Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 2683–2687

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Optimized fasting and OGTT-based simple surrogate methods for assessing insulin sensitivity

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ARTICLE INFO

Article history:
Received 21 June 2019
Accepted 10 July 2019

Keywords:
Oral glucose tolerance test
Insulin sensitivity
Metabolic syndrome
Evolutionary algorithm
Statistical analysis

ABSTRACT

Aims: Simple surrogate indices of insulin sensitivity have been conceived to deal with costly and complicated approaches, such as the hyperinsulinemic-euglycemic clamp; however, their use has not been widespread given their variabilities in different populations. In this paper, we present two simple surrogate indices, one that uses fasting glucose and insulin values and the other based on the values from the oral glucose tolerance test.
Materials and methods: The proposed methods integrate easy-to-obtain anthropometric measures. Evolutionary algorithms were used to optimize the proposed methods by maximizing its correlation with the Stumvoll MCR method.
Results and conclusion: When the proposed indices were applied to three study groups (control subjects, metabolic syndrome, marathon runners), a reduction in the intergroup variability of the insulin sensitivity was obtained. Moreover, the proposed index based on the oral glucose tolerance test (OGTT), which considers the glucose metabolism process and the hepatic and peripheral insulin sensitivity, showed stronger correlations with the Stumvoll method and lower intergroup variability than the fasting one.

1. Introduction

Insulin, an anabolic hormone produced and secreted by the pancreas, is in charge of the regulation of glucose in the human body. Insulin sensitivity is the cells' capacity to respond to insulin and process circulating glucose. When the insulin sensitivity decreases, that is, when the cells do not respond appropriately to insulin, the condition of insulin resistance occurs [1,2]. Insulin resistance is an important predisposing risk factor for the development of type 2 diabetes [1,3]. Moreover, insulin resistance and hyperinsulinemia (high blood insulin levels) are key factors in the prevalence of the metabolic syndrome, a cluster of metabolic conditions including dyslipidemia (high blood lipid levels), hypertension (high blood pressure), hyperglycemia (high blood glucose levels) and abdominal obesity (excessive fat around the waist), which increase the risk of cardiovascular diseases and type 2 diabetes. However, the metabolic syndrome can still be diagnosed even if insulin resistance does not occur [4].

The hyperinsulinemic-euglycemic clamp [5], the insulin suppression test [6,7] and the minimum model of the intravenous glucose tolerance test [8,31] are the most accurate and precise methods for assessing insulin sensitivity, but these methods involve very expensive and risky protocols, which makes them impractical for application to large population groups and in follow-up tasks. In this sense, over the last four decades, simple surrogate methods have been conceived to quantify insulin sensitivity by using the glucose and/or insulin values either in fasting (one sample), such as HOMA-IR [9], Raynaud [10] and QUICKI [11], or from several samples of the oral glucose tolerance test (OGTT), such as Belfiore [12], Matsuda [13], Avignon [14], Gutt [15], Stumvoll [16] and OGIS [17]. Nevertheless, a large variability in the insulin sensitivity index of simple surrogate methods has been observed in different populations [18–20], being the case, for example, of the HOMA-IR method which is accurate and precise in patients with insulin resistance but not in diabetic patients with β-cell deficiency [9,21]. Although surrogate methods are less accurate and precise, their ease of application, low cost and minor discomfort favor their use in large-scale clinical studies and follow-up

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https://doi.org/10.1016/j.dsx.2019.07.022
1871-4021/

tasks.

In clinical practice, the HOMA-IR index is the most widely used to assess insulin resistance [22], but this method, like those that use fasting insulin and/or glucose, does not take into account the process of glucose metabolism and only reflect the sensitivity to hepatic insulin, whereas OGTT-based methods take into account both hepatic and peripheral insulin sensitivity. Moreover, a recent meta-analysis study has shown that OGTT-based surrogate measures are more correlated with the hyperinsulinemic-euglycemic clamp, which is considered the gold standard for insulin sensitivity assessment, than fasting surrogate ones [23]. Specifically, the Stumvoll MCR, OGIS and Matsuda are the three OGTT-based indices most correlated with the hyperinsulinemic-euglycemic clamp, whereas QUICKI is the fasting surrogate measure most correlated with the hyperinsulinemic-euglycemic clamp.

