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Association between angiotensin-1 converting enzyme gene polymorphism and the metabolic syndrome in a Mexican population

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Abbreviations: ACE, angiotensin-1 converting enzyme; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; I/D, insertion/deletion; LDL-C, low density lipoprotein cholesterol; MS, metabolic syndrome; RAS, renin angiotensin system; SBP, systolic blood pressure; WC, waist circumference

Abstract

Metabolic Syndrome (MS) is recognized as a cluster of cardiovascular risk factors. All components of MS have a genetic base. Genes of the renin angiotensin system are potential candidate genes for MS. We investigated whether angiotensin converting enzyme (ACE) gene polymorphism increases susceptibility to MS as an entity in a Mexican population. In a cross-sectional study, 514 individuals were studied including 245 patients with MS and 269 subjects without MS criteria. ACE gene polymorphism was detected using PCR. MS was defined according to The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) criteria, except that the raised fasting plasma glucose $\geq$ 100 mg/dl criterion for identification of intolerance fasting glucose was modified in accordance with the suggestion of the American Diabetes Association. Patients with MS were significantly different from subjects without MS in relation to mean body mass index (BMI), waist circumference (WC), systolic blood pressure, diastolic blood pressure, glucose, total cholesterol (C), triglycerides, HDL-C, and LDL-C ($P < 0.0001$). The differences in the mean BMI, WC, glucose, total cholesterol, triglycerides, LDL-C, and HDL-C were maintained in patients with the MS and DD genotypes ($P < 0.01$). The DD genotype was strongly associated with MS (adjusted OR = 5.48, 95% CI 3.20-9.38, $P < 0.0001$). We concluded that the DD genotype increases susceptibility to MS in a Mexican population. These results indicate that pharmacological and non-pharmacological treatment and a reduction in body fat will have important therapeutic implications in this disease.

Keywords: metabolic syndrome X; obesity; peptidyl-dipeptidase A; polymorphism, genetic; renin-angiotensin system; risk factors

Introduction

Metabolic Syndrome (MS) is recognized as a cluster of cardiovascular risk factors that frequently coincide with central obesity, dyslipidemia, hypertension, and hyperglycemia (Timar *et al.*, 2000) with a frequent occurrence in various ethnic groups. Its presence is associated with a high risk of developing cardiovascular disease (CVD) (Isomaa *et al.*, 2001).

Recent estimates show the prevalence of MS in the adult population as 32% for Hispanic Americans, 22% for Afro-Americans, and 24% for Caucasian populations (Ford *et al.*, 2002). This prevalence increases more than 70% in patients with type 2 diabetes (Ilanne-Parikka *et al.*, 2004). All components of MS have a genetic base (Scott *et al.*, 2000). As a consequence, there is an interaction or multiplying effects of polymorphism in a growing number of genes potentially involved in this disease.

The renin angiotensin system (RAS) is a coordinated cascade that starts with the synthesis and secretion of renin from juxtaglomerular cells in the afferent renal artery (Boucher *et al.*, 1977). The angiotensin converting enzyme (ACE) key for RAS catalyzes the conversion of angiotensin I to angiotensin II (AngII), a potent vasocontrictor, and promotes the degradation of bradykinin (Erdos and Skidgel, 1987). The insertion/deletion (I/D) polymorphism of the ACE gene is characterized by the presense (I) or absence (D) of an alu repetitive sequence of 287 bp in intron 16 of the ACE gene. Individuals with the insertion (I) have a fragment of 490 bp and individuals with the deletion (D) have a fragment of 190 bp in PCR amplification (Rigat *et al.*, 1992). The ACE gene is related to the inter-individual variability of plasma ACE levels. Individuals with the DD genotype have higher ACE plasma levels, compared with individuals with the II or I/D genotypes (Rigat *et al.*, 1990).

RAS is essential in cardiovascular hemodynamics and plays an important role in the development of CVD (Harrap, 1996). Several studies have demonstrated that ACE gene polymorphism is a risk factor for ischemic cardiopathy (Ruiz *et al.*, 1994), hypertension (Caulfield *et al.*, 1994) and type 2 diabetes (Feng *et al.*, 2002); however, cross-sectional studies have yielded conflicting results depending on several factors, including ethnic differences, sample size, and patient characteristics (Cambien *et al.*, 1994; Iwai *et al.*, 1994; Panahloo *et al.*, 1995; Chiu and McCarty, 1997). Many studies have investigated the associations between genetic polymorphisms and the various components of MS. In contrast, few studies have explored this association with MS as an entity. Therefore, the aim of our study was to determine whether ACE polymorphism increases susceptibility to MS as an entity in a Mexican population.

