Evaluation of two new surrogate indices including parameters not using insulin to assess insulin sensitivity/resistance in non-diabetic postmenopausal women: A MONET group study

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Received 4 November 2011; received in revised form 23 January 2012; accepted 23 January 2012

Abstract

Aim. – The study evaluated and compared, with other surrogate indices of insulin sensitivity/resistance (IS/R), the relevance of the TyG index, a product of fasting glucose and triglyceride (TG) levels, and the EGIR index, which includes TG, high-density lipoprotein cholesterol (HDL-c) and waist circumference in its formula to estimate IS/R, in non-diabetic postmenopausal women.

Methods. – A secondary analysis was performed using the baseline data for 163 non-diabetic postmenopausal women from the Montreal–Ottawa New Emerging Team (MONET) population database. The subjects participated in hyperinsulinaemic–euglycaemic (HIEG) clamp and oral glucose tolerance (OGTT) tests. Correlations and comparisons between surrogate indices were performed in addition to inter-rater agreement tests. The optimal value of surrogate indices for diagnosis of IS/R was established on a receiver operating characteristic (ROC) scatter plot.

Results. – A significant correlation was found between the HIEG clamp and all IS/R surrogate indices tested \( r = -0.370 \) (TyG index) to \( 0.608 \) (SIisOGTT index); \( P < 0.001 \). On ROC curve analysis, a higher AUROC was found for SIisOGTT (0.791) than for TyG and EGIR (0.706 and 0.675, respectively; \( P = 0.07 \) and \( P < 0.05 \), respectively).

Conclusion. – The TyG and EGIR IS/R indices were only relatively modestly related to the HIEG clamp. In contrast, both fasting- and OGTT-derived IS/R surrogate indices, which include insulin values in their formulae, appeared to be more accurate in estimating IS/R in our study population. Thus, the TyG and EGIR IS/R indices need to be tested and validated more extensively in different populations before being put to large-scale clinical use.

Keywords: Glucose; Insulin; Triglyceride; Hyperinsulinaemic–euglycaemic clamp; Surrogate index

Résumé

Évaluation de deux nouveaux indices simples de mesure de la sensibilité/résistance à l’insuline (IS/R) n’intégrant pas l’insulinémie dans leur équation dans une cohorte de femmes non diabétiques ménopausées: une étude du groupe MONET.

But. – Évaluer et comparer la pertinence de l’utilisation de deux nouveaux indices d’estimation de l’IS/R dans une population de femmes ménopausées non diabétiques : les indices TyG qui résulte du produit de la glycémie et de la triglycéridémie à jeun et EGIR qui prend en compte les triglycérides (TG), les lipoprotéines de haute densité (HDL-c) et la circonférence de la taille dans sa formule.

Méthodes. – Nous avons réalisé une analyse secondaire à partir des résultats de 163 femmes ménopausées non diabétiques de la base de données de l’Équipe Émergente Montréal Ottawa (MONET). Les sujets ont participé à une épreuve de clamp hyperinsulinémique euglycémique (CHE) et

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doi:10.1016/j.diabet.2012.01.004
une hyperglycémie provoquée par voie orale (HGPO). Les corrélations et les comparaisons entre des indices d’IS/R ont été réalisées. La pertinence de l’utilisation de ces indices de mesure d’IS/R comparés au CHE a été appréciée par l’analyse des courbes ROC.

Résultats. Nous avons observé des corrélations significatives entre les données du CHE et tous les indices d’estimation de l’IS/R évalués ($r = -0.370$ indice TyG) à $0.608$ indice SIisOGTT, $P < 0.001$). L’analyse des courbes ROC a montré que l’aire sous la courbe pour l’indice SIisOGTT (0,791) était plus élevée que pour les indices TyG (0,706) ou EGIR (0,675), ($P = 0.07$ et $P < 0.05$) respectivement.


Mots clés : Glucose ; Insuline ; Triglycéride ; Clamp hyperinsulinémique euglycémique ; Indice d’insulinorésistance

