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Influence of *CYP1A1*2C* on High Triglyceride Levels in Female Mexican Indigenous Tarahumaras

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Background and Aims. High triglyceride levels are closely related to cardiovascular disease. Its development lays on age, diet, physical activity, ethnicity and genetic factors. Among the last, the *CYP1A1*2C* allele has an influence on the metabolism of cholesterol and other fatty acids. We undertook this study to determine the frequency of *CYP1A1*2C* and its association with triglyceride levels in Mexican indigenous Tarahumaras and Tepehuanos.

Methods. Anthropometric and biochemical data were recorded. Genotyping of *CYP1A1*2C* by RT-PCR was done in 110 Tepehuano, 69 Tarahumara and 64 Mestizo.

Results. Significant differences in age, waist diameter, BMI, creatinine, glucose, cholesterol, triglycerides, HDL and VLDL measurements were found between Tarahumaras and Tepehuanos ($p < 0.05$). Additionally, Tarahumara women showed the highest values of waist diameter, BMI and triglycerides ($p < 0.05$). It was found that Tarahumaras showed a significant association between high triglyceride levels and *CYP1A1*2C* allele (OR = 2.57; 95% CI 1.12–5.88, $p = 0.024$) under a recessive inheritance model. However, the Tepehuano group showed a significant protective association between normal triglyceride levels and *CYP1A1*2C* polymorphism (OR = 0.28; 95% CI 0.10–0.80, $p = 0.015$) following a dominant inheritance model. The same pattern was observed after analysis with females of both ethnicities.

Conclusion. A significant association between *CYP1A1*2C* and high triglyceride levels in Amerindian Tarahumaras from Chihuahua has been found; this allele was significantly associated with normal triglyceride levels in Tepehuanos from Durango, Mexico. Further studies are needed to elucidate the genetic role of *CYP1A1* in cardiovascular disease susceptibility.

Key Words: High triglyceride levels, Tarahumaras, Tepehuanos, *CYP1A1*.

Introduction

Because the liver plays a fundamental role in the synthesis and transport of fatty acids, it can be associated with triglyceride disorders. Hypertriglyceridemia is a frequent lipid disorder, which can be defined as an abnormal increase of triglyceride concentration in the blood (1). Primary hypertriglyceridemia has a genetic etiology and is inherited. Secondary hypertriglyceridemia, on the other hand, has underlying causes such as diabetes or alcoholism. A study revealed that primary and secondary hypertriglyceridemia are often associated with other lipid abnormalities (2). High triglyceride levels are compelling factors of atherogenic dyslipidemia and can increase cardiovascular risk (3).

Hypertriglyceridemia, abdominal obesity along with a large waist, genetics, low metabolism, null physical activity, a diet rich in saturated fat and very high caloric content and

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ethnicity are important risk factors for cardiovascular disease (4,5).

The enzyme CYP1A1 plays an important role in the metabolism of cholesterol and other fatty acids such as arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (6). CYP1A1 acts both as an epoxygenase and ω-1 hydroxylase when converting EPA in 17(*R*), 18(*S*) enantiomers of epoxyeicosatetraenoic acid (17[R]-EETeTr, 18[S]-EETeTr), and 19-OH-EPA metabolites (7,8). CYP1A1 exclusively epoxidizes the ω-3 double bond of EPA and produces 19,20-EDP (9). Furthermore, important contributions of CYP1A1 in the production of signalling and vasoreactive molecules from fatty acids and steroids have been described (10). This suggests that allelic variants of CYP1A1 may affect triglyceride concentrations.

A number of *CYP1A1* allelic variants have been associated with a higher inducibility and/or activity of the enzyme. Among these, *CYP1A1**2C (2455A > G rs1048943, Ile462Val) affects EPA metabolism by altering both, the catalytic efficiency and region specificity of the enzyme (8). Furthermore, CYP1A1*2C has been associated with a 6- to 12-fold higher hydroxylation capacity that forms 17β-estradiol and estrone (11).

Lipid-associated diseases are among the leading causes of morbidity and mortality worldwide. Those conditions have reached populations traditionally considered as healthy such as indigenous groups in Mexico. The ethnic group Tarahumara lives in a mountainous region of Chihuahua in the north of Mexico and represents the second largest Amerindian group in the country (12). Recently, an increase in migration rate to larger settlements because of harsh environmental, social and economic conditions have forced Tarahumaras to adopt a more westernized lifestyle (12,13).

Similarly, the Southern Tepehuano group is also settled in the mountainous region of Durango, Mexico and as happened with Tarahumaras, they have adopted a mestizo lifestyle (14). Thus, this study aimed to investigate the frequencies of *CYP1A1*2C* in Tarahumaras and Tepehuanos and their association with triglyceride levels.

Materials and Methods

Study Subjects and Definitions

We conducted a descriptive and association study including 69 Tarahumara volunteers from ‘‘Choguita’’ community in Chihuahua State and 110 volunteers from the South Tepehuano group with residence in ‘‘Duraznitos’’ community from El Mezquital, Durango and 64 rural Mestizo volunteers from Llano Grande town belonging to the Durango municipality in the state of Durango in the north of Mexico. Moreover, the Amerindian ancestry of the studied groups was confirmed through the analysis of 15 short tandem repeats (STRs) loci (15). This study was approved by the local Ethics Committee of the Hospital General de Durango, Durango, Mexico. All volunteers were thoroughly informed of the study and provided written consent. A questionnaire including dietary habits, alcohol and smoking consumption was applied to all participants. Due to cultural and language barriers, alcoholism was dichotomically evaluated as positive or negative consumption without considering the amount and frequency of consumption; the same criteria were applied for smoking. Family history and a complete medical evaluation were obtained from each volunteer. Each procedure was carried out by the same trained personnel: questionnaire application, medical history, and blood sampling/processing and genotyping.

Biochemical Testing Measurements

Biochemical profile analyses were performed at the Biomedical Research Institute from Universidad Juarez de Durango, Mexico. Normal values are shown in Table 1. Those measurements were done by enzymatic methods (16).

DNA Extraction and Genotyping

Five mL of peripheral venous blood from each volunteer were collected in an EDTA supplemented tube. Genomic DNA was extracted from whole venous blood using a QIAmp DNA Blood Kit according to the manufacturer's instructions (Qiagen, Hilden, Germany). DNA integrity was confirmed by 1% agarose gel electrophoresis and quantified in a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA). Genotyping was done by semi-quantitative Real Time Polymerase Chain Reaction (qRT-PCR) in a StepOne Real Time PCR system (V.2.2, Applied Biosystems, Foster City, CA) under standard conditions. MGB TaqMan probes were used to identify *CYP1A1*2C* (C_25624888_50) polymorphism (17).

Statistical Analysis

Data are presented as mean ± standard deviation or proportions. Median, maximum and minimum values were also

Table 1. Reference values for biochemical testing measurements (16)

Test	Reference values
Creatinine	0.6–1.3 mg/dL
Glucose	70–105 mg/dL
Cholesterol	0–200 mg/dL
Triglycerides	0–150 mg/Dl
AST	0–41 U/L
ALT	0–40 U/L
LDL	35–100 mg/dL
HDL	35–60 mg/Dl
VLDL	0–35 mg/Dl

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein cholesterol.