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Misclassification of subjects with insulin resistance and associated cardiovascular risk factors by homeostasis model assessment index. Utility of a postprandial method based on oral glucose tolerance test

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Abstract

Different methods are available for assessing insulin sensitivity in the fasting state. However, insulin resistance (IR) is initially a postprandial disturbance; and usually, when basal (fasting) disturbance appears, the process has been in progress for some time. Our aim was to investigate if a postprandial measurement, performing an oral glucose tolerance test (OGTT), is more sensitive than fasting values. We wished to identify early IR states in healthy, nonobese individuals and ascertain if this situation was associated with other cardiovascular risk factors. A total of 90 nonobese, nondiabetic, and nonsmoker individuals were studied. They were divided into 3 groups according to IR state—group 1: non-IR—homeostasis model assessment of IR ($HOMA_{IR}$) and insulin sensitivity index of Matsuda-De Fronzo (ISI-Mat) were normal ($HOMA_{IR}$ <3.2 and ISI-Mat >4.0); group 2: with IR post-OGTT (ISI-Mat ≤4.0 and $HOMA_{IR}$ <3.2); and group 3: subjects with IR in basal conditions ($HOMA_{IR}$ ≥3.2). An intravenous glucose tolerance test to compare both indices was also performed. In 14.4% of subjects, the fasting $HOMA_{IR}$ values failed to identify IR (false-negative results). The ISI-Mat values were better correlated than $HOMA_{IR}$ (r = 0.875, P = .0001 and r = −0.631, P = .0001, respectively) with insulin sensitivity index obtained with intravenous glucose tolerance test. Subjects with IR had higher prevalence of a cluster of cardiovascular risk factors than non-IR subjects. These data show that that a significant percentage of subjects were misclassified with $HOMA_{IR}$. Early identification of IR by OGTT was associated with other cardiovascular risk factors. The OGTT is a simple method that could be applied to accurately identify IR subjects in the general population.

1. Introduction

Cardiovascular diseases are the leading cause of death in developed countries. In the last years, insulin resistance (IR) has been identified as an important cardiovascular risk factor. It is a pathologic situation with a genetic background and important influence of abdominal obesity and sedentary habits. Insulin resistance is characterized by the absence of physiologic response of peripheral tissues to insulin action, leading to the metabolic and hemodynamic disturbances known as the *metabolic syndrome* [1]. The main features of this condition include dyslipidemia (high triglyceride and low high-density lipoprotein cholesterol [HDL-C] levels), hypertension, glucose intolerance or type 2 diabetes mellitus, hyperuricemia or gout, abdominal obesity, hypercoagulability and defects in the fibrinolytic system, hyperandrogenism, fatty liver, and an increased incidence of coronary heart disease [2].

The interest of IR and metabolic syndrome lies in their high prevalence in the population and the associated high death rate, fundamentally through coronary heart disease, even in nondiabetic subjects [3,4]. The connection between

The research was approved by the appropriate committee of our institution. Patients gave written informed consent.

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IR, hyperinsulinemia, and cardiovascular disease has been established by several studies [5,6]; and IR has been identified as an independent risk factor [7]. Therefore, a simple test for identifying early insulin-resistant individuals is important both for population-based research and in clinical practice to prevent type 2 diabetes mellitus and cardiovascular disease.

Different methods are available for assessing insulin sensitivity. However, IR is initially a postprandial disturbance; and usually, when basal (fasting) disturbances appear, the process has been in progress for some time. Therefore, studies based in basal measurements could fail to identify individuals who are already insulin resistant. Our aim was to investigate if a postprandial approach, following an oral glucose tolerance test (OGTT), is more sensitive than basal (fasting) methods, usually performed in clinical practice. Our purpose was to identify early IR state in healthy nonobese individuals and ascertain if this situation was associated with other cardiovascular risk factors.

