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ORIGINAL ARTICLE

Early Decrease of Insulin Sensitivity in Offspring of Individuals with Type 2 Diabetes. The Mexican Diabetes Prevention Study

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Background and Aims. Defects in insulin sensitivity (IS) and insulin secretion have been recognized as risk factors for type 2 diabetes (T2D) and its complications. We undertook this study to establish the relationship between healthy type 2 diabetic offspring (OFD) from a Mexican population with IS.

Methods. A total of 602 Mexican subjects, 359 first-degree offspring of T2D (OFD+) and 243 first-degree non-offspring of T2D (OFD−) were classified as young adults (age range, 18−44 years) and middle-aged adults (age range, 45−65 years). Groups were clinically and biochemically characterized. Quantitative insulin sensitivity check index (QUICKI) was used to estimate IS and the homeostasis model assessment B (HOMA-B) was used to estimate B cell function.

Results. IS decreased significantly ($p < 0.05$) in OFD+ middle-aged (QUICKI 0.330 ± 0.03) compared with OFD− (0.370 ± 0.03). Middle-aged adults (OFD+) had the highest prevalence of increased fasting insulin levels (FIL) (13.6%) and decreased IS (22.9%) compared with OFD− groups (3.2%). A binary regression analysis showed the association of OFD+ with increased FIL (odds ratio [OR], 3.71; 95% confidence interval [95% CI], 1.68−8.2; $p = 0.001$), and QUICKI (OR, 10.87; 95% CI, 2.36−44.69; $p < 0.01$) adjusted by gender, age, and obesity.

Conclusions. Our results suggest that decreased IS itself could be recognized as one of the earliest detectable abnormalities in middle-aged adults. Moreover, prevalence increases with age and is associated with type 2 diabetic offspring, regardless of obesity. © 2014 IMSS. Published by Elsevier Inc.

Key Words: Insulin sensitivity, Family history, Type 2 diabetes.

Introduction

Over 371 million people are diagnosed with diabetes, with possible only half of the cases identified (1,2). The Mexican Diabetes Prevention (MexDiab) Study was a population-based study to evaluate strategies for preventing Type 2 diabetes (T2D) in high-risk individuals and to provide information on the prevalence of metabolic glucose disorders in a Mexican population (3). In Mexico, it is estimated that 10.6 million persons directly suffer from diabetes and its complications (4,6). The disease is characterized as either Type 1 (T1D) or Type 2 (T2D), both having a genetic predisposition that depends on the first-degree relative history of the disease. The Mexican National Health Survey (5) reported that the prevalence of first-degree non-offspring T2D (OFD−), an individual not having parents, siblings,

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or children with diabetes, is 6.1%. If the individual had one parent (OFD+), the prevalence of the disease was 10.2% and if both parents had the disease, the prevalence was 19.5% (5). Therefore, genetic factors elevate the risk of developing T2D (7).

Decreased insulin sensitivity (IS) and increased fasting insulin levels (FIL) are recognized as two important risk factors for determining T2D and its complications (8,9). However, other factors also play an important role in the physiopathology of the disease such as environmental changes (10) and lifestyle (11). Furthermore, it has been also demonstrated that certain clinical and metabolic risk factors such as dyslipidemia and obesity are associated with T2D development (12,13).

Therefore, it is important to determine how these factors influence each other at the onset of T2D.

One of the major environmental factors associated with T2D is a poor diet, which can lead to obesity (11,14). Obesity and abdominal body fat distribution has been associated with increased FIL and decreased IS in non-obese healthy OFD+ adults (15,16). Moreover, increased FIL and decreased IS are related with cardiovascular disorders independent of obesity (17). Thus, central obesity and overall adiposity cannot satisfactorily explain increased FIL and decreased IS. Given the remarkable increase in the prevalence in the Mexican population of T2D and obesity the aim of this study was to determine the relationship between healthy OFD+ with IS.

Materials and Methods

Subjects and Setting

The study was approved by the Scientific Research Committee of the Instituto Mexicano del Seguro Social (IMSS) and all participants were required to sign an informed consent form to participate in the study in accordance with the Declaration of Helsinki (18). In this report, we included a population of males and non-pregnant females aged 18–65 years residing in the city of Puebla in central Mexico. OFD+ was defined by a previous diagnosis of T2D in at least one first-degree relative (mother, father, or sibling). To establish diagnosis of T2D in family relatives, we used the criteria according to the American Diabetes Association (ADA) (1). There were a total of 359 first-degree offspring of T2D eligible subjects (OFD+) and 243 first-degree non-offspring of T2D (OFD−). Study population was classified as young (aged 18–44 years) and middle-aged (45–65 years of age) adults. Diagnoses of acute or chronic disease (except hypertension and hyperlipidemia) were exclusion criteria.

Clinical and Metabolic Characterization

A standardized clinical history including a history of diabetes was performed. With the subject under fasting conditions, wearing light clothing, and without shoes and socks, height, weight, and percentage of total body fat (%TBF) were measured using an electronic digital scale with bioelectrical impedance (Tanita, TBF-215, Tokyo, Japan; 200 g ± 100 kg). Reference values of %TBF range from 15–25% in women and 10–20% in men. Body mass index (BMI) was calculated as kilograms per square meter (kg/m^2) (19). Obesity was defined by BMI >30 kg/m^2. Waist circumference (WC) was measured with a non-elastic anthropometric tape (seca, Hamburg, Germany) (20). Central adiposity was defined by WC as >80 cm in women and >90 cm in men (21). Waist-hip ratio (WHR) was calculated as WC (cm) divided by hip circumference (cm) with cut-off point of >0.9 and >0.8 for males and females, respectively (21).

Assays

A whole blood sample was collected from an antecubital vein after an overnight fast of 10–12 h. All subjects underwent an oral glucose tolerance test as previously described (22). Glucose-equivalent oral glucose challenge (75 g) was administered and a blood sample was drawn 2 h (±15 min) later. Samples were used to the follow determinations: fasting glucose, fasting insulin, and triglycerides (TAG mg/dL) levels. Plasma glucose and triglycerides levels were determined with the Beckman Synchron CX4 Chemistry system using a timed endpoint method (Beckman Coulter, Fullerton, CA). Glucose was measured by the hexokinase enzymatic assay determination method. Triglycerides were quantified by the enzyme-based method described by Trinder. Plasma insulin was measured by the enzyme immunoassay method with the Beckman Synchron CX4 system (Beckman Coulter). All assays were performed at the GRUMID Information System Central Laboratory. Samples were frozen at −20°C and sent weekly for analysis. Hyperinsulinemia was defined as FIL >12 μIU/mL (23). Decreased IS was evaluated by the Quantitative Insulin Sensitivity Check Index (QUICKI) as 1/(log fasting Insulin + log fasting glucose mg/dL) cut-off values as <0.357 (24). TAG cut-off values <150 mg/dL. The homeostatic model assessment (HOMA) used to evaluate β-cell function is a value expressed as % of function (100% is normal) (25,26).

Statistical Analysis

Differences between groups were estimated using the unpaired, two-tailed Student t test. For statistical analysis, all skewed numerical data were log(n) transformed to obtain symmetrical distribution. The Kolmogorov-Smirnov test was employed to test whether any variable would significantly deviate from a normal distribution. Prevalence is expressed by percentage (χ^2 test was utilized). To report the prevalence of obesity, WHR, increased FIL, and decreased IS, we estimated the age-adjusted rates. Age-adjusted conditional logistic regression forward step