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RESEARCH

Diabetes Research and Metabolism

Oral Glucose Tolerance Test with Insulin Assay and the evaluation of Insulin Resistance and Impaired Beta-cell function in primary prevention for Type 2 Diabetes

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Abstract

Background: *Insulin resistance and impaired beta-cell function are associated with type 2 diabetes mellitus (T2DM). Many insulin resistance and beta-cell function indices have been developed using the data from an oral glucose tolerance test (OGTT) with insulin assay. However, insulin assays are not widely used along with the OGTT in primary prevention outpatient clinics. We aimed to evaluate the association of having impaired fasting glucose (IFG), impaired glucose tolerance (IGT), isolated or combined, with insulin resistance and impaired beta-cell function in subjects at risk for T2DM.*

Methods: This is a cross-sectional study that included 376 subjects who underwent an OGTT who had at least two risk factors for T2DM without any chronic disease.

Results: Participants were 51.6±8.2 years old, 71.8% were women, had a mean body mass index (BMI) of 30.1±6.5 kg/m2, 42.4% had obesity and 26.7% hypertension. A HOMA-IR ≥2.5 was independently associated with male sex, BMI>25kg/m2, and with isolated-IFG, isolated-IGT, or combined ($p<0.05$ for all).

On the other hand, only overweight, but not obesity, was independently associated with impaired beta-cell function (disposition index <1.24). Additionally, combined IFG and IGT had 29.7 higher odds to have impaired beta-cell function compared with those that had a normal OGTT.

Conclusions: IFG alone, IGT alone, or the presence of both, are associated with higher odds to have insulin resistance and impaired beta-cell function in asymptomatic subjects at risk for T2DM without any chronic disease. Further studies are needed to evaluate this associations with the risk to develop T2DM, cardiovascular events and mortality.

Keywords: *type 2 diabetes; insulin resistance; beta-cell function; primary prevention; oral glucose tolerance test.*

Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the major disease burdens worldwide [1,2]. Despite that modern therapies have been developed recently, the incidence of T2DM and its complications, such as cardiovascular events, have increased over the last decades [1–4]. As consequence of the pandemic of T2DM, global public health policies have placed massive efforts to reduce its development or diminish its progression, including health programs focused on controlling known cardiovascular risk factors, such as insulin resistance and obesity [3–5]. Therefore, primary prevention of T2DM aims to reduce that burden to global health economies, and aims to improve quality of life and survival of subjects at high risk of developing diabetes [2,3].

Increased visceral adiposity and the development and progression of insulin resistance are one of the main etiologies of T2DM, which can be present several years prior to meet laboratory criteria for its diagnosis [3,6–9]. As a matter of fact, increased visceral, rather than subcutaneous adiposity seen in patients with obesity, has shown to induce insulin resistance through several molecular pathways, including peripheral glucose intolerance, impaired first- and late-insulin secretion, and reduced beta-cell function [8,10–13]. However, impaired insulin secretion and beta-cell dysfunction have a slow silent progression, which in consequence delays the diagnosis of diabetes [3,4,13].

The gold standard method for measuring insulin resistance is the euglycemic-hyperinsulinemic clamp, however this is an invasive and costly test [14]. Therefore, several insulin resistance and beta-cell function indices have been developed using dynamic insulin and glucose concentrations measured every 30 minutes through an oral glucose tolerance test (OGTT) [15–18]. These surrogate indices are good predictors for future diabetes [15,19]. However, this test is not widely used in primary prevention outpatient clinics, mostly for the high cost of dynamic insulin assays, the duration of the OGTT and, the limited resources to adequately perform the test [16,20]. Thus, the aim of the present study is to assess the relationship of impaired fasting and/or impaired glucose tolerance, combined or alone, with insulin resistance and beta-cell function surrogates in asymptomatic subjects with high risk to develop T2DM in the context of primary prevention.

Methods

Subjects

The population studied was selected from the Internal Medicine and Endocrinology outpatient clinics of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) that received attention between March 2007 and July 2010. The study included 376 subjects that met selection criteria and were recruited for this retrospective cross-sectional study. The study included subjects of both genders between 40 to 75 years old, that had a 75 g OGTT with insulin assay, and at least two risk factors for type 2 diabetes as stated by the American Diabetes Association (ADA; Table 1) [21]. Patients that had a newly diagnosis of T2DM after performing the OGTT were excluded from the study, using the ADA criteria [21]. Patients with current use of medications that could influence glucose and insulin values during the OGTT such as steroids, oral glucose lowering drugs (such as metformin, sulfonylureas, thiazolidinediones, acarbose, dipeptidyl peptidase-4 inhibitors, and glinides), subcutaneous insulin, and thyroid hormones, and patients with established chronic diseases, such as HIV infection, hepatitis C infection, systemic lupus erythematosus, rheumatoid arthritis, seizures, major depression, hospitalization in the past 6 months, active cancer or under treatment for cancer, and pregnant women, were excluded from the present study.

