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Metabolic syndrome and ALA54THR polymorphism of fatty acid–binding protein 2 in obese patients

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Abstract

The prevalence of metabolic syndrome (MS) has been estimated to be approximately 25% of the population at large. A transition G to A at codon 54 of fatty acid–binding protein 2 (*FABP2*) results in an amino acid substitution (ala54 to Thr54), and this polymorphism was associated with some cardiovascular risk factors. The aim of our study was to investigate the relationship between MS and Thr54 polymorphism in the *FABP2* gene in obese patients. A population of 750 (body mass index >30) obese patients was analyzed in cross-sectional survey. Bioimpedance, blood pressure, and serial assessment of nutritional intake with 3-day written food records and biochemical analysis were performed. The statistical analysis was performed for the combined Ala54/Thr54 and Thr54/Thr54 as a mutant group and wild-type Ala54/Ala54 as second group. Prevalence of MS with Adult Treatment Panel III definition was 49.7% (373 patients; 24.9% male and 75.1% female), and 50.3% of the patients had no MS (n = 377; 34.2% male and 65.8% female). Prevalence of *FABP* genotypes was similar in patients with MS (55.5% wild genotype and 44.5% mutant genotype) and without MS (54.6% wild genotype and 45.4% mutant genotype). Prevalence of each criteria of MS was calculated in wild- and mutant-type genotypes, without statistical differences. No differences in anthropometric and biochemical parameters were detected between genotypes in the same group of MS. The finding of our study is the lack of association of the Thr54/Ala54 and Thr54/Thr54 *FABP2* genotypes with MS.

1. Introduction

The prevalence of metabolic syndrome (MS) has been estimated to be approximately 25% of the population at large [1]. People with MS have a 2-fold higher risk of mortality and a 3-fold higher risk of experiencing a cardiovascular event as compared with people without MS [2]. The definitions most widely used are those of Adult Treatment Panel (ATP) III [3] because they are based on easily obtained biochemical and anthropometric measurements [4], including among their criteria estimations of abdominal obesity, high blood pressure [BP], dyslipidemia, and hyperglycemia. According to recent surveys, approximately two thirds of the population of Spain is overweight [5]. The etiology of this common obesity is complex because many genetic, environmental, and metabolic factors might act. For example, the fatty acid–binding protein 2 (*FABP2*) gene codes for intestinal FABP and plays an important role in several steps of unsaturated and saturated long-chain fatty acids, protection of the cell from the cytotoxic effects of free fatty acids, and modulation of the enzyme additive involved in lipid metabolism [6,7]. A transition G to A at codon 54 of *FABP2* results in an amino acid substitution (ala54 to Thr54) [8]. This polymorphism is common, with a Thr54 allelic frequency of 30% in most populations. This amino acid substitution was associated with high insulin resistance and fasting insulin concentrations [8], which supports the role of the *FABP2* Ala54Thr polymorphism in the etiology of metabolic disorders such as insulin resistance [9].

The aim of our study was to investigate the relationship between MS and Thr54 polymorphism in the *FABP2* gene in obese patients.

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2. Subjects and methods

2.1. Subjects

A population of 750 (body mass index [BMI] >30) obese patients was analyzed in cross-sectional survey. The recruitment of subjects was a nonprobabilistic method of sampling among patients sent from primary care physicians with obesity from a Northwest area of Spain (Castilla y León). Exclusion criteria included history of cardiovascular disease or stroke during the previous 36 months, malignant tumor or major surgery during the previous 6 months, as well as the use of glucocorticoids, antineoplastic agents, and drinking and/or smoking habit. This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving patients were approved by the Hospital Universitario Rio Hortega ethics committee. Written informed consent was obtained from all patients and signed.