Following these previous studies, in this paper we propose two simple surrogate methods for insulin sensitivity assessment, one that uses fasting values and the other that uses OGTT values. We have included anthropometric measures in the calculation of insulin sensitivity, as the Stumvoll MCR does. The parameters of the proposed surrogate indices are optimized through real-valued evolutionary algorithms by maximizing the correlation with the Stumvoll MCR method. The Stumvoll MCR method was selected as the gold standard since hyperinsulinemic-euglycemic clamp insulin sensitivity values were not available given its complexity and risk of use in the population under study. Our fasting surrogate index is based on the QUICKI method whereas the OGTT-based index is based on the Matsuda's method. We have chosen QUICKI and Matsuda's methods given their strong correlations with the hyperinsulinemic-euglycemic clamp; in addition, Matsuda is an easy to calculate index of whole-body insulin sensitivity, with strong correlation with the rate of whole-body glucose disposal [13].

Insulin resistance is a condition that can be reversed with appropriate actions, such as a healthy diet and physical activities; whereas it is not possible to reverse type 2 diabetes [24,25]. Hence the importance of correctly estimating insulin sensitivity as well as diagnosing this dangerous metabolic condition in time.

2. Materials and methods

2.1. Subject database

Forty male subjects underwent an OGTT, in which, after a fasting period, a blood sample was taken, and four additional blood samples were subsequently taken, at intervals of 30 min, after ingesting a solution with 75 g of anhydrous glucose. From the blood samples, the concentrations of insulin and glucose were determined in each phase of the OGTT, that is I_0, I_{30}, I_{60}, I_{90}, I_{120} and G_0, G_{30}, G_{60}, G_{90}, G_{120}, where I_x and G_x correspond to the level of insulin and glucose at time instant x of the OGTT. The level of triglycerides (*Tri*) and HDL cholesterol (*Cho*) were estimated in the fasting state. Additionally, the height (h), weight (w), abdominal circumference (C) and blood pressure (P) were measured [30].

The database was divided into three groups: 15 subjects with the metabolic syndrome, 15 marathon runners, and 10 control subjects. The subjects were diagnosed with metabolic syndrome if they had the presence of at least three of the following factors [26]: *i*) abdominal obesity ($C > 102$ cm), *ii*) elevated triglycerides ($Tri \geq 150$ mg/dL), *iii*) reduced HDL cholesterol ($Cho < 40$ mg/dL), iv) hypertension ($\geq 130/85$ mmHg), v) fasting hyperglycemia ($G_0 \geq 100$ mg/dL). The group of marathon runners was composed of professional marathon runners who trained between 180 and 240 km per week. The subjects in the control group did not perform any physical activity on a regular basis and did not meet with the metabolic syndrome condition. The clinical protocol was performed in accordance with the ethical standards of the University Hospital of Caracas. All subjects agreed to the study by signing an informed consent.

Clinical details of the subjects are given in Table 1. The table also details the variables that showed statistically significant differences between the groups. The statistical analysis will be described later on.

2.2. Assessment of insulin sensitivity

As previously stated, two simple surrogate methods were proposed in this paper. The first, a fasting surrogate index based on the QUICKI method, and the second, an OGTT-based surrogate index based on the Matsuda's method. The QUICKI index is described according to equation (1) and the Matsuda's index is described according to equation (2), where $\bar{I}$ and $\bar{G}$ are the average value of plasma insulin and glucose concentrations along the OGTT, respectively.

$$ISI_{QUICKI} = \frac{1}{\log G_0 + \log I_0} \tag{1}$$

$$ISI_{Matsuda} = \frac{10000}{\sqrt{G_0 \times I_0 \times \bar{G} \times \bar{I}}} \tag{2}$$

We have employed these equations as base for the indices proposed, in which we have included anthropometric measures and a set of parameters (α, β, γ, δ and ε) that are tuned through evolutionary algorithms to provide an optimal correlation with the gold standard selected. The anthropometric measures correspond to the ratio of the area that represents the abdominal circumference, i.e. $A = \frac{C}{4\pi}$, and the body surface area according to the model of Mosteller [27], i.e. $S = \sqrt{\frac{wh}{3600}}$. The proposed fasting and OGTT-based simple surrogate indices are shown in equations (3) and (4), respectively. Numerators in these equations were empirically chosen to provide values much greater than zero.

