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Measuring insulin sensitivity in postmenopausal women covering a range of glucose tolerance: comparison of indices derived from the oral glucose tolerance test with the euglycemic-hyperinsulinemic clamp

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Abstract

This study compares indices of insulin sensitivity derived from fasting and oral glucose tolerance test (OGTT) glucose and insulin measurements, with respect to the reference measure (*M*/*I*), obtained from the euglycemic-hyperinsulinemic clamp, in postmenopausal women with varying glucose tolerance status. Fasting plasma insulin index, homeostasis model assessment index, and OGTT-derived indices (insulin 120-minute, Matsuda, metabolic clearance rate [MCR] of glucose, insulin sensitivity [ISI], and Cederholm indices) were calculated and compared with the *M*/*I* value in 112 postmenopausal women. All indices examined were significantly correlated with *M*/*I* ($0.28 \leq r^2 \leq 0.56$). Association studies revealed that on average, 48% of women were grouped in the same tertile of insulin sensitivity when using *M*/*I* and fasting plasma insulin index, and 54% when using *M*/*I* and insulin 120-minute index. However, concordance with *M*/*I* tertiles were 57%, 58%, 64%, 64%, and 68% for homeostasis model assessment, Matsuda, MCR, ISI, and Cederholm indices, respectively. Finally, correlation coefficients between *M*/*I* and insulin sensitivity indices were generally lower in women with normal glucose tolerance compared with women with impaired glucose tolerance or type 2 diabetes mellitus. These results suggest that in postmenopausal women, surrogate indices of insulin sensitivity obtained from OGTT data and incorporating a measurement of body weight or body mass index) (Cederholm, ISI, and MCR indices) appear to be superior to those without OGTT data or body weight-body mass index measurements and, therefore, could offer a better estimate of insulin sensitivity, allowing an improved clinical evaluation of this population at higher risk of cardiovascular disease and type 2 diabetes mellitus.

1. Introduction

Women with type 2 diabetes mellitus are significantly more at risk of developing cardiovascular disease (CVD) than nondiabetic women [1]. Menopause in women is associated with an increased risk of CVD. This increased CVD risk after menopause has been partly attributed to the worsening of insulin-stimulated glucose disposal observed during the menopause transition [2]. Insulin resistance is a common metabolic abnormality that characterizes individuals with type 2 diabetes mellitus and obesity [3]. Furthermore, insulin resistance is present in approximately 20% to 25% of the nondiabetic population and has been suggested as an important risk factor in the development of the metabolic syndrome, a cluster of abnormalities including glucose intolerance, dyslipidemia, high blood pressure, and impaired fibrinolysis activity, known to increase risk for type 2 diabetes mellitus and CVD development [4]. Because insulin resistance is an underlying feature of these common

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clinical disorders and could be seen in individuals with a normal glucose tolerance (NGT), there is a growing interest in the development of accurate, reproducible, and simpler methods to assess insulin sensitivity in clinical practice. In addition, with the increased use of nonpharmacologic and pharmacologic treatments that can target insulin sensitivity, a reliable measurement of this important clinical parameter could allow better risk assessment in the patient [5,6].

Insulin resistance can be measured by using the euglycemic-hyperinsulinemic clamp and the intravenous glucose tolerance test with *minimal modeling* techniques [7,8], which are regarded as the reference methods for an accurate assessment of insulin sensitivity. However, these methods are laborious, expensive, time-consuming, and therefore difficult to use in clinical practice and in epidemiologic studies. The homeostasis model assessment (HOMA) represents a simple index for evaluating insulin sensitivity that has been widely used in epidemiologic studies, although some limitations restricting its clinical use have been reported [9]. One limitation of HOMA is the model assumption that insulin sensitivity in the liver and peripheral tissue are equivalent, whereas it is known that they can differ considerably [10]. Furthermore, some data suggest that the accuracy of HOMA may be limited by the presence of fasting hyperglycemia [11,12]. Recently, several new insulin sensitivity indices calculated from plasma glucose and plasma insulin concentrations after an oral glucose tolerance test (OGTT) have been described. These indices have been shown to correlate closely with the insulin sensitivity value obtained with the euglycemic-hyperinsulinemic clamp method [13]. Hence, in a single test, it is possible to obtain reliable information both on insulin sensitivity and glucose tolerance.