2. Subjects and methods

Participants were recruited by voluntary participation through advertisement among hospital staff and personnel. After clinical screening (medical history, physical examination, and laboratory tests), only healthy subjects who fulfilled inclusion criteria were included into the study.

2.1. Subjects

A total of 90 subjects, 66 men and 24 women, aged 18 to 65 years, were studied. The inclusion criteria were as follows: normal glucose metabolism (fasting blood glucose <6.1 mmol/L, 2-hour postprandial glucose <7.8 mmol/L), fasting plasma triglyceride level less than 2.25 mmol/L, and general analytical evaluation (hepatic, renal, thyroid function, complete blood count, uric acid, and standard urine analysis) within normal limits. All subjects were nonsmokers (never smoked or absence of smoking for at least the preceding 2 years) and were not taking medication for at least the preceding 3 months. Alcohol consumption was less than 30 g/d. Body weight and physical activity habits were stable for 3 months preceding the study. The absence of clinical manifestations of cardiovascular disease was determined.

Clinical history was obtained from all subjects, including age, sex, personal medical history, smoking and alcohol consumption, levels of physical exercise, previous history of high blood pressure or diabetes, and symptoms of coronary heart disease, ischemic stroke, or peripheral vascular disease. Family history of high blood pressure, diabetes, coronary heart disease, or dyslipidemia was also ascertained.

The study was approved by the ethical committee of our hospital, and the subjects gave written informed consent.

2.2. Methods

2.2.1. Clinical and anthropometric parameters

In all participants, body weight and height, body mass index (BMI), and waist circumference were measured using standard methods. Blood pressure was measured after a rest period of 10 minutes, and readings were recorded at 5-minute intervals in the sitting position. Blood samples were collected after a 12-hour overnight fast and deposited in dry tubes with EDTA. The plasma was separated immediately using refrigerated centrifugation at 2500 rpm for a period of 10 minutes. The samples were processed either immediately or during the first week after conservation at −20°C. As previously described [8], plasma total cholesterol, triglyceride, and glucose levels were determined using enzymatic methods; HDL-C was measured after precipitation with polyanions. Apolipoprotein B was determined by immunoturbidimetry and insulin by radioimmunoassay.

2.2.2. Insulin resistance determination

All tests were performed in the Metabolic Unit adjacent to the laboratory, with a clinician or a nurse in attendance, in accordance with standard procedures.

Basal method: At 8:00 AM, following a 12-hour overnight fasting, plasma glucose and insulin were determined to calculate the homeostasis model assessment index ($HOMA_{IR}$), which is defined as fasting insulin (in microunits per milliliter) × fasting plasma glucose (in millimoles per liter)/22.5 [9].

Postprandial method: An OGTT with 75 g of glucose was performed at 8:00 AM following a 12-hour overnight fasting. Blood samples were collected at −15, 0, 30, 60, 90, and 120 minutes for measurement of plasma glucose and insulin concentrations. Insulin sensitivity index of Matsuda-De Fronzo (ISI-Mat) was calculated as previously described [10]: ISI-Mat = 10 000/T (fasting plasma glucose × fasting plasma insulin) × (mean plasma glucose × mean plasma insulin). The mean values of glucose and insulin were obtained during OGTT at 30, 60, 90, and 120 minutes.

In addition, a direct index for the measurement of IR was calculated. An intravenous glucose tolerance test (IVGTT) was performed in a group of 30 of these subjects (random selection). Multiple blood sample extractions for the measurement of glucose and insulin were conducted following 12-hour fast, with the patient resting supine for at least 15 minutes before the beginning of the test. Two baseline venous blood samples ($t = -15$ and $t = -5$ minutes) for glucose and insulin were taken. At $t = 0$, a bolus of 300 mg glucose per kilogram body weight in a 50% glucose-saline solution was administered over a period of approximately 60 seconds. At $t = 20$ minutes, a bolus of 0.03 U/kg body weight of insulin (Actrapid, Novo Nordisk Pharma, Bagsvaerd, Denmark) was administered. Following the 2 baseline samples, 26 more blood samples were taken for the determination of glucose and insulin at times $t = 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 25, 27, 30, 40, 50, 60, 70, 90,$

100, 120, 140, 160, and 180 minutes [11]. The indices of insulin sensitivity (Si) and utilization of glucose independent of insulin were calculated following the method/methodology described by Pacini and Bergman [12] using the MINMOD program [8].

