Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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β-cell function is associated with metabolic syndrome in Mexican subjects

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Aims: The clinical diagnosis of metabolic syndrome does not find any parameters to evaluate the insulin sensitivity (IS) or β-cell function. The evaluation of these parameters would detect early risk of developing metabolic syndrome. The aim of this study is to determine the relationship between β-cell function and presence of metabolic syndrome in Mexican subjects.

Material and methods: This study is part of the Mexican Survey on the Prevention of Diabetes (MexDiab Study) with headquarters in the city of Puebla, Mexico. The study comprised of 444 subjects of both genders, aged between 18 and 60 years and allocated into two study groups: (1) control group of individuals at metabolic balance without metabolic syndrome and (2) group composed of subjects with metabolic syndrome and diagnosed according to the criteria of the Third Report of the National Cholesterol Education Program Expert Panel on Defection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Anthropometric, biochemical, and clinical assessments were carried out.

Results: Average age of the subjects in the control group (n = 254) was 35.7 ± 11.5 years and 42.0 ± 10.7 years for subjects in the metabolic syndrome group (n = 190). Subjects at metabolic balance without metabolic syndrome showed decreased IS, increased insulin resistance (IR), and altered β-cell function. Individuals with metabolic syndrome showed a high prevalence ($P \leq 0.05$) of family history of type 2 diabetes (T2D). This group also showed a significant metabolic imbalance with glucose and insulin levels and lipid profile outside the ranges considered safe to prevent the development of cardiovascular disease and T2D.

Conclusion: The main finding in this study was the detection of altered β-cell function, decreased IS, an increased IR in subjects at metabolic balance, and the progressive deterioration of β-cell function and IS in subjects with metabolic syndrome as the number of features of metabolic syndrome increases.

Keywords: insulin sensitivity, insulin resistance, family history of type 2 diabetes mellitus, metabolic syndrome, b-cell function

Introduction

In recent decades, Mexico has seen a rapid increase in the prevalence of chronic degenerative diseases, particularly those of cardiovascular origin.[1] Among these diseases, the metabolic syndrome is highlighted. Metabolic syndrome, considered as a public health problem worldwide, has been defined as a set of metabolic abnormalities consisting of central obesity distribution, decreased levels of cholesterol linked to low-density lipoprotein cholesterol (LDL-C), high levels of triacylglycerides (TAG), increased blood pressure (BP), and hyperglycemia.[2] Different criteria have been proposed to clinically define this syndrome. The definition used to date is that proposed by the third report from the Adult Treatment Panel (ATP-III) of National Cholesterol

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Education Program (NCEP).[3] This was proposed as a means of identifying individuals with increased coronary risk. Insulin resistance (IR) has been proposed as a key player in the pathophysiology of the metabolic syndrome and is considered as the root cause.[4] However, there are studies that cast doubt on IR as an etiological factor responsible for the development of the metabolic syndrome and its complications.[5]

The interaction between defects in insulin sensitivity (IS) and β-cell function has been proposed as a mechanism for the development of the metabolic syndrome.[5] It has been suggested that β-cell function should be assessed relative to IS because it has been shown that subjects with type 2 diabetes (T2D), subjects at risk for T2D, and those subjects that are in a state of normoglycemia or hyperglycemia have poor β-cell function compared with controls with normal glucose tolerance.[5] β-cell function has been estimated by various groups and shown to be clearly demonstrated that subjects at high risk of developing T2D (older individuals, women with a history of gestational diabetes or polycystic ovary syndrome, subjects with impaired glucose tolerance, and first-degree relatives of individuals with T2D) have impaired β-cell function. Furthermore, the progression from normal glucose tolerance to impaired glucose tolerance and T2D is associated with declining insulin secretion.[5,6] In overweight Latino adolescents with family history of T2D (FH-T2D), impaired fasting glucose is associated with impaired β-cell function and therefore, may identify children likely to be at risk for progression to T2D.[6]

Decreased β-cell function and decreased IS are the two major risk factors for the development of T2D.[7] The β-cell ability to compensate for a decrease in IS enables these individuals to maintain normal glucose levels, notwithstanding β cell can no longer compensate.[8] However, it is still unknown whether β-cell dysfunction, decreased IS, or combination of both defects are the primary abnormalities leading to T2D.[9]

However, the factors that may mediate the physiopathology of the metabolic syndrome are not entirely clear and, to the best of our knowledge, are not well described in Latin American subjects. The scarcity of information currently available regarding these mechanisms hinder our understanding of the primary events leading to the cascade of disorders that characterize this disease. To this end, we studied the relationship between β-cell function and the presence of metabolic syndrome in subjects from Mexico and observed that the assessment of β-cell function in apparently healthy subjects may detect early stages of metabolic abnormalities.