Materials and Methods

Patients

Using a cross-sectional study from January 2005 to December 2005, we studied 514 individuals of both sexes including 245 patients with MS and 269 subjects without MS criteria. The sample size was calculated using a formula for cross-sectional studies with a confidence level of 95%, an acceptable error of $\pm$ 2.3%, and an expected proportion of patients with MS of 50% (Lwanga and Lemeshow, 1991). The calculated sample size was 473 patients plus 10% additional to cover for possible lost. All patients were born in the state of Michoacán, which is located in the central part of Mexico. All were mestizos in origin as a result of admixture between Europeans and Native Mexicans. All patients were treated at the Unidad de Medicina Familiar No. 80 Instituto Mexicano del Seguro Social (IMSS) in Morelia, Michoacán, Mexico. A complete clinical history of all patients was taken, including gender, age, body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP) glucose, total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C). The BMI was calculated according to the Quetelet equation. Blood pressure was registered twice using a calibrated mercury Baumanometer (Model 88030054; Mercurial Sphygmomanometer, American Diagnostic Corp.) with the patient seated, at rest for at least 5 min, without having ingested caffeinated drinks or having smoked cigarettes 30 min prior to the reading. The average of the two measurements was reported.

MS was defined according to The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, ATP III) criteria. The definition in 2001 of ATP III identified a fasting plasma glucose level of $\geq$ 110 mg/dl as elevated. This definition was modified in 2004 to be $\geq$ 100 mg/dl according to the American Diabetes Association update of the definition of the intolerance fasting glucose level (IFG) (Grundy *et al.*, 2004). MS was determined by the presence of at least three of the following abnormalities: central obesity (waist circumference $>$ 102 cm in men or $>$ 88 cm in women), triglycerides $\geq$ 150 mg/dl, or drug treatment for elevated triglycerides, HDL-C $<$ 40 mg/dl in men or $<$ 50 mg/dl in women or drug treatment for reduced HDL-C, blood pressure $\geq$ 130/85 mmHg without antihypertensive treatment or with antihypertensive drug treatment in a patient with a history of hypertension, and raised IFP $\geq$ 100 mg/dl or previously diagnosed type 2 diabetes. Diabetes was defined according to the American Diabetes Association criteria and hypertension was defined according to the Seven Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (DC report 2004; Chobanian *et al.*, 2003).

The protocol was approved by the Research and Ethics Committee of the Hospital General Regional No. 1, IMSS, Morelia, Michoacán, México. Informed consent for genetic studies was obtained from all patients.

Biochemical measurements

Glucose, total cholesterol, triglycerides, HDL-C, and LDL-C levels were measured in all subjects using equipment for chemical analysis (Dimension AR/ AVL Clinical Chemistry System, Newark, NJ).

Dyslipidemia was considered as a total cholesterol level of $\geq$ 200 mg/dl, triglyceride $\geq$ 150 mg/dl, low HDL-C $<$ 40 mg/dl for men and $<$ 50 mg/dl for women, and high LDL-C $\geq$ 130 mg/dl concentrations.

DNA analysis and PCR

DNA was extracted from leucocytes obtained from peripheral blood samples of the subjects using the technique of Miller *et al.* (1988) with minor modifications.

Two hundred μl of blood was placed in a 1.5-ml tube. Two hundred μl SDS at 1.6% was added, the immersion was mixed, and 80 μl of lysozyme (20 mg/ml) was added to the mixture and left for 20 min at 37°C. Next, 290 μl of ammonium acetate (7 M) was gently mixed and left for an additional 5 min. Then, 770 μl of phenol was added, the tube was shaken vigorously and centrifuged at 10,000 rpm. The excess was placed in another 1.5-ml tube, 850 μl absolute ethanol was added, the immersion was mixed, left for 5 min on ice, centrifuged at 10,000 rpm during 10 min, dried and dissolved once again in 50 μl of DNA stabilizing solution. The concentration was determined spectrophotometrically at 260 nm and the integrity of the DNA was checked by agarose gel electrophoresis (1%) with 1$\times$TAE buffer at 80 V and staining with ethidium bromide (0.5 g/ml).

