

The *Ala54Thr* polymorphism of the fatty acid-binding protein 2 gene is associated with a change in insulin sensitivity after a change in the type of dietary fat¹⁻³

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ABSTRACT

Background: Insulin resistance, a condition associated with type 2 diabetes, results from the interaction of environmental and genetic factors.

Objective: We examined the influence of the intestinal fatty acid-binding protein 2 (*FABP2*) *Ala54Thr* polymorphism on insulin sensitivity.

Design: Fifty-nine healthy young subjects (28 were *Ala54/Ala54*, 27 were *Ala54/Thr54*, and 4 were *Thr54/Thr54*) completed 3 diets, each of which lasted 4 wk. The first diet, which all subjects consumed, was a high-saturated fatty acid (SFA) diet (38% of energy as fat and 20% of energy as SFAs). The second and third diets were administered according to a randomized crossover design, and they consisted of a low-fat and high-carbohydrate diet (CHO diet; 28% of energy from fat and <10% of energy from SFAs) and a high-monounsaturated fatty acid (MUFA) diet (called the Mediterranean diet; 38% of energy from fat and 22% of energy from MUFAs). All food and drinks were prepared and provided in the research kitchen. We determined in vivo insulin resistance by using the insulin suppression test with somatostatin.

Results: Steady state plasma glucose concentrations were significantly higher in *Ala54Thr* subjects after the SFA diet than after the CHO diet or the Mediterranean diet. The plasma free fatty acid concentrations in these subjects were significantly lower after the CHO and Mediterranean diets than after the SFA diet. However, no significant differences between the 3 diets were observed in the *Ala54* allele homozygotes.

Conclusion: Insulin sensitivity decreased in subjects with the *Thr54* allele of the *FABP2* polymorphism when SFAs were replaced by MUFAs and carbohydrates. *Am J Clin Nutr* 2005;82:196-200.

KEY WORDS *Ala54Thr* polymorphism, steady state plasma glucose, Mediterranean diet, insulin sensitivity, dietary fat

INTRODUCTION

Insulin resistance is considered a risk factor for both diabetes and coronary heart disease, and it is measured by using the interaction between genetic and environmental factors. In general, high intakes of dietary fat have been associated with obesity and its comorbid conditions, including heart disease and type 2 diabetes. In most cases, the clinical expression of the disease can be prevented by dietary and lifestyle modifications (1). On the

other hand, the genetic base of type 2 diabetes 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 (2), the insulin receptor substrate 1 (3), the Rad protein (4), glycogen synthase (5), and the β_3 -adrenergic receptor (6) are the best known. However, the genetic background of insulin resistance and type 2 diabetes is more complex and can also involve other genes that seemingly are unrelated to carbohydrate metabolism.

The fatty acid (FA)-binding protein 2 (*FABP2*) gene codes for intestinal FABP (IFABP), which is a member of a family of small (14-15-kDa) intracellular lipid-binding proteins. The gene located at 4q28-q31 has the conserved 4 exons and 3 introns that are characteristic of this family of genes (7, 8). IFABP plays important roles in several steps of fat absorption and transport: the uptake and trafficking of saturated and unsaturated long-chain fatty acids (LCFAs), the targeting of free FAs (FFAs) toward different metabolic pathways, protection of the cytosol from the cytotoxic effects of FFAs, and modulation of the enzyme additive involved in lipid metabolism (9, 10). Besides FFAs, IFABP may bind other ligands such as phenolic antioxidants, and it is abundant in the enterocyte, representing 2-3% of the cytoplasmic mass of those cells (11). It has been found that the expression of IFABP mRNA is under dietary control (12).

In 1995, Baier et al (13) reported a new G/A mutation. A transition (G→A) at codon 54 of *FABP2* results in an amino acid substitution (*Ala54*→*Thr54*). This polymorphism is very

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common, with a *Thr54* allelic frequency of $\approx 29\%$ in most populations. This amino acid substitution was found to be associated with high fasting insulin concentrations, high insulin resistance, and high FA binding in Pima Indians (13).

In the current study, we investigated the possible influence of *Thr54* polymorphism in the *FABP2* gene on insulin sensitivity in a healthy young population. In addition, we investigated the interaction between this polymorphism and diet for insulin sensitivity.