The present study was approved by the INCMNSZ Human Biomedical Research Institutional Committee (REF 1650) and was conducted according to the 1975 Declaration of Helsinki. Written informed consent was obtained from each patient included in the study.

Anthropometric measurements were obtained by trained staff. Current smoking status was defined when subjects self-reported that had smoked any tobacco in the previous 12 months and included those who had quit within the past year. Former smokers were defined as those who had quit more than a year earlier [5]. The body mass index (BMI) was calculated as the weight in kilograms (kg) divided by the square meters of body height (m2); normal weight was defined as BMI <25 kg/m^2, overweight as BMI between 25-29.9 kg/m^2, and obesity as BMI≥30 kg/m^2. Systolic/diastolic blood pressure was measured three times in a sitting position within a ten-minute interval, and the average of the three measurements was used for the analysis [22]. Hypertension was defined as blood pressure values ≥ 140/90 mmHg or prior documented diagnosis [22]. Cardiovascular risk was estimated with the Globorisk Laboratory-based risk score which has specific coefficients for the Mexican population [23].

Biochemical analysis

The central laboratory of the INCMNSZ performed all biochemical laboratory measurements. Blood samples from the patients were collected after at least 10 hours of fasting. The measurements were carried out with commercially available standardized methods. Plasma glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured using the Synchron CX analyzer (Beckman Systems, Fullerton CA). Plasma insulin concentrations were estimated using a radioimmunoassay method (MEIA, Abbott Laboratories). To perform the OGTT, subjects ingested a solution containing 75 g of dextrose, and venous samples were obtained at 0, 30, 60, 90 and 120 min for determination of plasma glucose and plasma insulin. Based on the results of the OGTT, subjects were categorized as normal (normal fasting glucose [<100 mg/dL] with normal glucose tolerance [120-min glucose value <140 mg/dL]), isolated impaired fasting glucose (IFG; fasting glucose between 100 and 125 mg/dL with normal glucose tolerance), isolated impaired glucose tolerance (IGT; 120-min glucose value between 140 and 199 mg/dL, with normal fasting glucose) and combined IFG-IGT, using the ADA criteria [21].

Table 1. *American Diabetes Association criteria for testing for diabetes in asymptomatic adults*

1. Testing should be considered in adults with overweight or obesity (BMI ≥ 25 kg/m^2 or ≥ 23 kg/m^2 in Asian Americans) who have one or more of the following risk factors:
• First-degree relative with diabetes
• High-risk race/ethnicity (e.g, African American, Latino, Native American, Pacific Islander)
• History of CVD
• Hypertension (≥ 140/90 mmHg or on therapy for hypertension)
• HDL cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
• Women with polycystic ovary syndrome
• Physical inactivity
• Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

BMI: Body Mass Index; CVD: Cardiovascular Disease; HDL: High-Density Lipoprotein Cholesterol; IGT: Impaired Glucose Tolerance; IFG: Impaired Fasting Glucose.

Insulin resistance indices

Published formulas were used to calculate the homeostasis model assessment of insulin resistance (HOMA-IR) (basal insulin x basal glucose) / 22.5) [24], and Matsuda index (10^4 / (basal glucose [mg/dL] x basal insulin [mIU/mL] x mean glucose [mg/dL] x mean insulin [mIU/mL])$^{0.5}$) [15]. In this last formula, mean glucose and mean insulin concentrations indicate average glucose and insulin concentrations based on sampling times at 0, 30, 60, 90 and 120 min. Stumvoll et al. insulin secretion indices were used to evaluate the first-phase insulin secretion (S1PhOGTT) and the second-phase insulin secretion (S2PhOGTT) [17]. A HOMA-IR reference value of ≥ 2.5 was used to determine insulin resistance, because it has been widely considered to have the highest specificity to predict incident diabetes [24,25].