However, to our knowledge, no study has assessed these different measures in the same population to evaluate their respective performance compared with the gold standard. In addition, these relationships have been examined mainly from sample populations including men and premenopausal women and have not been confirmed in postmenopausal women. Furthermore, validation of these insulin sensitivity indices over a broad range of glucose tolerance status including de novo diagnosed type 2 diabetes mellitus and impaired glucose tolerance (IGT) in women has not been demonstrated. Therefore, in this study, we compared several insulin sensitivity indices calculated from the OGTT or fasting values of glucose and insulin with the euglycemic-hyperinsulinemic clamp method to evaluate the ability of each index to predict insulin sensitivity in postmenopausal women.

2. Patients and methods

2.1. Patients

One hundred twelve white postmenopausal women (aged between 46 and 68 years) from the Quebec City metropolitan area were recruited by solicitation through newspapers between 1999 and 2003. Each woman was individually interviewed to evaluate if she corresponded to the study's criteria for age, menopausal status, hormone therapy (HT), and other medication. Those who reported that they had not had their menses for at least 1 year were considered as postmenopausal and were included in the study. A measure of the follicule-stimulating hormone (value between 28 and 127 IU/L) was used to confirm the menopausal status. Women who participated in the study were not using any type of HT and were not under treatment for coronary heart disease, diabetes, dyslipidemias, or endocrine disorders (except stable thyroid disease). Five women included in our study were smokers. One woman had important menopausal symptoms and started HT during the testing period. Analyses were therefore conducted with and without this woman for comparison purposes. None of the participants had received a diagnosis of type 2 diabetes mellitus or glucose intolerance before the study. Among these postmenopausal women, 64 were classified as having NGT (fasting plasma glucose [FPG] concentrations <6.1 mmol/L and 2-hour plasma glucose [2hPG] concentrations of <7.8 mmol/L), 30 women were characterized by IGT (FPG <6.1 mmol/L and 2hPG between 7.8 and 11.0 mmol/L), and finally, 18 had type 2 diabetes mellitus (FPG concentration ≥7.0 mmol/L or 2hPG ≥11.1 mmol/L) [14]. Among women with type 2 diabetes mellitus, 6 were characterized by both FPG concentrations of 7.0 mmol/L or greater and 2hPG of 11.1 mmol/L or greater, and 12 were characterized by isolated 2hPG of 11.1 mmol/L or greater. FPG concentration was calculated as the average of 2 baseline samples taken on the morning of the OGTT. Systolic and diastolic blood pressure were measured in the right arm of seated participants, as previously described [15]. All participants signed a written informed consent before entering the study, which was approved by the Laval University and by the CHUL Research Ethics Committees.

2.2. Anthropometric measurements

Height, body weight, and body mass index (BMI) were determined following the procedures recommended at the Airlie Conference [16]. Height was measured to the nearest millimeter with a stadiometer, and body weight was measured to the nearest 0.1 kg on a calibrated balance.

2.3. Oral glucose tolerance test

A 75-g OGTT was performed in the morning after an overnight fast. Blood samples were collected in EDTA-containing tubes (Becton Dickinson, Franklin Lakes, NJ) through a venous catheter from an antecubital vein at −15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 minutes for the determination of plasma glucose and insulin concentrations. Plasma glucose was measured enzymatically, whereas plasma insulin was measured by radioimmunoassay with

polyethylene glycol separation [17,18]. Women with plasma insulin antibody (2% or more) after insulin measurements were excluded from all analyses (n = 3). The interassay coefficient of variation was 1.0% for a basal glucose value set at 5.0 mmol/L. Means of glucose and insulin were defined as the summation of glucose or insulin concentrations during each point of the OGTT, divided by 10 (total number of measures during the OGTT). We used several indices derived from fasting state and OGTT to evaluate insulin sensitivity [12,19-21]. These indices, shown in Table 1, have been correlated with more precise insulin sensitivity measurements in previous studies [12,19-21]. We used 1/fasting plasma insulin, 1/HOMA, and 1/120-minute insulin as insulin sensitivity indices because these indices were originally defined to measure insulin resistance.