SUBJECTS AND METHODS

Subjects and diets

Fifty-nine healthy normolipidemic subjects (total plasma cholesterol concentration: < 5.2 mmol/L) who were attending the University of Cordoba volunteered to participate in the study. Of these subjects, 28 were homozygous for the most common *Ala54* allele, and 31 were carriers of the *Thr54* allele (*Ala54/Thr54*, $n = 27$; *Thr54/Thr54*, $n = 4$). All subjects underwent a comprehensive medical history, physical examination, and clinical chemistry analysis before enrollment. Subjects were < 30 y old ($\bar{x} \pm$ SD age: 21 ± 2 y) and had no evidence of any chronic illness such as hepatic, renal, thyroid, or cardiac dysfunction and no unusually high physical activity values. Mean initial body mass index (in kg/m^2) was 21.4 ± 0.7 for *Ala54* homozygotes, 21.7 ± 0.5 for *Ala54/Thr54* heterozygotes, and 21.1 ± 0.5 for *Thr54* homozygotes. This measure remained constant at the end of each diet.

Dietary information, including alcohol consumption, was collected over 7 consecutive days. Individual energy requirements were calculated by taking into consideration each subject's weight and physical activity level. The subjects were encouraged to maintain their regular physical activity and lifestyle and were asked to record in a diary any event that could affect the outcome of the study, such as a stressful experience, a change in smoking habits, and consumption of alcohol or foods not included in the experimental design.

The study design included an initial 28-d period during which all subjects consumed a saturated FA (SFA)-enriched diet with 15% of energy as protein, 47% of energy as carbohydrates, and 38% of energy as fat [20% SFAs, 12% monounsaturated FAs (MUFAs), and 6% polyunsaturated FAs (PUFAs)]. All subjects were then randomly assigned in a crossover design to 2 new dietary periods: a low-fat, high-carbohydrate diet (CHO diet) and a high-MUFA diet enriched with olive oil (Mediterranean diet). The 2 groups of subjects were assigned in random sequence order to 1 of the 2 dietary regimens for 28 d each. Group 1 (29 subjects) began with the Mediterranean diet and then switched to the CHO diet. In group 2 (30 subjects), the order of diets was reversed. The CHO diet (14) contained 15% of energy as protein, 57% of energy as carbohydrate, and 28% of energy as fat ($< 10\%$ SFAs, 12% MUFAs, and 6% PUFAs). The Mediterranean diet contained 15% of energy as protein, 47% of energy as carbohydrate, and 38% of energy as fat ($< 10\%$ SFAs, 22% MUFAs, and 6% PUFAs). Virgin olive oil provided 75% of total MUFAs consumed during the Mediterranean diet period. Each dietary period lasted 28 d. Dietary cholesterol was kept constant in our experimental design, and the mean cholesterol intake was 115 mg/1000 kcal during the 3 periods.

Written informed consent was obtained from all participants. The Human Investigation Review Committee at the Reina Sofia University Hospital approved this study.

The composition of the experimental diets was calculated by using the US Department of Agriculture 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 Mediterranean diet and palm oil and butter during the high-SFA diet. During the CHO diet, biscuits, bread, and jam replaced some olive oil or palm oil. Lunch and dinner were consumed in the hospital dining room, and breakfast and an afternoon coffee break were eaten in the medical school cafeteria. A dietitian supervised all meals. Duplicate samples from each menu were collected, homogenized, and stored at -80°C . The protein, fat, and carbohydrate contents of the diet were analyzed by using standard methods (15). Evaluation of dietary compliance was also performed by examining the food diaries and by analyzing the FA content of the cholesterol ester fraction in LDL (16).

Blood sampling and biochemical determinations

Venous blood for insulin, glucose, lipid and lipoprotein analysis was collected from the subjects into EDTA-containing tubes after a 12-h overnight fast at the end of each dietary period. Each analysis was performed 3 times. Total cholesterol and triacylglycerols were assayed by enzymatic procedures (17, 18). HDL cholesterol was measured by analyzing the supernatant obtained after precipitation of a plasma aliquot with dextran sulfate- Mg^{++} (19). LDL-cholesterol concentrations were calculated from the total and HDL-cholesterol and triacylglycerol values by using the formula of Friedewald et al (20). Unesterified free FA concentrations were measured by using an enzymatic colorimetric assay (Boehringer Mannheim, Mannheim, Germany) as described by Shimizu et al (21). To reduce interassay variation, plasma for biochemical determinations was stored at -80°C and analyzed in duplicate at the end of the study.