Material and methods

Subjects and setting

Based on the Mexican Diabetes Prevention Study (MexDiab Study), which randomly enrolled individuals from urban and rural communities, the study population was selected during the first stage. Inclusion criteria were Mexican subjects who resided in the city of Puebla, Mexico, of both genders (excluding women who were pregnant or breastfeeding) and aged between 18 and 60 years with or without a FH-T2D. The study population was selected from patients attending the Family Medical Unit No. 2 (UMF-2) of the Instituto Mexicano del Seguro Social (IMSS) in Puebla, Mexico. The protocol was approved by the Scientific Research and Ethics Committee of the IMSS.

Clinical characterization

Participants who accepted to be included in the study were interviewed. A complete clinical history and physical examination were carried out, aimed at detecting the presence of a personal history of chronic or acute use of medications, alternative treatments, smoking, physical activity, obesity, cardiovascular disease (CVD), and FH-T2D. The latter concept was considered positive where there were first-degree relatives (mother, father, siblings, and children) with disease.

Smoking was considered positive if subjects were active smokers (one or more cigarettes daily) and alcoholism if subjects had an alcohol intake >10 beers of 325 mL each or 300 mL of liquor (tequila, wine, whiskey, vodka, rum, and brandy) per month. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and anthropometric measurements (weight, height, and waist circumference [WC]) were measured in a standardized manner.

BP was determined in a sitting position and after 5 minutes of rest in accordance with the Mexican Official Standard (NOM-030-1999-SSA2) for prevention, treatment, and control of hypertension[10] using a Baumanometer (Microlife AG, Heerbrugg, Switzerland) and stethoscope (3M LITTMAN Classic II, Neuss, Germany). The size, weight, and percentage body fat (%BF) were determined using an electronic digital scale (Tanita Body Composition Analyzer, Model TBF-215, Tokyo, Japan) with a capacity of 200 g ± 100 kg. WC was established around the waist (using a fiberglass tape with SECA mark) in a position parallel to the floor at the midpoint between the lower edge of the last rib and the edge of the iliac crest, at the end of expiration. Body mass index (BMI) was calculated using the Quetelet

formula (weight in kilograms divided by height in meters squared).

Assay

Blood sample obtained by venipuncture was taken in all participants after a 12-hour fast. We performed the determination of fasting glucose (Gluc0h) and fasting insulin (Ins0h), total cholesterol (TC), TAG, high-density lipoprotein cholesterol (HDL-C) and 2 hours after a 75-g glucose load for measuring levels of glucose (Glc2h) and insulin (Ins2h). All biochemical determinations were performed according to conventional laboratory protocols using the periodic end point method (enzymatic spectroscopic methods). The levels of plasma glucose and lipid profile were determined using the Synchron CX5 Analyzer System from Beckman Coulter (Fullerton, CA). The determination of insulin was performed by chemiluminescence in a sandwich enzyme immunoassay using anti-insulin mouse monoclonal antibodies with alkaline phosphatase. Luminometer used was the Beckman Coulter Access System.

IR was assessed by homeostatic model assessment (HOMA)-IR using the following formula: ([Glc0h (mmol/L)] × [Ins0h (μU/mL)])/22.517). IR was defined by a HOMA-IR > 2.5.[11] IS was calculated from the index to check the quantitative insulin sensitivity (QUICKI) by the following formula: QUICKI = 1/(log Ins0h + log Glc0h mg/dL) and in accordance with the 0.357 cut-off point; lower numbers represent lower IS.[12]

Determination of β-cell function was performed using the homeostatic model HOMA-β, through the formula: HOMA-β = [20 × Ins0h]/[Gluc0h (mmol/dL) − 3.5].