2.4. Euglycemic-hyperinsulinemic clamp

Insulin sensitivity was determined with a euglycemic-hyperinsulinemic clamp performed after a 12-hour overnight fast, as previously described by DeFronzo et al [7]. An intravenous catheter was placed in an antecubital vein for the infusion of insulin and glucose (20% dextrose). A second catheter was placed in the other arm for sampling of blood to permit determination of plasma insulin and glucose levels. A primed continuous infusion of insulin (Humulin R) (40 mU/m^2 per minute) was then started. Adjustments in glucose infusion rate were done to reach the FPG values and a steady state of about 5.5 mmol/L for women with FPG above the reference range (FPG ≥6.1 mmol/L). Once the steady state of insulin and glucose was reached, the insulin infusion was continued for the next 2 hours. The duration of the insulin infusion was such that the rate of infused glucose reached a constant value during the last hour of the clamp. Blood samples were collected from time −15 minutes and then every 5 minutes during the test to measure blood glucose concentrations by using an Elite Bayer glucometer (3903-E). Blood samples were collected every 10 minutes, centrifuged for plasma, and stored at −20°C for later analyses of glucose using a hexokinase method, and for plasma insulin using a radioimmunoassay with polyethylene glycol separation [17,18]. The exogenous glucose infusion rate divided by kilograms of body weight during the last 30 minutes of the 120-minute clamp was averaged as an index of insulin-stimulated glucose disposal rate or *M* value. Insulin sensitivity (*M*/*I*) was defined as the *M* value divided by the mean insulin concentration during the last 30 minutes of the clamp, as defined previously [7].

2.5. Other measurements

Presence of the metabolic syndrome was defined by the National Cholesterol Education Program (NCEP)/Adult Treatment Panel III (ATP-III) as having 3 or more of the following criteria: triglyceride concentrations of 1.7 mmol/L or greater, high-density lipoprotein cholesterol less than 1.3 mmol/L, FPG 6.1 mmol/L or greater, waist circumference greater than 88 cm, and blood pressure 130/85 mm Hg or higher [22].

2.6. Statistical analyses

Statistical analyses were performed using software (version 8.2) from the SAS Institute (Cary, NC). Pearson correlation coefficients were calculated to quantify the univariate associations between insulin sensitivity value measured with the euglycemic-hyperinsulinemic clamp (*M*/*I*) and insulin sensitivity indices derived from fasting and OGTT measurements. Differences between correlation coefficients were obtained using MedCalc software version 7.6 (Braekstraat, Mariakerke, Belgium). Agreement analyses were performed to determine the degree of concordance between *M*/*I* and insulin sensitivity indices in identifying subjects separated into tertiles of insulin sensitivity. For that purpose, tertiles of insulin sensitivity were determined for each insulin sensitivity index. For each woman, the concordance between the measures (*M*/*I* vs insulin sensitivity indices) was assessed. The percentage of concordance was calculated as the percentage of women who fell in the same tertile for 2 given parameters. The level of agreement ranges from slight (κ = .0-.2), fair (κ = .21-.40), moderate (κ = .41-.60), substantial (κ = .61-.80) to almost perfect (κ = .81-1.00) according to Landis and Koch [22]. To further explore the associations between insulin sensitivity measurements according to the glucose tolerance status, women were separated into 3 groups: (1) women with NGT, (2) women with IGT, and (3) women with type 2 diabetes mellitus. Pearson correlations were performed to evaluate the relationship between insulin sensitivity indices and the euglycemic-hyperinsulinemic clamp according to the glucose

Table 1
Indices of insulin sensitivity derived from fasting and OGTT measurements of glucose and insulin

Index	Formula	Reference
Fasting plasma insulin index	1/Fasting plasma insulin	
HOMA index	1/[(fasting insulin × fasting glucose)/22.5]	[19]
Insulin 120-minute index	1/Insulin 120 min	
Matsuda index	10 000/[fasting glucose × fasting insulin × (mean glucose × mean insulin)]$^{1/2}$	[12]
Cederholm index	[75 000 + (fasting glucose − 2hPG) × 1.15 × 180 × 0.19 × body weight]/[120 × log(mean insulin) × mean glucose]	[21]
MCR OGTT index	18.8 − (0.271 × BMI) − (0.0052 × insulin 120 min) − (0.27 × glucose 90 min)	[20]
ISI OGTT index	0.226 − (0.0032 × BMI) − (0.0000645 × insulin 120 min) − (0.00375 × glucose 90 min)	[20]

