

Diagnosing Insulin Resistance by Simple Quantitative Methods in Subjects With Normal Glucose Metabolism

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OBJECTIVE — To identify a reliable yet simple indirect method for detection of insulin resistance (IR).

RESEARCH DESIGN AND METHODS — A total of 65 subjects (44 men and 21 women aged 30–60 years) were selected by a simple random sampling method. Inclusion criteria were voluntary participation from staff and hospital personnel, absence of abnormal glucose tolerance, and normal results of lipid profile and basic blood chemistry. A blood sample was taken after a 12-h overnight fast to determine plasma lipid, glucose, and insulin levels. An intravenous glucose tolerance test with administration of insulin after 20 min and extraction of multiple blood samples for glucose and insulin measurements and calculation of the minimal model approximation of the metabolism of glucose (MMAMG) S_i value were performed. Three indirect indexes used to predict insulin sensitivity or IR were calculated, and metabolic syndrome was diagnosed using the Adult Treatment Panel III (ATP III) criteria. All results were correlated with those of the MMAMG.

RESULTS — The 75th percentile value as the cutoff point to define IR corresponded with a fasting plasma glucose level of 12 mU/l, a homeostasis model assessment of 2.6, a 25th percentile for S_i value of 21, and QUICKI (quantitative insulin sensitivity check index) and McAuley indexes of 0.33 and 5.8, respectively. The S_i index correlated ($P < 0.001$) with all the indirect indexes and parameters of the metabolic syndrome.

CONCLUSIONS — When compared with the S_i index, the most sensitive and specific indirect method was the score proposed by McAuley et al. (specificity 0.91, sensitivity 0.75, 9.2 probability ratio of a positive test), followed by the existence of metabolic syndrome (specificity 0.91, sensitivity 0.66, 7.8 probability ratio of a positive test).

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Insulin resistance (IR) is a pathological situation characterized by a lack of physiological 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 HDL cholesterol levels), hyper-

tension, glucose intolerance or type 2 diabetes, hyperuricemia or gout, abdominal obesity, hypercoagulability and defects in the fibrinolytic system, hyperandrogenism, fatty liver, and an increased incidence of coronary heart disease (1).

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 (2,3). The connection between IR, hyperinsulinemia, and coronary heart disease has been established by several transverse, prospective, and experimental studies (4–8). Difficulties in measuring insulin sensitivity, however, prevent identification of insulin-resistant individuals in the general population.

The quantification of IR can be performed by evaluating the peripheral insulin sensitivity in vivo with methods such as the pancreatic suppression test (9), the hyperinsulinemic-euglycemic clamp technique (9), and the minimal model approximation of the metabolism of glucose (MMAMG) (10). They are complicated, time-consuming, and expensive methods suitable only for studies with a small number of subjects.

For epidemiologic and clinical studies, more simple, indirect methods have been advocated for quantification of IR, based on measuring plasma insulin levels during fasting or after glucose stimulus and on the insulin-glucose ratio calculated with different mathematical formulas. Such methods include measurement of fasting plasma insulin levels and 2-h post-75-g oral glucose load, the homeostasis model assessment (HOMA) (11), and the mathematical calculations known as the QUICKI (quantitative insulin sensitivity check index) (12) and McAuley (13) indexes. In addition, several components of the metabolic syndrome (type 2 diabetes, abdominal obesity, or dyslipidemia) are pathophysiologically related to IR and indicate a high probability of its existence.

The goal of this study is to identify a reliable yet simple indirect method for detection of IR, a disturbance with high prevalence in the general population of nondiabetic subjects.

RESEARCH DESIGN AND

METHODS — Participants were recruited by voluntary participation through advertisement among hospital

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Abbreviations: ATP III, Adult Treatment Panel III; HOMA, homeostasis model assessment; IR, insulin resistance; MMAMG, minimal model approximation of the metabolism of glucose; QUICKI, quantitative insulin sensitivity check index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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staff and personnel. The sample selection was performed using a random sampling method (14). After clinical screening (medical history, physical examination, and laboratory tests), only healthy subjects with inclusion criteria were randomized into the study. A total of 65 subjects, 44 men and 21 women aged 30–60 years, were studied.

