Surrogate indexes vs. euglycaemic-hyperinsulinemic clamp as an indicator of insulin resistance and cardiovascular risk factors in overweight and obese postmenopausal women

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SUMMARY

Background: There is considerable interest in validating the most convenient method to estimate insulin sensitivity in clinical research protocols that could best indicate cardiovascular risk factors. To address this issue we examined the interrelationships of several cardiovascular risk factors with surrogate indexes such as fasting insulin, the homeostasis model assessment (HOMA), the quantitative insulin sensitivity check index (QUICKI) and the revised QUICKI vs. the euglycaemic-hyperinsulinemic (EH) clamp in a non-diabetic overweight or obese postmenopausal female population.

Design: Cross-sectional study involving 88 obese postmenopausal women (age: 57.5±5.0 yrs; body mass index: 32.52±4.4 kg/m²; percent body fat: 46.35±4.9%).

Methods: Insulin sensitivity was determined by the EH clamp technique as well as by surrogate indexes such as fasting insulin, HOMA, log HOMA, QUICKI and revised QUICKI. Body composition and body fat distribution were measured using dual energy x-ray absorptiometry and computed tomography, respectively.

Results: Correlations between insulin resistance indexes (fasting insulin, revised QUICKI, QUICKI, log HOMA, HOMA) vs glucose disposal were similar (range of r’s=0.40 to 0.49), suggesting that no index was superior to another with respect to its relationship with the EH clamp. Correlations between the insulin resistance indexes with plasma lipids were comparable among all indexes, however, systolic blood pressure, visceral fat and C-reactive protein were moderately superior with index vs the EH clamp.

Conclusion: Surrogate measures of insulin resistance, in particular fasting insulin, are simple tools appropriate for epidemiological studies that can be used as substitutes for the EH clamp to estimate glucose disposal and cardiovascular risk factors in overweight and obese postmenopausal women.

Key-words: HOMA · QUICKI · Revised QUICKI · Fasting insulin · Insulin resistance.

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RÉSUMÉ

Comparsion de la mesure directe de la sensibilité à l’insuline à son évaluation par des index comme indicateur de la résistance à l’insuline et du risque cardiovasculaire chez des femmes en surpoids ou obèses post-ménopausiques

Introduction: L’évaluation de la sensibilité à l’insuline est primordiale dans les protocoles de recherche clinique. Bien que plusieurs index soient couramment utilisés, il existe peu de comparaison de ces index avec la technique de référence, le clamp euglycémique hyperinsulinémique. Nous avons évalué l’association de ces index et du clamp avec l’utilisation du glucose ainsi que de multiples facteurs de risque cardiovasculaire.

Matériaux et méthodes: Étude transversale d’une cohorte (n = 88) de femmes obèses post-ménopausiques non diabétiques dont le phénomène a été étudié en détail : composition corporelle, profil lipique, pression artérielle et sensibilité à l’insuline grâce au clamp hyperinsulinémique-euglycémique. Comparaison de différents index d’évaluation de la sensibilité : insulémie, HOMA, Log HOMA QUICKI, QUICKI révisé avec les résultats du clamp hyperinsulinémique-euglycémique pour leur association avec l’utilisation du glucose ainsi que de multiples facteurs de risque cardiovasculaire : cholestérol total, cholestérol LDL, triglycérides, cholestérol HDL à jeun, pression artérielle, tissu adipeux viscéral et protéine C-réactive (CRP).

Résultats : Tous les index sont corrélés de façon comparable avec le clamp hyperinsulinémique-euglycémique pour l’utilisation du glucose (r compris entre 0,40 et 0,49). La corrélation avec les paramètres du bilan lipidique est comparable pour toutes les méthodes de mesure de la sensibilité à l’insuline. En revanche, la corrélation entre la pression artérielle ou la CRP et les index est légèrement supérieure à celle observée avec le clamp hyperinsulinémique-euglycémique.

Conclusion : Ces résultats suggèrent que les index, y compris l’insulémie à jeun, sont des outils acceptables dans les études épidémiologiques pour évaluer tant l’utilisation du glucose que la plupart des facteurs de risque cardiovasculaire chez les femmes obèses post-ménopausiques.

Mots-clés : HOMA · QUICKI · QUICKI-révisé · Clamp hyperinsulinémique-euglycémique · Insulinémie à jeun · Insulinorésistance.

