)	4.965	NS	15.3	0.011
Sex (male or female)	3.795	NS	22.2	0.002
Obesity (yes or no)	85.901	< 0.0001	31.9	< 0.0001
Different degrees of glucose tolerance[2]	3.596	<0.0001	17.8	0.001
Type of oil consumed (olive + mixture vs sunflower)	—	—	2.4	NS
Interactions				
Thr54 allele × obesity	29.8	<0.0001	18.1	0.006
Thr54 allele × different degrees of glucose tolerance	—	—	5.9	0.081
Thr54 allele × oil	—	—	11.5	0.028
Different degrees of glucose tolerance × obesity	—	—	7.4	0.046

[1] Dependent variable is HOMA-IR.
[2] Different degrees of glucose tolerance include the categories of normal oral-glucose-tolerance test, impaired fasting glucose, and impaired glucose tolerance.

model 1). When the type of oil consumed was introduced into the analysis of variance model, the Thr54 allele accounted for a significant part of the variance in HOMA-IR ($P = 0.01$), noting a significant interaction between the Thr54 allele and the type of oil consumed ($P = 0.02$; model 2 in Table 3), as well as an interaction between the polymorphism and obesity ($P = 0.006$). The same analysis of model 2 but separating the obese persons from the nonobese persons showed how the interaction between polymorphism and the type of oil was significant only in the nonobese persons (data not shown).

For the population as a whole, without taking into consideration the type of oil consumed, no significant differences were found in insulin resistance (measured by the HOMA-IR) depending on the Ala54Thr polymorphism of *FABP2* (2.83 ± 2.9 Ala/Ala compared with 2.89 ± 2.7 for carriers of Thr54). However, when the participants were separated according to the type of cooking oil consumed, those persons who consumed sunflower oil and who also had the Thr54 allele had higher HOMA-IR concentrations than did those who consumed olive oil or a mixture of the 2 oils ($P = 0.01$). Likewise, the HOMA-IR values were significantly different between the carriers of the Thr54 allele according to the type of oil consumed, with those who consumed olive oil having the lowest values ($P = 0.02$). These differences remained both in the persons with normal glucose tolerance and after excluding the persons who had diabetes (**Table 4**).

DISCUSSION

The most important finding in the present study was the interaction between the Ala54Thr polymorphism of *FABP2* and the type of dietary fat in the explanation of the general pattern of insulin resistance. Numerous studies have shown the effect of dietary fat on insulin resistance (20, 28). Clinical intervention studies have shown that replacement of dietary saturated fatty acids by MUFAs improves insulin sensitivity (29, 30).

Intestinal FABP2 is very abundant in enterocytes, and one of the most common polymorphisms of its gene (Ala54Thr) has been associated with insulin resistance (4, 12, 31). Another series of studies has examined the fatty acid absorption differential of this protein (15, 32). However, few studies have shown a gene-diet interaction with the Ala54Thr polymorphism of *FABP2*; moreover, these studies may not be comparable because of differences in design and the variable phenotypes of the study subjects. A recent study that compared 3 diets (saturated, MUFAs, and carbohydrate-rich) showed that carriers of the Thr54 variant had lower peripheral insulin sensitivity and an increased concentration of free fatty acids after the intake of a diet rich in saturated fats (17). Another recent study of the gene-environment interaction by Weiss et al (33) noted how nondiabetic sedentary persons who consumed a low-fat diet and were carriers of the Thr54 allele had a lower glucose tolerance and lower insulin action than did Ala54 homozygotes.

In a study undertaken in rats, Richieri et al (32) showed that the FABP protein had a greater affinity for linoleic acid than for oleic acid, which suggests that protein affinity changes according to the type of fatty acid consumed. Others have associated the presence of the Thr54 allele with the different absorption of fatty acids, finding a significant increase in chylomicrons and VLDL after a 14–18-carbon fatty acid loading test, whereas a similar increase was not observed with Ala54 homozygotes (34). Another study of the composition of chylomicrons after an oral fat-loading test with different fatty acids found a significant increase in chylomicron cholesterol in the carriers of the Thr54 allele after they consumed olive oil (16).

Numerous studies have shown the beneficial effect of olive oil on health and on certain biochemical parameters (35, 36). A previous study undertaken in the same population noted greater insulin sensitivity in persons who consumed olive oil than in those who consumed sunflower oil (37); that study also noted an interaction between the Pro12Ala polymorphism of the peroxisome-proliferator activated receptor γ 2 gene and the intake of MUFAs (20). In the present study, we showed that this

TABLE 4
Homeostasis model assessment insulin resistance index values according to the type of oil consumed and the genotype distribution of the Ala54Thr polymorphism of the fatty acid–binding protein 2 gene[1]

