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ACE, APOA5, and MTP Gene Polymorphisms Analysis in Relation to Triglyceride and Insulin Levels in Pediatric Patients

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Background and Aims. Obesity is a complex, chronic, and multifactorial disease that has become a major, and worldwide, public health problem contributing to an increased number of pathologies, including type 2 diabetes, cardiovascular disease, hyperlipidemia, and metabolic syndrome, thus suggesting a commolon origin. A diet high in sugar and fats coupled with a sedentary lifestyle has a major role in the development of obesity. However, the genetic background has also been associated with body fat accumulation. The aim of this study was to assess the effect ofACE-rs4646994, APOA5-rs662799, and MTP-rs1800591 gene polymorphisms on clinical and biochemical parameters and to evaluate the association with body phenotypes in children and adolescent population of Saltillo, Coahuila, Mexico.

Methods. Anthropometric, clinical, biochemical parameters and BMI were obtained from 405 children and adolescents. The BMI was used to determine the body phenotype. The rs4646994 gene polymorphism was determined by PCR, whereas rs662799 and rs1800591 were determined by PCR-RFLP. The obtained results were analyzed to determine their association of these single nucleotide polymorphisms with body phenotype and biochemical parameters.

Results. TT genotype for APOA5-rs662799 was associated with increased levels of HDL-C in the analyzed population ($p < 0.05$). The ACErs4646994gene polymorphism is associated with high Insulin levels, HOMAIR index, and triglyceride levels, mainly when presenting a I/I genotype ($p < 0.05$).

Conclusion. The polymorphic allele of the ACE gene is capable of modulating triglyceride levels, insulin levels and HOMA-IR index in the evaluated population; it must be highlighted that this has not been reported in other studied populations elsewhere.

Key Words: Gene polymorphisms, Triglyceride and insulin levels, Mexican population, PCR-RFLP.

Introduction

Obesity has become a major public health problem, with the global prevalence of childhood obesity increasing over the past three decades, especially in developing countries (1,2). In Mexico, obesity has reached epidemic rates, and it is now within the top rank of Latin American countries with the highest percentage of childhood obesity (3).

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There is evidence indicating that the accumulation of body fat has a genetic basis (4), and it is estimated that between 40−75% of the variation in body mass index (BMI) could be attributed to the interaction of multiple susceptibility genes, as well as to behavioral and environmental factors (5). The genetic composition could determine not only how the food is processed, but its influence in related chronic and degenerative diseases, such as diabetes mellitus type 2 (DM2), cardiovascular disease, some types of cancer, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), among other pathologies (6−8), resulting in decreased quality and overall life expectancy of the obese individuals (9).

Currently, more than one hundred genes are associated with obesity (7,10); however, there are still some genes whose participation in the development of this disease is not yet understood. In this regard, the ACE gene (locus 17q23) (11), coding the angiotensin-converting enzyme, allows the production of angiotensin II and thus is a crucial regulator of the Renin-Angiotensin-Aldosterone system, influencing blood pressure homeostasis (12). ACE gene polymorphism I/D (rs4646994) has been associated with the development of cardiovascular diseases, as well as increased adiposity and blood pressure in obese children and adolescents (13).

The APOA5 gene, located within the apolipoprotein APOA1/C3/A4 gene cluster (locus 11q23), is predominantly expressed in hepatocytes and secreted into the bloodstream (14), where its main function is to contain and transport lipids through the blood, thus determining triglyceride levels (TG) (15). Some polymorphisms in this gene (genetic variants) are considered as a risk factor for vascular disease (16), obesity, and dyslipidemia (17−20). The single nucleotide polymorphism (SNPs) rs662799 of the APOA5 gene, one of the most studied polymorphisms of this gene (21), results in a T > C shift at promoter region -1131, modifying promoter activity (22). This SNP has been associated with dyslipidemia in European, Japanese, Chinese, and American populations (14,23). This polymorphism has been associated with high levels of TG and LDL-C, and lower HDL-C levels. However, the relation between this polymorphism and obesity development has been little explored (17,24); until now, the presence of the C allele (SNP rs662799) represents a risk factor in the development of obesity in Chinese child population.

Further, the MTP gene (locus 4q24) encodes the microsomal triglyceride transfer protein, involved in the transfer of triglycerides towards chylomicrons and nascent VLDL (25). Some alterations of this gene have been associated with variation in levels of LDL-Cholesterol and the presence of obesity, metabolic syndrome, non-alcoholic steatohepatitis (NASH), and hyperinsulinemia (26,27). Moreover, the -493G/T polymorphism (rs1800591) could impact NASH syndrome by modulating post-prandial lipemia and lipoprotein metabolism (28), influencing cholesterol absorption and lipid levels (29,30).

The aim of this study was to determine the genotype distribution of ACE-rs4646994 (I/D), APOA5-rs662799 (-1131 T/C,) and MTP-rs1800591 (-493G/T) polymorphisms, and assess the effect of these polymorphisms on clinical and biochemical data, and to evaluate the association with body phenotypes in children and adolescent populations in the state of Coahuila (Mexico).

Methods

Design

A cross-sectional, observational and descriptive study was performed in adolescent population from Saltillo, Coahuila (Mexico) who participated willingly. This study included a background interview as well as biochemical and anthropometric measurements. The study protocol was performed in accordance with the ethical standards, approved by our Institutional Review Board of the University Hospital in Saltillo, and registered under the code 01-2011. Informed consent was obtained from all the participants or their fathers/legal tutors.

Subjects and Classification of Body Phenotypes

A total of 405 adolescents, age range between 11−19 years old and including both genders were analyzed. Subjects who reported in the interview with chronic or endocrine disorders were excluded from the study. Body phenotypes were classified using the standards established by the WHO. The adolescents were divided into 4 groups according to BMI, and *Z* score (BMIz), calculated using percentile boy/girl table BMI for age (5−19 years).

Biochemical Analyzes

The biochemical parameters of glucose, total cholesterol, LDL-C, HDL-C, triglycerides, and insulin, were determined from 5 mL of peripheral blood samples extracted from the participants after a 12 h fast. These biochemical values were used to calculate the homeostatic model assessment for Insulin Resistance (HOMA-IR) and the atherogenic index. All biochemical analyses were made using a SLFIA immolunoassay in a TOSOH AIA-600 analyzer (Tokyo, Japan) for insulin, and an InCCA model Diconex Clinical Chemistry Analyzer (Intelligent Clinical Chemistry Analyzer) (Diconex, USA).

Genotyping

Genomic DNA was isolated from the blood samples by phenol-chloroform, precipitated in ethanol, resuspended in Tris-EDTA (pH 7.8) at a concentration of 0.1−1.0 μg/μL, and stored at −20°C until analysis.

Genotype and allele frequencies for the ACE-rs662799, APOA5-rs662799, and MTP-rs1800591 SNPs were performed by polymerase chain reaction−restriction fragment