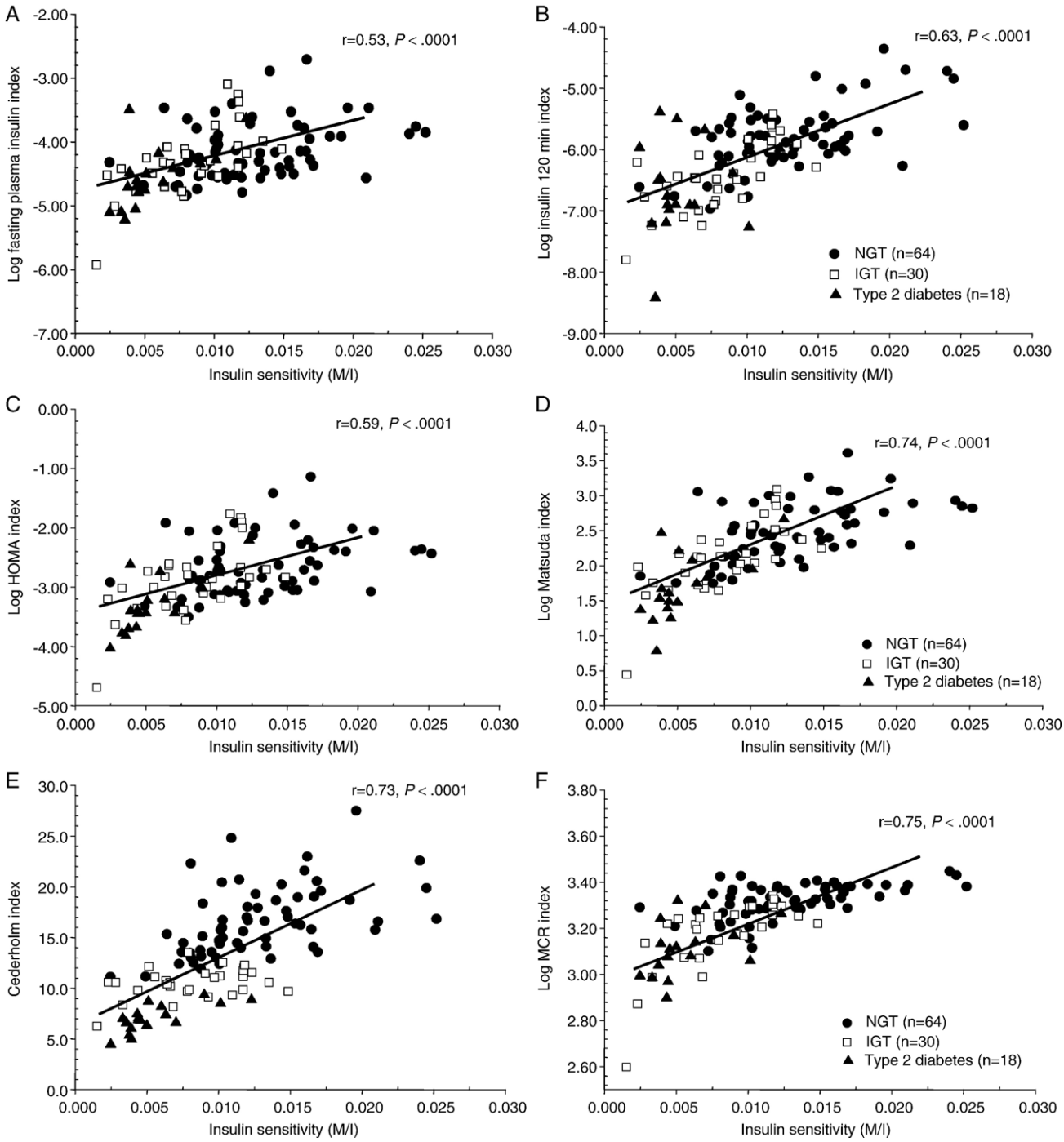

Fig. 1. Linear regression analyses relating insulin sensitivity (*M*/*I*) to fasting plasma insulin index (A), insulin 120-minute index (B), HOMA index (C), Matsuda index (D), Cederholm index (E), MCR (F), and ISI index (G) in 112 postmenopausal women not receiving HT.

tolerance status. Finally, the prevalence of the metabolic syndrome (percent of women with metabolic syndrome) was assessed by tertiles of Celerholm, metabolic clearance rate (MCR) and insulin sensitivity (ISI) indices. The critical *P* value for significance was set at .05. Several variables required log transformation to normalize their distribution (BMI, FPG, fasting plasma insulin, and 120 minute-insulin, HOMA, Matsuda, MCR, and ISI indices).