2.2. Procedure

Weight, BP, basal glucose, insulin, insulin resistance (homeostasis model assessment [HOMA]), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, blood triglycerides, and adipocytokines (leptin, adiponectin, resistin, tumor necrosis factor [TNF] α, and interleukin [IL] 6) levels were measured in fasting condition. A tetrapolar bioimpedance and a prospective serial assessment of nutritional intake with 3-day written food records were realized. Genotype of *FABP2* gene polymorphism was studied. To estimate the prevalence of MS, the definitions of the ATP III was considered [3]. The cutoff points for the criteria used are 3 or more of the following: central obesity (waist circumference >102 in male and >88 cm in female subjects), hypertriglyceridemia (triglycerides >150 mg/dL or specific treatment), hypertension (systolic BP >130 mm Hg or diastolic BP >85 mm Hg or specific treatment), or fasting plasma glucose greater than 100 mg/dL or drug treatment of elevated blood glucose.

2.3. Genotyping of FABP2 gene polymorphism

Oligonucleotide primers and probes were designed with the Beacon Designer 4.0 (Premier Biosoft International, Los Angeles, CA). The polymerase chain reaction was carried out with 50 ng of genomic DNA, 0.5 μL of each oligonucleotide primer (primer forward: 5′-CAG TTC CGT CTG CTA GAT TGT-3′; primer reverse: 5′-GCT GAC AAT TAC ACA AGA AGG AA-3′), and 0.25 μL of each probe (wild probe: 5′-Fam-CAA AGA ATC AAG CAC TTT TCG AAA CA-BHQ-1-3′; mutant probe: 5′-Hex-AGA ATC AAG CGC TTT TCG AAA CA-BHQ-1-3′) in a 25-μL final volume (Termociclador iCycler IQ; Bio-Rad, Hercules, CA). DNA was denaturated at 95°C for 3 minutes; this was followed by 50 cycles of denaturation at 95°C for 15 seconds and annealing at 59.3° for 45 seconds. The polymerase chain reaction was run in a 25-μL final volume containing 12.5 μ of IQTM Supermix (Bio-Rad) with hot start Taq DNA polymerase. Hardy-Weinberg equilibrium was assessed.

2.4. Assays

Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, New York, NY), whereas HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. Low-density lipoprotein cholesterol was calculated using the Friedewald formula.

Plasma glucose levels were determined by using an automated glucose oxidase method (Glucose Analyzer 2; Beckman Instruments, Fullerton, CA). Insulin was measured by radioimmunoassay (RIA Diagnostic, Los Angeles, CA) with a sensitivity of 0.5 mUI/L (reference range, 0.5-30 mUI/L) [10], and the HOMA for insulin sensitivity was calculated using these values [11]. C-reactive protein was measured by immunoturbidimetry (Roche Diagnostics, Mannheim, Germany) with a reference range of 0 to 7 mg/dL and analytical sensitivity 0.5 mg/dL.

2.5. Adipocytokines

Resistin was measured by enzyme-linked immunosorbent assay (ELISA) (Biovendor Laboratory, Brno, Czech Republic) with a sensitivity of 0.2 ng/mL and a reference range of 4 to 12 ng/mL [12]. Leptin was measured by ELISA (Diagnostic Systems Laboratories, Webster, TX) with a sensitivity of 0.05 ng/mL and a reference range of 10 to 100 ng/mL [13]. Adiponectin was measured by ELISA (R&D Systems, Minneapolis, MN) with a sensitivity of 0.246 ng/mL and a reference range of 8.65 to 21.43 ng/mL [14]. Interleukin-6 and TNF-α were measured by ELISA (R&D Systems) with a sensitivity of 0.7 and 0.5 pg/mL, respectively. Normal values were 1.12 to 12.5 pg/mL for IL-6 and 0.5 to 15.6 pg/mL for TNF-α [15,16].

2.6. Anthropometric measurements and dietary habits

Body weight was measured to an accuracy of 0.5 kg, and BMI was computed as body weight/(height^2). Waist (narrowest diameter between xiphoid process and iliac crest) and hip (widest diameter over greater trochanters) circumferences to derive waist-to-hip ratio (WHR) were measured, too. Tetrapolar body electrical bioimpedance was used to determine body composition with an accuracy of 5 g [17]. Blood pressure was measured twice after a 10-minute rest with a random zero mercury sphygmomanometer and averaged.

Patients received prospective serial assessment of nutritional intake with 3-day written food records. All enrolled subjects received instruction to record their daily dietary intake for 3 days including a weekend day. Records were analyzed with a computer-based data evaluation system. National composition food tables were used as reference [18].