According to the method of Modan et al[13] hyperinsulinemia was defined as levels of Ins0h equal to or greater than the 75th percentile (≥11.25 μU/mL).

LDL-C was determined using the formula of Friedewald[14] where very low-density lipoprotein (VLDL-C) = TAG/5 and LDL-C = TC − (VLDL-C + HDL-C).

To determine whether there was risk of developing CVD in the subjects, we calculated the rate of Castelli Cardiovascular Index (CVI) with the formula: TC/HDL-C.

TAG/HDL-C index was calculated by dividing the concentration of TAG on HDL-C as determined by Boizel et al.[15] The cut-off point for cardiovascular risk was determined by TAG/HDL-C > 3.

Exclusion criteria were applied to subjects who did not sign informed consent, did not conclude the clinical history or blood sampling, or who had chronic proinflammatory diseases (arthritis, rhinitis, and trauma), endocrine diseases (hyperthyroidism and hypothyroidism), or any chronic diseases (except hypertension and hyperlipidemia). Smoking and alcoholism were also considered as exclusion criteria, as well as subjects who had previous diagnosis of T2D.

Metabolic syndrome was defined according to the criteria of the NCEP ATP-III[3] with WC values adjusted according to the Mexican population as suggested by Zimmet et al[16] (NCEP ATP-III). Diagnosis of metabolic syndrome was established if 3 or more of the following risk factors were present: BP ≥ 130/85 mm Hg, Gluc0h ≥ 100 mg/dL, TAG ≥150 mg/dL, HDL-C in men <40 and women <50 mg/dL, WC ≥ 90 in men and in women ≥80 cm.

Subjects were classified into two study groups: (1) metabolic syndrome group comprised of subjects with metabolic syndrome according to the criteria of NCEP ATP-IIIm and (2) control group comprised of subjects at metabolic balance without disabling physical illness and not using any medications. The control group met the following biochemical parameters: Gluc0h < 100 mg/dL, TAG ≤ 150 mg/dL, HDL-C ≥ 40 mg/dL, and BP < 130/<85 mm Hg. The control group was divided into subjects with low IS (QUICKI index <0.357) and subjects with normal IS (QUICKI index ≥0.357). Metabolic syndrome subjects were divided into three groups according to the number of features of metabolic syndrome according to NCEP ATP-IIIm criteria.

Subsequently, all subjects were grouped according to the cut-off point of QUICKI index to determine the relationship between IS and the presence of metabolic syndrome.

Statistical analysis

The results were expressed as mean ± standard deviation. Differences between groups were considered significant at $P \leq 0.05$. To assess the normality, Kurtosis Normality of Residuals test was used. Continuous variables with normality and equal variances were analyzed using one-way analysis of variance. Differences between groups were analyzed by Tukey–Kramer test or. If there were not normality but equal variances, Kruskal–Wallis test was used and differences between groups were determined by Kruskal–Wallis multiple comparisons of Z value. Nonparametric continuous variables were analyzed using Mann–Whitney *U* test and to establish their proportions, Fisher's exact test was used. Spearman correlation test was used for variables. Data were analyzed with SPSS software (v. 12.0 for Windows; SPSS Inc., Chicago, IL).

Results

Of the subjects participating in the MexDiab Study and who were residents of the city of Puebla, Mexico, only 444 met the inclusion criteria to remain in the study. This population was assigned, according to previously established guidelines, to a control group (n = 254) and to the metabolic syndrome group (n = 190). Average age of the subjects in the control group was 35.7 ± 11.5 years and 42.0 ± 10.7 years for the metabolic syndrome group, with significant statistical difference between groups ($P \leq 0.05$).

Metabolic syndrome subjects compared with control group subjects had higher levels of SBP (115 ± 15 vs 103 ± 12 mm Hg) and DBP (77 ± 10 vs 69 ± 8.0 mm Hg; $P \leq 0.05$). In addition, metabolic syndrome subjects had a higher prevalence of FH-T2D compared with control group (70.0% vs 52.4%; $P \leq 0.05$).

