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Original Research

Beta-cell function and insulin resistance among Peruvian adolescents with type 2 diabetes

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ABSTRACT

Objective: To characterize and compare the beta-cell function and insulin resistance among Peruvian adolescents with type 2 diabetes (T2D) and their non-diabetic, overweight and lean peers.
Methods: Cross-sectional study of 54 adolescents aged 10–19 years, distributed in three sex- and age-matched groups (n = 18): (i) adolescents with T2D; (ii) overweight adolescents without T2D; and (iii) lean adolescents without T2D, at the Diabetes, Obesity and Nutrition Research Center in Lima, Peru. Fasting glucose, insulin, C-peptide, and glycated hemoglobin were measured for all participants. In addition, a two-hour oral glucose tolerance test (OGTT, 1.75 mg of glucose/kg body weight) was performed, during which glucose and C-peptide were quantified. The homeostasis model assessment of insulin resistance (HOMA-IR) and beta-cell function (HOMA-B) were derived for all participants, and beta-cell function was further examined by the area under the curve (AUC) of C-peptide.
Results: The median HOMA-IR score was higher in adolescents with T2D compared to lean adolescents (6.1 vs. 2.1; $p = 0.002$), but was not different from that of overweight adolescents (6.1 vs. 4.0; $p = 0.322$). The median HOMA-B was higher in overweight adolescents than in lean adolescents (256.9 vs. 134.2; $p = 0.015$), and adolescents with T2D (256.9 vs. 119.8; $p = 0.011$). The mean AUC of glucose in adolescents with T2D was 1.8-fold higher than that of overweight adolescents, and 1.9-fold higher than that of lean adolescents ($p < 0.001$). Although the median AUC of C-peptide in adolescents with T2D was lower than that of overweight and lean adolescents, this difference was not statistically significant (230.7 vs. 336.6 vs. 267.3 nmol/l120 min, respectively; $p = 0.215$).
Conclusion: Among Peruvian adolescents with T2D, insulin resistance is the most prominent characteristic, rather than beta-cell dysfunction.
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Introduction

Type 2 diabetes (T2D) in youth is a serious public health problem that has exhibited an epidemic growth in recent decades [1,2]. Pediatric T2D is associated with both acute and chronic complications [3], which occur more prematurely than in pediatric type 1 diabetes [4,5]. Although initially noted in affluent settings [6], the rise in pediatric T2D has spread to low- and middle-income countries (LMICs) around the world [7]. The increased vulnerability of several of the ethnic groups living in LMICs, combined with the current epidemic of childhood obesity, will likely make the contribution of LMICs to the global T2D caseload significant. Indeed, about 80% of the 370 million of patients with diabetes will live in LMICs by 2030 [8].

Despite the importance of pediatric T2D in LMICs, the pathogenesis of T2D in non-Caucasian adolescents is still unclear [9], preventing the development of effective therapeutic strategies for these groups. In general, T2D is thought to arise from beta-cell

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dysfunction and increased insulin resistance [10–13], usually resulting from obesity [14]. However, the relative contribution of insulin resistance and beta-cell dysfunction to the pathogenesis of T2D in adolescents is uncertain [9], partly due to the complex metabolic changes occurring in puberty [15,16]. Furthermore, ethnic variations in glucose metabolism exist [17,18], and add to the uncertainty about the pathophysiology of T2D in non-Caucasian adolescents.

Delineating the specific metabolic defects underlying T2D in non-Caucasian adolescents is critical for the development of effective therapeutic strategies targeting the specific metabolic defects in each ethnic group. This is apparent in adults, with African-Americans exhibiting a greater response to insulin sensitizers (e.g. thiazolidinediones), given their diminished insulin sensitivity [19].

Hispanic adolescents have a high prevalence of obesity [20,21], type 2 diabetes [22,23], and its complications [24]. This increased vulnerability has been linked to both environmental and genetic factors, expressed as a low disposition index [25], and higher insulin resistance than their Caucasian peers [26]. Despite these observations, evidence on ethnic variations in glucose metabolism in Hispanics is very limited [26], particularly for Latin American adolescents. Latin Americans share a common genetic ancestry, which may affect their risk of T2D and the pathogenesis of the disease. Nevertheless, the extent to which this genetic background affects the role of insulin resistance and impaired beta-cell function in the pathogenesis of T2D in Latin American adolescents is currently unknown.

In this context, we aimed to assess the beta-cell function and insulin resistance in three groups of adolescents aged 10–19 years in Peru: adolescents with T2D, overweight adolescents without T2D, and lean adolescents without T2D. This evidence will improve our understanding of the pathogenesis of diabetes in Latin American adolescents and, more importantly, it will contribute to tailor effective and safe therapeutic strategies targeting the main metabolic defects underlying diabetes in this population.