3. Results

Postmenopausal women had a mean weight of 72.9 kg, a mean BMI of 28.7 kg/m^2 and a mean age of 56.8 years. Mean levels for FPG and 2hPG were 5.6 and 8.0 mmol/L, respectively. In addition, mean insulin sensitivity value, as obtained with the euglycemic-hyperinsulinemic clamp, was 0.0104 mg kg^{-1} min^{-1} (pmol/L)$^{-1}$. Fig. 1 shows the

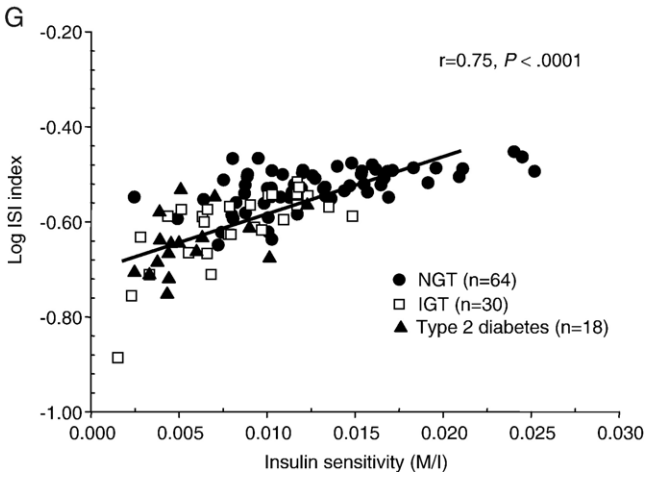

Fig. 1 (*continued*)

relationships between insulin sensitivity (*M*/*I*) and the insulin sensitivity indices examined. In the total sample, Pearson correlation coefficients between *M*/*I* and all insulin sensitivity indices were statistically significant ($P < .0001$), with significantly lower correlation coefficients for fasting plasma insulin and HOMA indices with *M*/*I* compared with correlation coefficients for the relationship between Matsuda, MCR, and ISI indices with *M*/*I* ($P < .05$).

The concordance between insulin sensitivity obtained from the euglycemic-hyperinsulinemic clamp (*M*/*I*) and each insulin sensitivity index was investigated (Table 2). Percentage of agreement with *M*/*I* varied from 60% for fasting plasma insulin index to 82% for Cederholm index for the lowest tertile of insulin sensitivity, and from 50% for fasting plasma insulin index to 69% for MCR and ISI indices for the top tertile of insulin sensitivity (data not shown). Cederholm, MCR, and ISI indices showed the higher degree of concordance (moderate) with *M*/*I*.

To further explore the potential effect of glucose tolerance status on association between *M*/*I* and insulin sensitivity indices, women were separated into 3 groups according to their glucose tolerance status. Table 3 shows that women with type 2 diabetes mellitus were characterized by reduced insulin sensitivity, as defined by *M*/*I*, HOMA, Matsuda, Cederholm, MCR, and ISI indices, compared with women with NGT and IGT ($P < .05$). Fasting plasma insulin and insulin 120-minute concentrations were significantly increased in women with type 2 diabetes mellitus compared with women with NGT ($P < .05$). Women with IGT also showed lower insulin sensitivity, as defined by *M*/*I*, HOMA, Matsuda, Cederholm, MCR, and ISI indices, compared with women with NGT ($P < .05$). However, fasting plasma insulin concentrations were not significantly different between these groups. Relationships between insulin sensitivity as measured with the euglycemic-hyperinsulinemic clamp (*M*/*I*) and indices derived from OGTT (Matsuda, Cederholm, MCR, and ISI) were all significant in women with NGT, IGT, or type 2 diabetes mellitus ($0.33 \le r \le 0.74$), except for insulin 120-minute index in women with type 2 diabetes

Table 3
Insulin sensitivity indices in postmenopausal women separated into groups

Glucose-insulin homeostasis variables	Women with NGT (n = 64)	Women with IGT (n = 30)	Women with T2D (n = 18)
Fasting glycemia (mmol/L)	5.3 ± 0.5	5.6 ± 0.5 [a]	6.5 ± 1.3 [a, b]
2-h glycemia (mmol/L)	5.9 ± 1.1	9.3 ± 1.0 [a]	13.1 ± 1.9 [a, b]
M/*I* (mg kg^{-1} min^{-1} [pmol/L]$^{-1}$)	0.0128 ± 0.005	0.0083 ± 0.0035 [a]	0.0055 ± 0.0026 [a, b]
Fasting plasma insulin (pmol/L)	67.9 ± 26.0	84.5 ± 62.3	104.2 ± 42.5 [a]
HOMA index	0.079 ± 0.049	0.066 ± 0.040 [a]	0.041 ± 0.023 [a, b]
Insulin 120 min	378.4 ± 193.0	721.3 ± 455.3 [a]	1002.8 ± 964.5 [a]
Matsuda index	13.1 ± 5.9	9.4 ± 4.6 [a]	6.2 ± 3.2 [a, b]
Cederholm index	16.6 ± 3.5	10.5 ± 1.5 [a]	7.0 ± 1.3 [a, b]
MCR index	27.7 ± 2.0	24.3 ± 3.3 [a]	21.6 ± 5.1 [a, b]
ISI index	0.59 ± 0.03	0.55 ± 0.04 [a]	0.51 ± 0.06 [a, b]

Data are means ± SD. Statistical analyses were performed on age-adjusted values. T2D indicates type 2 diabetes mellitus.
[a] Significantly different from women with NGT ($P < .05$).
[b] Significantly different from women with IGT ($P < .05$).