Table 1 describes the anthropometric and biochemical characteristics of study subjects with significant differences ($P \leq 0.05$) between groups according to the following variables: %BF, BMI, and WC. Moreover, taking into account data from the biochemical analysis, we found that metabolic syndrome group subjects showed a significant metabolic imbalance with levels of glucose, insulin, and lipid profile outside the ranges considered safe to prevent the development CVD and T2D. Table 1 also shows the variables of IR, IS, as well as β-cell function. One can see that the β-cell function is increased in subjects with metabolic syndrome and that matches with the lower IS present in these subjects. In addition, metabolic syndrome group presented a higher cardiovascular risk (assessed with CVI) compared with the control group ($P \leq 0.05$). This is supported by determining the TAG/HDL-C index, which was higher in the metabolic syndrome group compared with the control group ($P \leq 0.05$; Table 2); 161 subjects with metabolic syndrome had TAG/HDL-C > 3.

Control group was divided according to the cut-off point of the QUICKI index (≥0.357 and <0.357; Table 3) in order to show the metabolic parameters to try to define the "premetabolic syndrome group". We note that subjects at metabolic balance without metabolic syndrome but with IS low, showed levels of IR and β-cell function increased compared with the group of subjects at metabolic balance with adequate IS.

The prevalence of the features of the metabolic syndrome according to the criteria of NCEP ATP-IIIm was as follows: abdominal obesity (98.95%), hypertriglyceridemia (74.74%), low HDL-C (90.53%), hypertension (23.16%), and altered gluc0h (55.26%). Table 4 shows the characteristics of the subjects in the metabolic syndrome group by number of features of metabolic syndrome according to the criteria of NCEP ATP-IIIm. It is demonstrated that with increased number of features of metabolic syndrome, there is increased abdominal obesity, BP, and glucose, insulin and TAG levels. It is also important to note that the degree of IR and IS, as well as β-cell function, is different between groups ($P \leq 0.05$).

Correlation analysis showed a strong relationship ($P \leq 0.05$) between the following variables that are

Table 1 Anthropometric and biochemical characteristics of study groups

	Study groups	
	Control n = 254	Metabolic syndrome n = 190
%BF	31.7 ± 8.3	36.7 ± 6.9*
BMI (kg/m^2)	26.6 ± 4.6	30.9 ± 4.7**
WC (M) (cm)	90.1 ± 14.8	103.7 ± 11.5**
WC (W) (cm)	88.1 ± 10.8	98.7 ± 10.4**
Gluc0h (mg/dL)	88.6 ± 6.4	105.4 ± 25.6*
Gluc2h (mg/dL)	104.1 ± 20.6	143.3 ± 57.0*
Ins0h (μU/mL)	6.7 ± 3.3	11.9 ± 5.8*
Ins2h (μU/mL)	44.4 ± 29.4	86.1 ± 66.1*
HOMA-IR	1.5 ± 0.8	3.1 ± 1.9*
HOMA-β	98.9 ± 55.8	115.2 ± 62.3**
QUICKI	0.37 ± 0.03	0.33 ± 0.03*

Notes: Results are expressed as mean ± standard deviation.
*P # 0.05, Mann–Whitney *U* test; **P # 0.05, Kruskal–Wallis one-way analysis of variance.
Abbreviations: M, men; W, women; %BF, % body fat; BMI, body mass index; WC, waist circumference; Glc0h, fasting glucose; Gluc2h, glucose 2 hours after a 75-g oral glucose load; Ins0h, fasting insulin; Ins2h, insulin 2 hours after a 75-g oral glucose load; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; QUICKI, index to check the quantitative insulin sensitivity.

Table 2 Lipid profile of study groups

	Study groups	
	Control n = 254	Metabolic syndrome n = 190
TC (mg/dL)	186.4 ± 36.8	201.3 ± 42.2*
HDL-C (mg/dL)	47.4 ± 12.0	37.0 ± 8.5**
LDL-C (mg/dL)	117.9 ± 29.8	124.1 ± 36.8
VLDL-C (mg/dL)	21.1 ± 7.9	40.1 ± 17.5**
TAG (mg/dL)	105.3 ± 39.3	200.5 ± 87.5**
CVI	4.1 ± 1.0	5.6 ± 1.3**
TAG/HDL-C	2.4 ± 1.0	5.8 ± 3.0**

Notes: Results are expressed as mean ± standard deviation.
*P # 0.05, Kruskal–Wallis one-way analysis of variance; **P # 0.05, Mann–Whitney *U* test.
Abbreviations: TC, total cholesterol; HDL-C, cholesterol combined with high-density lipoprotein; LDL-C, cholesterol combined with low-density lipoprotein; VLDL-C, cholesterol combined with very low-density lipoprotein; TAG, triacylglycerides; CVI, Castelli Cardiovascular Index.