Glucose suppression test

At the end of each dietary period, all subjects underwent a modified insulin suppression test (22, 23). Somatostatin (214 nmol/h), insulin ($180 \text{ pmol} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$), and glucose ($13.2 \text{ mol} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$) were infused into the same vein at 0800 after a 12-h fast. Somatostatin was used to inhibit endogenous insulin secretion. Blood was sampled every 30 min for the first 2.5 h, by which time steady state plasma glucose (SSPG) and steady state plasma insulin (SSPI) concentrations were achieved. Blood was then sampled at 10-min intervals for the last 30 min (ie, at 150, 160, 170, and 180 min) for measurement of plasma glucose and insulin concentrations. These 4 values determined the SSPG and SSPI concentrations. Because SSPI concentrations were similar in all subjects, SSPG concentrations provided a measure of the ability of insulin to promote the disposal of infused glucose. Subjects with high SSPG are significantly more insulin resistant than are those with lower SSPG.

Genotyping of *FABP2* gene polymorphism

A polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) assay was developed for genotyping. The genomic DNA fragment flanking the *Ala54/Thr54* polymorphism was amplified by using 2 primers flanking exon 2



TABLE 1
Daily intakes during the experimental diets¹

	SFA diet	CHO diet	Mediterranean diet
Protein (% of energy intake)			
Calculated	15	15	15
Analyzed	18.1 ± 2.5 ²	17.6 ± 1.5	17.5 ± 2.0
Fat (% of energy intake)			
Saturated			
Calculated	20	10	10
Analyzed	22.6 ± 4.1	9.2 ± 3.5	9.2 ± 4.2
Monounsaturated			
Calculated	12	12	22
Analyzed	10.1 ± 2.9	13.5 ± 1.2	24.4 ± 2.2
Polyunsaturated			
Calculated	6	6	6
Analyzed	5.0 ± 1.5	5.2 ± 2.0	4.8 ± 1.1
Carbohydrates (% of energy intake)			
Calculated	47	57	47
Analyzed	44.2 ± 8.3	54.5 ± 8.6	44.1 ± 7.8
Cholesterol (mg/dL)			
Calculated	115	115	115
Analyzed	112 ± 39	113 ± 48	117 ± 42
Energy (MJ)			
Calculated	10.2	10.2	10.2
Analyzed	10.8 ± 1.1	10.6 ± 1.0	10.8 ± 1.5

¹ *n* = 5. SFA diet, saturated fatty acid–enriched diet; CHO diet, low-fat and high-carbohydrate diet; Mediterranean diet, high–monounsaturated fatty acid diet.

² $\bar{x} \pm$ SD (all such values).

of the *FABP2* gene. The PCR was carried out with 250 ng genomic DNA and 0.2 μ mol of each oligonucleotide primer (primer 1: 5'-CTACCGAGTTTTCTTCCACC-3'; primer 2: 5'-AATTAACCATCCAATGAAATAGAGC-3') in a 50- μ L final volume. DNA was denatured at 94 °C for 5 min; this was 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 it concluded with a final extension at 72 °C for 10 min. The PCR product (10 μ L) was digested with 5 units of restriction enzyme *HhaI* (New England Biolabs Inc, Beverly MA) in a total volume of 35 μ L. The digested PCR products were resolved on 2% agarose gels. *HhaI* digested the wild type, alanine (GCT), which yielded 2 products of 200 and 175 base pairs, respectively (A allele). The G-to-A substitution (threonine; ACT) destroyed the *HhaI* site (*Thr* allele).