1. Introduction

The gold standard for measuring insulin sensitivity/resistance (IS/R) is the hyperinsulinaemic–euglycaemic (HIEG) clamp [1]. However, numerous surrogate indices to estimate IS/R have been developed over the past 20 years, as the HIEG clamp is not routinely applicable in clinical practice [2–4]. These indices usually take into account insulin and glucose, and are sometimes combined with measurements of lipid parameters such as triglycerides (TG) and non-esterified fatty acids (NEFA) [5–8]. However, insulin assay is currently not standardized [9] and not always easily measurable (such as in lower-income countries). Moreover, it is not the best factor for assessing IS/R in diabetic patients with significant insulinopenia, including both type 1 (T1D) and most type 2 (T2D) diabetes cases. For this reason, new IS/R surrogate indices that do not use insulin measurement have been developed, including the TyG index, a product of the levels of both fasting glucose and fasting TG [5,6], and the estimated glucose infusion rate (EGIR) index, which includes fasting TG, high-density lipoprotein cholesterol (HDL-c) and waist circumference (WC) in its formula [10]. The TyG index was initially developed in comparison to the homoeostasis model assessment (HOMA) index [5], and its relevance was confirmed with the HIEG clamp in a Mexican population with a wide range of insulin resistance, including obese subjects with and without T2D [6]. The EGIR index was developed in a Japanese population that included controls, T1D and T2D subjects against the HIEG clamp, and has been shown to be applicable in diabetic patients even in cases where the more classical HOMA index to assess IS/R was little successful [10]. However, as these surrogate indices have been population-specific (validated only in a specific population), the present study aimed to evaluate both the TyG and EGIR indices in comparison to the gold standard HIEG clamp to estimate IS/R in a homogeneous population of non-diabetic postmenopausal women with varying degrees of insulin sensitivity.

2. Research design and methods

The secondary analysis performed in the present study used baseline data pooled from two low-calorie dietary interventional studies [11,12] of similar populations of non-diabetic overweight and obese postmenopausal women, performed by our research team from 2003 to 2007: the Montreal–Ottawa New Emerging Team (MONET) Study ($n = 137$); and the Complications Associated with Obesity (CAO) Study ($n = 37$). Both studies were approved by the University of Montreal ethics committee, and all subjects gave their written informed consent before the study began. The HIEG clamp was performed in non-diabetic postmenopausal overweight and obese women. The cohort included women who had been weight-stable for 2 months prior to the study and who met the following criteria:

- body mass index (BMI) more than 27 kg/m²;
- no menstruation for more than 1 year and follicle-stimulating hormone levels greater or equal to 30 U/L;
- sedentary lifestyle (<2 h/week of structured exercise);
- non-smoker;
- low-to-moderate alcohol consumption (<2 drinks/day);
- no known inflammatory disease;
- no use of hormone replacement therapy within the last 3 months.

Also, all participants had no history or evidence of:

- cardiovascular disease, peripheral vascular disease or stroke;
- diabetes [2-h plasma glucose less than 11.0 mmol/L after a 75-g oral glucose tolerance test (OGTT)];
- body weight fluctuation of ± 2 kg within the last 2 months;
- thyroid or pituitary disease;
- infection according to a medical questionnaire examination and complete blood count;
- taking medication that might affect cardiovascular function and/or metabolism.

From this database of subjects, 163 out of 174 women had complete datasets of the required study parameters, including fasting lipid profiles, fasting and OGTT values of glucose and insulin, and HIEG clamp data. Subjects underwent the HIEG clamp (insulin infusion rate: 75 mU/m²·min) for 180 min, as previously described [13–15]. Insulin sensitivity was expressed as the glucose disposal rate (M; mg/min/kg of fat-free mass), as calculated from measurements taken during the final 30 min of the clamp. Fasting glucose, total cholesterol, HDL-c and TG were measured with a COBAS INTEGRA 400 analyzer (Roche Diagnostics Corp., Indianapolis, IN, USA). Insulin was measured in duplicate by using a radioimmunoassay (RIA) kit (Medi-corps Inc., Montreal, Quebec, Canada). Fat-free mass (FFM)
Correlations between fasting biological parameters, and fasting and oral glucose tolerance test surrogate indices, and the hyperinsulinaemic–euglycaemic clamp test.

2.1. ISI–Matsuda [20] $104/[\text{fasting glucose} \times \text{insulin}]^{22.5}$ was evaluated by dual-energy X-ray absorptiometry (version 6.10.019; GE Lunar Corp., Madison, WI, USA). Fasting-derived IS/R indices, including the HOMA [16], quantitative insulin sensitivity check index (QUICKI) [17], McAuley index [7], TyG index [5,6], EGIR index [10] and TG/HDL-c ratio [18], was evaluated by dual-energy X-ray absorptiometry (version 6.10.019; GE Lunar Corp., Madison, WI, USA). Fasting-derived IS/R indices, including the HOMA [16], quantitative insulin sensitivity check index (QUICKI) [17], McAuley index [7], TyG index [5,6], EGIR index [10] and TG/HDL-c ratio [18], a simple index assessing insulin sensitivity derived from OGTT (SlisOGTT) [19] and insulin sensitivity index from Matsuda and De Fronzo [20] (ISI–Matsuda) were calculated as previously published (Table 1).