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Introduction

Insulin resistance is associated with deleterious health outcomes, such as type 2 diabetes mellitus and cardiovascular diseases (CVD) [1-3]. Therefore, it is important to develop clinically useful methods to estimate insulin resistance to potentially understand the risk for cardiovascular and metabolic disease. The euglycaemic-hyperinsulinemic (EH) clamp technique is the gold standard method to measure insulin sensitivity because it directly measures insulin action on glucose utilization under steady-state conditions [4,5]. However, this method is invasive and time consuming and thus not suitable for large scale trials [6]. Therefore, there is considerable interest to evaluate more convenient methods to measure insulin resistance levels in targeted populations.

A number of surrogate indexes have been derived from fasting plasma insulin and glucose levels to evaluate insulin sensitivity [7,8] such as HOMA, QUICKI and revised QUICKI. Their major advantages are their simplicity and their validation vs the EH clamp [9-14]. However, there remains considerable debate about the validity of these surrogate indexes to evaluate insulin resistance in specific populations and to predict cardiovascular events [15-18]. Thus, it is important to validate these indexes in well described populations (i.e. obese postmenopausal women) with a large spectrum of CVD risks (dyslipidemia, dysglycaemia and hypertension).

Therefore, the aims of this study were to: (1) examine the relationship with measured indexes of insulin sensitivity (fasting insulin, revised QUICKI, QUICKI, log HOMA, HOMA) and glucose disposal measured with the EH clamp and (2) to determine the relationship between measured indexes of insulin sensitivity and a large spectrum of cardiovascular disease risk factors in overweight and obese postmenopausal women.

Methods

Subjects

The study population consisted of 88 non-diabetic overweight and obese postmenopausal women aged between 46 and 73 years old. The study was approved by the University of Montreal ethics committee. After reading and signing the consent form, each participant was invited to the Metabolic Unit in the fasting state at 07 h30 for a series of tests. Inclusion criteria and methods for blood pressure, body composition and fat distribution were determined as previously described [19].

Euglycaemic-hyperinsulinemic clamp

Insulin sensitivity was measured as previously described using an insulin doses of 75 mU/m²/min for 180 min [19]. Glucose disposal was calculated as the mean rate of glucose infusion measured during the last 30 min of the clamp (steady state) and is expressed as mg/min x kg fat free mass.

Blood Samples

Blood samples were measured as previously described [19]. Briefly, insulin levels were determined in duplicate by radioimmunoassay (Linco research Inc, St-Charles, MO USA). There was <0.2% of cross reactivity for human pro-insulin. Homeostasis model assessment (HOMA) was calculated according to the formula: \[ \text{HOMA} = \frac{I_0(\mu U/ml) \times G_0 \text{ (mmol/liter)}}{22.5} \]. QUICKI according to the formula: \[ \frac{1}{\log (I_0)+\log (G_0)} \], where \( G_0 \) represents fasting glucose and \( I_0 \) represents fasting insulin. Revised QUICKI was calculated as described by Perseghin et al. [14]. Fasting glucose and insulin were determined using the mean of three basal values.

Statistical Analysis

We verified the normality of the distribution of variables with a Kolmogorov-Smirnov test and found that CRP was not normally distributed. Therefore, we used the log of CRP for this variable. Data are presented as mean ± SD. Pearson correlations were performed to examine the relationship between insulin resistance indexes and metabolic/cardiovascular risk factors (i.e. body composition, lipid profile). Significance was accepted at P<0.05.

Results

Physical characteristics of apparently healthy overweight and obese postmenopausal women showed a broad range of age, adiposity, body fat distribution and blood pressure (table I). When assessing metabolic profile and insulin sensitivity (table II), we observed a five-fold range in glucose disposal despite high levels of body fat, suggesting that some obese women have high insulin sensitivity. Relative to the first aim, correlations between insulin resistance indexes (fasting insulin, revised QUICKI, QUICKI, log HOMA, HOMA) vs glucose disposal (table III) were comparable among all indexes (i.e., fasting insulin vs revised QUICKI, vs QUICKI vs log HOMA vs HOMA vs the EH clamp). No significant correlation was noted between revised QUICKI with HDL-cholesterol and total cholesterol/HDL-cholesterol, nor between total cholesterol and LDL-cholesterol with either the EH clamp or surrogate indexes.