The following inclusion criteria were used in this study: normal glucose metabolism (fasting blood glucose <6.1 mmol/L, 2-h postprandial glucose <7.8 mmol/L), fasting plasma triglyceride level <2.25 mmol/L, and general analytical evaluation (hepatic, renal, and thyroid function, complete blood count, uric acid, and standard urine analysis) within normal limits. All subjects were non-smokers (never smoked or absence of smoking for at least the preceding 2 years) and were not taking any medications. Alcohol consumption was <35 g per day. Body weight and physical activity habits had been stable for 3 months preceding the study.

The following exclusion criteria were used in this study: age outside the range of 30–60 years, consumption of a hypocaloric diet, or weight gain or loss $>10\%$ in the 3 months preceding the study. Other exclusion criteria included hypothyroidism; liver, kidney, or heart failure; and neoplasia.

Clinical history was obtained from all subjects, including age, sex, personal medical history, intake of drugs, 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. In all participants, blood pressure was measured after a 10-min rest period, and readings were recorded at 5-min intervals. Body weight and height, BMI, and waist circumference were measured using standard methods.

Blood samples were collected after a 12-h overnight fast and deposited in dry tubes with EDTA. The plasma was separated immediately using refrigerated centrifugation at 2,500–3,000 rpm for a period of 10 min. The samples were processed either immediately or during the first week after conservation at -20°C .

As previously described (15), plasma

total cholesterol, triglyceride, free fatty acid, and glucose levels were determined using enzymatic methods; HDL cholesterol was measured after precipitation with polyanions. Apolipoprotein B was determined by immunoturbidimetry and insulin by radioimmunoassay.

Clinical methods

All tests (oral glucose tolerance test and intravenous glucose tolerance test) were performed in the Metabolic Unit near the laboratory with a clinician or a nurse in attendance, in accordance with standard procedures (15).

The intravenous glucose tolerance test, with the extraction of multiple blood samples for measurement of glucose and insulin levels, calculation of the MMAMG indexes of S_i , and use of glucose independent of insulin (S_g), was conducted after a 12-h fast and with the patient resting supine for at least 15 min before initiation of the test. Two baseline venous blood samples ($t = -15$ min and $t = -5$ min) for measurement of plasma glucose and insulin levels were collected. At $t = 0$, a bolus of 300 mg glucose/kg body wt in a 50% glucose-saline solution was administered over a period of ~ 60 s. At $t = 20$ min, a bolus of 0.03 units/kg body wt of regular insulin (Actrapid; Novo Nordisk, Princeton, NJ) was administered intravenously. After the two baseline samples, 26 additional blood samples were collected for measurement of glucose and insulin levels 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 min (10,16). The S_i index was calculated using the MINMOD computer program (15).

In addition, three indirect indexes for the assessment of IR were calculated. The HOMA index uses the formula described by Matthews et al. (11): $\text{insulin } (\mu\text{U}/\text{m}) \times [\text{glucose } (\text{mmol}/\text{L})/22.5]$. The QUICKI index is based on the logarithmic transformation: $1/(\log \text{insulin} + \log \text{glycemia in mg}/\text{dl})$ (12). Finally, the IR index described by McAuley et al. (13), based on the increase of plasma triglycerides and insulin, using the equation $= \exp [2.63 - 0.28 \ln(\text{insulin in mU}/\text{L}) - 0.31 \ln(\text{triglycerides in mmol}/\text{L})]$ for the quantification of peripheral insulin sensitivity, was also calculated.

The Adult Treatment Panel (ATP III) (17) diagnostic criteria were used to establish the presence of the metabolic syndrome.

Statistical analysis

For the descriptive analysis, and after having checked the normality of the variables using the Kolmogorov-Smirnov test, the usual central and dispersion methods were used: average, SD, and 95% CI. We used the Mann-Whitney U test to compare the quantitative variables, χ^2 test was used to compare proportions, and the correlation between two variables was studied with the Spearman test. Sensitivity, specificity, and probability ratio were calculated with the usual methods (18). All statistical analyses were performed using the statistical program SPSS (version 10; SPSS, Chicago, IL).