Table 3 Comparison of metabolic variables in control group according to the cut-off point 0.357 of the QUICKI index

	Control study group	
	QUICKI ≥ 0.357 n = 175	QUICKI < 0.357 n = 79
Age (years)	35.6 ± 11.3	34.6 ± 11.5
BMI (kg/m²)	25.4 ± 3.7	28.8 ± 5.2*
SBP (mm Hg)	101.2 ± 11.9	103.2 ± 10.5
DBP (mm Hg)	68.1 ± 8.3	70.4 ± 7.4**
Gluc0h (mg/dL)	86.6 ± 6.5	91.3 ± 5.3*
Gluc2h (mg/dL)	99.7 ± 19.5	108.1 ± 15.7**
Ins0h (μU/mL)	4.7 ± 1.5	9.7 ± 2.8***
Ins2h (μU/mL)	33.0 ± 20.8	60.4 ± 29.9***
HOMA-IR	1.0 ± 0.3	2.2 ± 0.6***
HOMA-β	77.0 ± 36.3	132.2 ± 69.5***
TC (mg/dL)	182.9 ± 35.8	181.6 ± 34.1
HDL-C (mg/dL)	50.0 ± 12.9	42.7 ± 10.2*
TAG (mg/dL)	92.4 ± 29.7	102.8 ± 29.7*
TAG/HDL-C	2.0 ± 0.8	2.6 ± 1.0***
CVI	3.8 ± 0.9	4.4 ± 0.9*

Notes: Results are expressed as mean ± standard deviation.
*P # 0.05, Kruskal–Wallis one-way analysis of variance; **P # 0.05, one-way analysis of variance; ***P # 0.05, Mann–Whitney *U* test.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Glc0h, fasting glucose; Gluc2h, Glucose 2 hours after a 75-g of glucose oral load; Ins0h, fasting insulin; Ins2h, insulin 2 hours after 75-g of oral glucose load; TC, total cholesterol; HDL-C, cholesterol combined with high-density lipoprotein; TAG, triacylglycerides; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; QUICKI, index to check the quantitative insulin sensitivity; FH-T2D, family history of type 2 diabetes mellitus; CVI, Castelli Cardiovascular Index.

highly relevant to this study: BMI showed a correlation with HOMA-IR (r = 0.5389), QUICKI (r = −0.5392), and HOMA-β (r = 0.2555). The relationship between BMI and IS change among the groups: control group (r = −0.2728, $P \leq 0.01$), subjects with metabolic syndrome diagnosed with three criteria (r = −0.4066, $P \leq 0.01$), and subjects with metabolic syndrome diagnosed with five criteria (r = −0.5778, $P \leq 0.01$). Among these groups, there was no change in the relationship between BMI and HOMA-β. In subjects with metabolic syndrome, HOMA-β correlated significantly ($P \leq 0.01$) with TAG (r = 0.1682), glc0h (r = −0.4200), HDL-C (r = −0.2315), and WC (r = 0.2017). In addition, the diagnosis of metabolic syndrome correlated with HOMA-β (r = 0.1473) and QUICKI (r = −0.5809), and between HOMA-β and QUICKI, there was a significant inverse relationship (r = −0.6234, $P \leq 0.01$).

Both study groups were divided according to the cut-off point of the QUICKI index (≥0.357 and <0.357; Table 5) in order to determine the relationship among IS, β-cell function, and presence of metabolic syndrome. We found

Table 4 Characteristics of the subjects of the metabolic syndrome group according to number of features of metabolic syndrome according to the criteria of the NCEP ATP-IIIm