Statistical analysis

Statistical analyses were carried out by using SPSS statistical software (version 11.0; SPSS Inc, Chicago, IL). Repeated-measures analysis of variance was used to analyze the effect of differences in plasma lipid, glucose, and SSPG concentrations between dietary phases. The general linear model for repeated-measures procedures was used to test the main effects of genes and diet and gene \times diet interactions. When significant effects were observed, Tukey's post hoc test was used to identify between-group differences. Because the *Thr54/Thr54* group was small, the statistical analysis was performed for the combined *Ala54/Thr54* and *Thr54/Thr54* groups. Correlation was performed with Pearson's correlation coefficient. *FABP2* genotypes were dichotomized for these analyses. A *P* value of < 0.05 was

TABLE 2
Fatty acid composition of plasma LDL-cholesterol esters during each diet.¹

Fatty acid	SFA diet	CHO diet	Mediterranean diet
	<i>% of the total</i>		
16:0	27.2 ± 1.4 ^a	18.9 ± 3.9 ^b	15.1 ± 0.4 ^b
16:1	2.2 ± 0.9	2.3 ± 0.3	1.9 ± 0.2
18:0	2.8 ± 1.1	2.4 ± 0.8	2.5 ± 0.4
18:1	45.5 ± 4.4 ^{a,b}	38.5 ± 9 ^b	49.7 ± 4.7 ^a
18:2	20.2 ± 3.6 ^a	33.6 ± 16 ^b	26.4 ± 4.8 ^{a,b}

¹ All values are $\bar{x} \pm$ SD. SFA diet, saturated fatty acid–enriched diet; CHO diet, low-fat and high-carbohydrate diet; Mediterranean diet, high–monounsaturated fatty acid diet. Means in a row with different superscript letters are significantly different, *P* < 0.05 (repeated-measures ANOVA and Tukey's test).

considered significant. All data are given in the text and tables as means \pm SDs.

RESULTS

Dietary composition was analyzed in duplicate meal portions, and results are shown in **Table 1**. The results were in good agreement with values obtained from the food-composition tables. Analysis of the cholesterol ester fraction of plasma LDL showed good adherence to the different diets (**Table 2**). During consumption of the SFA diet, there was a significantly higher concentration of palmitic acid (16:0) than that recorded during consumption of the CHO and Mediterranean diets (*P* < 0.05 for both). We also observed a significant increase in the concentrations of oleic acid (18:1) when subjects switched from the CHO diet to the Mediterranean diet (*P* < 0.05).

The baseline characteristics of the subjects according to the *FABP2 Ala54/Thr54* polymorphism are shown in **Table 3**. There were no significant differences between subjects in any of the lipid variables after the 3 dietary periods.

SSPI and SSPG concentrations for the 3 genotypes of *FABP2 Ala54/Thr54* polymorphism in response to each diet are shown in **Table 4**. Carriers of the *Thr54* allele showed significantly (*P* < 0.05) higher concentrations of SSPG after an SFA diet than after

TABLE 3

Baseline anthropometric characteristics and plasma lipid and apolipoprotein (apo) concentrations according to *FABP2* genotype¹

	<i>Ala54/Ala54</i> (<i>n</i> = 28)	<i>Ala54/Thr54</i> (<i>n</i> = 27)	<i>Thr54/Thr54</i> (<i>n</i> = 4)
BMI (kg/m ²)	21.4 ± 0.7	21.7 ± 0.5	21.1 ± 3.5
Total cholesterol (mmol/L)	4.22 ± 0.59	4.21 ± 0.75	3.74 ± 0.76
Triacylglycerol (mmol/L)	0.71 ± 0.30	0.71 ± 0.26	0.52 ± 0.14
LDL cholesterol (mmol/L)	2.45 ± 0.61	2.53 ± 0.73	2.17 ± 0.64
HDL cholesterol (mmol/L)	1.44 ± 0.42	1.35 ± 0.31	1.33 ± 0.21
Apo A-I (g/L)	1.50 ± 0.16	1.49 ± 0.18	1.46 ± 0.11
Apo B (g/L)	0.72 ± 0.09	0.75 ± 0.16	0.68 ± 0.11

¹ All values are $\bar{x} \pm$ SD. *FABP2*, fatty acid–binding protein 2 gene; SFA diet, saturated fatty acid–enriched diet; CHO diet, low-fat and high-carbohydrate diet; *Ala54*, alanine-encoding allele in codon 54 of the intestinal *FABP2* gene; *Thr54*, threonine-encoding allele. Because the *Thr54/Thr54* group was small, the statistical analysis was performed for the combined *Ala54/Thr54* and *Thr54/Thr54* groups. There were no significant differences between genotype groups by repeated-measures ANOVA.