RESULTS — The general characteristics of the group studied, 65 subjects comprising 44 men and 21 women aged 30–60 years, are shown in Table 1. Mean values for systolic and diastolic blood pressure; BMI; waist circumference; plasma leptin, total cholesterol, triglyceride, HDL cholesterol, apolipoprotein B, fasting glucose, and insulin levels; S_i index; and indirect indexes to measure IR (HOMA, QUICKI, and McAuley) are included in these data. Statistically significant differences between the men and women were found for blood pressure; waist circumference; triglyceride, HDL cholesterol, apolipoprotein B, and insulin levels; S_i index; and indirect formulas of IR.

The same parameters are shown in Table 2, separating the subjects according to presence or absence of abdominal obesity (waist circumference >102 or <102 cm in men and >88 or <88 cm in women). Significant differences were found in all parameters, with the exception of plasma total cholesterol, free fatty acids, fasting glucose, and glucose 2-h post-glucose loading test.

We selected the 75th percentile value as the cutoff point to define IR (Table 3). This point corresponded to a fasting plasma insulin level of 12 mU/L and a HOMA of 2.6. The 25th percentile for the S_i value was $2.1 \times 10^{-4} \text{ mU} \cdot \text{L}^{-1} \cdot \text{min}^{-1}$, and QUICKI and McAuley indexes were 0.33 and 5.8, respectively.

The results of calculating the Spearman correlation between the S_i index obtained using the MMAMG technique and the calculated indirect indexes of IR are shown in Table 4. A statistically significant

Table 1—General characteristics of the group studied

	Men	Women	Total
n	44	21	65
Age (years)	43.8 (9.3)	42.1 (8.7)	43.2 (9.1)
Systolic blood pressure (mmHg)*	129.9 (14.2)	111.1 (10.5)	123.8 (15.7)
Diastolic blood pressure (mmHg)*	77.9 (9.3)	71.7 (6.9)	75.9 (9.3)
BMI (kg/m ²)	26.7 (2.5)	25.4 (3.6)	26.2 (2.9)
Waist circumference (cm)*	103.7 (7.6)	78.7 (12.4)	94.5 (15.3)
Total cholesterol (mmol/l)	5.69 (1.35)	5.22 (0.99)	5.54 (1.26)
Triglycerides (mmol/l)*	1.51 (0.45)	1.02 (0.38)	1.34 (0.48)
HDL cholesterol (mmol/l)*	1.07 (0.16)	1.43 (0.33)	1.19 (0.28)
Apolipoprotein B (g/l)*	1.14 (0.29)	0.86 (0.22)	1.05 (0.30)
Leptin (μmol/l)	400.2 (159.8)	404.6 (140.8)	401.6 (152.8)
Fasting plasma glucose (mmol/l)	5.02 (0.47)	4.97 (0.52)	4.99 (0.51)
Fasting plasma glucose at 120 min (mmol/l)	5.75 (1.55)	5.09 (1.59)	5.56 (1.57)
Fasting plasma insulin (mU/l)*	11.5 (4.6)	8.7 (5.8)	10.5 (4.8)
Fasting plasma insulin at 120 min (mU/l)*	54.6 (31.9)	34.6 (33.0)	48.5 (33.7)
S _i × 10 ⁻⁴ mU · l ⁻¹ · min ⁻¹ *	2.9 (1.3)	5.0 (1.9)	3.6 (1.8)
HOMA*	2.5 (1.1)	1.8 (1.1)	2.3 (1.1)
QUICKI*	0.33 (0.02)	0.36 (0.02)	0.34 (0.02)
McAuley*	6.5 (1.4)	8.2 (1.5)	7.1 (1.6)

Data are means (SD). *P < 0.01 between men and women.

cant correlation was found with all the parameters.

When confronted with the results obtained with the MMAMG technique, the sensitivity and specificity diagnosis were higher for the indirect, calculated index proposed by McAuley, followed by the

existence of metabolic syndrome (Table 5).

CONCLUSIONS— The goal of this study was to identify a reliable yet simple indirect method for detection of IR, a disturbance with high prevalence in the gen-

eral population of nondiabetic subjects. Recent results from our group have shown that IR can be detected in up to 31.8% (19) of an adult population, in agreement with figures observed in other populations (20). Moreover, the metabolic syndrome, a condition pathophysi-