The cutoff for IR of $HOMA_{IR}$ was based on the 75th percentile of the general population (HOMA ≥3.2) as previously described [13]. The cutoff for insulin sensitivity of ISI-Mat was calculated as the 25th percentile of our healthy subjects without abdominal obesity (ISI-Mat ≤4.0).

After completion of these tests, we classified the subjects in 3 groups according to the presence or absence of IR:

Group 1: non-IR. The $HOMA_{IR}$ and ISI-Mat were normal ($HOMA_{IR}$ <75th percentile and ISI-Mat >25th percentile).
Group 2: with IR post-OGTT (ISI-Mat ≤25th percentile). The $HOMA_{IR}$ was normal (<75th percentile).
Group 3: Subjects showed criteria for IR in the fasting measurements ($HOMA_{IR}$ ≥75th percentile).

The Adult Treatment Panel III diagnostic criteria were used to establish the presence of the metabolic syndrome [14].

2.3. Statistical analyses

All analyses were conducted using the SPSS 15 version (SPSS, Chicago, IL), and the results were expressed as the mean ± standard deviation. Because of the sample size and the measurement of variables that do not fulfill the criteria of normality, we used nonparametric tests for the statistical analyses. For the comparison of means, we used the Mann-Whitney *U* test to compare 2 variables or the test of Kruskal-Wallis for 3 or more variables. For the comparison of proportions, we used the Fisher exact test. The degree of relationship between 2 quantitative variables was analyzed by Spearman correlation coefficient. Multiple regression analysis was performed to assess possible differences between the ISI-Mat group and $HOMA_{IR}$ group.

3. Results

Clinical and biochemical characteristics of the 3 groups (non-IR, IR post-OGTT, and basal IR) are shown in Table 1. The percentage of subjects included in each group was as follows (χ^2 = 0.0001): 68.9% had no IR, 14.4% were only classified as insulin resistant with the OGTT index, and 16.7% were identified with both methods (OGTT and basal). In accordance with the classification criteria, there were significant differences in fasting insulin, $HOMA_{IR}$, and ISI-Mat. There were no differences in age, sex, and BMI between groups. We found statistical differences in waist circumference between groups. However, the results were maintained after the correction by waist circumference. There were no statistical differences between groups 2 and 3 (only in fasting insulin and $HOMA_{IR}$ index because of inclusion criteria). On the contrary, group 1 showed statistical differences compared with IR groups in most of the clinical and biochemical parameters studied (Table 1).

The correlations between the different methods showed that $HOMA_{IR}$ ($r = -0.631$, $P = .0001$) and ISI-Mat obtained

Table 1
Anthropometric, clinical characteristics, plasma lipid values, glucose, insulin, and IR index in the studied subjects

