Original Article

Association between the *Xba* I polymorphism of *APOB* gene and plasma lipid level in Mexican patients with coronary artery disease

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Some studies, that consider polymorphisms of the apolipoprotein B (*APOB*) gene as risk factors for coronary artery disease (CAD), have reported discordant results. The aim of the present study was to search for associations between plasma lipid profiles with the DNA *Xba* I polymorphism of the *APOB* gene in CAD patients diagnosed by angiography (CAD+). In the present study we compared 114 Mexican patients (80 men and 34 women) with CAD+ and 132 control patients (59 men and 73 women) without evidence of ischemia or arterial damage (CAD-). The frequency of *X+/X+* genotype of *Xba* I polymorphism, in CAD+ group, was 23% (26/114) compared with 8% (11/132) in the CAD- (OR 3.25, $p = 0.002$). The patients with *X+/X+* for the *Xba* I genotype *APOB* gene had higher concentration of triglycerides (TG) and VLDL in plasma than CAD- ($p < 0.05$). The genotype *X+/X+* in the CAD had an effect increasing the TG and VLDL plasma levels when compared with individuals with *X-/X-* and *X-/X+* genotypes. The present study indicated that the *X+X+* genotype of *Xba* I polymorphism is associated with CAD+ patients and high plasma levels of TG and VLDL, in the Mexican population.

Key Words: apolipoprotein B, cholesterol, polymorphism, plasma lipids, Mexican

INTRODUCTION

The constituent lipids of the human body are mainly phospholipids, cholesterol, triglycerides (TG) and cholesteryl esters; they are transported through blood forming lipoprotein complexes of lipids and one or more proteins, called apolipoproteins, and are under a continuous synthesis/degradation turnover. Low density lipoprotein (LDL) is the product of metabolism of very low density lipoprotein (VLDL), and LDL is built by 75% lipid (cholesteryl esters and cholesterol) and remaining 25% protein. Increased LDL levels are associated with cardiovascular disease.[1] It is known that dyslipidemia results from interactions between genetics and environmental (particularity diet, exercise and tobacco smoking) factors, in different populations. The biological, genetics and diet risk factors, may explain the differences in the coronary artery disease (CAD) risk in several populations. It has been observed that there exist factors in the diet that can be altering the lipids concentrations such as: high concentration of lipids, low ingest of vegetables and fruits.[2]

APOB is essential in the maintenance of cholesterol homeostasis, and is the major protein element of LDL. It serves as the ligand for the recognition and catabolism of plasma LDL by LDL-receptor.[3] Elevated levels of serum APOB are associated with an increased risk of premature atherosclerosis.[4] APOB circulates in two distinct forms (apoB100 and apoB48), encoded by a single gene

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Manuscript received 3 February 2011. Initial review completed 16 November 2011. Revision accepted 26 December 2011.

localized in chromosome 2 p23-25. ApoB100, the larger form, is synthesized in the liver as a translational product of the entire *APOB* mRNA.[5]

The smaller form, apoB48, is produced from the small bowel by a novel posttranscriptional RNA editing a CAA (glutamine) to a UAA (stop) codon in *APOB* mRNA.[5] Thus, apoB48 terminates at amino acid residues 2153 and consists of the N-terminal 48% of apoB100. ApoB48 lacks the C-terminal domain of apoB100. As a result, it does not bind to the LDL-receptor .[1] Different polymorphisms in the *APOB* gene have been identified, and some of them have been associated with total cholesterol, LDL cholesterol, high density cholesterol (HDL) and VLDL cholesterol levels.[6-10]

The restriction fragment length polymorphism detected with the restriction enzyme *Xba* I, represents a synonymous variation in the coding region of the *APOB* gene, located within exon 26 of the gene, at the 2,488th nucleotide (ACC_ACT). The substitution of cytosine by thymine, which does not change the amino sequence, creates an *Xba* I restriction site that characterize the *X+* allele, and conversely its absence determines the *X-* allele.[6,11] There are polemical studies that have reported the allele lacking the *Xba* I site (*X-*) and/ or its homozygous genotype (*X-/X-*) as more frequent in survivors of myocardial infarction and in patients with CAD than in controls (12). However other reports correlated the allele X+ with CAD patients.[13-14] In the present study, the *APOB* alleles detected with the *Xba* I restriction enzymes were examined for association with CAD by evaluating their frequency distributions in patients with CAD (CAD+) and compared to patients with the confirmed absence of this disease (CAD-).