PCR was performed at a final volume of 25 μl with 100 ng of genomic DNA, 50 pmol of each oligonucleotide of the ACE gene with the following sequences: sense 5'-CTGGAGACCACTCCCATCCTTTCT-3', antisense 5'-GATGTGGCCATCACATTCGTCAGAT-3' (Asamoah *et al.*, 1996), 3 mM $MgCl_2$, 2.5 μl of 10$\times$ buffer (100 mM/l KCl, 100 mM/l Tris-HCl, pH 8.3), 2 μl of the mixture of dNTPs (2.5 mM), 1 U of *Taq* polymerase and 25 μl distilled, deionized water (cbp). Amplification was carried out in a thermocycler (Eppendorff, Mastercycler Gradient) with 30 cycles under the following conditions: 1 min at 94°C for denaturation, 1 min at 58°C for aligning and 2 min at 72°C for extension, and a final extension at 72°C for 5 min. To exclude mistyping of heterozygotes, all DD homozygote samples were confirmed using a pair of specific flanked oligonucleotides for insertion with the following sequences: sense 5'-TGGGACCACAGCGCCCGCCACTAC-3', antisense 5'-TCGCCAGCCCTCCCATGCCCATAA-3' (Shanmugan *et al.*, 1993). PCR products used were similar to the ones used for obtaining I/D except for the time and temperature of alignment, which was 45 s at 67°C. PCR products were electrophoresed in 1% agarose gel and visualized by staining with ethidium bromide. Genotype II was characterized by a 490-bp band, genotype DD by a 190-bp band, and genotype ID by the presence of both bands.

Statistical analysis

Data are presented as mean $\pm$ SD. The Hardy-Weinberg equilibrium was estimated by comparing observed and expected genotype frequencies of ACE gene polymorphism using χ^2. Differences between and within-groups of the continuous variables were analyzed using Student's *t*-test, ANOVA and Tukey's post hoc test, respectively. Nominal variables were analyzed using χ^2. A multiple logistic regression model was used to test the effect of ACE genotypes on the likelihood of MS while controlling the confounding effects of age and gender. The odds ratio (OR) together with the 95% confidence interval (95% CI) for the allelic frequency in the study

Table 1. Clinical and biochemical variables in individuals with and without metabolic syndrome.

Variables	With metabolic syndrome	Without metabolic syndrome
n (%)	245 (47.7)	269 (52.3)
Gender (M/F)	117/128	127/142
Age (years)	57 $\pm$ 7	58 $\pm$ 9
BMI (kg/m^2)	30.0 $\pm$ 3.2*	26.0 $\pm$ 3.0
WC (cm)	102.3 $\pm$ 9.9*	85.1 $\pm$ 8.7
SBP (mmHg)	142 $\pm$ 15*	131 $\pm$ 18
DBP (mmHg)	86 $\pm$ 7*	81 $\pm$ 8
Glucose (mg/dl)	172.4 $\pm$ 55.8*	83.4 $\pm$ 10.7
Total cholesterol (mg/dl)	243.3 $\pm$ 52.6*	210.8 $\pm$ 35.2
Triglycerides (mg/dl)	181.2 $\pm$ 63.6*	136.6 $\pm$ 47.8
HDL-C (mg/dl)	43.5 $\pm$ 10.0*	49.5 $\pm$ 11.1
LDL-C (mg/dl)	153.3 $\pm$ 28.4*	131.5 $\pm$ 26.4

Data expressed as mean $\pm$ SD. Gender is reported in number. n, Number of individuals; M, Male; F, Female. BMI, Body mass index [weight (kg)/height (m^2)]; WC, Waist circumference; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HDL-C, HDL-Cholesterol. LDL-C: LDL-cholesterol. *P $<$ 0.0001.

Table 2. Clinical and biochemical variables in individuals with and without metabolic syndrome analyzed for genotype.