Table 1
Clinical features of each study group. Results are presented as median (interquartile range).

Variable	Control	Metabolic syndrome	Marathon Runners
Age (years)	27.5 (8)	33 (8.75)	35 (13.25)
w (kg)[a,c]	70.7 (18.5)	102.3 (15.15)	61.6 (10.4)
C (cm)[a,c]	82.3 (15)	108.8 (18.33)	71.9 (9.28)
h (cm)	178.5 (4)	176 (7.98)	174 (8.98)
Tri (mg/dL)[a,c]	71 (32)	194 (96.75)	56 (25)
Cho (mg/dL)	46.5 (9)	41 (9.75)	48 (8)
P (mmHg)[a,c]	116/73 (10/8)	137/88 (8.3/16)	110/72 (10/15)
G_0 (mg/dL)[b,c]	96.5 (6)	103 (10.25)	86 (11)
G_{30} (mg/dL)[c]	145.5 (31)	161 (37)	112 (39.75)
G_{60} (mg/dL)[c]	129 (13)	165 (51.5)	90 (34.75)
G_{90} (mg/dL)[a,c]	90 (34.75)	146 (40.5)	84 (34.25)
G_{120} (mg/dL)[a,c]	96 (20)	131 (30)	71 (27.25)
I_0 (μIU/mL)[a,c]	3 (3)	11 (6.5)	2 (1.41)
I_{30} (μIU/mL)[c]	39 (32)	70 (85.5)	28.8 (12.53)
I_{60} (μIU/mL)[a,c]	28.5 (27)	70 (143)	24 (14.93)
I_{90} (μIU/mL)[a,c]	29.5 (42)	75 (91.75)	21.4 (17.98)
I_{120} (μIU/mL)[c]	28.5 (12)	94 (93)	16.6 (12.11)

[a] Statistically significant difference between control and metabolic syndrome.
[b] Statistically significant difference between control and marathon runners.
[c] Statistically significant difference between metabolic syndrome and marathon runners.

$$ISI_{Fasting} = \frac{50}{\log\left(\frac{A}{S} + \alpha\right) + \log(G_0 + \beta) + \log(I_0 + \gamma)} \quad (3)$$

$$ISI_{OGTT} = \frac{350000}{\sqrt{\left(\frac{A}{S} + \alpha\right)(G_0 + \beta)(I_0 + \gamma)(\bar{G} + \delta)(\bar{I} + \varepsilon)}} \quad (4)$$

2.3. Parameter optimization based on evolutionary algorithms

The set of parameters of the insulin sensitivity indices must be adapted to provide the best insulin sensitivity assessment. This adaptation problem can be viewed as the maximization of a nonlinear multi-parameter objective function, i.e. the maximization of the absolute value of the Spearman's rank correlation coefficient (ρ) between the proposed insulin sensitivity index and the Stumvoll MCR index. Evolutionary algorithms, optimization methods inspired by theories of evolution and natural selection, are well-suited for this type of problem [28]. The Stumvoll MCR method is shown in equation (5), where BMI is the body mass index (expressed in units of kg/m^2).

$$ISI_{Stumvoll} = 18.8 - 0.271BMI - 0.03611I_{120} - 0.015G_{90} \quad (5)$$

The parameters to be optimized were largely increased and decreased from possible extreme values of each variable that goes with it to create the initial population. Standard operators for real-valued chromosomes (simple, arithmetic and heuristic crossovers, and multi-non-uniform and non-uniform mutations) and the ranking selection were addressed in the evolutionary algorithm.

Three parameters (α, β and γ) were optimized in the proposed fasting surrogate index and five parameters (α, β, γ, δ, and ε) were optimized in the proposed OGTT-based surrogate index. Evolutionary algorithms were applied for 500 generations with 100 individuals, with 0.7 for crossover probability and high mutation probability during the first generations and low at the end [29].

2.4. Statistical analysis

To determine the statistically significant differences between the study groups, both for insulin sensitivity values and for the variables that were shown in Table 1, we used the Kruskal-Wallis nonparametric hypothesis test followed by the Dunn's test. A value of $p < 0.05$ was considered statistically significant.

The degree of association between the insulin sensitivity indices was assessed using the Spearman's rank nonparametric test. In addition, a linear regression analysis was carried out to visualize the relationship between the proposed indices and the Stumvoll MCR method both for all subjects and for each group.