MATERIAL AND METHODS

Study population

A total of 114 (80 men and 34 women) CAD+ patients and 132 control patients (59 men and 73 women) without ischemia or arterial damage (CAD-) were diagnosed by coronary angiography at the Servicio de Cardiología, Hospital de Especialidades, Centro Médico Nacional de Occidente (CMNO), Instituto Mexicano del Seguro Social (IMSS), Guadalajara, Jalisco; México.

The CAD+ group comprised patients with recurrent acute ischemic syndrome and angiographically proven CAD (with at least one coronary stenosis with ≥50% of narrowing of the luminal diameter). The CAD- group comprised consecutive patients being catheterized for clinical reasons and presenting non-cyanogenic congenital cardiopathy or valvulopathies. All patients in the CAD- group had angiographically normal coronaries. All coronary angiograms were analyzed visually by two experienced interventional cardiologists according to conventional American Heart Association methods.

All participants in the study signed the consent form. This study was approved by the Ethics Committee of the Centro de Investigación Biomédica de Occidente, CMNO, IMSS, Guadalajara, Jalisco; México.

Whole blood (5 ml) was collected without anticoagulant and the serum was used for the determination of lipids and lipoproteins. The blood sample was taken after 12 hour of fasting. The levels of total cholesterol (TC) and TG were obtained by an enzymatic procedure (Roche Diagnostic GmbH, Mannheim, Germany) using a Cobas Mira S autoanalyzer (Roche). HDL-cholesterol (HDL) was measured by an enzymatic method (Roche) in the supernatant after precipitation with phosphotungstate-MgCl2 (Roche). LDL-C (LDL) levels were estimated by the method of Friedewald *et al.*[15]

Determination of DNA polymorphism

Genomic DNA was extracted from peripheral blood samples (4ml with EDTA anticoagulant) according to standard protocols.[16] The presence of *X-* allele in exon 26 of the *APOB* gene was determined by PCR amplification in a total volume of 15 µL containing 200 µM dNTPs, 1 pmol of primers, 1.5 mM $MgCl_2$ and 2.5 U *Taq* polymerase. The primers were 5′-GGAGACTATTCAG AAGCTAA-3′ and 5′-TCAGTCAGAAGTCCGAGAAG-3′. These primers amplify the exon 26 of the human a*poB* gene, yielding a 710-bp fragment. Cycling conditions consisted of an initial melting temperature of 94°C (4 min), followed by 35 cycles of melting (94°C, 1 min), annealing (58°C, 3 min), and extension (72°C, 3 min). The amplified product was subjected to restriction enzyme analysis with *Xba* I (New England Biolabs, Beverly, MA), according to the manufacturer's instructions. The PCR products were separated by electrophoresis using 6% polyacrylamide gels (29:1), followed by silver staining. The wild-type allele (*X-*) produced a single 710-bp fragment, while the mutant allele (*X+*) produced 433-bp and 277- pb fragments.[17]

Statistical analysis

Differences in means values between CAD patients and control group were analyzed by Student t-test and present as means ± standard deviation (SD), chi-square test was used to compare discrete variables. Allelic frequencies were calculated by gene counting. Comparison of observed and expected genotypes was analyzed by Hardy-Weinberg equilibrium. The means and standard deviations of plasma level lipids were analyzed by parametric analysis, to determine differences using an independent sample t-test and a two-way ANOVA. The odds ratio (OR) was calculated as a measure of relative risk. A multivariate logistic regression was performed considering CAD as dependent variable and the following independent variables: *Xba I* genotypes, gender, hypertension, tobacco consumption, TC, and TG. For this analysis numbers were assigned to the variables (CAD- = 0, CAD+ = 1; female = 0, male = 1; absence of hypertension = 0, presence = 1; absence of tobacco consumption = 0, presence = 1). The *Xba* I genotypes were classified as *X+/X+* (= 1) and other genotypes as 0. TC and TG were classified as 0 when plasma levels were below to 200 mg/dL and 150 mg/dL, respectively, and as 1 when plasma levels were equal or over to 200 mg/dl for TC and 150 mg/dL for TG. HDL was classified as 1 when plasma levels were below 35 mg/dL, and as 0 when they were equal or over 35 mg/dL. LDL was classified as 0 when plasma levels were below 100 mg/dL, and as 1 when plasma levels were equal or over 100 mg/dL. VLDL was classified as 0 when plasma levels were below 26 mg/dL, and as 1 when levels were equal or over. A *p*-value of less than 0.05 is consid-