2.7. Statistical analysis

Sample size was calculated to detect differences greater than 45% of prevalence of MS with 90% power and 5% significance. The results were expressed as average ± standard deviation. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a 2-tailed, paired Student *t* test. Nonparametric variables were analyzed with the Mann-Whitney *U* test. Qualitative variables were analyzed with the χ^2 test, with Yates correction as necessary, and Fisher test. The statistical analysis was performed for the combined Ala54/Thr54 and Thr54/Thr54 as a group and wild-type Ala54/Ala54 as second group. A P value < .05 was considered statistically significant.

3. Results

Seven hundred fifty patients gave informed consent and were enrolled in the study. The mean age was 42.8 ± 14.9 years and the mean BMI was 36.21 ± 6.0, with 222 (29.6%) male and 528 (70.4%) female.

Four hundred thirteen patients (55.1%) had the genotype Ala54/Ala54 (wild group), whereas 337 (44.9%) had either the genotype Ala54/Thr54 (274 patients, 36.5%) or the genotype Thr54/Thr54 (63 patients, 8.4%) (mutant group). Age was similar in both groups (wild type, 42.6 ± 12.3 years vs mutant group, 43.4 ± 15.2 years; P = not significant). Sex distribution was similar in both groups (wild- vs mutant-type group): male (31.5% vs 27.3%) and female (68.5% vs 72.7%).

Prevalence of MS with ATP III definition was 49.7% (373 patients; 24.9% male and 75.1% female), and 50.3% of patients had no MS (n = 377; 34.2% male and 65.8% female). Prevalence of FABP genotypes was similar in patients with MS (55.5% wild genotype and 44.5% mutant genotype) and without MS (54.6% wild genotype and 45.4% mutant genotype). Prevalence of each criteria of MS was calculated in wild- and mutant-type genotypes, without statistical differences. Elevated waist circumference was detected in 92.0% of patients with wild-type genotype and 89.5% of patients with mutant-type genotype. Elevated levels of triglycerides or specific treatment was detected in 25% of patients with wild-type genotype and 26.5% of patients with mutant-type genotype. Elevated levels of BP or specific treatment was detected in 56.9% of patients with wild-type genotype and 60.4% of patients with mutant-type genotype. Elevated levels of glucose or specific treatment was detected in 37.6% of patients with wild-type genotype and 36% of patients with mutant-type genotype.

Table 1
Anthropometric and biochemical variables, MS vs no MS

Characteristics	MS (n = 373)	No MS (n = 377)
BMI	37.2 ± 6.4	35.1 ± 5.5*
Weight (kg)	98.4 ± 20.1	93.4 ± 17.1*
Fat mass (kg)	42.6 ± 14.1	39.6 ± 12.6*
WC (cm)	113.9 ± 14.5	107.1 ± 11.4*
WHR	0.94 ± 0.07	0.90 ± 0.06*
Systolic BP (mm Hg)	135.9 ± 15.4	123.3 ± 13.3*
Diastolic BP (mm Hg)	86.0 ± 10.2	78.5 ± 9.2*
Glucose (mg/dL)	110.7 ± 31.1	91.7 ± 10.8*
Total ch (mg/dL)	208.7 ± 38.3	196.4 ± 40.3*
LDL ch (mg/dL)	125.4 ± 37.1	117.1 ± 40.3*
HDL ch (mg/dL)	54.2 ± 24.6	56.6 ± 18.3
TG (mg/dL)	150.8 ± 80.1	100.3 ± 40.9*
Insulin (mUI/L)	20.5 ± 17.2	13.8 ± 8.2*
HOMA	5.85 ± 5.6	3.07 ± 2.0*

Ch indicates Cholesterol; TG, triglycerides; WC, waist circumference.
* P < .05, between groups.