2.1. Statistical analysis

Differences between groups were determined using one-way analysis of variance (Anova), followed by Fisher’s protected least significant difference test for pair-wise differences. Pearson’s correlation coefficient was calculated to express the strength of the relationship between continuous values. Comparison of correlations was made using the method described by Dawson and Trapp [21] and elsewhere [15,22]. Fasting insulin, TG, HOMA, TyG, EGIR and SlisOGTT indices and the HIEG clamp were stratified into tertiles, and the degree of agreement estimated according to the inter-rater agreement $k$ test, set from 0.00 (no agreement) to 1.00 (full agreement). The sensitivity and specificity of fasting insulin, TG, HOMA, TyG and SlisOGTT indices were then estimated as a function of the threshold (11.56 mg/kgFFM/min) used to define insulin resistance by HIEG clamp. The optimal value of all these indices for diagnosis of insulin resistance was established on a receiver operating characteristic (ROC) scatter plot. The area under the ROC curve (AUROC) was estimated, with the best markers having ROC curves shifted to the left with AUROCs near 1. The threshold for significance was set at $P = 0.05$. 3. Results

A secondary analysis was performed using baseline data from 163 non-diabetic overweight or obese postmenopausal women aged 57.3 ± 0.4 years with a mean BMI of 33.1 ± 0.3 kg/m². Based on the OGTT, subjects were classified as having normal glucose tolerance (NGT, fasting glucose less than 5.6 mmol/L and 2-h glucose less than 7.8 mmol/L, $n = 104$), impaired glucose tolerance (IGT, fasting glucose less than 5.6 mmol/L and 2-h glucose 7.8–11.1 mmol/L, $n = 22$), impaired fasting glucose (IFG, fasting glucose 5.6–7.0 mmol/L and 2-h glucose less than 7.8 mmol/L, $n = 26$) or combined glucose intolerance (CGI, fasting glucose 5.6–7.0 mmol/L and 2-h glucose 7.8–11.1 mmol/L, $n = 11$), according to American Diabetes Association criteria [23]. Fasting insulin, TG, HDL-c and HOMA were included in the present study. Interestingly, the SlisOGTT was better correlated with the HIEG clamp than all the other surrogates tested ($P < 0.01$ for all except HOMA, which was $P < 0.05$) except for fasting insulin. In fact, the correlation with the HIEG clamp was higher for fasting insulin than for fasting HDL-c ($P < 0.05$), fasting TG, HDL-c, EGIR, TyG and McAuley indices ($P < 0.01$). In addition, the correlations between the TyG and HIEG clamp and between the fasting TG and HIEG clamp were similar (Table 1).

Subjects were then categorized by tertiles of fasting insulin, TG, HIEG clamp, HOMA, EGIR, TyG, ISI–Matsuda and SlisOGTT indices. The weighted $k$ test showed only fair agreement between TG, TyG, EGIR, HOMA and fasting insulin.
and the HIEG clamp with $k$ at 0.232, 0.232, 0.294, 0.315 and 0.371, respectively, whereas agreement was better and considered moderate between the SIsOGTT and ISI–Matsuda indices and the HIEG clamp ($k = 0.407$ and 0.405, respectively). As expected, agreement was also very good between TG and the TyG index ($k = 0.834$), and between fasting insulin and the HOMA index ($k = 0.820$). The median value of the HIEG clamp at 11.56 mg/kgFFM/min was arbitrarily used in our population to define IR and to perform the ROC scatter plot for fasting insulin, TG, EGIR, TyG, HOMA and SIsOGTT indices. AUROCs of 0.675, 0.704, 0.706, 0.773, 0.783, 0.789 and 0.791 ($P < 0.001$) were found for EGIR, TG, TyG, HOMA, ISI–Matsuda, fasting insulin and SIsOGTT indices, respectively. On comparing ROC curves, the AUROC for the EGIR index was significantly lower than those for the fasting insulin, HOMA, ISI–Matsuda and SIsOGTT indices ($P < 0.05$; Fig. 1). In addition, the ROC curves for both fasting TG and the TyG index tended to be lower than the AUROC for either fasting insulin ($P = 0.08$) or the SIsOGTT index ($P = 0.07$; Fig. 1).

When studying subjects according to glycaemic status, the fasting surrogate indices that included either fasting glucose or fasting insulin, or both, in their formulae showed significant differences in the IFG, IGT and CGI groups compared with the NGT group (Table 2). In contrast, fasting insulin, TG, TG/HDL-c ratio and the EGIR were less informative as discriminating indicators of glycaemic status in our study population. Interestingly, the SIsOGTT changed more closely in parallel with the HIEG clamp (Table 2).
4. Discussion

The relevance of two new recently described surrogate indices that do not include insulin values in their formulae to evaluate IS/R was assessed in the present study. Both TyG and EGIR indices were significantly related to the HIEG clamp. However, this relationship was relatively weak for the TyG index and similar to that observed with fasting TG levels. This observation was confirmed by the results from the ROC curve analysis and estimation of the degree of agreement with the HIEG clamp. Thus, the use of such an index in our population of overweight or obese postmenopausal women did not improve IS/R estimation and classification compared with fasting TG levels and the other, more classical, surrogate indices.