	Olive	Mixture	Sunflower	*P*
Whole population[2–4]				
Ala54Ala	2.8 ± 2.3 [161][5]	2.6 ± 2.0 [59]	2.9 ± 1.9 [63]	NS
Ala54Thr	2.6 ± 2.7 [112]	3.3 ± 2.4 [47]	4.1 ± 4.7 [58]	
Thr54Thr	3.7 ± 3.8 [19]	3.0 ± 2.9 [8]	3.4 ± 2.2 [11]	
P[6]	NS	NS	0.017	
Population excluding persons with diabetes[7,8]				
Ala54Ala	2.4 ± 1.9 [134]	2.0 ± 1.3 [49]	2.3 ± 1.2 [52]	NS
Ala54Thr	2.1 ± 1.3 [98]	2.6 ± 1.5 [36]	3.2 ± 2.3 [47]	
Thr54Thr	2.0 ± 0.9 [13]	2.9 ± 3.0 [8]	3.1 ± 1.7 [7]	
P[6]	NS	NS	0.004	
Persons with NGT[9,10]				
Ala54Ala	1.8 ± 1.2 [86]	1.9 ± 1.4 [36]	2.3 ± 1.2 [34]	NS
Ala54Thr	1.8 ± 1.0 [67]	2.3 ± 1.6 [25]	2.6 ± 1.9 [32]	
Thr54Thr	2.0 ± 0.8 [12]	1.8 ± 0.6 [5]	2.8 ± 1.8 [6]	
P[6]	NS	NS	NS	

[1] All *P* values are for subjects with Thr allele combined (Ala54Thr/Thr54Thr) compared with Ala54Ala subjects. NGT, normal glucose tolerance.
[2] Oil × polymorphism × diabetes interaction = NS.
[3] Oil × genotype interaction = 0.049, adjusted for age and sex.
[4,8,10] ANOVA between oils, adjusted for age and sex (Bonferroni adjustment for comparisons): [4]$P = 0.028$, [8]$P = 0.001$, [10]$P = 0.031$.
[5] $\bar{x}$ ± SD; the number of cases is in brackets (all such values).
[6] ANOVA between alleles, adjusted for age and sex.
[7] Oil × genotype interaction = 0.031, adjusted for age and sex.
[9] Oil × genotype interaction = NS, adjusted for age and sex.

effect is not independent of the Ala54Thr polymorphism, as suggested by the interaction seen between the type of oil consumed and the presence of the Thr54 allele. These results support those of other studies that suggest a protective role for monounsaturated fats in metabolic control and the risk of diabetes (36, 38–40), as well as other risk factors related with insulin resistance, such as hypertension (18). The results of this study could also partly explain the contradictory observations noted concerning the type of dietary fat as a risk factor for metabolic or cardiovascular diseases. Thus, the Ala54Thr polymorphism of *FABP2* would be associated with greater insulin resistance, as has been noted previously, in those persons who have a high intake of sunflower oil. A high consumption of olive oil, on the other hand, would counter this effect. The interaction between the Thr54 allele and the type of oil consumed in the explanation of the HOMA-IR was only present in nonobese persons. This interaction could help account for the development of diabetes in nonobese persons.

The present study was undertaken within the context of an epidemiologic study representative of a culturally homogeneous ethnic population in whom 20% of dietary calories come from the consumption of MUFAs (20), with the cases and the controls all from the same population, thereby avoiding the possibility of selection bias. Nevertheless, the study does have certain limitations inherent to cross-sectional studies.

Baier et al (4) suggested that the increased absorption of dietary fat in persons with the Ala54Thr polymorphism could lead to adipocyte hypertrophy associated with an increased calorie balance. The increase in free fatty acids would reduce the uptake of glucose by the adipocyte (2, 3). The enlarged adipocyte, on the other hand, would imply a reduced density of insulin receptors. Finally, a selective absorption of dietary fatty acids would lead to a change in the fatty acid profile to be incorporated into the tissues. This change in the fatty acid composition of the membrane phospholipids would modify their fluidity and thus modify the peripheral sensitivity to the action of insulin (41, 42). The results of the present study incorporate to this hypothesis the specific interaction between genetic and nutritional variability. On the other hand, they also warn of the difficulty of extrapolating risk associations outside the particular social and nutritional context studied. Additionally, it would be interesting to reproduce these results with controlled intervention studies. In conclusion, our results suggest that the effect of dietary fatty acids on the general pattern of insulin resistance is not independent of the Ala54Thr polymorphism of *FABP2*, there being an interaction between the polymorphism and the dietary intake of fat in a population with a high intake of monounsaturated fatty acids.

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The authors' responsibilities were as follows—FS: designed the study, analyzed and interpreted the data, and wrote the manuscript; SM: contributed to the collection, analysis, and interpretation of the data and to writing the manuscript; FC: contributed to the analysis and interpretation of data; MCA, MSRdA, IC, and IE: contributed to the collection of data; GR-M: designed the study and contributed to the collection of data; and all authors: reviewed the manuscript. None of the authors had any conflict of interest, either financial or personal, with the present study.

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