Variables	ACE I/D genotype					
	With metabolic syndrome			Without metabolic syndrome		
	II	ID	DD	II	ID	DD
n (%)	36 (14.7)	111 (45.3)	98 (40.0)	82 (30.5)	144 (53.5)	43 (16.0)
Gender (M/F)	16/20	57/54	44/54	39/43	73/71	15/28
Age (years)	56 ± 9	57 ± 7	58 ± 6	59 ± 9	57 ± 7	57 ± 9
BMI (kg/m^2)	29.3 ± 2.4	29.0 ± 2.7	31.5 ± 3.6*	25.5 ± 2.9	26.2 ± 2.9	25.9 ± 3.4
WC (cm)	99.2 ± 10.9	100.3 ± 8.3	105.6 ± 10.3*	84.2 ± 8.2	85.4 ± 8.8	85.9 ± 9.6
SBP (mmHg)	139 ± 12	141 ± 14	146 ± 16	129 ± 17	132 ± 18	131 ± 21
DBP (mmHg)	85 ± 8	86 ± 6	87 ± 8	79 ± 8	82 ± 8	82 ± 9
Glucose (mg/dl)	164.5 ± 51.7	161.9 ± 50.3	187.3 ± 59.6*	83.6 ± 10.3	82.6 ± 11.5	84.3 ± 11.2
Total cholesterol (mg/dl)	228.9 ± 32.5	232.9 ± 47.0	260.5 ± 59.8*	213.4 ± 32.2	210.1 ± 38.8	207.5 ± 24.1
Triglycerides (mg/dl)	159.4 ± 34.8	171.0 ± 45.8	200.7 ± 81.9*	127.0 ± 34.8	140.7 ± 48.4	141.4 ± 66.7
HDL-C (mg/dl)	48.4 ± 12.0	44.8 ± 10.0	40.3 ± 8.1*	49.8 ± 11.4	49.1 ± 10.6	49.8 ± 13.2
LDL-C (mg/dl)	141.7 ± 18.0	148.0 ± 27.4	164.0 ± 29.6*	130.9 ± 27.4	130.9 ± 27.4	128.7 ± 21.7

Data expressed as mean ± SD. Gender is reported in number. n, Number of individuals; M, Male; F, Female; BMI, Body mass index [weight (kg)/height (m^2)]. WC, Waist circumference; SBP, Systolic blood pressure; DBP, diastolic blood pressure; HDL-c, HDL-cholesterol; LDL-c, LDL-cholesterol; II, Insertion/Insertion; ID, Insertion/Deletion; DD, Deletion/Deletion. * $P < 0.01$.

Table 3. Distribution of ACE genotype and allele frequencies in the individuals with and without metabolic syndrome.

Variable	With metabolic syndrome (*n* = 245)	Without metabolic syndrome (*n* = 269)
Genotypes		
II	36 (14.7)*	82 (30.5)
ID	111 (45.3)	144 (53.5)
DD	98 (40.0)*	43 (16.0)
Alleles		
I	183 (37.3)	308 (57.2)
D	307 (62.7)*	230 (42.8)

Data are *n* (%). II, Insertion/Insertion; ID, Insertion/Deletion; DD, Deletion/Deletion. * $P < 0.0001$ compared with individuals without MS.

Table 4. Association of metabolic syndrome and polymorphism, adjusted by gender and ege.

Genotype ratio	Adjusted Odds	95% CI	
		Lower limit	Upper limit
DD *	5.48	3.20	9.38
ID **	1.79	1.12	2.87

The II genotype was considered as reference. *$P < 0.0001$; **$P = 0.01$.

groups were calculated. A value of $P < 0.05$ was considered statistically significant. SPSS software v.10.0 for Windows (Chicago, IL) and Stata software 8.0 special version (College Station, Texas), were used to perform statistical analyses.

Results

A total 514 subjects was included, 245 patients with MS and 269 without MS criteria. Among the patients with MS, type 2 diabetes was found in 190 (77.6%), hypertension in 155 (63.3%), obesity in 138 (56.3%), and dyslipidemia in 90 (36.7%). In the subjects without MS, type 2 diabetes was found in 5 (1.9%), hypertension in 65 (24.2%), obesity 37 (13.8%), and dyslipidemia in 11 (4.1%).

Table 1 shows the clinical and biochemical variables in individuals with and without MS. Patients with MS were significantly different from subjects without MS in relation to the mean BMI, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose, total cholesterol, triglycerides, HDL-C, and LDL-C ($P < 0.0001$). Differences in the mean BMI, WC, glucose, total cholesterol, triglycerides, HDL-C, and LDL-C, were maintained in patients with MS and the DD genotype in comparison with patients with