Beta-cell function indices

The HOMA of beta-cell function (HOMA-B; [basal insulin [mIU/mL] × 20] / [basal glucose [mmol/L] - 3.5]) and the disposition index were used to evaluate the beta-cell function [19,26]. In the last formula, the insulinogenic index (ΔI0–30/ΔG0–30; (insulin [pmol/L] at 30min–basal insulin [pmol/L]/glucose [mmol/L] at 30min–basal glucose [mmol/L]) was used to measure the beta-cell function with insulin secretion/insulin resistance index (ΔI0–30 / ΔG0–30 × 1/fasting insulin [pmol/L]), the so-called disposition index. Then, a cut-off value of < 1.24 was considered to determine impaired beta-cell function, because it is strongly associated with T2DM [19].

Statistical analysis

Values are expressed as mean ± standard deviation or median (interquartile range) for continuous values and frequencies (%) for categorical values. Means and medians were compared using Student's T, ANOVA, Mann-Whitney's U or Kruskal Wallis tests when needed, and frequencies with chi-squared test. Multiple logistic regression analysis was used to evaluate independent factors associated with insulin resistance and beta-cell dysfunction.

Analyses were performed using the SPSS v.21.0 statistical package (SPSS Chicago, II.). All values with p <0.05 and 95% confidence intervals (95% CI) that excluded the unit, were considered statistically significant.

Results

The study included 376 subjects with at least two risk factors for T2DM. The mean age of all the subjects was 51.6 ± 8.2 years, 71.8% were women, had a mean BMI of 30.1 ± 6.5 kg/m2, 42.4% had obesity, and mean waist circumference was 99.6 ± 14.9 cm. Hypertension was present in 26.7% of the subjects, 57.8% have never smoked, and 76.8% had cardiovascular risk between 0-9% estimated by Globorisk lab calculator. Likewise, based on the OGTT result, 58.0%, 16.3%, 13.5%, and 12.2% had normal OGTT, isolated-IFG, isolated-IGT and combined IFG-IGT, respectively. As mentioned above, no patient had any other chronic disease or were under any drug that could impair the OGTT.

Table 2 shows the clinical and biochemical characteristics of the subjects classified by the OGTT result. Overall, patients with

Table 2. *Clinical and biochemical characteristics of subjects at high risk for Type 2 Diabetes at primary prevention.*

Variable	Normal (n= 219)	IFG Alone (n= 60)	IGT Alone (n= 51)	Combined IFG and IGT (n= 46)	p value
Age (years)	50.8 ± 8.8	51.9 ± 7.2	52.3 ± 8.6	53.4 ± 9.0	0.247
Female sex (%)	77.3	65.4	62.8 [a]	69.2	0.128
Body Mass Index (kg/m^2) <25 kg/m^2 (%) 25 – 29.9 kg/m^2 (%) ≥ 30 kg/m^2 (%)	 29.2 ± 5.8 23.8 36.2 40	30.3 ± 7.3 23.1 36.5 40.4	29.9 ± 5.92 16.3 44.2 39.5	32.9 ± 8.47[a] 15.4 35.9 48.7	0.014 0.81
Waist Circumference (cm) Waist-to-Hip Ratio	96.9 ± 14.4 0.92 ± 0.09	101.0 ± 16.4 0.93 ± 0.08	101.4 ± 14.0 0.97 ± 0.08 [a]	105.0 ± 14.3[a] 0.97 ± 0.11[a]	0.006 <0.001
Smoking history (%) Never Former Current	 57.9 19.1 23	 55.8 13.5 30.8	 69 14.3 16.7	 51.3 23.1 25.6	 0.557
Globorisk (%) 0 – 9 % ≥ 10 %	 83.8 16.2	 75 25	 79.1 20.9	 79.5 20.5	 0.509
Blood pressure ≥ 140/90 mmHg (%)	20.5	27.5	34.9 [a]	30.8	0.166
Systolic blood pressure (mmHg)	119 ± 14	121 ± 15	125 ± 16	126 ± 14[a]	0.004
Diastolic blood pressure (mmHg)	78 ± 9	78 ± 9	79 ± 10	81 ± 9	0.471
Cholesterol (mg/dL) Total Low-density lipoprotein High-density lipoprotein	 198.9 ± 36.8 111.3 ± 49.9 41.8 ± 11.2	 197.5 ± 38.6 114.8 ± 48.2 40.3 ± 9.1	 194.9 ± 42.4 95.5 ± 56.25 38.1 ± 10.1	 202.7 ± 39.0 111.3 ± 50.24 39.0 ± 8.5	 0.852 0.306 0.163
Triglycerides (mg/dL)	142 (114-194)	150 (118-200)	164 (121-225)	169 (130-198)	0.207
Serum creatinine (mg/dL)	0.81 ± 0.29	0.81 ± 0.17	0.82 ± 0.24	0.86 ± 0.22	0.88
HOMA-IR	1.73 (1.10-2.72)	2.87 (1.97-4.24)[a]	2.53 (1.62-3.76)[a]	3.59 (2.80-5.52)[a,b,c]	<0.001
Matsuda index	5.18 (3.30-8.06)	2.93 (2.30-5.07)[a]	3.09 (2.20-4.67)[a]	2.41 (1.59-3.09)[a,b,c]	<0.001
$S1Ph_{OGTT}$	1040 (758-1476)	1073 (586-1588)	1027 (652.82-1415)	997 (590-1246)	0.464
$S2Ph_{OGTT}$	279 (215 – 386)	289 (184-420)	294 (199-371)	276 (197-348)	0.861
HOMA-B	79.9 (50.6-115.6)	78.4 (49.4-114.1)	101.2 (69.8-145.4)[a,b]	86.5 (65.9-137.4)	0.027
$\Delta I_{0-30}/\Delta G_{0-30}$	0.95 (0.61-1.45)	0.84 (0.55-1.33)	0.72 (0.42-1.06)[a]	0.67 (0.40-0.88)[a,b]	<0.001
Disposition index	2.24 (1.33-3.56)	1.32 (0.87-1.98)[a]	1.04 (0.63-1.59)[a]	0.72 (0.55-1.04)[a,b,c]	<0.001

IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance; HOMA-IR: Homeostatic Model Assessment Of Insulin Resistance; S1PhOGTT and S1PhOGTT: Stumvoll's first phase and second phase insulin release, respectively; $\Delta I_{0-30}/\Delta G_{0-30}$: Delta Insulin/Delta Glucose ratio. Variables are shown as mean ± SD or median (interquartile range) or percentages.

p value: T-student test, ANOVA, U-Mann-Whitney, Kruskal Wallis, or chi2. a p<0.05 vs normal group; b p<0.05 vs IFG Alone, and c p<0.05 vs IGT Alone.

Table 3. *Pearson bivariate correlations coefficients for variables of interest.*

	HOMA-IR †	Matsuda Index †	$S1Ph_{OGTT}$ †	$S2Ph_{OGTT}$ †	HOMA-B †	$\Delta I_{I0-30}/\Delta G_{0-30}$ †	Disposition index †
Age (y) *p*	-0.042 0.433	0.025 0.678	-0.1 0.065	-0.105 0.051	-0.157 0.003	-0.065 0.226	-0.004 0.946
Globorisk (%) *p*	0.161 0.002	-0.135 0.026	-0.174 0.001	-0.132 0.014	-0.052 0.335	-0.162 0.002	-0.21 <0.001
Smoke (%) *p*	0.6 0.262	-0.019 0.762	0.031 0.568	0.038 0.482	0.032 0.555	0.032 0.558	-0.006 0.908
Hypertension (%) *p*	0.06 0.265	-0.163 0.007	-0.045 0.409	-0.052 0.330	0.007 0.903	-0.036 0.504	-0.066 0.223
WC (cm) *p*	0.418 <0.001	-0.379 <0.001	0.152 0.005	0.189 <0.001	0.393 <0.001	0.031 0.567	-0.261 <0.001
W-H Ratio *p*	0.263 <0.001	-0.228 <0.001	0.039 0.473	0.041 0.440	0.217 <0.001	-0.066 0.225	-0.233 <0.001
BMI (kg/m^2) *p*	0.475 <0.001	-0.41 <0.001	0.215 <0.001	0.243 <0.001	0.451 <0.001	0.07 0.193	-0.26 <0.001
Fasting Glucose (mg/dL) *p*	0.542 <0.001	-0.503 <0.001	-0.235 <0.001	-0.21 <0.001	-0.079 0.14	-0.316 <0.001	-0.545 <0.001
120-min Glucose (mg/dL) *p*	0.431 <0.001	-0.446 <0.001	-0.235 <0.001	-0.251 <0.001	0.089 0.095	-0.419 <0.001	-0.609 <0.001

† log transformed variables.