Table 2
Circulating adipocytokines, MS vs no MS

Characteristics	MS (n = 373)	No MS (n = 377)
IL-6 (pg/mL)	2.10 ± 2.7	2.43 ± 1.6
TNF-α (pg/mL)	5.47 ± 3.7	6.24 ± 4.0
Adiponectin (μg/mL)	26.64 ± 32.4*	35.64 ± 31.3*
Resistin (ng/mL)	3.85 ± 1.74	3.94 ± 1.78
Leptin (ng/mL)	74.4 ± 69.1	86.2 ± 51.1

* P < .05, between groups.

Table 1 shows the subjects' differences in anthropometric and cardiovascular variables with and without MS. Patients with MS had higher weight, BMI, waist circumference, WHR, systolic and diastolic BP, glucose, HOMA, insulin, total cholesterol, LDL cholesterol, and triglycerides than patients without MS. Table 2 shows the subjects' levels of adipokines. Patients with MS had lower adiponectin levels than patients without MS. Adiponectin (in microgram per milliliter) levels were higher in women than men in patients with MS (36.14 ± 22.3 vs 20.23 ± 19.8, P < .05) and patients without MS (47.13 ± 21.3 vs 21.12 ± 13.4, P < .05).

Subject's nutritional intake was similar in both groups (MS vs no MS): calorie (1940 ± 661 vs 1882 ± 778 cal/d), carbohydrate (198.1 ± 85 vs 182.5 ± 83 g/d), fat (85.1 ± 39 vs 84.1 ± 45 g/d), protein (91.4 ± 26 vs 91.7 ± 38 g/d), and fiber intakes (15.38 ± 6.4 vs 14.81 ± 6.9 g/d). Hours of exercise per week were similar (1.76 ± 2.9 vs 1.43 ± 2.8 h/wk), too.

Table 3 shows the subjects' differences in anthropometric and cardiovascular variables secondary to genotype in those with MS and those without MS. Patients with MS, in both genotypes, had higher weight, BMI, waist circumference, WHR, systolic and diastolic BP, glucose, HOMA, insulin, total cholesterol, LDL cholesterol, and triglycerides than patients without MS. No differences in these parameters were detected between genotypes in the same group of MS.

Table 4 shows the subjects' levels of adipokines in both genotypes in those with MS and those without MS. Patients with MS, in both genotypes, had lower adiponectin levels than patients without MS. No differences in adipocytokines levels were detected between genotypes in the same group of MS. Adiponectin (in micrograms per milliliter) levels were higher in women than men in patients with MS and wild-type

Table 3
Anthropometric and biochemical variables

Characteristics	MS		No MS	
	WT	MT	WT	MT
BMI	37.3 ± 7.0	36.9 ± 5.7	34.9 ± 5.2†	35.1 ± 5.2†
Weight (kg)	99.0 ± 20.9	97.5 ± 19.5	93.5 ± 16.1†	93.3 ± 14.2†
Fat mass (kg)	43.2 ± 15.4	42.0 ± 13.2	37.8 ± 10.1†	38.4 ± 10.1†
Waist circumference	113.1 ± 15.2	114.9 ± 13.3	107.5 ± 13†	106.8 ± 11.8†
WHR	0.93 ± 0.1	0.94 ± 0.07	0.90 ± 0.1	0.90 ± 0.09
Systolic BP (mm Hg)	135.1 ± 14	136.8 ± 15.3	118.4 ± 11.6	119.4 ± 11.3
Diastolic BP (mm Hg)	86.4 ± 9.3	85.5 ± 11.4	78.0 ± 8.6	78.9 ± 9.7
Glucose (mg/dL)	110.7 ± 30	110.7 ± 32.1	91.4 ± 12.1†	92.1 ± 11.2†
Total ch (mg/dL)	208.3 ± 38	207.0 ± 39.1	195.2 ± 38	197.8 ± 42
LDL ch (mg/dL)	124.9 ± 38	126.1 ± 37	115.6 ± 40	118.8 ± 32
HDL ch (mg/dL)	53.1 ± 18.7	55.1 ± 28.1	58.2 ± 22.1	56.0 ± 13.8
TG (mg/dL)	150.2 ± 70	151.7 ± 90.3	99.6 ± 35.1†	101.5 ± 46†
Insulin (mUI/L)	19.9 ± 18.3	21.1 ± 16.8	14.1 ± 7.9†	13.5 ± 8.7†
HOMA	5.6 ± 5.1	6.1 ± 6.4	3.1 ± 1.9†	3.2 ± 2.3†

No statistical differences between WT and MT in each allele group. WT indicates wild-type genotype Ala54/Ala54); MT, mutant-type genotype (Ala54/Thr54 or Thr54/Thr54).