Table 1. Characteristic of the study groups

	CAD+ (n=114)			CAD- (n=132)		
	Male (n=80)	Female (n=34)	*p*-value	Male (n=59)	Female (n=73)	*p*-value
Characteristics						
Age (years)± SD	64.0±9.5	62.6±10.8	0.509 ‡	55.3±5.8	54.8±5.8	0.580‡
Arterial hypertension						
Yes (%)	41 (51)	18 (53)	0.516 †	13 (22)	15 (21)	0.830 †
No (%)	39 (49)	16 (47)		46 (78)	58 (79)	
Diabetes mellitus						
Yes	39 (49)	12 (35)	0.22 †	17 (29)	18 (25)	0.690†
No	41 (51)	22 (65)		42 (71)	55 (75)	
Smoking habit						
Yes	55 (69)	21 (62)	0.51 †	35 (59)	29 (40)	0.035†
No	25 (31)	13 (38)		24 (41)	44 (60)	
TC (mg/dL)	183±38.3	179±43.6	0.60 ‡	186±42.5	180±42.0	0.370 ‡
TG (mg/dL)	188±86.1	182±103	0.73 ‡	119±69.9	104±43.0	0.137 ‡
HDL (mg/dL)	36.6±13.3	38.5±10.4	0.44 ‡	51.0±45.5	26.8±15.3	0.140 ‡
LDL (mg/dL)	105±39.8	94.4±36.8	0.17 ‡	115±36.0	113±40.5	0.704 ‡
VLDL (mg/dL)	38.5±18.1	38.6±22.1	0.97 ‡	23.8±5	20.9±8.1	0.125 ‡

Total cholesterol (TC), triglycerides (TG), High Density Lipoprotein-cholesterol (HDL), Low Density Lipoprotein-cholesterol (LDL), Very Low Density Lipoprotein (VLDL)t, †Fisher's exact test, ‡Student's *t-test*, SD, standard deviation

Table 2. *Xba I* genotype frequency and their interaction with lipid levels in CAD+ and CAD- patients

Genotypes	CAD+	CAD-	CAD+ vs. CAD-		
	n (%)	*n* (%)	OR	(95% CI)	*p value*
X-/X-(reference) †	57 (50)	59 (45)	1.00		
X+/X- †	31 (27)	62 (47)			
X+/X+	26 (23)	11 (8)	3.25	(1.45-7.6)	0.002
Allele					
X-	145 (64)	180 (68)			0.32
X+	83 (36)	84 (32)			0.32

	CAD+ (mean±SD) mg/dL			CAD- (mean±SD) mg/dL			*p* value
X+/X+							
TC	183.8	±	36.6	176.2	±	41.2	0.580
TG	212.2	±	112.4	110.2	±	28.5	0.006
LDL	38.1	±	10.7	42.5	±	8.31	0.240
HDL	94.2	±	34.9	121.6	±	48.1	0.060
VLDL	47.1	±	25.7	21.9	±	5.5	0.002
X+/X-							
TC	178.1	±	37.28	188.0	±	38.3	0.154
TG	183.5	±	85.95	113.0	±	57.2	0.000
LDL	37.2	±	14.75	52.0	±	27.3	0.000
HDL	98.9	±	37.12	113.7	±	36.3	0.031
VLDL	37.99	±	17.27	22.2	±	11.4	0.000
X-/X-							
TC	188.0	±	46.8	178.1	±	45.8	0.332
TG	170.3	±	78.3	108.5	±	59.7	0.000
LDL	36.3	±	9.2	44.8	±	13.9	0.003
HDL	114.2	±	44.1	112.8	±	39.2	0.874
VLDL	32.4	±	14.8	22.3	±	11.3	0.001

†This reference category combined the two genotypes, because the odds ratio (OR) showed and equal risk for each group. CI: confidence interval

ered statistically significant. All tests were performed using the SPSS version 11 (Chicago IL) for windows.