Materials and methods

Study design and setting

We conducted a cross-sectional study to assess the metabolic defects in Peruvian adolescents with type 2 diabetes mellitus, by comparing the metabolic parameters of sex- and age-matched patients with T2D, overweight and lean adolescents aged 10–19 years at the Diabetes, Obesity and Nutrition Research Center (CIDON), in Lima, Peru.

Participants

This study included three groups of adolescents between 10 and 19 years, matched by sex and age (within one year), in a 1:1:1 scheme: (i) adolescents with T2D, (ii) overweight or obese adolescents without T2D, and (iii) lean adolescents without T2D. Adolescents with T2D were selected randomly from a list of patients aged 10–19 years, and with T2D attending CIDON. The diagnosis of T2D was based on the diagnostic criteria of the International Society for Pediatric and Adolescent Diabetes, and included: symptoms of diabetes plus casual plasma glucose ≥200 mg/dl, fasting plasma glucose ≥126 mg/dl or two-hour plasma glucose ≥200 mg/dl during an oral glucose tolerance test (OGTT) [27]. For the comparison groups, lean and overweight adolescents fulfilling the eligibility and matching criteria were systematically selected from adolescents consecutively attending CIDON. Overweight was defined as a Body Mass Index (BMI) for age and sex at or above the 85th percentile of the 2000 clinical growth charts of the Center for Disease Control and Prevention [28]. Normal weight was defined as a BMI for age and sex within the 5th and 84th percentiles of the same standard. Adolescents with a diagnosis of with type 1 diabetes and the presence of markers of beta-cell autoimmunity (antibodies against glutamic acid decarboxylase, islet antigen 2, and insulin; and islet cell autoantibodies) were excluded from the study. Participants with active concurrent illnesses were excluded from the study.

Data collection and variables

Metabolic testing took place between January 8th and March 15, 2014 at CIDON. As instructed, participants arrived at CIDON at 08:00 h on their scheduled date, after a 12-hour overnight fast. Insulin treatment was discontinued 48 hours prior to metabolic testing, but oral antidiabetic therapy was not modified, because close follow-up was not possible.

A short survey was conducted to collect basic demographic data (age, sex) and relevant clinical antecedents (family history of diabetes, age at diagnosis and duration of diabetes). Weight and height were measured by experienced health professionals, using a previously-calibrated scale and stadiometer, respectively. Vital signs were checked prior to initiating metabolic testing. A peripheral catheter was placed in the forearm and 4 ml of fasting venous blood was collected for measuring glucose, insulin, HbA1C and C-peptide. Fifteen minutes later, a two-hour oral glucose tolerance test (OGTT) using 1.75 g of glucose per kilogram of body weight (up to a maximum of 75 g) was performed, and C-peptide and glucose were measured at baseline, and 15, 30, 60 and 120 minutes after the glucose load. Glucose, fasting insulin and HbA1C were measured using kinetic methods (ByoSystems, Barcelona, Spain), and C-peptide was measured by radioimmunoassay (C-PEP II-RIA-CT, DIAsource ImmunoAssays S.A., Louvain-la-Neuve, Belgium).

Beta-cell function was assessed by calculating the area under the curve (AUC) of C-peptide levels during an OGTT, using the trapezoidal method [29]. The post-stimulation C-peptide concentrations constitute a widely-accepted, accurate marker of beta-cell function among children and adolescents with T2D [30,31]. In addition, we analyzed the 15-minute C-peptide concentration during OGTT as a measure of beta-cell function [31]. Finally, we also calculated the Homeostasis Model Assessment of Beta-cell function (HOMA-B) index, which is based on the fasting glucose and insulin levels [32,33]. This index has been shown to characterize beta-cell function accurately in adolescents [34].

Insulin resistance was measured using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index [32,33]. The HOMA-IR index has been shown to correlate closely with well-established methods for assessing insulin resistance, including the hyperinsulinemic-euglycemic clamp and minimal models, in patients with T2D and lean and obese children and adolescents without T2D [34–37].

Statistical analysis

Initially, we evaluated the distribution of variables using numeric and graphic methods, and checked for the presence of outliers. Non-normally distributed, numeric variables were transformed using simple power functions (logarithmic, inverse, square-root, square, cubic, etc.), and their distribution was re-checked after transformation. Variables that were not normalized after transformation were analyzed in their original form, using non-parametric tests. Normally-distributed variables were summarized using the mean and standard deviation (the geometric mean and geometric standard deviation were used for log-transformed numeric variables), and the median and interquartile range was used for non-normally distributed variables. In the bivariate analysis, we compared the distribution of age, anthropometric and metabolic parameters across

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