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Genetic susceptibility to pre diabetes mellitus and related association with obesity and physical fitness components in Mexican-Mestizos

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ABSTRACT

Pre diabetes mellitus (pre-DM) is considered an early-reversible condition that can progress to Type 2 diabetes mellitus (T2DM) which is the main cause of death for adult Mexican population. Gene variants influencing fasting glucose levels may constitute helpful tool for prevention purposes in pre-DM condition. Physically active Mexican-Mestizo adults (n = 565) were genotyped for 6 single nucleotide polymorphisms (SNPs) (ADIPOQ rs2241766, ACSL1 rs9997745, LIPC rs1800588, PPARA rs1800206, PPARG rs1801282 and PPARGC1A rs8192678) related to lipid and carbohydrate metabolism. Fasting glucose was measured and values classified as pre-DM (≥100 mg/dL) or normal fasting glucose. Logistic models were used to test associations between pre-DM condition and SNPs, and interaction with Body Mass Index (BMI) and physical fitness components. The A allele of ASCL1 rs9997745 conferred increased risk (OR = 3.39, p = 0.001) of pre-DM which is modulated by BMI. The A allele of the PPARGC1A rs8192678 showed significant SNP*BMI (OR = 1.10, p = 0.008) interaction effect for pre-DM risk, meaning that obese subjects showed

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higher pre-DM risk but normal weight subjects showed lower risk. The effect increased with age and was attenuated by higher cardiorespiratory values. We found that both ACSL1 rs9997745 and PPARGC1A rs8192678 are associated with pre-DM, and that BMI significantly modified their association.

1. Introduction

Pre diabetes mellitus (Pre-DM) is a condition characterized by elevated blood glucose, but does not reach the levels to diagnose Type 2 diabetes mellitus (T2DM). Pre-DM is a reversible condition; however, without treatment, 37% of individuals with pre-DM develop T2DM within a four-year span [1].

In Mexican-Mestizos, T2DM prevalence reach 10% in adults and the disease has become the first cause of death of both women and men between 45 and 65 years old [2,3].

Fasting glucose level is one of the most employed tests for the diagnosis of diabetes, as it represents low-cost and self-monitoring means for that purpose [4,5].

Fasting glucose variation depends on genetic and environmental factors; the former are considered to account for around 30% of the final estimated glycemic values [6]. A well-established association of 14 single nucleotide polymorphisms (SNPs) to fasting glucose concentration explains around 10% of variation in glucose levels in Caucasian populations [7]. In the Mexican population over 20 genes have presented variants associated with T2DM [8–17], but only one, PPARG (Pro12Ala), has been associated with higher fasting glucose levels in obese subjects [18]. Thus, identification of additional gene variants influencing fasting glucose levels may improve our understanding of pre-DM and how the effect could be modified by obesity and/or physical fitness.

The most prevalent environmental factors contributing to pre-DM are obesity (Body Mass Index; BMI $\geq 30\,kg/m^2$) and physical inactivity. The genetic susceptibility to pre-DM (or T2DM) conferred by some gene variants may interact with obesity; this means that some genetic variants may confer a pre-DM or T2DM risk in obese people but not in non-obese people or vice versa, suggesting that the genetic architecture of the disease may differ from obese to non-obese individuals [19–21].

The fundamental aspect to manage pre-DM is imposing strict control of glycemia through lifestyle intervention via diet, exercise and, often, medication. A regular exercise program prevents or delays the transition from pre-DM to T2DM, enhancing insulin sensitivity, and increasing glucose uptake from blood [5]. However, the effect of BMI and physical fitness components (such as muscle endurance ability or cardiorespiratory capacity) on pre-DM has not been studied in the Mexican population. We aimed to analyze the genetic risk associated with pre-DM in regard to 6 common genetic variants related with lipid and carbohydrate metabolism, and the respective interaction with BMI and physical fitness components.

2. Materials and methods

2.1. Study design, data and sample collection

Subjects who voluntarily took part of the study were members of a fitness company (Sport City S.A. de C.V., Grupo Marti) in Mexico City, Mexico. They met the following criteria: they were between 18 and 55 years of age, all of Mexican-Mestizo ancestry (a minimum of 3 non-related grandparents born in Mexico), they were non-smokers, had not been diagnosed for T2DM, and could not be receiving weight-loss medication. In order to obtain a homogenous sample in terms of physical activity, subjects should be sedentary and become physically active 3 months before sample collection, as such requisite ensures time enough for neuromuscular adaptations to occur as a result of training [22]. Highly trained individuals were not enrolled in this study. During those three months, participants followed the same exercise routine: 3 times a week with the goal of losing weight or adopting a healthy life. Details of the exercise protocol can be found in Ref. [23].

Measurements of physical fitness components were obtained following the American College of Sport Medicine (ACSM) guidelines [5]. Cardiorespiratory fitness was measured through the evaluation of maximal oxygen uptake consumed in a minute of exercise (VO_{2max}) [5], expressed in mL/kg × min, calculated after Cooper's test (the largest possible distance run or walked in 12 min) [24]. Muscle endurance (ME) was regarded as the ability of a muscle or group of muscles to exert force to overcome resistance in repeated bouts. ME was measured as the maximum number of abdominal crunches performed in one minute [5].

Participants covered a range of BMI (calculated as weight over squared height in kg/m^2) from 20 to $55\,kg/m^2$, which included both obese (BMI $\geq 30\,kg/m^2$) and non-obese individuals height and weight were measured while subjects were wearing light clothing and no shoes. Venous blood samples were drawn at early morning from all participants after an 8-h fast. Subjects with ≥100 mg/dL fasting glucose concentration were classified as pre-DM (case group), and those with values <100 mg/dL were classified as normal fasting glucose NFG (control group) [25]. The order of the steps in the sampling procedure were: recording anthropometric measurements, taking blood samples, performing the ME test and, after a 10-min full pause, the indirect VO_{2max} test.

This project was approved by the ethics committee of Regional Hospital Lic. Adolfo Lopez Mateos, from Institute for Social Security and Services for State Workers, Mexico (193.2017), and by the Institute of Biomedical Science, University of São Paulo (USP), Brazil. PROTOCOL N. All participants

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