On the other hand, our present study has confirmed that fasting plasma insulin as well as surrogate indices including insulin levels in their formulae were better related to the HIEG clamp, suggesting that insulin values at either fasting or during OGTT are essential for estimating IS/R, as previously shown in a subset of the present study population [14]. Indeed, on ROC curve analysis, it was found that fasting insulin, HOMA, ISI–Matsuda and SIisOGTT indices were better at estimating IS/R than the EGIR index, and tended to be better than the TyG index. Moreover, a stronger degree of agreement was observed between the SIisOGTT and HIEG clamp, as was also previously shown in this population [19]. However, this result was not surprising, as the SIisOGTT index was originally described in a clamp study of 107 subjects who were also included in the present analysis. Nevertheless, these results have confirmed that insulin either under fasting conditions or during OGTT is a key marker for estimations of IS/R in subjects without major insulinopenia.

It should also be noted that fasting insulin levels alone have already been shown to be good surrogates for assessing IS/R [14,24,25]. However, several drawbacks in using fasting insulin levels alone, such as the absence of insulin assay standardization, have recently been described [4], and also affect the simple indices that include fasting insulin in their calculations [4]. Perhaps the most important issue is the fact that using either fasting insulin or indices that include only fasting insulin, such as the Raynaud index [25], may be particularly inappropriate when insulin secretion is reduced in the face of hyperglycaemia, as observed in T2D patients, and could lead to false results, as previously discussed [3].

Also, the discrepancies observed between our results for the TyG index and previous studies [6,26] may be explained by several factors. The populations previously studied [6,26] included Mexican and Brazilian subjects who were different from ours: they included controls, obese and diabetic subjects, and both men and women, whereas our present study used data from a homogeneous population of non-diabetic overweight or obese postmenopausal women. In addition, in accordance with our results, Abbasi and Reaven [18] made similar observations in a homogeneous population of only NGT and IFG subjects, and showed that the TyG index was weakly correlated with steady-state plasma glucose according to the insulin suppression test (IST), while the insulin AUC during OGTT was strongly associated with IS/R as measured by IST. Furthermore, they also concluded that, although the TyG index was no better than other indices, such as the TG/HDL-c ratio and HOMA, for assessing insulin resistance, the TyG index might be of value for screening because of its low cost, being derived from routine clinical measurements [18]. It should also be noted that the values for the TyG index obtained by Abbasi and Reaven [18] were similar to our present findings and up to twice those presented initially by Guerrero-Romero et al. [6], for which no clear explanation was given.

In addition to the different characteristics of the populations studied, such discrepancies could have also been due to the use of different reference tests to assess IS/R (hyperglycaemic clamp, IST and HIEG clamp) and the different insulin infusion rates used, as recently reviewed [4]. For this reason, our present study used an insulin infusion rate that mostly allowed the assessment of muscle insulin sensitivity. This was illustrated by the results (Table 2) showing the lack of differences between the NGT and IFG groups, and between the IGT and CGI groups, which were similar to the observations obtained with the SIisOGTT index. Furthermore, the use of the EGIR index in our population was also relatively disappointing and, in our opinion, should not replace the most-validated HOMA index for assessing IS/R. However, the EGIR index might be useful in other populations such as diabetic patients [10].

In conclusion, although the TyG and EGIR indices showed promise for estimating IS/R in Mexican and Brazilian populations [5,6,26], and diabetics [10], respectively, these indices were very similar to fasting TG levels and TG/HDL-c, and were only relatively modestly related to the HIEG clamp in our study population. In contrast, the use of fasting insulin values or both fasting- and OGTT-derived surrogate indices including insulin values in their formulae appears to be more efficient in non-diabetic Caucasian overweight and obese postmenopausal women. Thus, it appears that surrogate indices might be applicable in different ways, depending on the population studied. Although less expensive than other surrogate indices, the TyG and EGIR indices have yet to be tested and validated more extensively in different populations before being clinically used at a larger scale.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

We thank the volunteers who took part in the different experimental protocols. This research was supported by the Canadian Institutes of Health Research (T0602145.02 to Denis Prud’homme and Remi Rabasa-Lhoret).

Funding source: This study was supported by grants from the Canadian Institutes of Health Research (CIHR) New Emerging Team in Obesity (University of Montreal and University of Ottawa MONET project) and from the Genome
Canada-Quebec Complications Associated with Obesity (CAO) project. Marie-Eve Lavoie was supported by a scholarship from the Fonds de la Recherche en Santé du Québec (FRSQ, Funding Agency for Health Research in Quebec). Dr Rabasa-Lhoret was also supported by the FRSQ and holds the J.-A. de Sève chair for clinical research at the IRCM (Montreal Institute for Clinical Research).

References