RESULTS

The characteristics of the CAD+ and CAD- groups, stratified by gender are listed in Table 1. The two groups contained middle-aged participants [mean in male 64.0±9.5 and female 62.6±10.8 in CAD+ group (p=0.509), and 55.3±5.8 and female 54.8±5.8 in CAD- group (p=0.580)]. The tobacco smoking status was significantly different (p=0.035) in the CAD- group stratified by gender.

The *APOB Xba* I genotypes of the study groups are

shown in the Table 2(up). The frequency of genotype *X+/X+* genotype was 8% (11/132) among CAD-, and 23% (26/114) among the CAD+. The CAD+ patients showed a significantly higher frequency of *X+/X+* genotype, with an OR of 3.25 (95% CI=1.44-7.4; p=0.002).

The CAD+ patients with the *X+/X+* genotype had statistically significant higher TG (212±112), and VLDL (47.2±25.1), than CAD- (110±28.6 and 21.9±5.59 respectively) (p<0.05). When the *X-/X-* participants was compared between the study groups we observed statistical significance in TG, LDL and VLDL levels (p<0.05) among CAD+ and CAD- participants. We also observed significant differences in TG, LDL, HDL and VLDL levels (p<0.05) between CAD+ and CAD- participants with the *X+/X-* genotype (Table 2(low)).

In the analysis of CAD+ and CAD- together with *Xba* I genotype association, we observed that, those individuals with *X+/X+* genotype had higher levels of TG (182±106) and VLDL (39.6±24.1) than those individuals with genotypes *X-/X-* and *X-/X+* (140±77.3 and 28.0±15.3) respectively (p<0.05) (Table 3).

The multivariable logistic regression analysis which considered gender as the dependent variable in the CAD+ and CAD- groups, showed as risk factor de both LDL level in CAD+ group with OR of 3.39 (95%CI=1.23-8.8; p=0.017) and tobacco in CAD- group with OR of 2.43 (95%CI=1.1-5.4; p=0.030) .

DISCUSSION

CAD is a multifactorial disease that may differ in each race or ethnic population. This way the prevalence of CAD vary widely among different population, and the frequencies of the *APOB* gene polymorphisms have been reported to vary among ethnics groups.[18] Thus, we investigated the association of plasma lipid levels with polymorphism *Xba* I of the *APOB* gene in Mexican CAD patients. Tobacco consumption, the conventional risk factor, was significantly different in our patients with CAD+ compared with the CAD- group by gender (p<0.05).

APOB mutations might affect the plasma lipid responses or the plasma APOB concentrations during dietary modifications by altering APOB secretion, structural stability, affinity for the LDL receptor, or interactions of APOB-containing lipoproteins with other lipoproteins, cells or enzymes. The physiologic role of the *APOB Xba I* polymorphism in the codon 2488 in exon 26 is still unclear, but it has been observed that this polymorphism may be associated with the Ag system, as well as with serum APOB, cholesterol, and TG levels in different studies.[19] The Ag systems are based on antigens a1/d, c/g, h/i, t/z, and x/y, which appeared to be products of five closely linked allele pairs. Different combinations of Ag system have been associated with serum lipid levels. It has also been observed that the changes in the polarity of the amino acids, in the protein structure and its relation to function, can influence the molecular function of the protein in lipid metabolism.[19-20]

The polymorphism alters plasma lipid concentrations[21-23] and LDL catabolism even though it does not alter the amino acid sequence. In our study, the genotype distribution of the CAD group showed association between the CAD+ group in comparison with the CAD- group (p<0.05). These data are in accordance with some previous studies where the *X+* allele was associated with CAD.[13-14]

The lipid profile of the CAD+ group was more atherogenic than that of the CAD- group. It has been postulated that a high plasma TG concentration together with small dense LDL particles are associates with premature CAD,[24-29] the atherogenic LDL particles originating from VLDL. An increase in total TG, a decrease in HDL cholesterol levels and an association of elevated total, LDL cholesterol and TG and low HDL cholesterol with the increasing extension of CAD have been reported. A lowering of VLDL cholesterol and TG been reported to be associated with a slowing down of the progression of coronary atherosclerosis in young AMI survivors.[28-30]

