Diabetes & Metabolic Syndrome: Clinical Research & Reviews xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original article

The impact of parental history of type 2 diabetes on hyperinsulinemia and insulin resistance in subjects from central Mexico

Ana Paula Acevedo-Negrete[a], Leonardo M. Porchia[a], M. Elba Gonzalez-Mejia[b], Enrique Torres-Rasgado[b], Dania G. Solis-Cano[a], Guadalupe Ruiz-Vivanco[a,b], Ricardo Pérez-Fuentes[a,b,*]

[a] *Laboratorio de Investigación en Fisiopatología de Enfermedades Crónicas, Centro de Investigación Biomédica de Oriente, IMSS, Carretera Federal Atlixco-Metepec Km 4.5, C.P. 42730 Atlixco, Pue, Mexico*
[b] *Facultad de Medicina, Benemérita Universidad Autónoma de Puebla, Calle 13 Sur 2901 Colonia Volcanes, C.P. 72000, Puebla, Pue, Mexico*

ARTICLE INFO

Article history:
Received 17 June 2017
Accepted 1 July 2017
Available online xxx

Keywords:
Family history
Type 2 diabetes
Insulin resistance
Hyperinsulinemia
Mexico

ABSTRACT

Aims: Hyperinsulinemia and insulin resistance are both associated with the development of Type 2 Diabetes and other pathologies; however, the influence of parental history of Type 2 diabetes (PH-T2D) has yet to be investigated. Therefore, this study was conducted to determine the effect of PH-T2D has on the risk of developing hyperinsulinemia and IR.

Materials and methods: 1092 subjects (703 non-pregnant females and 389 males) were enrolled for a cross-sectional study. Clinical and biochemical parameters were collected. Subjects were allocated according to their PH-T2D: no parents, one parent, or both parents. Insulin resistance was calculated using the HOMA1 equation (HOMA1-IR). Logistic regression was used to determine the association (odds ratio) between PH-T2D and hyperinsulinemia or insulin resistance.

Results: Increasing degrees of PH-T2D were associated with significant increases in fasting plasma glucose, insulin, and HOMA1-IR ($p < 0.05$). Subjects having one or both parents were associated with an increase risk of developing hyperinsulinemia (odds ratio = 1.53, 95%CI: 1.12–2.09, and odds ratio = 1.92, 95%CI: 1.21–3.06, respectively) and insulin resistance (odds ratio = 1.47, 95%CI: 1.08-2.00 and odds ratio = 1.77, 95%CI: 1.09–2.87, respectively), when adjusting for age, sex, BMI, fasting plasma glucose, and triglycerides.

Conclusion: The presences of PH-T2D significantly increased the risk of developing hyperinsulinemia and insulin resistance.

1. Introduction

Obesity and diabetes incidence has increased throughout this century. The most likely causes are cultural and dietary changes in the population [1]. Here in Mexico, the rate of obesity has increased 70% in the past few years and the prevalence of Type 2 Diabetes (T2D) has increased 9.2% [2,3]. With many different possible mechanisms leading to the presentation of insulin resistance or obesity, ranging from genetic susceptibility [1,4], hormone treatment [5], or even the use of sugar substitutes [6], understanding how family history can identify disease development remains a concern in many developing countries [7,8].

The compensatory mechanism for elevated glucose levels by the body is to augment the production of insulin. This results in increased ß-cell function and hyperinsulinemia, if prolonged will lead to ß-cell dysfunction and the eventually onset of T2D [9]. In addition, hyperinsulinemia is considered a risk factor for the development of certain forms of cancer [10] and other pathologies, such as Alzheimer's [11] and polycystic ovary syndrome [12]. Moreover, hyperinsulinemia is a precursor state before the development of insulin resistance, which is defined as a diminished insulin response by muscle and adipose tissues. Consequently, insulin resistance increases the risk of developing T2D and cardiovascular disease [13]. Therefore, examining factors that affect the development of hyperinsulinemia can aid in the understanding and prevention of T2D and other pathologies.

Family history is defined as the presence of an affected first-degree relative (mother, father, or sibling) or second degree relative (grandparents, aunts, uncle, or cousins) and is currently

* Corresponding author at: Facultad de Medicina, Benemérita Universidad Autónoma de Puebla, 13 Sur 2901 Col. Volcanes, C.P. 72420, Puebla, Pue, Mexico.
E-mail address: rycardoperez@hotmail.com (R. Pérez-Fuentes).

http://dx.doi.org/10.1016/j.dsx.2017.07.012
1871-4021/

considered a risk factor for a large number of chronic diseases [8,14,15]. Family history has been used as an indicator to guide and personalize the prevention and timely care of a disease [15,16]. Furthermore, it can be used to identifying high-risk families for targeted intervention [17]. For Mexicans and Mexican Americans, having a positive parental history for T2D augments the risk for T2D. Velasco et al. demonstrated that there is a 1.6–2.4 and 3.2–4.5 fold increased risk of developing T2D if one or two parents were a diabetic, respectively [18]. However, most studies have yet to examine precursor states, such as hyperinsulinemia and insulin resistance.

Even though no specific gene or a set genes for diabetes or obesity has been found, it has been hypothesized that a genetic component exists and that the family history of a disease could be used as a diagnostic risk factor. Currently in Mexico, 8.60% of men and 9.67% of women are diabetic, which is equivalent to 2.84 million men and 3.56 million women [2]. This would suggest that a large portion of the Mexican population is at risk. Therefore, the purpose of this study was to determine the effect of having at least one parent with T2D for developing hyperinsulinemia and insulin resistance.