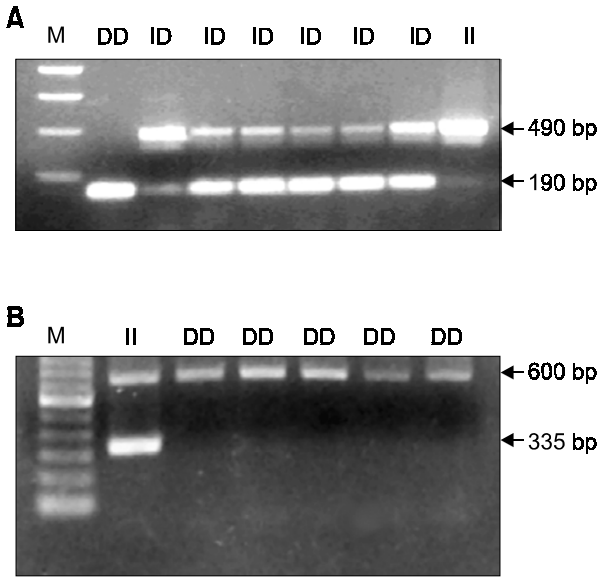

Figure 1. (A) Individuals homozygous for the D allele (DD genotype) were identified by the presence of a single 190 bp product. Individuals homozygous for the I allele (II genotype) were identified by the presence of a single 490 bp product. Heterozygous individuals (ID genotype) were identified by the presence of both the 190 bp and the 490 bp products. M = 1 kb marker Benchtop, Promega. (B) The II homozygous state was identified by the presence of the 335 bp product. M = 100 bp marker Invitrogen.

MS and either the II or ID genotypes of ACE gene polymorphism ($P < 0.01$, Table 2).

Table 3 shows the distribution of the ACE genotype and allele frequencies in individuals with and without MS. The DD genotype (40.0% *vs* 16.0%, $P < 0.0001$) and the D allele (62.7% *vs* 42.8%, $P < 0.0001$) were significantly more frequent in patients with MS than without MS. In contrast, the II genotype (30.5% *vs* 14.7%, $P < 0.0001$) was more frequent in subjects without MS than with MS. The distributions of the ACE genotypes observed were in agreement with the Hardy-Weinberg equilibrium. Table 4 shows the multiple logistic regression model adjusting for the confounding effects of gender and age. The results revealed a strong association of the DD genotype with MS (adjusted OR 5.48, 95% CI 3.20-9.38, $P < 0.0001$). These results indicate that subjects with the DD genotype have an increased susceptibility for developing MS. Figure 1 shows representative gel images of the ACE gene.

Discussion

We examined the relationship between ACE gene polymorphism in 245 patients with MS and 269 subjects without MS using the ATP III criteria with modification in the IFG criteria in accordance with the American Diabetes Association's (Grundy *et al.*, 2004).

Our study reveals that the DD genotype is strongly associated with an increased susceptibility to MS as an entity. To our knowledge this is the first study that shows a relationship between ACE gene polymorphism with MS in a Mexican population. Our results are in accordance with a previous study in other populations (Lee *et al.*, 2002) that has shown that the DD genotype confers an increased risk for MS. In a large Chinese population-based study with type 2 diabetes using the 1998 World Health Organization (WHO) criteria for diagnosis of MS, the DD genotype was associated with increased risks for MS, dyslipidemia, and albuminuria. In contrast, in other studies (Costa *et al.*, 2002) performed in a Brazilian population of European ancestry self-classified as white with type 2 diabetes and MS using the WHO criteria, an association between ACE gene I/D polymorphism and MS was not found. The reasons for this discrepancy is not known. One possible explanation is ethnic differences. It is well known that the allele frecuency of ACE gene polymorphism varies according to ethnic group (Barley *et al.*, 1994). The DD genotype is more frequent in a Caucasian population than in an Asian population. In the Mexican population, mestizas comprise 80% of the total, with 20% corresponding to Mexican Indian groups and a reduced group (less than 1.0%) of a white population formed by inmigrant Europeans (mainly Spanish) and North-Americans (from the United States of America and Canada). A Mexican mestizo has been defined by the National Institute of Anthropology as a person who was born in the country, has a Spanish-derived last name, and a family of Mexican ancestors of at least three generations (Gorodezky *et al.*, 2001). Our results support this hypothesis because a high prevalence of the DD genotype has been reported in previous studies in a Spanish population with nephropathy (Ortiz *et al.*, 2003). Another explanation may be related to possible interactions with other genes or enviromental factors, although further study is necessary to verify this explanation. Previously, Zhu *et al.* (2003) performed genotyping of single-nucleotide polymorphisms in the RAS genes ACE, angiotensinogen (AGT) angiotensin II receptor, subtype 1 (AGTR1), and renin in a biracial population sample. Evidence was found that inter-individual variation in the RAS genes contributes to a hypertension risk. Marre *et al.* (1997) studied the contribution of genetic polymorphism in RAS to the development of renal complications in insulin-dependent diabetes in a European population.