	Total group (N = 90)	Group 1 (n = 62)	Group 2 (n = 13)	Group 3 (n = 15)	*P* Kruskal-Wallis
Age (y)	46.5 ± 9.3	45.2 ± 9.0	48.9 ± 10.2	49.6 ± 9.0	.101
Sex (male/female)	66/24	46/16	8/5	12/3	χ^2 .926
BMI (kg/m^2)	26.2 ± 2.1	26.1 ± 2.0	25.9 ± 2.9	26.9 ± 1.7	.119
Waist circumference (cm)	92.0 ± 9.5	90.5 ± 8.6	92.5 ± 11.6	98.1 ± 9.3*	.001
Systolic blood pressure (mm Hg)	127.7 ± 12.6	124.4 ± 9.6	133.3 ± 13.8*	136.9 ± 16.3*	.328
Diastolic blood pressure (mm Hg)	75.7 ± 8.0	73.4 ± 7.3	80.5 ± 6.7*	81.0 ± 7.9*	.877
TC (mmol/L)	5.2 ± 0.9	5.0 ± 1.0	5.7 ± 0.9*	5.5 ± 0.7	.478
TG (mmol/L)	1.5 ± 0.7	1.3 ± 0.6	1.7 ± 0.7	1.7 ± 0.6	.146
HDL-C (mmol/L)	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3*	1.0 ± 0.1*	.001
LDL-C (mmol/L)	3.3 ± 0.9	3.1 ± 0.9	3.7 ± 0.7	3.7 ± 0.8	.146
Apo B (g/L)	0.9 ± 0.2	0.9 ± 0.1	1.1 ± 0.2*	1.1 ± 0.2*	.037
Fasting glucose (mmol/L)	5.1 ± 0.4	5.0 ± 0.4	5.2 ± 0.4	5.5 ± 0.5*	.001
Glucose 120-min OGTT (mmol/L)	5.6± 1.8	5.1 ± 1.0	6.1 ± 1.4	7.4 ± 3.1*	.145
Fasting insulin (mU/L)	11.2 ± 4.2	9.8 ± 1.7	10.8 ± 1.9	17.1 ± 6.9*,†	.258
Insulin 120-min OGTT (mU/L)	45.4 ± 40.5	29.9 ± 11.4	69.2 ± 31.1*	88.7 ± 73.9*	.355
$HOMA_{IR}$ index	2.5 ± 1.1	2.2 ± 0.4	2.4 ± 0.4	4.2 ± 1.9*,†	.331
ISI-Mat index	4.8 ± 2.0	5.7 ± 1.8	3.2 ± 0.6*	2.5 ± 0.6*	.073

The results were adjusted by waist circumference. Group 1 = non-IR ($HOMA_{IR}$ <3.2 and ISI-Mat ≥4.0); group 2 = IR post-OGTT ($HOMA_{IR}$ <3.2 and ISI-Mat <4.0); and group 3 = basal IR ($HOMA_{IR}$ ≥3.2 and ISI-Mat <4.0). TC indicates total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; Apo B, apolipoprotein B.

* Significant differences with non-IR: $P < .02$.

† Significant differences with IR post-OGTT: $P < .02$.