Table 2
Degree of agreement among the insulin sensitivity measurements

Variables	κ	Agreement
Insulin sensitivity (*M*/*I*) vs		
1/Fasting plasma insulin	.22	Fair
HOMA index	.36	Fair
1/Insulin 120 min	.32	Fair
Matsuda index	.37	Fair
Cederholm index	.52	Moderate
MCR index	.46	Moderate
ISI index	.46	Moderate

The κ statistic, on a scale from 0 to 1, reflects the degree of agreement between 2 variables. The level of agreement ranges from slight (κ = .0-.2), fair (κ = .21-.40), moderate (κ = .41-.60), and substantial (κ = .61-.80) to almost perfect (κ = .81-1.00) according to Landis and Koch [22].

Table 4
Correlations coefficients (*r*) for the associations of insulin sensitivity (*M*/*I*) with insulin sensitivity indices derived from fasting and OGTT measurements in women separated into groups

Variables	Insulin sensitivity (*M*/*I*)		
	Women with NGT (n = 64)	Women with IGT (n = 30)	Women with T2D (n = 18)
1/Fasting insulin	0.33**	0.65***	0.66**
HOMA index	0.38**	0.56**	0.73**
1/Insulin 120 min	0.43**	0.69***	0.10
Matsuda index	0.54***	0.73***	0.67**
Cederholm index	0.58***	0.31	0.73**
MCR index	0.58***	0.74***	0.60**
ISI index	0.58***	0.73***	0.60**

Significant> correlation, **$P < .01$, ***$P < .0001$.

mellitus and Cederholm index in women with IGT, which were not significantly correlated with *M*/*I*. The magnitude of the relationships between *M*/*I* and insulin sensitivity indices differs slightly according to the glucose tolerance status as illustrated in Table 4. In fact, correlation coefficients between *M*/*I* and insulin sensitivity indices for fasting plasma insulin index, HOMA, and Matsuda indices were generally lower in women with NGT compared with women with IGT or type 2 diabetes mellitus.

Finally, the prevalence of the metabolic syndrome was assessed by tertiles of Cederholm, MCR, and ISI indices (Fig. 2); 28.1% of women in the first tertile of Cederholm index had the metabolic syndrome, whereas 58.6% and 86.1% of women, respectively, had the metabolic syndrome in the second and the third tertile of Cedelholm index. Similar results were observed for the MCR (24.3%, 55.9%, and 88.9%) and ISI (21.6%, 58.8%, and 88.9%) indices.