It is difficult to provide explanation of a mecha-

nism by which ACE gene polymorphism promotes susceptibility to MS. One possible explanation is related to participation of RAS in the components of MS. It is generally accepted that RAS participates in the long-term complications of diabetes (Gilbert *et al.*, 2003) and previous findings have reported an association of the DD genotype with the development of type 2 diabetes in several populations (Feng *et al.*, 2002; Lee and Tsai, 2002; Ergen *et al.*, 2004).

We found that patients with the MS and DD genotypes were associated with obesity. These results are interesting because of the strong association between RAS and the mechanisms of obesity. Obesity leads to hypertension and increases the cardiovascular risk (Mikhail *et al.*, 1999). RAS has been implicated in obesity by several authors (Giacchetti *et al.*, 2002), which is supported by recent investigations that show high plasma concentrations of angiotensinogen (ANG) (Umemura *et al.*, 1997) and a rise in the expression of the ANG gene in obese humans (Van Harmelen *et al.*, 2000). The plasma ANG decrease was highly correlated with the WC decline and with one reduction in the systolic ambulatory blood pressure (Engeli *et al.*, 2005). These data suggest that a reduction in body weight can lead to a reduced RAS in plasma and adipose tissue. In addition, targeted expression of 11 β-hidroxyesteroid dehydrogenase-1 (11-β-HSD1) in adipocytes and a direct relationship with obesity have been recently reported. In adipocytes, 11-β-HSD1 caused an increased plasma AGT level and increased blood pressure. In adipose tissue, the AGT gene was expressed in mice with a wild-type generic background (Alsaeid *et al.*, 2004). Higher ACE activity in obese individuals and a decrease in ACE activity with weight loss have been described previously (Keidar *et al.*, 1994) as has the DD genotype predicting central obesity and an increase in body weight and blood pressure with aging in men (Keidar *et al.*, 1996). The DD genotype has influence on blood pressure and body weight.

Dyslipidemia in MS is characterized by an increase in triglycerides, LDL-C, and low HDL-C. These alterations contribute to an increase in the risk for CVD in individuals with MS. We found a relationship between dyslipidemia and ACE gene polymorphism with the DD genotype in patients with MS. This is related to previous studies that identified the DD genotype in patients with type 1 (Masuzaki *et al.*, 2003) and type 2 diabetes (Lee and Tsai, 2002), showing the important role of RAS as a likely contributor to MS. Experiments *in vitro* have suggested that ANG participates in the growth, development, and metabolic functioning of fatty tissue once it is converted into Ang II, which connects specifically to LDL-C (Harp *et al.*, 2002) and produces another modified form of LDL-C that is captured by the macrophage. This provokes an accumulation of cholesterol (Strazzullo *et al.*, 2003).

Other possibility that may have significant clinical implications is the insulin resistance (IR) that appears to be a central feature of this syndrome associated with type 2 diabetes, obesity, dyslipidemia, hypertension, and recently with hypercoagulability, inflammation, atherosclerosis, and CVD (Dandona *et al.*, 2002; Festa *et al.*, 2002; Doelle, 2004). RAS has been implicated in IR as RAS inhibits the metabolic actions of insulin and promotes its proliferative effects for cellular interactions with the signal transduction pathways. These pathways include the phosphatidylinositol 3 and MAPK pathways that are dependent on tyrosine phosphorylation of insulin receptor sustrates 1 and 2 after binding to their respective receptors (Prasad and Quyyumi, 2004). However, the principal relationship between IR, ACE plasma levels, and the DD genotype in patients with MS requires more study in this and other populations.

In conclusion, we present evidence that the DD genotype of the ACE gene increases susceptibility to the MS entity in a Mexican population, providing genetic evidence of MS components in the Mexican population and an increased risk for CVD. These results indicate that pharmacological and non-pharmacological treatment and a reduction of body fat will have important therapeutic implications for this disease.

Additional studies will be necessary for investigating the association between the ACE gene and energy metabolism, vascular disregulation, the proinflamatory state, the prothrombothic state, and hormonal factors.

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