3. Results

Table 2 shows optimal values of the set of parameters of the proposed simple surrogate indices and the attained correlation coefficient with the Stumvoll MCR method. The best individuals of the last generation for ten different realizations of the evolutionary algorithm were selected as optimal parameters. The table shows that our proposed OGTT-based surrogate index has stronger significant correlation ($\rho = 0.95$) with the Stumvoll MCR index than our fasting one ($\rho = 0.90$).

Table 3 shows the values of insulin sensitivity indices and its correlation with the Stumvoll MCR index for each study group. We can observe that, for each group, our proposed indices show stronger correlations with the gold standard index compared with the method used to derive each proposed index. Moreover, the correlations obtained with our proposed OGTT-based index are stronger, for each group, than with our fasting proposed index. Only with our proposed OGTT-based index, a significant correlation was obtained for the marathon runners compared with the other indices. On the other hand, the insulin sensitivity indices provided statistically significant differences between control and metabolic syndrome, and between metabolic syndrome and marathon runners; no statistically significant differences were observed between control and marathon runners.

Figs. 1 and 2 depict the associations between our proposed fasting and OGTT-based surrogate indices, respectively, with the Stumvoll MCR method, for each study group. In these figures, we can visualize the associations reported in Tables 2 and 3, as well as the distributions of the subjects in the graph. For instance, larger variabilities were observed for all groups in the fasting proposed index than in the OGTT-based proposed one. On the other hand, in the fasting proposed method, the linear regression analysis for each group revealed almost parallel regression lines, but shifted down, to the global regression line, for control and marathon runners, whereas in the OGTT-based proposed method, control subjects showed almost parallel regression lines to the global regression line; in other words, metabolic syndrome showed different slope in the regression line compared with the overall regression line in the fasting proposed method, and metabolic syndrome and marathon runners showed different slope in the regression line compared with the overall regression line in the OGTT-based proposed method.

Table 2
Correlation coefficient with the Stumvoll MCR method and optimal values of the set of parameters for each proposed index.

Method	ρ	α	β	γ	δ	ε
$ISI_{Fasting}$	0.90	−2.76	−60.3	3.29		
ISI_{OGTT}	0.95	1.6	188.7	88.9	−21.1	37.2

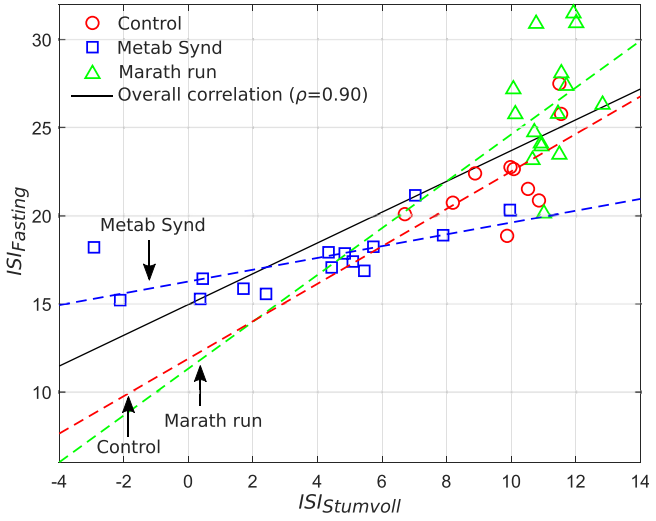

Fig. 1. Correlation between the proposed fasting and Stumvoll MCR indices of insulin sensitivity. The solid line denotes the linear regression line between the proposed fasting and Stumvoll MCR for all subjects ($\rho = 0.90$; $p = 0$), and the dashed lines denote the linear regression lines for each group: $\rho = 0.68$ ($p = 0.04$) for control subjects, $\rho = 0.72$ ($p = 0.004$) for subjects with the metabolic syndrome, and $\rho = 0.42$ ($p = 0.12$) for marathon runners.