TABLE 4

Steady state plasma insulin and glucose (SSPI and SSPG) values for each genotype in response to each diet¹

Genotype and diet	SSPI	SSPG
	pmol/L	mmol/L
<i>Ala54/Ala54</i> (n = 28)		
SFA diet	97.3 ± 22.8	6.4 ± 2.8
CHO diet	100.4 ± 23.9	5.6 ± 2.4
Mediterranean diet	99.2 ± 23.5	5.5 ± 2.8
<i>Ala54/Thr54</i> (n = 27)		
SFA diet	99.3 ± 25.3	7.8 ± 4.2 ^a
CHO diet	97.5 ± 21.8	6.7 ± 3.1 ^b
Mediterranean diet	99.7 ± 25.3	6.1 ± 2.5 ^b
<i>Thr54/Thr54</i> (n = 4)		
SFA diet	98.6 ± 30.7	7.4 ± 3.3
CHO diet	99.2 ± 23.5	5.0 ± 1.3
Mediterranean diet	97.2 ± 30.5	6.6 ± 0.9
<i>P</i> ¹		
Diet	0.316	0.207
Genotype	0.898	0.012
Interaction	0.285	0.050

¹ All values are $\bar{x} \pm$ SD. SFA diet, saturated fatty acid–enriched diet; CHO diet, low-fat and high-carbohydrate diet; *Ala54*, alanine-encoding allele in codon 54 of the intestinal fatty acid–binding protein 2 gene; *Thr54*, threonine-encoding allele. Because the *Thr54/Thr54* group was small, the statistical analysis was performed for the combined *Ala54/Thr54*+*Thr54/Thr54* groups and is reported only on the *Ala54/Thr54* means. Means in a column with different superscript letters are significantly different, $P < 0.05$ (repeated-measures ANOVA and Tukey's test).

the Mediterranean or CHO diet (Table 4). Nevertheless, homozygotes for the *Ala54* allele showed no significant differences in SSPG after consumption of any of the 3 diets.

Analysis of the fasting nonesterified FAs found that the *Thr54* allele carriers had lower concentrations of FFAs with consumption of the CHO diet and the Mediterranean diet ($P < 0.05$) than with that of the SFA diet (Figure 1). Likewise, we noted a positive correlation between the SSPG and nonesterified FA concentrations during the Mediterranean ($r = 0.278$, $P < 0.05$)

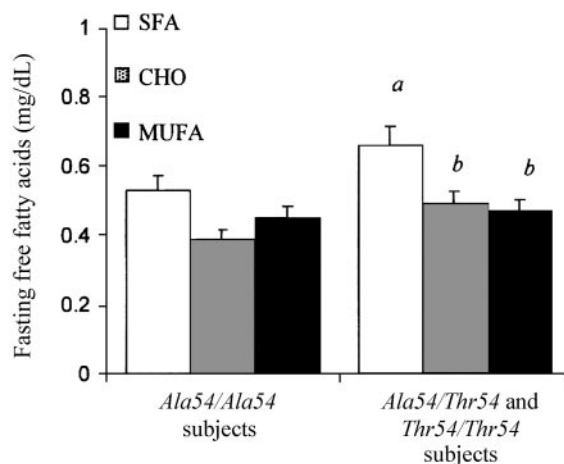


FIGURE 1. Mean (\pm SD) plasma concentrations of fasting free fatty acids according to fatty acid–binding protein 2 genotype. $P = 0.238$, 0.002, and 0.015 for genotype effect, diet effect, and genotype \times diet interaction, respectively. Means with different letters are significantly different, $P < 0.05$ (repeated-measures ANOVA and Tukey's test). There were no significant differences between the diets for persons with *Ala54/Ala54*.

and CHO ($r = 301$, $P < 0.05$) diets. However, there was no significant correlation between the SSPG and nonesterified FA concentrations during the SFA diet ($r = 0.114$, $P = 0.397$).