	Study groups		
	3 n = 86	4 n = 81	5 n = 23
Age (years)*	38.0 ± 10.0[a]	46.1 ± 9.9[b]	46.3 ± 10.9[b]
BMI (kg/m²)**	30.6 ± 4.6	30.7 ± 4.7	32.6 ± 5.0
WC (cm)**	98.7 ± 11.2[a]	100.6 ± 11.0[ab]	103.5 ± 8.7[b]
SBP (mm Hg)*	112.2 ± 12.0[a]	113.8 ± 15.9[a]	127.0 ± 13.3[b]
DBP (mm Hg)*	75.5 ± 9.3[a]	76.5 ± 9.4[a]	84.3 ± 7.7[b]
Gluc0h (mg/dL)**	100.7 ± 27.3[a]	109.1 ± 26.6[b]	109.5 ± 7.6[c]
Gluc2h (mg/dL)**	129.9 ± 53.3[a]	150.1 ± 60.6[b]	169.7 ± 44.7[c]
Ins0h (μIU/mL)**	11.5 ± 5.9	11.8 ± 5.6	13.5 ± 6.4
Ins2h (μIU/mL)**	77.1 ± 57.1[a]	87.6 ± 67.2[ab]	114.0 ± 85.6[b]
HOMA-IR**	2.9 ± 2.0[a]	3.2 ± 1.7[ab]	3.7 ± 1.8[b]
HOMA-β**	129.2 ± 73.3[a]	103.5 ± 48.1[b]	104.1 ± 52.3[ab]
QUICKI*	0.34 ± 0.03[a]	0.33 ± 0.02[ab]	0.32 ± 0.02[b]
TC (mg/dL)**	191.2 ± 37.5[a]	208.3 ± 44.5[b]	214.4 ± 43.6[b]
HDL-C (mg/dL)**	35.6 ± 9.8[a]	38.4 ± 7.3[b]	37.6 ± 6.6[ab]
LDL-C (mg/dL)**	120.5 ± 30.3	126.1 ± 42.9	130.9 ± 35.7
VLDL-C (mg/dL)**	35.1 ± 15.9[a]	43.7 ± 18.3[b]	45.8 ± 15.9[b]
TAG (mg/dL)**	175.7 ± 79.5[a]	218.7 ± 91.6[b]	229.2 ± 79.3[b]
TAG/HDL-C**	5.3 ± 2.8	6.1 ± 3.3	6.3 ± 2.3
CVI**	5.6 ± 1.4	5.6 ± 1.3	5.8 ± 1.1

Notes: Results are expressed as mean ± standard deviation.
*P # 0.05, one-way analysis of variance/Tukey–Kramer; **P # 0.05, Kruskal–Wallis one-way analysis of variance/Kruskal–Wallis multiple comparisons. Different letters (a, b, c) in a row indicate significant difference (P # 0.05) between groups.
Abbreviations: NCEP ATP-IIIm, third expert panel of the national cholesterol education program-modified; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; Glc0h, fasting glucose; Gluc2h, Glucose 2 hours after a 75-g of glucose oral load; Ins0h, fasting insulin; Ins2h, insulin 2 hours after 75-g of oral glucose load; TC, total cholesterol; HDL-C, cholesterol combined with high-density lipoprotein; LDL-C, cholesterol combined with low-density lipoprotein; VLDL-C, cholesterol combined with very low-density lipoprotein; TAG, triacylglycerides; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; QUICKI, index to check the quantitative insulin sensitivity; CVI, Castelli Cardiovascular Index.

that there was a significant difference between groups ($P \leq 0.05$) with regard to anthropometric and biochemical variables. It was further noted that the QUICKI ≥ 0357 group showed the least number of subjects diagnosed with metabolic syndrome and a better β-cell function compared with the QUICKI < 0.357 group (15.6% vs 62.4%, respectively, $P \leq 0.05$). FH-T2D was not different between these groups.

In this study, besides evaluating the IS using the QUICKI index, it was also assessed with HOMA-S% index. Similar results were found to apply to both indexes.