Our study confirms the earlier associations between the presences of the *Xba* I cutting site and the elevated TG levels, and part of the effect might be due to the slightly lower LDL catabolic rate in the individuals with the *Xba* I cutting site. It has been demonstrated that the *Xba* I polymorphism modifies dietary fat and cholesterol responses in individuals with the *Xba* I cutting site. This individuals are more responsive to a low-fat, low cholesterol diet than those lacking the cutting site.[6-15] This could, in part, explain the differences in the lipoprotein composition associated with the *Xba* I polymorphism.

When the CAD+ and CAD- participants were classified by genotype, it was observed that these with genotype *X+/X+* had low levels of LDL and higher levels of VLDL than those with heterozygote and *X-/X-* genotypes. A possible explanation is that in the presence of the X+/X+ genotype, statin treatment has major effect on the LDL particle; however the VLDL particles remain high, probably due to this polymorphism because this gene may play an important role in the mechanism of drug action. Then the cardiovascular damage could be the VLDL endothelium accumulation. Very low density lipoprotein receptors have been shown to be expressed *in vivo* in vascular endothelium as well as in foam cells in atherosclerotic plaques.[31] These receptors are markedly upregulated during atherogenesis in rabbits. By its affinity for lipoproteins, lipoprotein lipase, the VLDL receptor

Table 3. Plasma lipid (mean±SD) of CAD (+ and-) by *XbaI* genotypes

	X+/X+ (n=37)	*X+/X- and X-/X-*(n=209)	*p*-value
	Mean±SD(mg/dL)	Mean±SD(mg/dL)	
TC	182±37.9	183±41.6	0.897
TG	182±106.0	140±77.3	0.004
LDL	39.4±10.1	43.6±19.6	0.211
HDL	102±40.6	110±38.8	0.306
VLDL	39.6±24.1	28.0±15.3	<0.001

may therefore serve an important function in regulating metabolic processes relating to lipid homeostasis, atherogenesis, and hemostasis.[31]

We would like to point out that in our study, we did not consider the nutritional status of the patients; however it is well known that the Mexican diet is rich in lipids and deficient in bran and vegetables.

In conclusion, the results of this study suggest that, at least in the Mexican population, the *APOB Xba* I polymorphism of the *APOB* gene is to be a useful marker for CAD patients.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Norma Patricia Esquivel Vázquez for sample support. Financial support of this work was provided by Centro de Investigación Biomédica de Occidente, IMSS

AUTHOR DESCLUOSURES

The manuscript has been seen and approved by all of the authors. There is no conflict of interest with regards to this manuscript.

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罹患冠心病的墨西哥患者之脂蛋白酶元 B 基因 *Xba* I 多型性與血脂濃度的相關性

有些研究認為脂蛋白酶元 B(APOB)的基因多型性為冠狀動脈疾病的危險因子，但其研究結果並不一致。而此研究的目的在於尋找出由血管攝影診斷有冠心病的患者，其脂蛋白酶元 B 基因上的 *Xba* I 多型性與血脂的相關性。在此研究中比較 114 位(80 位男性；34 位女性)罹患冠心病(CAD+)的墨西哥患者與 132 位(59 位男性；73 位女性)沒有心肌缺血及動脈損傷的控制組(CAD-)。在患有冠心病的組別，其 *Xba* I 多型性的基因型為 *X+/X+*的比例為 23%，而控制組為 8% (OR=3.25；p=0.002)。在 *Xba* I 基因型為 *X+/X+*的 CAD+患者相較於控制組，有較高的血漿三酸甘油酯以及極低密度脂蛋白(VLDL)(p<0.05)。當與基因型為 *X-/X-*或 *X-/X+*的冠心病患者比較時，*X+/X+*基因型的 CAD+患者，顯現較高的血漿三酸甘油酯及極低密度脂蛋白濃度。本研究指出在墨西哥族群中，*Xba* I 的基因型為 *X+/X+*者，與冠心病患者的高濃度血漿三酸甘油酯和極低密度脂蛋白具有相關。

關鍵字：脂蛋白酶元 B、膽固醇、基因多型性、血脂、墨西哥人