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; S1PhOGTT and S1PhOGTT: Stumvoll's First Phase and Second Phase Insulin Release, Respectively; $\Delta I_{I0-30}/\Delta G_{0-30}$: Delta Insulin/Delta Glucose Ratio; WC: Waist Circumference; W-H Ratio: Waist-to-Hip Ratio; BMI: Body Mass Index. Hypertension was defined as blood pressure levels ≥140/90 mmHg.

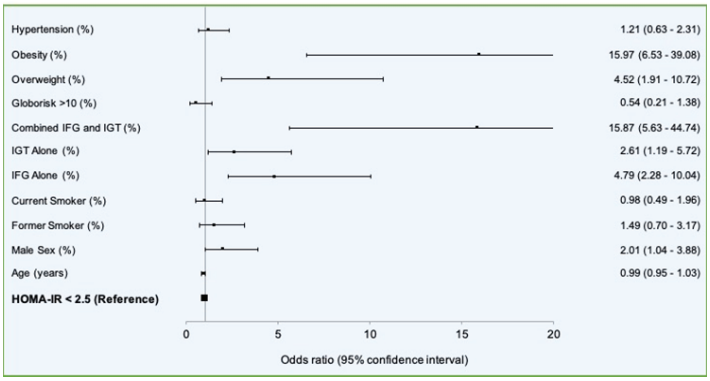

Figure 1. *Variables associated with Insulin resistance in subjects at high risk for Type 2 Diabetes*

Insulin resistance defined as homeostasis model assessment of insulin resistance (HOMA-IR) ≥ 2.5. IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance. Hypertension, obesity, overweight, cardiovascular risk estimated with the Globorisk formula, IFG and IGT (alone or combined), smoking status, sex and age were used as covariates.

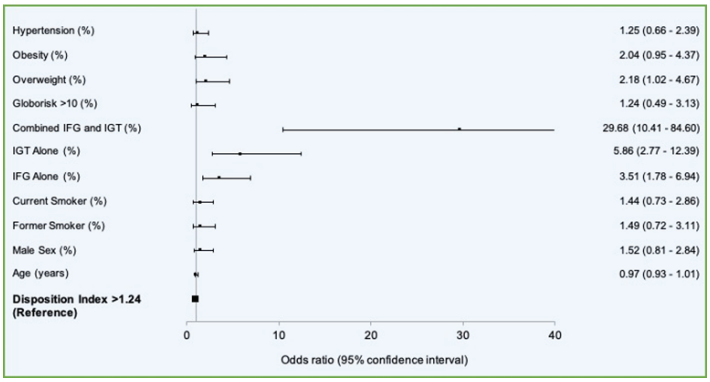

Figure 2. *Variables associated with Impaired beta-cell function in subjects at high risk for Type 2 Diabetes*

Impaired beta-cell function defined as Disposition Index ≥ 1.24. IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance. Hypertension, Obesity, Overweight, cardiovascular risk estimated with the Globorisk formula, IFG and IGT (alone or combined), smoking status, sex and age were used as covariates.

combined IFG and IGT had significantly higher BMI, higher waist circumference, higher waist-to-hip ratio, and higher systolic blood pressure levels. Although subjects with a normal fasting and glucose tolerance test tended to be younger, more likely to be women, and to have lower cardiovascular risk, the univariate analysis showed no significant difference. Regarding the insulin sensitivity indices, patients with combined IFG and IGT had higher HOMA-IR, and lower Matsuda index among all groups ($p<0.05$ for all). The S1PhOGTT and the S2PhOGTT were similar among all groups. Moreover, when the indices of beta-cell function were evaluated, those with normal fasting and glucose tolerance had lower HOMA-B, $\Delta I_{0-30} / \Delta G_{0-30}$, and higher disposition index ($p<0.05$ for all).

Table 3 shows Pearson bivariate correlations between clinical and biochemical characteristics of the subjects and the results of the insulin resistance/secretion and beta-cell function indices. Overall, Globorisk was positively correlated with the HOMA-IR, and negatively correlated with the Matsuda, $S1Ph_{OGTT,}$ $S2Ph_{OGTT}$, $\Delta I_{0-30} / \Delta G_{0-30}$, and the disposition indices ($p<0.05$ for all). Except from $\Delta I_{0-30} / \Delta G_{0-30}$, waist circumference, waist-to-hip ratio and BMI were significantly correlated with all the insulin resistance/secretion and beta-cell function indices.