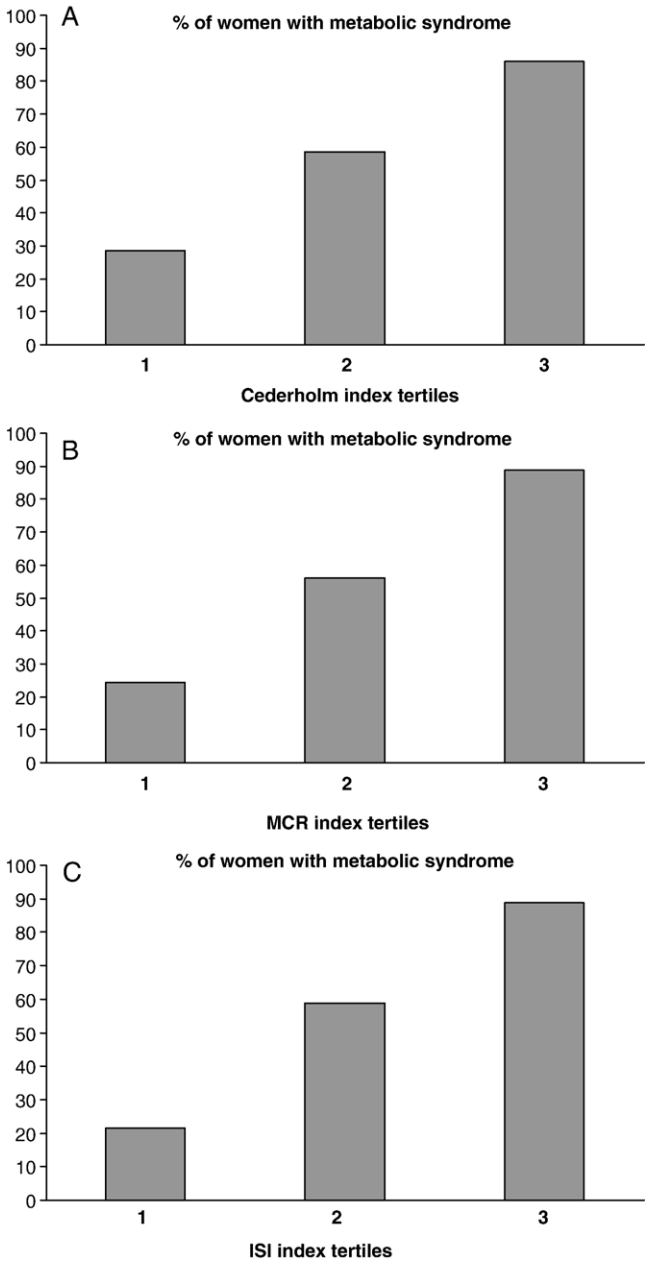

Fig. 2. Prevalence of the metabolic syndrome as defined by the NCEP/ATP-III guidelines separated into tertiles of Cederholm index (A), MCR (B), and ISI index (C).

4. Discussion

In this study, we examined how surrogate measures of insulin sensitivity were associated with insulin sensitivity obtained using the euglycemic-hyperinsulinemic clamp technique in postmenopausal women. To our knowledge, our study is the first to extensively examine the associations between different surrogate insulin sensitivity indices derived from fasting and OGTT measurements with insulin sensitivity obtained from the euglycemic-hyperinsulinemic clamp in a sample of postmenopausal women with varying degrees of glucose tolerance.

Our results show that all insulin sensitivity indices measured in this study were significantly correlated with insulin sensitivity obtained from the euglycemic-hyperinsulinemic clamp. These associations were also observed in other studies [12,20,23]. Indices derived from fasting plasma insulin and insulin 120-minute concentrations (especially in type 2 diabetic women), which are commonly used as indicators of insulin resistance, were found to be less concordant with *M*/*I* than Cederholm, MCR, and ISI indices when using κ analysis. In addition, the fasting plasma insulin index was significantly less correlated with *M*/*I* than the other indices. Hence, these findings weaken the rationale for the use in clinical practice of fasting plasma insulin and insulin 120-minute concentrations. These results were consistent with those of other studies, which showed that fasting plasma insulin and insulin 120-minute indices correlate only mildly with more direct indices of insulin resistance [24,25]. In addition, Kuo et al [26] observed that insulin 120-minute index was less correlated with insulin sensitivity obtained from the euglycemic-hyperinsulinemic clamp in type 2 diabetic subjects than in subjects with NGT, because insulin 120-minute levels mainly reflect impaired insulin secretion. Interestingly, HOMA (derived from fasting measurements) and Matsuda (derived from mean glucose and insulin values obtained after an OGTT) indices showed similarly fair concordance with *M*/*I* and were also moderately correlated with it. Bonora et al [24] also observed a similar correlation between HOMA and insulin sensitivity measured by the euglycemic-hyperinsulinemic clamp in subjects with various degrees of glucose tolerance. Therefore, our results suggest that the HOMA index, which performs better than fasting plasma insulin alone, may represent an alternative method to the euglycemic-hyperinsulinemic clamp in the evaluation of insulin sensitivity when only fasting measures are available. That HOMA showed a better concordance than fasting plasma insulin

alone demonstrates the importance of considering FPG in relation with fasting plasma insulin (as done in the HOMA model) to estimate the degree of insulin sensitivity.

In our study, insulin sensitivity indices that had the higher degree of concordance with *M*/*I* were those defined by Cederholm and Stumvoll (MCR and ISI indices) [20,21]. These indices use postload glucose and insulin concentrations and anthropometric measurements (body weight or BMI). The stronger concordance between MCR and ISI with *M*/*I* could be explained by the fact that estimates for MCR and ISI indices were originally obtained by determining the best model derived from multiple linear regression analyses as measured with the euglycemic-hyperinsulinemic clamp. Similarity in BMI (19.7-45.8 kg/m^2) of subjects used to define these 2 indices and our subjects (19.0-59.7 kg/m^2) could also potentially explain the relatively good performance of these indices to predict insulin sensitivity in our sample [20]. Because the measurements needed to derive these indices are relatively easy to obtain in the context of the OGTT, these indices represent interesting surrogate measures of insulin sensitivity during a test that also clearly defines glucose tolerance.