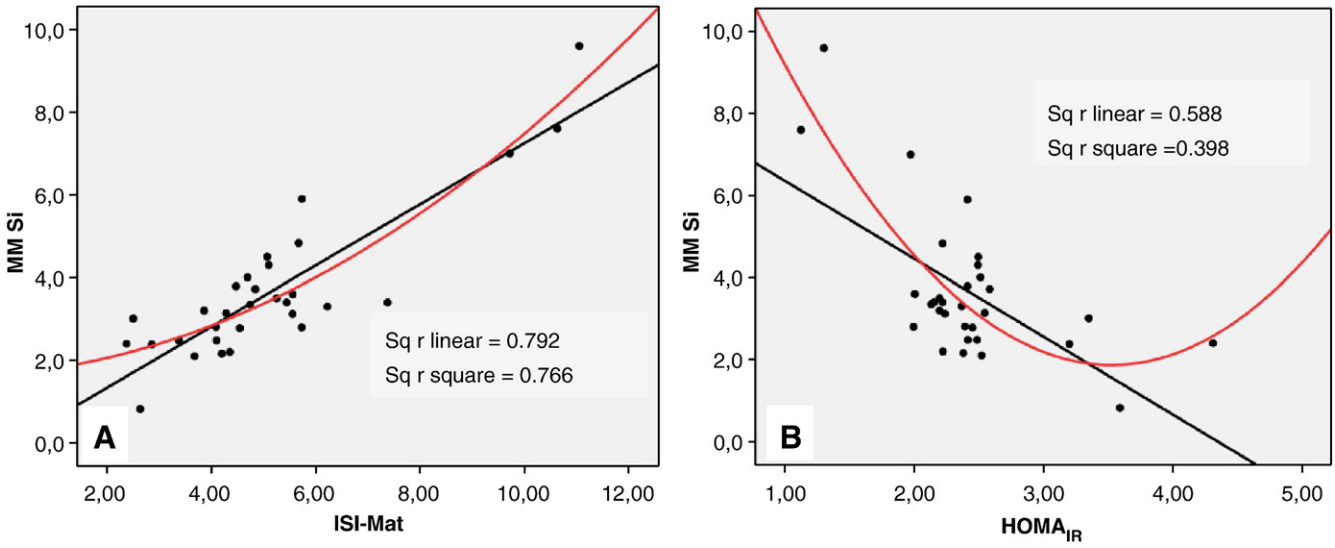

Fig. 1. Interrelation coefficient of MMSi with ISI-Mat (A) and $HOMA_{IR}$ (B).

from OGTT (r = 0.875, P = .0001) correlated well with insulin sensitivity index obtained from the IVGTT. The ISI-Mat and $HOMA_{IR}$ also had a good correlation (r = −0.791, P = .0001) between each other. However, ISI-Mat was better correlated than $HOMA_{IR}$ with the IVGTT (Fig. 1). Moreover, ISI-Mat remained significantly correlated with IVGTT, even in a model with both ISI-Mat and $HOMA_{IR}$ (Table 2).

When we studied the presence of cardiovascular risk factors according to IR state (Table 3), we found that non-IR individuals had lower prevalence of hypertension, abdominal obesity, high apolipoprotein B, impaired fasting glucose, and metabolic syndrome than IR groups. However, we did not find differences between both IR groups. Moreover, IR state (IR post-OGTT and basal IR) was associated with higher prevalence of cluster of cardiovascular disease risk factors (hypertension, low HDL-C, impaired fasting glucose, and high apolipoprotein B; Fig. 2).

4. Discussion

Insulin resistance is a common condition, recognized to be a central feature of the metabolic syndrome, and is strongly associated with an increased risk of diabetes, preceding and predicting the disease for several years [15]. Furthermore, in recent years, different studies have documented an independent association between IR and subclinical or clinical cardiovascular disease in both nondiabetic and diabetic subjects [5,6,15,16].

In aggregate, IR and related conditions are very common, affecting as many as 20% to 40% of subjects in the general population, most of them being apparently healthy subjects [10,16]. However, difficulties in measuring IR prevent identification of insulin-resistant individuals. A variety of methods are available for assessing IR state. The hyperinsulinemic-euglycemic clamp technique, considered "the criterion standard," and other direct methods such as IVGTT are complicated, time consuming, and expensive, suitable only for studies with a small number of subjects. For epidemiological and clinical studies, simpler indirect methods have been advocated for quantification of IR [10,17,18].

We have evaluated 2 indirect indices ($HOMA_{IR}$ and ISI-Mat) and compared them with a more standardized measure, IVGTT (a well-accepted alternative to the clamp technique) [19,20]. Our results show that $HOMA_{IR}$ correlated well (r = −0.631, P = .0001) with insulin sensitivity index obtained from the IVGTT. However, ISI-Mat obtained from OGTT was better correlated (r = 0.875, P = .0001) (Fig. 1). The ISI-Mat and $HOMA_{IR}$ also had a good correlation (r = −0.791, P = .0001) between each other. Previous studies have evaluated the accuracy of different methods to assess IR. All them were significantly correlated with the results obtained with the euglycemic-hyperinsulinemic clamp. However, the indices obtained after an OGTT showed higher degree of concordance with the clamp technique [21-24]. In our study, the correlation between ISI-Mat and insulin sensitivity index obtained from IVGTT (MMSi) was

Table 2
Multiple regression analysis between the ISI-Mat and MMSi after adjusting for HOMAIR

Model	Unstandardized coefficients		Standardized coefficients	t	Significance
	B	SE	β		
1 (constant)	−0.144	0.421		−0.342	.735
ISI-Mat	0.740	0.076	0.875	9.751	.0001
2 (constant)	−1.902	1.621		−1.173	.251
ISI-Mat	0.849	0.123	1.005	6.883	.0001
$HOMA_{IR}$	0.494	0.440	0.164	1.123	.271

Dependent variable: MMSi.