Figure 1 shows the variables independently associated with insulin resistance assessed with a threshold of HOMA-IR ≤ 2.5 in subjects at primary prevention for T2DM. Compared with subjects who have a HOMA-IR ≤ 2.5 (reference), those with insulin resistance were more likely to be men, and to have higher prevalence of overweight and obesity. Although IFG alone, IGT alone and combined IFG and IGT were significantly associated with higher probability of having a HOMA-IR ≤ 2.5, those with combined IFG and IGT had 15.9 higher odds compared with the rest of patients. On the other hand, figure 2 shows the variables independently associated with impaired beta-cell function in subjects at high risk for T2DM. Compared with subjects who have a disposition index ≤ 1.24 (reference), overweight, but not obesity, was independently associated with impaired beta-cell function. In addition, combined IFG and IGT had 29.7 higher odds to have impaired beta-cell function compared with those that had a normal OGTT.

Discussion

Cardiovascular disease is the leading cause of death in patients with diabetes, and the burden of T2DM and its complications are alarmingly increasing around the world [1–3]. Primary prevention programs are focused on reducing that burden with global strategies directed to timely screen those apparently healthy subjects that are at high risk for developing T2DM, promoting healthier lifestyles, achieving a normal BMI, or in some cases, starting pharmacological treatment [1–4]. As noted, insulin resistance and impaired beta-cell function are considered one of the main pathophysiological mechanism of T2DM, and despite vast knowledge has been reported on the molecular insights of these pathways [6–8,10–13], the incidence of T2DM and its metabolic comorbidities continue to exponentially increase in most countries [1,2,9]. Thus, the early identification of subjects with insulin resistance and reduced beta-cell function in the setting of primary care outpatient clinics is needed. The aim of this cross-sectional study was to report the characteristics of asymptomatic subjects, without any chronic disease, and naïve to any medication for metabolic diseases, who met the criteria to undergo an OGTT by the ADA [21], and to identify which factors could be associated to present impaired beta-cell function and increased insulin resistance. After the patients were classified by the result of the OGTT, the present study found that, although patients with IFG and IGT, alone or combined, have increased insulin resistance and decrease beta-cell function, there was no significant difference on first and late insulin secretion phases. After multiple logistic regression analysis, a BMI >25 kg/m2 and male sex were independently associated with increased insulin resistance. Interestingly, patients with IFG alone had significantly higher risk for insulin resistance than IGT alone, which could suggest that increased hepatic gluconeogesis at night could have a more important role in the whole-body insulin resistance, than the impaired peripheral-tissue glucose intake, as seen in the 120-min glucose result [27]. Moreover, when the beta-cell function was evaluated in the multiple logistic regression analysis, only overweight, but not obesity, was independently associated with decreased beta-cell function. Likewise, patients with IFG alone, IGT alone and combined IFG and IGT had 3.51-, 5.86- and 29.68-fold higher probability to present impaired beta-cell function, respectively.

Despite the glucose clamp techniques are considered to be the gold standard to assess whole-body insulin sensitivity and beta-cell function [14,20], these methods are reserved to research purposes due to its unpracticable use and expensive cost in common clinical practice [16,19–21]. In consequence, several indices have been developed derived from a much simpler OGTT with insulin assay [15,17,19,20]. Using the data from this dynamic test, HOMA-IR and Matsuda indices have shown a high correlation to measure insulin sensitivity in both patients with and without T2DM [15,18,20,24], and more recently the Stumvoll's indices are good surrogates to evaluate first and second phase of insulin secretion [17]. Interestingly, although the threshold values for HOMA-IR in previous reports are quite different [20,24,28], a cut-off point of 2.5 has been consistently to predict diabetes in populations similar to the one in the present study [24,25]. Esteghamati et al, suggested that these inconsistent reports of HOMA-IR reference values are consequence of the assorted clinical methods and the diversity of populations studied in terms of ethnicity, as well as the lack of a worldwide standardized assay for insulin, therefore the distinct assays for insulin would conclusively bring different results for HOMA-IR [24].