2. Methods

2.1. Subjects and settings

We designed a cross-sectional study that included subjects from central Mexico. All subjects were recruited from Mexican Social Security Institute (IMSS) Clinic 2, located in the City of Puebla, Mexico, from February 2002 to July 2013. The subjects were selected using random sampling. When the subjects attended the clinic, they were asymptomatic; however, subjects were excluded from the study, if it was suspected they had an acute or chronic illness that would interfere with the analysis, did not know their family history of diabetes, were anorexic ($<18.5\,kg/m^2$) or severely obese ($>40\,kg/m^2$), were younger than 18 or older than 65 years-old, had irregular insulin levels (below 2 μU/ml or above 60 μU/ml), or the subjects failed to complete any part of the study. The protocol was approved by the Scientific Research Committee of the Mexican Social Security Institute. All participants provided informed consent to participate in the study protocol, conducted in accordance with the Declaration of Helsinki.

2.2. Clinical characterization and biochemical assays

Subjects were clinically evaluated according to a standardized protocol including personal and family medical history. With the subjects in fasting conditions, wearing light clothing and without shoes, their height (m) and weight (kg) were measured using the body composition analyzer (TBF-215, Tanita, Tokyo, Japan). BMI was calculated as weight/height^2 (kg/m^2). Whole blood samples were collected from the antecubital vein following a 10–12 h overnight fast. The samples were kept at room temperature to allow clotting. The serum fraction was recovered and frozen at −20 °C until use. Samples were used for the following endpoints: fasting plasma glucose, insulin, glycated hemoglobin (HbA1c), high-density lipoprotein, low-density lipoprotein, and triglycerides. An additional blood sample was obtained 2 h after oral glucose administration (75 g) for the oral glucose tolerance test. Fasting plasma glucose and oral glucose tolerance were determined, in duplicate, using the enzymatic method/spectrophotometric glucose oxidation (Beckman Instruments, Brea, CA). Insulin levels were determined by automated immunoassay (Access, Beckman). The HbA1c levels were determined by the turbidimetric inhibition immunoassay. To determine high-density lipoprotein, low-density lipoprotein, and triglycerides, serum samples were sent to the Central Laboratory of the Multidisciplinary Research Group (IMSS). Insulin resistance was assessed by the homeostatic model assessment (HOMA1-IR) formula: (Glucose in mg/dL x Insulin in μU/ml)/405 [19].

2.3. Allocation of subjects into groups and subgroups

Patients were grouped based on their Parental History of T2D (PH-T2D), either as having no parents, one parent, or both parents. According to their BMI, subjects were also allocated into subgroups: normal weight ($18.5–24.9\,kg/m^2$), overweight ($25–29.9\,kg/m^2$), or obese ($30–39.9\,kg/m^2$). Using the American Diabetes Association recommendations [20], subjects were classified as either normal glucose tolerance (NGT; fasting plasma glucose: <100 mg/dL; oral glucose tolerance: <140 mg/dL; HbA1c: <5.6%), prediabetics (PT2D; fasting plasma glucose: 100–125 mg/dL; oral glucose tolerance: 140–199 mg/dL; HbA1c: 5.6–6.4%) and T2D (fasting plasma glucose: ≥126 mg/dL; oral glucose tolerance: ≥200 mg/dL; HbA1c: ≥6.5%; or taking Glucose Control medicine). Subjects were evaluated for hyperinsulinemia (insulin levels >11 μU/ml) [21] and insulin resistance (HOMA1-IR score ≥2.5) [22].

2.4. Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences program, version 19 (SPSS, Chicago, IL) or Medcalc Statistical Software, version 13.3.3 (Medcalc, Ostend, Belgium). The normality of the data was assessed by the Shapiro-Wilk test. Differences between categorical data were assessed with the Chi-Square test. Homogeneity in parametric data was determined with the Levene's test. For heterogeneous and homogeneous data, differences between groups were determined with Welch's test or ANOVA, respectively. Difference between each group was determined with a *post hoc* Dunnet't T3 or the Bonferroni test, according to their homogeneity. For non-parametric data, differences between groups were determined with the Kruskal-Wallis Test with a *post hoc* Dunn's test. Linear contrast was used to determine a trend for parametric data and Jonckheere-Terpstra Test was used for non-parametric data. The Pearson correlation coefficient (r) was used to determine the association between variables for continuous data. Simple and multiple logistic regressions were used to determine the Odds Ratio (OR), evaluating the level of association. The Cochran-Armitage test was used to determine if a trend exists between increasing degrees of PH-T2D and hyperinsulinemia or insulin resistance. The results were expressed as mean ± standard error. P-values <0.05 were considered statistically significant.

3. Results

Initially, 1707 participants were approached for this study (600 males and 1131 non-pregnant females). Two hundred forty-five patients, whom initially chose to participate, did not obtained fasting glucose values. Of the remaining participants, 94 were found to exceed the age range, 216 did not obtain fasting insulin, whereas 11 had insulin values not within the range. Forty participants BMI's were calculated as being anorexic (n = 9) or as being Morbid Obese (n = 31) and therefore removed. Four participants were removed for not knowing their family history of diabetes. Thus, our cohort consisted of 1092 subjects (63.1% of the original sample). The cohort's clinical and metabolic characteristics stratified by PH-T2D are depicted in Table 1.

There was a significant difference between subjects with no parents, one parent, and both parents with T2D with respect to fasting plasma glucose levels and HbA1c ($p < 0.05$). Significant

Please cite this article in press as: A.P. Acevedo-Negrete, et al., The impact of parental history of type 2 diabetes on hyperinsulinemia and insulin resistance in subjects from central Mexico, Diab Met Syndr: Clin Res Rev (2017), http://dx.doi.org/10.1016/j.dsx.2017.07.012