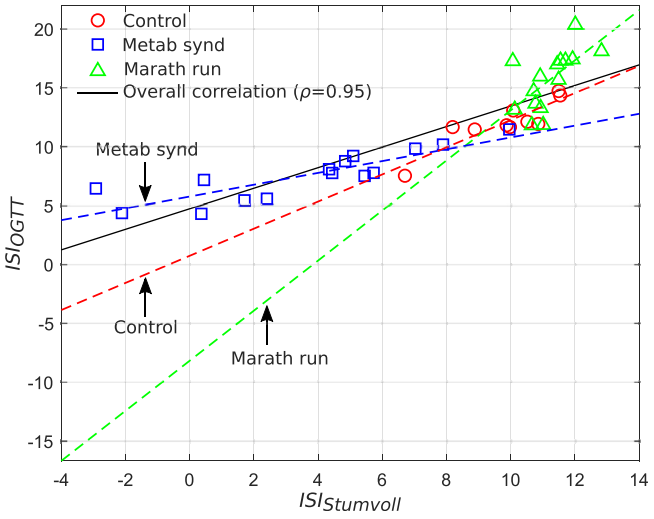

Fig. 2. Correlation between the proposed OGTT-based and Stumvoll MCR indices of insulin sensitivity. The solid line denotes the linear regression line between the proposed OGTT and Stumvoll MCR for all subjects ($\rho = 0.95$; $p = 0$), and the dashed lines denote the linear regression lines for each group: $\rho = 0.88$ ($p = 0.002$) for control subjects, $\rho = 0.87$ ($p = 0$) for subjects with the metabolic syndrome, and $\rho = 0.73$ ($p = 0.003$) for marathon runners.

Table 3
Insulin sensitivity and correlation values for each study group. Insulin sensitivity is presented as median (interquartile range).

Method	Control		Metabolic syndrome		Marathon runners	
	SI	ρ	SI	ρ	SI	ρ
$ISI_{Fasting}$[a,b]	21.96 (2.02)	0.68[c]	17.39 (2.22)	0.72[c]	25.78 (3.92)	0.42
ISI_{OGTT}[a,b]	11.88 (1.41)	0.88[c]	7.77 (3.30)	0.87[c]	15.96 (3.93)	0.73[c]
$ISI_{Matsuda}$[a,b]	9.84 (8.06)	0.87[c]	2.95 (2.79)	0.83[c]	17.98 (9.63)	0.49
ISI_{QUICKI}[a,b]	0.41 (0.07)	0.52	0.33 (0.03)	0.75[c]	0.45 (0.05)	0.36

[a] Statistically significant difference in the insulin sensitivity value between control and metabolic syndrome.
[b] Statistically significant difference in the insulin sensitivity value between metabolic syndrome and marathon runners.
[c] Statistically significant correlation with the Stumvoll MCR index.

4. Discussion

Even if fasting insulin and glucose values furnish enough information for insulin sensitivity assessment, such as in the QUICKI method, the use of several glucose and insulin samples from the OGTT allows a better observation of the glucose metabolism process as well as the hepatic and peripheral insulin sensitivity. In addition, anthropometric measurements are easy to obtain and provide relevant information to the physician about the people's morphology and health and, as shown in this work, can be integrated in the assessment of insulin sensitivity.

In this paper, we proposed two simple surrogate indices for insulin sensitivity assessment, one in fasting and the other from the OGTT. The optimization of the methods, through real-valued evolutionary algorithms, allows to reduce the variability of the insulin sensitivity indices among the study groups (subjects are closer to the regression line in Figs. 1 and 2), and provides statistical significant differences of the indices between groups (control vs. metabolic syndrome, and metabolic syndrome vs. marathon runners), as observed in Table 3.

Correlations between the simple surrogate indices and the Stumvoll MCR method were in agreement to those reported in the literature. Moreover, the proposed OGTT-based index showed stronger correlation with the Stumvoll MCR index than the fasting one.

Thanks to the optimization process, the proposed indices showed better correlations with the gold standard than the methods from which they were derived, for each group.

5. Conclusions

This paper presented two simple surrogate insulin sensitivity indices that integrate anthropometric measures. The first index was derived from the QUICKI method and uses fasting insulin and glucose levels, and the second index was derived from the Matsuda's method and uses several glucose and insulin values from the OGTT. The optimization of the indices, performed using evolutionary algorithms, sought to maximize the correlation with the Stumvoll MCR index, a simple surrogate method highly correlated with the hyperinsulinemic-euglycemic clamp. The proposed methods minimized the intergroup variability of the insulin sensitivity index, particularly the OGTT-based index, and provide statistically significant differences between groups.

Conflicts of interest

The authors have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.07.022.

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