Although the HOMA-B and the insulinogenic index ($\Delta I_{0-30} / \Delta G_{0-30}$) were previously considered good markers to evaluate the beta-cell function, nowadays the disposition index is considered the gold standard to determine the remaining beta-cell function, with a cut off value of >1.24 to remain without diabetes in a lapse of 10 years [16,19,20,26,28,29]. Previous data suggest that BMI, adiponectin and IL-6 could independently influence the beta-cell function through the disposition index [8]. Compared with our data, only overweight, but not obesity, was found to be independently associated with impaired beta-cell function despite that BMI>25 kg/m^2 and waist circumference were significantly higher in patients with combined IFG and IGT in the univariate analysis. The last could suggest that BMI could not be useful to screen impaired beta-cell function, because it has been widely accepted that BMI is not a reliable marker of visceral adiposity nor dysfunctional adipose tissue [30]. Moreover, although there is evidence that beta-cells can mount a compensatory response to insulin resistance and overnutrition, the ability to compensate this metabolic disturbance is ephemeral in those subjects that progress from prediabetes to T2DM [7,13,26]. With the course of time, the overproduction of insulin by the compensating beta-cells wields continuous demand for protein synthesis and increased secretion [7,13]. Ultimately, the beta-cell is incapable to sustain the increased workload, and the initial adaptive responses become progressively maladaptive [13]. Either way, the data presented was

only measured with an OGTT, and not with a clamp technique, thus it remains entirely uncertain whether the disposition index threshold used can really resemble the remaining functionality of the beta-cell or not.

One of the strengths of the present study is that subjects selected did not have any comorbidity or other chronic disease different from hypertension and obesity. In addition, most of them had a low-cardiovascular risk estimated with specific coefficients for the Mexican population which considers age, gender, smoking status, systolic blood pressure and total cholesterol [23]. Another strength is that subjects had a complete OGTT with both glucose and insulin measurements performed every 30 minutes. To our knowledge, this is the first study to compositely evaluate HOMA-IR, Matsuda, $S1Ph_{OGTT}$, $S2Ph_{OGTT}$, HOMA-B and the disposition indices in a selected population at high risk for diabetes in Mexico. On the other hand, an important limitation is that authors could not measure other sociodemographic data, such as socioeconomical, biochemical, nutritional or physical activity, that could interfere with the associations that were seen. Additionally, the sample of subjects were selected from a single tertiary medical center in Mexico City, and results may not accurately represent the true behavior of the whole population with high risk for developing diabetes due to possible bias of ethnicity.

In conclusion, BMI >25 kg/m^2 and male sex were independently associated with insulin resistance in patients at risk for T2DM. Likewise, isolated IFG had higher odds to have insulin resistance than IGT alone in this study. On the other hand, isolated-IFG, isolated-IGT and the combination of both had 3.51-, 5.86- and 29.68-fold higher odds to present impaired beta-cell function compared with those subjects that had a normal OGTT. Our results could support the implementation of further studies that could evaluate the associations seen in the present study with the risk on developing T2DM, cardiovascular events and all-cause mortality.