Table 2—Classification of subjects according to presence of abdominal obesity

	Without abdominal obesity	With abdominal obesity	P
n (men/women)	37 (21/16)	24 (16/5)	
Age (years)	41.2 (9.7)	46.1 (9.4)	0.005
BMI (kg/m ²)	25.1 (2.9)	27.7 (2.4)	<0.001
Waist circumference (cm)	85.4 (12.8)	106.6 (8.5)	<0.001
Leptin (μmol/l)	18.8 (10.3)	27.5 (13.8)	0.013
Systolic blood pressure (mmHg)	119.1 (18.1)	129.9 (9.1)	<0.001
Diastolic blood pressure (mmHg)	73.0 (9.7)	79.7 (6.3)	0.001
Total cholesterol (mmol/l)	5.39 (1.30)	5.76 (1.20)	0.266
Triglycerides (mmol/l)	1.12 (0.45)	1.63 (0.36)	<0.001
HDL cholesterol (mmol/l)	1.28 (0.31)	1.08 (1.19)	0.006
Apolipoprotein B (g/l)	0.98 (0.31)	1.14 (0.25)	0.024
Fasting free fatty acids (μmol/l)	392.4 (145.2)	413.8 (164.4)	0.721
Fasting plasma glucose (mmol/l)	4.90 (0.50)	5.13 (0.49)	0.174
Fasting plasma glucose at 120 min (mmol/l)	5.29 (1.36)	5.89 (1.80)	0.153
Fasting plasma insulin (mU/l)	8.5 (4.1)	13.1 (4.4)	<0.001
Fasting plasma insulin at 120 min (mU/l)	37.0 (25.3)	61.8 (36.7)	0.001
S _i (× 10 ⁻⁴ mU · l ⁻¹ · min ⁻¹)	4.5 (1.8)	2.4 (0.9)	<0.001
HOMA	1.8 (0.8)	2.9 (1.1)	<0.001
QUICKI	0.38 (0.02)	0.33 (0.02)	<0.001
McAuley	7.9 (1.5)	6.0 (1.0)	<0.001

Data are means (SD).

Table 3— S_i values (MMAMG) and indirect insulin resistance tests for the different percentiles (entire group n = 65)

	P10	P25	P50	P75	P90
S_i	1.7	2.1	3.2	4.9	6.6
Fasting plasma insulin	5.0	6.5	10.0	12.0	17.2
HOMA	1.1	1.4	2.3	2.6	4.1
QUICKI	0.31	0.33	0.34	0.36	0.38
McAuley	5.2	5.8	6.7	8.5	9.8

ologically related to IR, also has an elevated prevalence in adult populations, varying from 0.8 to 35.3%, after adjustment for age (3) and depending on the criteria used for establishing the diagnosis. 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, dyslipidemia, hypertension, and high risk of coronary heart disease.

In the present study, we investigated the presence of IR in subjects with normal fasting glucose levels using Bergman's MMAMG, modified with administration of insulin (15). This technique has been widely validated versus the hyperinsulinemic-euglycemic clamp. A good correlation between the indexes calculated by both methods indicates that the MMAMG is an easier but still reliable method for calculation of the S_i index in normal subjects (21). As one of the indirect indexes for diagnosing IR, we have used the fasting plasma insulin values, considering the 75th percentile (P75) to be the IR index (P75 = fasting insulin value of 12 mU/l). For the 90th percentile, the corresponding insulin value was 17.2 mU/l fasting

Table 4—Correlation between IR measured by the S_i index (MMAMG) and the indirect methods

	r	P
HOMA	-0.660	<0.001
QUICKI	-0.660	<0.001
McAuley	0.718	0.001
Fasting plasma insulin	-0.690	<0.001
Waist circumference	-0.640	<0.001
Leptin	-0.270	0.030
Systolic blood pressure	-0.558	<0.001
Triglycerides	-0.631	<0.001
HDL cholesterol	0.520	<0.001
Fasting plasma glucose	-0.113	0.368

insulin, similar to the value (16.0 mU/l) previously found by us in a different group of subjects (15). In the Paris Prospective Study (7), hyperinsulinism was defined as fasting plasma insulin level >16 mU/l or a level of 62 mU/l 2 h after the oral glucose tolerance test. The existence of these values multiplied the risk of coronary heart disease by 1.6 in the subjects affected. Fasting plasma insulin levels ≥ 12 mU/l have also been proposed by other authors as the cutoff between subjects with and without IR (13).