Discussion

Metabolic syndrome is a disease that is considered as a growing public health problem worldwide and has been

Table 5 Comparison of metabolic variables in 444 study subjects according to the cut-off point 0.357 of the QUICKI index

	Study groups	
	QUICKI ≥ 0.357 n = 186	**QUICKI < 0.357 n = 258**
Metabolic syndrome (%)	15.6	62.4*
Age (years)	39.2 ± 10.9	37.8 ± 12.1
BMI (kg/m^2)	25.8 ± 3.8	30.3 ± 5.1**
WC (cm)	86.7 ± 10.0	98.3 ± 12.1***
%BF	29.9 ± 8.4	36.6 ± 6.7**
FH-T2D (%)	55.9	62.8
SBP (mm Hg)	103.8 ± 12.9	110.8 ± 14.4***
DBP (mm Hg)	69.4 ± 8.7	74.8 ± 9.5**
Gluc0h (mg/dL)	88.1 ± 8.1	100.8 ± 22.0**
Ins0h (μU/mL)	4.8 ± 1.4	11.9 ± 4.9**
HOMA-IR	1.1 ± 0.3	3.0 ± 1.6**
HOMA-β	76.5 ± 40.7	126.9 ± 61.3**
HDL-C (mg/dL)	47.6 ± 12.9	39.6 ± 9.6**
TAG (mg/dL)	109.7 ± 50.8	172.3 ± 86.5**
TAG/HDL-C	2.5 ± 1.5	4.8 ± 3.0**
CVI	4.2 ± 1.3	5.1 ± 1.3***

Notes: Results are expressed as mean ± standard deviation.
*$P \leq 0.05$, Fisher's exact test for two proportions; **$P \leq 0.05$, Mann–Whitney *U* test; ***$P \leq 0.05$, Kruskal–Wallis one-way analysis of variance.
Abbreviations: BMI, body mass index; WC, waist circumference; %BF, % body fat; SBP, systolic blood pressure; DBP, diastolic blood pressure; Glc0h, fasting glucose; Ins0h, fasting insulin; HDL-C, cholesterol combined with high-density lipoprotein; TAG, triacylglycerides; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; QUICKI, index to check the quantitative insulin sensitivity; FH-T2D, family history of type 2 diabetes mellitus; CVI, Castelli Cardiovascular Index.

associated with a five fold increase in the prevalence of T2D and a greater than two fold increase in CVD prevalence.[16,17] We found that the assessment of β-cell function in relation to IS in subjects at metabolic balance without metabolic syndrome may detect early stages of metabolic abnormalities that characterize the metabolic syndrome and not only achieve early detection, but also enable strategies for prevention.

A surprise finding in this study was the detection of subjects at metabolic balance from the control group who presented glucose, TAG, HDL-C, and TC values within the appropriate range, but higher β-cell function, increased IR and decreased IS, similar to those seen in participants with metabolic syndrome. Therefore, these findings suggested that this may be the initial phase of the metabolic syndrome (premetabolic syndrome phase) and these metabolic abnormalities may serve as indicators and enable early detection of this disease and may be considered as a tool to prevent its development.

When analyzing the number of features of metabolic syndrome in the group of subjects with metabolic syndrome, it was observed that as age increased, the number of features of metabolic syndrome also increased. We also found that metabolic disturbances of the initial metabolic syndrome (subjects with only three diagnostic criteria of metabolic syndrome) are alterations in lipid profile, increase in β-cell function, increase of IR, decrease in IS, and adaptive hyperinsulinemia. Subsequently, as the number of diagnostic criteria of metabolic syndrome increased, we observed a dramatically and statistically significant increased in the levels of BP and glucose, we detected the gradual decrease of β-cell function and the IS.

As in the metabolic syndrome (observed in this study), in T2D the hyperglycemia is clearly the result of the interaction of defects in both IS and β-cell function. Thus with the realization that IS is a major determinant of the degree of β-cell function, it has become clear that defects in β-cell function are absolutely critical to the development of T2D. Furthermore, it has been demonstrated that defects in β-cell function are present long before the diagnostic criterion for T2D has been met.[5]

This is supported by the study of Festa et al[18] in African-Americans, Hispanics, and white non-Hispanic study subjects. These authors found that in all three ethnic groups after a follow-up of 5.2 years, IS and β-cell function decreased in subjects on transition from tolerant to intolerant to glucose and glucose intolerant to T2D. They also report that subjects with glucose tolerance who remained as tolerant despite the increase in body weight had the highest levels of IS and appropriate β-cell function in comparison with other subjects.

In addition, Arslanian et al[19] found that children with FH-T2D compared with those who had no FH-T2D showed diminished IS and had a lower clearance of insulin as well as a disturbed relationship between the action of insulin and β-cell compensation. This is consistent with that reported in our study where subjects with metabolic syndrome had a higher prevalence of FH-T2D and lower IS and altered β-cell function in comparison with the control group.