† $P < .05$, statistical differences between MS and no MS groups in different allele groups (Lys656/Lys656 vs Lys656/Asn656 and Asn656/Asn656).

genotype (33.12 ± 21.1 vs 22.28 ± 16.4, $P < .05$) and patients with MS and mutant-type genotype (36.11 ± 20.8 vs 24.31 ± 11.2, $P < .05$). In the same way, adiponectin (in micrograms per milliliter) levels were higher in women than men in patients without MS and wild-type genotype (37.34 ± 19.3 vs 21.09 ± 12.1, $P < .05$) and patients without MS and mutant-type genotype (48.24 ± 19.1 vs 22.34 ± 11.2, $P < .05$).

No differences in dietary intakes or physical activity were detected in both genotypes in those with MS and those without MS.

4. Discussion

The main finding of this study is the lack of association of the Thr54/Ala54 and Thr54/Thr54 *FABP2* genotypes with MS.

The relation of this polymorphism with different criteria of MS is contradictory. Baier et al [8] concluded that threonine-containing protein may increase absorption dietary fatty acids by the intestine and therefore increase fat oxidation, which has been shown to reduce insulin action, with higher insulinemia, LDL cholesterol, apolipoprotein B levels, BMI, and triglycerides. However, in other studies [19,20], no differences were detected in basal values of insulin, glucose, triglycerides, or LDL cholesterol between wild and mutant patients; this fact does not have a clear explanation.

Prevalence of this polymorphism is different among studies. Sipilainen et al [21] showed a similar frequency of the Ala54 to Thr polymorphism in obese and control subjects (28% to 29%, respectively). The authors found that obesity is not associated with specific variants in the *FABP2* gene and that the Ala54 to Thr polymorphism did not influence insulin levels or basal metabolic rate in obese patients. Slightly lower frequency have been reported for other population such as nondiabetic Pima Indians (30%), Koreans (34%), Japanese (35%), Swedish (30%), and white individuals from the United States (32%) [22-26]. However, the frequency of mutant allele was higher in our study in patients with and without MS. Perhaps, these discrepant results could be explained by the inclusion criteria of subjects in previous studies of the literature or the lack of analysis of MS in these populations. For example, some authors have shown [27,28] higher levels of cholesterol and triglycerides in patients with Thr allele. Nevertheless, Georgoporlus et al [29] have shown lower total and LDL cholesterol levels in patients with Thr allele. These previous studies would require composition analysis of the diet to determine whether dietary components could be responsible for the lipid profile modifications. Our data have been controlled by dietary intake; and previous discrepancies could be explained by this uncontrolled factor, as detected in other studies [30-33].

In conclusion, the finding of our study is the lack of association of the Thr54/Ala54 and Thr54/Thr54 *FABP2* genotypes with MS.

Table 4
Circulating adipocytokines

Characteristics	MS		No MS	
	WT	MT	WT	MT
IL 6 (pg/mL)	2.20 ± 3.1	1.90 ± 2.3	3.05 ± 1.3	2.07 ± 2.0
TNF-α (pg/mL)	5.62 ± 3.9	5.29 ± 3.5	6.32 ± 4.6	6.13 ± 4.5
Adiponectin (μg/mL)	30.5 ± 41.2	29.6 ± 19.6	34.9 ± 33†	37.9 ± 28†
Resistin (ng/mL)	3.90 ± 1.9	3.79 ± 1.5	3.78 ± 1.5	4.31 ± 1.7
Leptin (ng/mL)	73.7 ± 41	75.3 ± 45	80.5 ± 59	90.8 ± 88

No statistical differences between WT and MT in each allele group.

† $P < .05$, statistical differences between MS and no MS groups in different allele groups (Lys656/Lys656 vs Lys656/Asn656 and Asn656/Asn656).

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