We also evaluated the variation in the relationship between insulin sensitivity indices and clamp according to the glucose tolerance status. In contrast with some studies, we observed strong associations between insulin sensitivity indices and *M*/*I* in women with IGT or type 2 diabetes mellitus [12,27]. The presence of women with de novo type 2 diabetes mellitus in our study could possibly explain the maintenance of strong associations between insulin sensitivity indices and *M*/*I*. In our subjects with newly diagnosed type 2 diabetes mellitus, the relationship between circulating insulin levels probably still reflects insulin resistance because insulin secretion is maintained to a certain degree, whereas in subjects who have long-standing type 2 diabetes mellitus, circulating insulin levels no longer reflect insulin resistance because of severely impaired insulin secretion [28]. On the other hand, the associations among fasting plasma insulin index, HOMA index, and insulin sensitivity as obtained from the euglycemic-hyperinsulinemic clamp were considerably reduced in women with NGT. Our results are somewhat different from those of McAuley et al [29], who demonstrated that fasting plasma insulin and ISI were highly correlated with the euglycemic-hyperinsulinemic clamp in subjects with NGT. To better understand these discrepant results in women with NGT, we separated our group of NGT women according to BMI (less than or 25.0 kg/m^2 or greater). We found that relationships between insulin sensitivity indices and *M*/*I* were not significant in women with NGT and BMI less than 25.0 kg/m^2, except for Matsuda (r = 0.47, P = .03) and Cederholm (r = 0.43, P = .04) indices, whereas all these associations were significant and similar in magnitude to those found in women with IGT or type 2 diabetes mellitus in women with NGT and BMI 25.0 kg/m^2 or greater (data not shown). Because these indices of insulin sensitivity were primarily developed to detect subjects with insulin resistance who usually have increased BMI, the lower correlations seen in our population probably reflect the presence of NGT women with lower BMI. Many insulin sensitivity indices could therefore be of limited use in studying subjects with insulin sensitivity values in the upper reference range. These results were supported by a recent study performed in a nondiabetic population of men and women [30]. In the total sample of women from our study, the various insulin sensitivity indices studied were strongly correlated with insulin sensitivity obtained from the euglycemic-hyperinsulinemic clamp. As shown in Fig. 1, the fact that women with IGT and type 2 diabetes mellitus were on the left side of each graph, whereas women with NGT were on the right side, contributes to the stronger overall group correlations despite the weaker correlations found in each glucose tolerance subgroup. We have also found that the prevalence of the metabolic syndrome was increased with decreasing insulin sensitivity index tertiles (Cedelholm, MCR, and ISI), suggesting that deteriorated insulin sensitivity is strongly associated with the presence of the metabolic syndrome.

Although it is the gold standard for the evaluation of insulin sensitivity, the euglycemic-hyperinsulinemic clamp is a laborious, expensive, time-consuming method and would be of very limited use in the clinical setting. However, the determination of insulin sensitivity derived from postload glucose and insulin concentrations after an OGTT in combination with adiposity measures would be easier to use in clinical practice, less expensive, and less time-consuming. Because the OGTT is clearly a better test to evaluate glucose tolerance status and diabetes mellitus risk in patients, it is often recommended by many organizations and performed frequently in the evaluation of patients. From the same test, measures of insulin sensitivity can be derived as shown in our results, giving important information with potential impact on treatment. However, this remains to be demonstrated in prospective studies with evaluation of cost-effectiveness and clinical outcomes.

In conclusion, our results indicate that indices of insulin sensitivity derived from postload glucose and insulin concentrations after an OGTT and using anthropometric variables in their definition (Cederholm, MCR, and ISI) display the best correlations and agreement with insulin sensitivity measured by the gold standard clamp method. All indices examined in our study were significantly correlated with insulin sensitivity obtained by the reference method in women with varying glucose tolerance status, except in nonobese women with NGT. Finally, these results reinforce the effectiveness of using the OGTT in combination with a measure of adiposity in clinical practice to improve the identification of subjects characterized by insulin resistance, who are at increased risk of type 2 diabetes mellitus and CVD, the leading cause of death in these populations. One limitation of our study is the rather small sample size that prevents generalization of results obtained. Therefore, results will need to be corroborated in a larger study.

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