According to the results reported in this study and others,[20,21] one can see that the variation in the insulin released in response to changes in the IS are the result of changes in the secretory capacity of β cell, this is observed in the different study groups. Thus, subjects with reduced IS have increased responses to glucose. On the other hand, insulin responses are small when IS is high. As expected, there was an inverse relationship between

β-cell function and the IS in subjects both with and without metabolic syndrome. This relationship was also reported by Dixon et al[22] in nondiabetic subjects both before and after weight loss.

The importance of IS, as a modulator of β-cell function, is the detection of subjects with high risk of development of T2D, altered β-cell function is evident at a time when the fasting plasma glucose concentration is still well within the normal range.[5]

β-cell function is influenced throughout the life by a number of factors, some of which are potentially reversible. Abnormal β-cell function often has a genetic basis and precedes the development of T2D. β-cell function deteriorates with age, but more rapidly in those with impaired glucose tolerance.[22–26] Impaired insulin action and hyperglycemia adversely affect peripheral organ function and promote the development of other metabolic abnormalities characteristic of the metabolic syndrome.[27]

In this study, metabolic syndrome group subjects compared with control group are in a state of compensatory hyperinsulinemia to the state of low IS, which is consistent with the increase in β-cell function present in these individuals. In addition, the group of subjects with decreased IS showed a higher prevalence of metabolic syndrome in comparison with the group with normal IS. This has also been reported in other studies,[12] in which the population was of Czech origin and was initially divided into several groups depending on the metabolic alterations that had, like hyperlipidemia, glucose intolerance or both alterations, the QUICKI index <0.357 distinctly identified patients with manifestations of metabolic syndrome.

Quantifying IS and β-cell function in humans is of great importance for epidemiological studies, clinical and basic science investigations, and eventual use in clinical practice. Direct and indirect methods of varying complexity are currently employed for these purposes. Some methods rely on steady-state analysis of glucose and insulin, whereas others rely on dynamic testing. Thus, optimal choice and employment of a specific method depend on the nature of the studies being performed.

Simple surrogate indexes for IS and β-cell function are available that are derived from blood insulin and glucose concentrations under fasting conditions (steady state) or after an oral glucose load (dynamic). In particular, QUICKI index has been validated extensively against the reference standard glucose clamp method.[28] QUICKI index is a simple, robust, accurate, reproducible method that appropriately predicts changes in IS.[29] This index has been widely used[30–32] and validated and has shown an excellent linear correlation with the glucose clamp index of IS and was significantly better than the minimal model index of IS at predicting IS, based on data from 116 glucose clamps obtained from nonobese, obese, T2D, and hypertensive subjects.[33]

On the other hand, the HOMA-β index is the result of a computer model. This model has been used to predict the homeostatic concentrations of glucose and insulin which arise from varying degrees β-cell deficiency and IR.[34] Comparison of a patient's fasting values with the model's predictions allows a quantitative assessment of the contributions of IR and deficient β-cell function to the fasting hyperglycemia (HOMA).[34] The accuracy and precision of the estimate have been determined by comparison with independent measures of IR and β-cell function using hyperglycemic and euglycemic clamps and an intravenous glucose tolerance test.[34] This index has been widely used.[35–37]

Conclusion

In conclusion, this study detected altered β-cell function, decreased IS, an increased IR in subjects at metabolic balance without metabolic syndrome, and the progressive deterioration of β-cell function and IS in subjects with metabolic syndrome as the number of features of metabolic syndrome increases. This study suggests that the assessment of β-cell function in relation to IS in subjects at metabolic balance may detect early stages of metabolic abnormalities (premetabolic syndrome phase) that characterize metabolic syndrome and not only detect at an early stage, but also enable prevention strategies. The indices QUICKI and HOMA-β can be used in clinical practice to easily and accurately estimate the IS and β-cell function, respectively, in subjects at risk.

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Prof María del Carmen Sánchez Guillén, MD, MSc, PhD, passed away on November 27, 2009 during the final preparations of this manuscript. Her friendship, collegiality, talent, and creativity will be sorely missed.

Disclosure

The authors report no conflicts of interest in this work.

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