Table 3
Prevalence of cardiovascular risk factors, expressed in percentages, according to IR state

	Group 1 non-IR (n = 62)	Group 2 IR post-OGTT (n = 13)	Group 3 basal IR (n = 15)	χ^2 Pearson	Fisher exact test (2-tailed)		
				Groups 1, 2, & 3	Group 1 vs 2	Group 1 vs 3	Group 2 vs 3
Hypertension	3 (4.8)	4 (30.8)	9 (60.0)	0.0001	0.015	0.0001	0.151
Abdominal obesity (cm)	7 (11.3)	4 (30.8)	7 (46.7)	0.005	0.09	0.004	0.46
TG ≥150 mg/dL	12 (19.4)	7 (53.2)	9 (60.0)	0.002	0.015	0.003	1
Low HDL-C	7 (11.3)	1 (7.7)	3 (20.0)	0.564	1	0.399	0.6
Apo B 120	2 (3.2)	5 (38.4)	5 (33.3)	0.0001	0.001	0.002	1
IFG	2 (3.2)	2 (15.4)	7 (46.7)	0.0001	0.137	0.0001	0.114
TC/HDL-C ≥6	4 (6.4)	2 (15.4)	3 (20.0)	0.228	0.277	0.13	1
Non–HDL-C ≥190 mg/dL	13 (20.9)	4 (30.8)	5 (33.3)	0.515	0.475	0.323	1
Metabolic syndrome	3 (4.8)	5 (38.5)	9 (60.0)	0.0001	0.003	0.0001	0.449

Group 1 = non-IR ($HOMA_{IR}$ <3.2 and ISI-Mat ≥4.0); group 2 = IR post-OGTT ($HOMA_{IR}$ <3.2 and ISI-Mat <4.0); and group 3 = basal IR ($HOMA_{IR}$ ≥3.2 and ISI-Mat <4.0). Metabolic syndrome was defined using Adult Treatment Panel III criteria. Apo B 120 = apolipoprotein B ≥1.2 g/L; low HDL-C = HDL-C <0.9 mmol/L in men and <1.0 mmol/L in women; TC/HDL-C = TC/HDL-C index ≥6; hypertension = systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg; IFG = fasting plasma glucose ≥6.1 mmol/L.

also stronger than the correlation between $HOMA_{IR}$ and MMSi (Table 2).

The ISI-Mat is a well-established index to assess IR state [10,21]. Our cutoff value for ISI-Mat was similar to values described for other populations [23,25,26]. Considering as a threshold of IR a $HOMA_{IR}$ of 3.2 and an ISI-Mat of 4.0 (75th and 25th percentile of our population, respectively), as many as 14.4% of individuals who were insulin resistant according to postchallenge plasma glucose had normal values of $HOMA_{IR}$ and therefore would not have been detected by a screening procedure based upon fasting glucose and insulin measurements alone. However, none of the subjects with abnormally elevated $HOMA_{IR}$ presented normal ISI-Mat. Although this observation could result from the fact that only a small number of subjects were studied, these results could be explained by natural history of the IR syndrome and the characteristics of both methods. The $HOMA_{IR}$ is based upon the evaluation of glucose and insulin concentrations during the fasting state. However, plasma glucose and insulin responses during OGTT reflect both the ability of pancreatic β-cells to secrete insulin and the sensitivity of tissues to insulin [27]. Moreover, the initial stages of IR are characterized by normal fasting glycemia, the earliest alteration being the rising of plasma glucose during the postprandial phase, and followed by compensatory hyperinsulinemia. As the disease progresses, impaired fasting glucose appears; and subsequently, diabetes mellitus will develop. There is increasing evidence supporting the fact that by the time glucose tolerance or fasting glucose levels become impaired, appreciable β-cell destruction may have already occurred [28]. Thus, the classification of IR with tests based on the oral glucose administration may allow earlier identification of IR than indices based on the fasting state of IR.

