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Heritability, parental transmission and environment correlation of pediatric-onset type 2 diabetes mellitus and metabolic syndrome-related traits

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ABSTRACT

Aim: To estimate the heritability, parental transmission and environmental contributions to the phenotypic variation in type 2 diabetes mellitus and metabolic syndrome-related traits in families of Mexican children and adolescents.

Methods: We performed a cross-sectional study of 184 tri-generational pedigrees with a total of 1160 individuals (99 families with a type 2 diabetes mellitus proband before age 19). The family history of type 2 diabetes mellitus in three generations was obtained by interview. Demographic, anthropometric, biochemical and lifestyle information was corroborated in parents and offspring. We obtained correlations for metabolic traits between relative pairs, and variance component methods were used to determine the heritability and environmental components.

Results: The heritability of early-onset of type 2 diabetes mellitus was 0.50 ($p < 1.0e{-}7$). The heritability was greater than 0.5 for hypertension, hypoalphalipoproteinemia, hypercholesterolemia, body mass index, waist circumference, blood pressure, 2-h insulin, and cholesterol ($p < 0.001$). In contrast, we observed a high environmental correlation (>0.50) for blood pressure, HbA1c and HDL-cholesterol after multivariate adjustment ($p < 0.05$). Several traits, such as type 2 diabetes mellitus and insulin resistance, were significantly correlated only through the mother and others, such as hypertriglyceridemia, were significantly correlated only through the father.

Conclusion: This study demonstrates that type 2 diabetes mellitus and metabolic syndrome-related traits are highly heritable among Mexican children and adolescents. Furthermore, several cardiometabolic factors have strong heritability and/or high environmental contributions that highlight the complex architecture of these alterations.

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1. Introduction

The prevalence rates of obesity, metabolic syndrome (MS) and type 2 diabetes mellitus (type 2 DM) have increased worldwide over the past decades. In Mexico, approximately 70% of adults and 34.4% of children (5–11 y) are overweight or obese, of which 26.6% and 20% have MS, respectively, and 9.17% of adults have diabetes [1]. Despite an increase in the incidence of childhood type 2 DM, its prevalence remains unknown. Nevertheless, it is expected that the increase will parallel the observed increases in the number of children who are overweight or obese.

Many studies identified environmental factors, including physical inactivity and caloric excess, that contribute to the pathogenesis of these diseases. Moreover, there is evidence that genetics plays an important role in these diseases [2]. The highest prevalence occurs in certain risk populations, and the family aggregation and heritability (h^2) support the involvement of genetic factors in these types of diseases. However, distinct populations exhibit different levels of genetic involvement, and the estimates of h^2 for type 2 DM are between 0.20 and 0.80 [3]. Moreover, there are differences in the heritability of other cardiometabolic factors between ethnic groups [4].

Most of the information about the genetic components of these complex diseases is derived from studies in adults, with little information on pediatric patients. The h^2 is not necessarily extrapolate from adults to children because the genetic and environmental contributions may be different over a lifetime. Specifically, the genetic contribution may be higher when these complex diseases affect a younger population [2].

One problem encountered when assessing the importance of genetic factors is that families also share environmental factors. This correlation can underlie any observed increase in disease prevalence among family members. Therefore, is important to include environmental factors in the estimation of h^2, which has been a weakness in other studies.

The genetic architecture and environmental contributions to childhood type 2 DM and MS are poorly delineated, and less is known about Mexican youth. Therefore, the objective of the present study was to estimate the heritability, parental transmission and environmental contributions to the phenotypic variation in type 2 DM and MS-related traits in families of Mexican children and adolescents.

2. Materials and methods

2.1. Subjects

This manuscript reports on a family-based cross-sectional study. We analyzed 99 families selected based on a proband with type 2 DM between ages 8 and 19 y who attended the Diabetes Clinic at Mexico's Children's Hospital Federico Gómez. We also included 85 population-based families of children and adolescents without type 2 DM, requesting the participation of friends, neighbors or family acquaintances. These families were considered for the analysis because they contribute to the evaluation of covariate effects and they have no family relationship with the proband's families. All families live in the Mexico City metropolitan area, and the past three generations were born in Mexico. The Research, Ethics, and Biosafety committees of the Mexico's Children's Hospital Federico Gómez approved this study. The enrolled children and parents gave written informed assent and consent.

2.2. Phenotype and covariate data

Phenotypic assessments were conducted at the hospital. We obtained family pedigree tri-generational information about demographic and medical histories by directly questioning the parents. The data available from the grandparents is age, sex and medical history of diabetes and other chronic diseases. Anthropometric, biochemical measurements, fitness, physical activity and food frequency consumption information were obtained for parents and offspring.

Both members of the families, with and without type 2 DM, underwent the same phenotypic assessment, except for the oral glucose tolerance test, which it was not performed in participants with type 2 DM.

2.2.1. Anthropometric measures

Trained personnel performed the anthropometric measurements, and patients were measured without shoes and while wearing light clothing. The weight was measured using a digital scale (Seca® 884, Hamburg, Germany) with 0.1 kg accuracy. The height was evaluated with a stadiometer (Seca® 225, Hamburg, Germany) with 0.1 cm precision. The waist circumference (WC) was measured at the end of exhalation with non-elastic flexible tape to the nearest 0.1 cm (Seca® 200, Hamburg, Germany) in standing position at the midpoint between the lower costal border and the iliac crest. The blood pressure was measured with a mercury sphygmomanometer in the right arm supported at heart level after being seated for 5 min with the appropriate cuff size. Using the first and fifth Korotkoff sounds, blood pressure was recorded three times to the nearest 2 mmHg and the mean value was calculated.

2.2.2. Blood samples

A blood sample after 12 h fasting was obtained to determine the following parameters: glucose (hexokinase method, Dimension RXL.MAX, Siemens), insulin (chemiluminescence, IMMULITE 1000, Siemens, Euro, DPC, Llanberis, UK), C-peptide (chemiluminescence, IMMULITE 1000, Siemens Euro, DPC, Llanberis, UK), HbA1c (Dimension RXL. MAX Siemens immunoassay), total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol) and triglycerides (Hitachi 902 analyzer. Hitachi, Ltd., Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-cholesterol) levels were obtained per the Friedewald formula (LDL-cholesterol = total cholesterol in mg/dL–HDL-cholesterol in mg/dL–triglycerides in mg/dL/5). The homeostatic model assessment-insulin resistance (HOMA-IR) index was calculated as ([fasting glucose in mg/dL × fasting insulin in mU/mL]/405). In participants without diabetes, an oral glucose tolerance test (OGTT) with 1.75 g/kg anhydrous glucose (up to 75 g) with glucose and insulin measurements at 2-h was performed.