Systolic blood pressure was correlated only with fasting insulin (\( r=0.24; \) P<0.05), HOMA (\( r=0.22; \) P<0.05) and...
Our results show moderate (r=0.40 to 0.49), but significant correlations between surrogate measures of insulin sensitivity and the EH clamp technique. These findings suggest that approximately 25% of the variation is accounted for by these surrogate indexes when compared with the EH clamp. The magnitude of these correlations (albeit statistically significant) are less robust than previous studies that found stronger relationships between the clamp and QUICKI in obese subjects (r=0.79) [12], in a mixed gender population (r=0.81) [13], in older men with normal glucose tolerance (r=-0.59) and in type 2 diabetic patients (r=-0.625) [18]. Although the cause of the differences in the magnitude of correlations among studies remains unclear, it is possible that the higher insulin doses used in this study (75 mU/m²/min), may explain, in part, the different correlations [13]. Collectively, our results suggest that surrogate measures of insulin sensitivity are acceptable markers of insulin sensitivity (as compared to the clamp).

**Correlations among indexes of insulin sensitivity with cardiovascular risk factors**

The present study proposes that in overweight or obese postmenopausal women, surrogate indexes are associated with most of the cardiovascular risk factors. In addition, it appears that fasting insulin (compared to other surrogates) provides as good a correlation with traditional cardiovascular disease risk factors. This raises the question as to whether other indexes are needed to predict cardiovascular disease risk in older obese postmenopausal women.

We examined correlations between insulin sensitivity indexes and measures of body composition as well as body fat distribution. We found similar correlations between surrogate indexes and the EH clamp for body mass index and waist circumference. These results are concordant with
those of Diamanti-Kandarakis [17] who reported similar correlations of surrogate indexes and the EH clamp with BMI (QUICKI (r=-0.3), HOMA (r=0.30) and the EH clamp (r=-0.40). Moreover, Vaccaro et al. [20] reported similar correlations between surrogate indexes and waist circumference. Interestingly, the correlations between visceral adipose tissue were higher in surrogate indexes than in the EH clamps. This could be due to the fact that the EH clamp assesses essentially peripheral (i.e. muscle) insulin sensitivity whereas surrogate indexes estimate global insulin sensitivity including hepatic insulin sensitivity which is closely linked to insulin resistance [21].

The correlations of surrogate indexes and the EH clamp with C-reactive protein were also evaluated. Again, similar correlations were observed with either the EH clamp or various surrogate indexes. In addition, our correlations appear to be line with previously published findings, where HOMA and QUICKI were reported to be significantly correlated with CRP in a population of men and women (r=0.30 and r=-0.26, respectively) [22]. Moreover, a significant relationship was observed between fasting insulin and CRP in a large non-diabetic cohort (r=0.33) [23].

Finally, we report correlations between surrogate indexes and the EH clamp with blood pressure. Systolic blood pressure was moderately but significantly correlated with fasting insulin (r=0.238), HOMA (r=0.225), while a negative relationship was observed between diastolic blood pressure and the EH clamp (r=-0.238). This lack of association with the other surrogate indexes might be explained by the fact that the majority of women enrolled in this study were normotensive. In accordance with our results, it should be noted that lower but significant correlations between fasting insulin, HOMA and QUICKI with blood pressure have been observed in two large populations [20,24].

So what new findings does this study bring to the literature? We would suggest that it may not be necessary to calculate the plethora of surrogate measures of insulin sensitivity as markers of insulin resistance or cardiovascular disease risk. Admittedly, this was an unanticipated finding. That is, fasting levels of insulin turned out to be as good a marker of insulin sensitivity and as powerful a predictor of cardiovascular risk as the other surrogate measures (HOMA, clamp, etc.). It is interesting that the simplest measure provided as robust a finding as the other surrogate measures. This is an encouraging finding for researchers who seek a simple and convenient method to evaluate insulin resistance and cardiovascular risk in their older patients.

Several limitations of our study should be noted. First, the cross-sectional nature of this study precludes any speculation about relationships of cause and effects. Second, the characteristics of the cohort reflect strict inclusion and exclusion criteria. Third, men were not examined in this study. Thus, our results are only applicable to overweight or obese postmenopausal women.

In conclusion, all surrogate indexes as well as fasting insulin were moderately and similarly correlated with either glucose disposal as measured by the EH clamp technique or with various cardiovascular risk factors. Moreover, fasting insulin alone may provide a reliable marker of insu-
lin sensitivity and cardiovascular disease risk as compared to other more complicated surrogate markers in overweight and obese postmenopausal women.

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References