Another indirect index studied, the HOMA index, has been validated with the hyperinsulinemic-euglycemic clamp technique by Bonora et al. (22), who found a highly significant correlation ($r = -0.820, P < 0.0001$). Therefore, HOMA is considered a valid method to assess peripheral insulin sensitivity in epidemiologic studies. In a group of adult subjects without clinical or biochemical IR parameters or family history of diabetes or dyslipidemia, we found a P75 HOMA value >3.2 and ≥ 3.8 for the P90 (19). These values are in the same range (3.3–4.0) as those described by Haffner et al. (23) in populations in which diabetes did not develop after years of monitoring. Other groups (24,25) have found HOMA values between 1.7 and 2.5 in subjects with normal glucose tolerance. These figures are in

Table 5—Validity of the indirect diagnostic tests and presence of the metabolic syndrome against the standard established as the S_i index obtained by the MMAMG method modified with insulin administration

	Sensitivity	Specificity	Probability ratio of a positive test
HOMA	0.65	0.87	5.1
QUICKI	0.65	0.87	5.1
McAuley	0.75	0.91	9.2
Fasting plasma insulin	0.57	0.81	5.32
Metabolic syndrome	0.66	0.91	7.8

agreement with the value of 2.6 at the 75th percentile found in the present study.

With respect to the QUICKI index, our value of 0.33 at the 25th percentile is in agreement with results published by Hrebicek et al. (26) in a sample of 253 healthy volunteers.

The index proposed by McAuley et al. (13) for the diagnosis of IR consists of a score based on weighted combinations of fasting insulin, BMI, and fasting triglycerides, using the equation previously shown. Our results show that, at the 25th percentile, the calculated McAuley index was 5.8. When compared with the S_i value obtained by the MMAMG method, the sensitivity of this index was significantly higher than that of the HOMA or QUICKI indexes. Therefore, our results are in agreement with those reported by McAuley et al. (13), who, when comparing the hyperinsulinemic-euglycemic clamp, found this indirect index to be most sensitive for predicting IR in euglycemic individuals. It seems possible that the inclusion in the McAuley score of two fundamental components of the IR syndrome, i.e., fasting hyperinsulinemia and elevated plasma triglyceride levels, contributes to the high sensitivity of this method.

The clinical and biochemical parameters independently related to the S_i index in our study were waist circumference (abdominal obesity), blood pressure, and plasma leptin, triglyceride, and HDL cholesterol levels. Our results coincide with those published by Boyko et al. (27), who found an independent predictive role for the development of diabetes in fasting plasma glucose levels, BMI, and waist-to-hip ratio and a nonlinear association with plasma triglyceride and leptin levels. We have not found any relation with

fasting plasma glucose, possibly due to our selection criteria, because our subjects had normal glucose tolerance. The presence of the metabolic syndrome, defined according to the ATP III criteria, showed a high specificity and sensitivity for the detection of IR. Recently, a simple score system has been proposed to identify subjects at high risk for type 2 diabetes, based on age, BMI, waist circumference, and hypertension, as well as other risk factors. The importance of these metabolic syndrome parameters is again emphasized (28).

In studying the correlation of these indirect methods with regard to the results obtained using the MMAMG technique, a significant correlation ($P < 0.001$) was observed, just as has been confirmed by authors (29) who have described and studied these tests. However, in studying the diagnostic sensitivity and specificity, we found that the sensitivity is low (Table 5), although specificity is high. The most sensitive and specific method is that proposed by McAuley et al. (13), with specificity of 0.91, sensitivity of 0.75, and probability ratio of a positive test of 9.2, followed by the existence of metabolic syndrome, defined by the criteria of the ATP III (17), with specificity of 0.91, sensitivity of 0.66, and probability ratio of a positive test of 7.8. Our results indicate that, as previously shown by Ferrannini and Balkau (30), it is possible to have IR without hyperinsulinemia and, conversely, it is possible to have hyperinsulinemia without IR.

In summary, the quantification of IR using the MMAMG technique has been shown to be a sensitive method in nondiabetic adult subjects. The three indirect indexes of IR evaluated in this study have shown a good correlation with the S_i value. Those that offered the best diagnostic sensitivity and specificity were the McAuley index (which includes fasting plasma insulin and triglyceride levels) and the presence of the metabolic syndrome, diagnosed by ATP III criteria. We conclude that, in clinical practice, these two simple methods could be applied to accurately identify IR subjects in our population.

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