DISCUSSION


Our study shows that carriers of the *Thr54* allele have less peripheral insulin sensitivity after the intake of an SFA diet than after that of an olive oil–rich, Mediterranean-type diet. Likewise, these subjects show an increase in FFA concentrations after consumption of an SFA diet than after that of a Mediterranean or CHO diet. However, in *Ala54* allele homozygotes, no significant differences in SSPG concentrations were observed after any of the diets. These 2 facts together would indicate a genotype \times diet interaction.

Reductions in SFA intake improve insulin sensitivity in patients with type 2 diabetes (24, 25), and these data agree with the results in healthy subjects in the current study. However, debate continues as to whether dietary SFA should be replaced with low fat and high carbohydrate or with MUFA. A study carried out in our laboratory showed that the CHO and Mediterranean diets are equally effective at promoting in vivo disposal of glucose, because they showed a similar decrease in SSPG (26). It is important to stress that the 3 diets in the current study provided the same fiber content. In addition, previous studies indicated that an increase in carbohydrates, without an increase in fiber, does not improve glucose metabolism (27). A study showed that diets with different carbohydrate content, but with an equal fiber content, improved glucose metabolism (28).

There is substantial evidence that lifestyle factors such physical activity and healthy diets reduce the risk of insulin resistance or type 2 diabetes. However, individual variability exists and is determined by genetic factors that influence tissue sensitivity to insulin.

Earlier studies carried out in Pima Indians by Baier et al (13) showed that carriers of the *Thr54* allele presented increased incidence of hyperinsulinemia and insulin resistance after an oral glucose overload, in addition to a higher fasting lipid oxidation rate. These findings were consistent with the hypothesis that the presence of the *Thr54* allele was associated with increased binding affinity to LCFAs, which resulted in enhanced intestinal absorption of FAs, higher plasma lipid concentrations, and, consequently, enhanced lipid oxidation rates, which would inhibit tissue sensitivity to insulin in vivo. It was later confirmed, in a healthy white population with normal glucose tolerance, that the *Thr54* allele was associated with insulin resistance. These data coincide with those observed in the current study, but we noted the different peripheral insulin sensitivity in the *Thr54* allele carriers only when the subjects consumed a diet rich in saturated fat, which suggested that an interaction between this polymorphism and the type of fat determined peripheral insulin sensitivity.

Previous studies showed that the *FABP2* gene is a candidate gene that may be implicated in insulin resistance because its product is involved in FFA absorption and because defects in FFA regulation have been hypothesized to play a role in insulin resistance (29). IFABP expression appears to be limited to the enterocytes of the small intestine, where it is extremely abundant. The restricted expression of this protein combined with its high affinity for both unsaturated and saturated LCFAs indicates that IFABP has a role in the absorption and intracellular transport of dietary LCFAs. With this in mind, Baier et al (13) hypothesized

that the *Ala54/Thr54* polymorphism results in increased FA uptake from the intestinal lumen. This hypothesis was based on in vitro findings that this polymorphism binds FAs with twice as much affinity as does the wild-type protein. Increased digestive absorption of fat could result in abnormally high postprandial plasma FA concentrations, which produce transient muscle cell insulin resistance via the glucose-FA cycle, and in high hepatic glucose production via increased gluconeogenesis. In the current study, we observed that subjects with the *Thr54* allele had higher FFA concentrations than did those who were homozygous for the *Ala54* allele when consuming the SFA diet. Considering the hypothesis proposed by Baier et al (13), these results suggested a plausible mechanism of the *FABP2 Ala54/Thr54* polymorphism \times diet interaction for determining insulin sensitivity. Thus, the presence of the *FABP2* gene *Ala54/Thr54* polymorphism impairs peripheral insulin sensitivity when the carriers consume an SFA diet. 

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CM was responsible for the collection of data, analysis of data, and writing of the manuscript. PG, YJ, MJG, and JD contributed to the collection and analysis of data. JAP, AL, and BC recruited and screened subjects. FPJ and JLM were responsible for the conception and design of the study, analysis of data, and writing of the manuscript. None of the authors had any personal or financial conflict of interest.

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