We have also found that subjects characterized with IR by OGTT but misclassified by $HOMA_{IR}$ present a cluster of cardiovascular risk factors, similar to individuals with abnormal $HOMA_{IR}$ (Table 3 and Fig. 2). Previous data have shown that during the initial insulin-resistant period, the metabolic and physiologic changes progress in parallel with the commencement of silent atherosclerosis and cardiovascular complications in genetically susceptible individuals, before the onset of diabetes [2,10]. These findings express the importance of detecting IR in the early stages.

In summary, the early identification of IR would be of clinical interest because its treatment might have beneficial effects on glucose control and on cardiovascular disease prevention [15]. In the present study, we have shown the utility of ISI-Mat obtained with an easily available

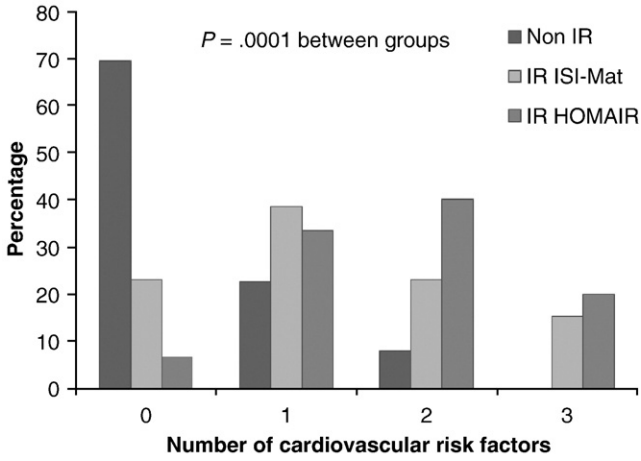

Fig. 2. Association of cardiovascular risk factors (hypertension, low HDL-C, impaired fasting glucose, and high apolipoprotein B) according to IR group classification. Cardiovascular risk factors considered: apolipoprotein B at least 1.2 g/L; HDL-C less than 0.9 mmol/L in men and less than 1.0 mmol/L in women; hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg); and fasting plasma glucose at least 6.1 mmol/L. Statistical significance: non-IR vs IR ISI-Mat, $P = .001$; non-IR vs IR $HOMA_{IR}$, $P = .001$; IR ISI-Mat vs IR $HOMA_{IR}$, $P = .558$.

postprandial method (OGTT) in the early detection of IR in nonobese subjects with normal fasting glucose levels. On the contrary, a high percentage of subjects were misclassified with $HOMA_{IR}$, the most common index used. Moreover, early diagnosis of IR by OGTT was associated with other cardiovascular risk factors. We have compared both methods with a well-accepted alternative to the clamp technique. However, a limitation of our study could be that the IVGTT is not as accurate as the euglycemic-hyperinsulinemic clamp to assess IR, and the small number of subjects studied.

The main clinical interest for the early detection of IR and the metabolic syndrome stems from its evolution over time toward the occurrence of type 2 diabetes mellitus, dyslipidemia, hypertension, and high risk of coronary heart disease. Identifying IR and associated cardiovascular risk factors when fasting blood glucose and insulin are still in the reference range may be important. Intervention programs could be more successful at this stage. However, this remains to be demonstrated in prospective studies with evaluation of cost-effectiveness and clinical outcomes.

We conclude that OGTT could be applied in clinical practice to accurately identify subjects with IR in the general population. However, further studies are required to confirm our findings.

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