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References

1. Wang H, Naghavi M, Allen C, Barber RM, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388: 1459–1544.
2. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380: 2197–2223.
3. Newman JD, Schwartzbard AZ, Weintraub HS, Goldberg IJ, Berger JS. Primary Prevention of Cardiovascular Disease in Diabetes Mellitus. J Am Coll Cardiol. 2017; 70: 883–893.
4. Green LW, Brancati FL, Albright A. Primary prevention of type 2 diabetes: Integrative public health and primary care opportunities, challenges and strategies. Fam Pract. 2012; 29 (SUPPL. 1).
5. Medina-Urrutia AX, Martínez-Sánchez FD, Posadas-Romero C, Jorge-Galarza E, Martínez-Alvarado M del R, et al. Metabolic control achievement in a population with premature coronary artery disease: results of the genetics of atherosclerotic disease study. Ther Adv Endocrinol Metab. 2020; 11: 204201882094337.
6. Di Pino A, Defronzo RA. Insulin Resistance and Atherosclerosis: Implications for Insulin-Sensitizing Agents. Endocr Rev. 2019; 40: 1447–1467.
7. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev. 2018; 98: 2133–2223.
8. Xiang AH, Black MH, Shu YH, Wu J, MacKay A, et al. Association of weight gain and fifteen adipokines with declining beta-cell function in Mexican Americans. PLoS One. 2018; 13: 1–10.
9. Isomaa B, Almgren P, Tuom T. Cardiovascular Morbidity and Mortality. Diabetes Care. 2001; 24: 683–689.
10. Lechner K, Mckenzie AL, Kränkel N, Von Schacky C, Worm N, et al. High-Risk Atherosclerosis and Metabolic Phenotype: The Roles of Ectopic Adiposity, Atherogenic Dyslipidemia, and Inflammation. Metab Syndr Relat Disord. 2020; 18: 176–185.
11. Vogelzangs N, van der Kallen CJH, van Greevenbroek MMJ, van der Kolk BW, Jocken JWE, et al. Metabolic profiling of tissue-specific insulin resistance in human obesity: results from the Diogenes study and the Maastricht Study. Int J Obes. 2020; 44: 1376–1386.
12. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med. 2014; 371: 1131–1141.
13. Hudish LI, Reusch JEB, Sussel L. β Cell dysfunction during progression of metabolic syndrome to type 2 diabetes. J Clin Invest. 2019; 129: 4001–4008.
14. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol Endocrinol Metab Gastrointest Physiol. 1979; 6.
15. Lorenzo C, Williams K, Haffner SM. Insulin secretion based on the late oral glucose tolerance test period and incident diabetes: The San Antonio Heart Study. Diabet Med. 2012; 29: 151–158.
16. Martínez-Sánchez FD, Vargas-Abonce VP, Guerrero-Castillo AP, Santos-Villavicencio MD los, Eseiza-Acevedo J, et al. Serum Uric Acid concentration is associated with insulin resistance and impaired insulin secretion in adults at risk for Type 2 Diabetes. Prim Care Diabetes. 2020.
17. Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Jarven H, et al. Use of the oral glucose tolerance test to assess insulin release and insulin s e n s i t i v ity. Diabetes Care. 2000; 23: 295–301.
18. Matsuda M, Defronzo RA. Insulin Sensitivity Indices Obtained From Comparison with the euglycemic insulin clamp. Diabetes Care. 1999; 22: 1462–1470.
19. Utzschneider KM, Prigeon RL, Faulenbach M V., Tong J, Carr DB, Boyko EJ, et al. Oral Disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. Diabetes Care. 2009; 32: 335–341.
20. Doi SAR, Ward GM. Examination of the fasting and 2-h plasma glucose in the light of impairment in beta-cell function: what does the epidemiological data tell us? Endocrine. 2014; 48: 170–178.
21. Care D, Suppl SS. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetesd2019. Diabetes Care. 2019; 42: S13–28.
22. Jorge-Galarza E, Martínez-Sánchez FD, Javier-Montiel CI, Medina-Urrutia AX, Posadas-Romero C, et al. Control of blood pressure levels in patients with premature coronary artery disease: Results from the Genetics of Atherosclerotic Disease study. J Clin Hypertens. 2020.
23. Ueda P, Woodward M, Lu Y, Hajifathalian K, Al-Wotayan R, et al. Laboratory-based and office-based risk scores and charts to predict 10-year risk of cardiovascular disease in 182 countries: a pooled analysis of prospective cohorts and health surveys. Lancet Diabetes Endocrinol. 2017; 5: 196–213.
24. Esteghamati A, Ashraf H, Esteghamati AR, Meysamie A, Khalilzadeh O, et al. Optimal threshold of homeostasis model assessment for insulin resistance in an Iranian population: The implication of metabolic syndrome to detect insulin resistance. Diabetes Res Clin Pract. 2009; 84: 279–287.
25. Salgado ALFDA, De Carvalho L, Oliveira AC, Dos Santos VN, Vieira JG, et al. Insulin resistance index (HOMA-IR) in the differentiation of patients with non-alcoholic fatty liver disease and healthy individuals. Arq Gastroenterol. 2010; 47: 165–169.

26. Gallwitz B, Kazda C, Kraus P, Nicolay C, Schernthaner G. Contribution of insulin deficiency and insulin resistance to the development of type 2 diabetes: Nature of early stage diabetes. Acta Diabetol. 2013; 50: 39–45.
27. Yip WCY, Sequeira IR, Plank LD, Poppitt SD. Prevalence of pre-diabetes across ethnicities: A review of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) for classification of dysglycaemia. Nutrients. 2017; 9: 1–18.
28. Ghasemi A, Tohidi M, Derakhshan A, Hasheminia M, Azizi F, et al. Cut-off points of homeostasis model assessment of insulin resistance, beta-cell function, and fasting serum insulin to identify future type 2 diabetes: Tehran Lipid and Glucose Study. Acta Diabetol. 2015; 52: 905–915.
29. Tang W, Fu Q, Zhang Q, Sun M, Gao Y, et al. The association between serum uric acid and residual β -cell function in type 2 diabetes. J Diabetes Res. 2014;2014.
30. Neeland IJ, Ross R, Després JP, Matsuzawa Y, Yamashita S, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol. 2019; 7: 715–725.

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