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Comparison of insulin sensitivity indices properties calculated from OGTT

Research Article

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Abstract: The aim of this study was to present the properties of insulin sensitivity indices formulas to justify selection of formulas to evaluate of insulin sensitivity for calculation from an oral glucose tolerance test (OGTT) data. Twelve of the most applicable formulae for ISI calculation were analyzed in the view of two sets of results: 1) point contrasts, calculated as the ratio of average ISI values in lean and obese groups of patients; and 2) interval contrasts, calculated as ratios of T from the two-sided t-test, evaluated as dimensionless, mutually comparable contrasts within a continuous scale. Statistical significance of individual ISIs in terms of their contrasts was evaluated by two-sided t-tests. $P<0.001$ was a considered statistically significance between a group of 59 healthy volunteers with BMI<25 kg/m^2 and a group of 63 volunteers with BMI≥ 25 kg/m^2 who underwent frequent OGTT sampling. To compare data of an individual subject with the standard, we recommend selecting the formulas with a high point contrast. To compare of data of several subject groups, we recommend using the formulas with a high interval contrast.

Keywords: *Insulin sensitivity indices • Point contrast • Interval contrast • Oral glucose tolerance test • Body mass index (BMI)*

1. Introduction

Insulin resistance especially that associated with central obesity is now recognized as one factor associated with a number of cardiovascular risk factors, such as dyslipidemia, hypertension, dysfibrinolysis, glucose intolerance, and also type 2 diabetes mellitus [1-3]. The insulin resistance syndrome, originally described by Reaven [1], is associated with a 2-fold greater relative risk for myocardial infarction and other cardiovascular diseases [4]. Resistance to insulin-stimulated glucose uptake affects the majority of patients with impaired glucose tolerance (IGT) or type 2 diabetes mellitus, as well as approximately 25% of non-obese individuals with normal oral glucose tolerance [1]. The sensitivity of body tissues to insulin indicates its physiological, pathophysiological, and therapeutic relevance.

The gold standard for measurement of insulin resistance is the hyperinsulinemic-euglycemic clamp technique proposed by DeFronzo et al. [5]. This technique directly measures whole body glucose disposal at a given level of hyperinsulinemia under steady-state conditions; however, it is expensive and time consuming. A wide variety of indices based on simple clinical measurements have been proposed for assessment of insulin resistance/sensitivity. The group of insulin sensitivity indices (ISIs) that are calculated from the oral glucose tolerance test (OGTT) correlated with the gold-standard technique includes the Matsuda index [6], Cederholm index [7], Gutt index [8], Belfiore indices [9], Avignon

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indices [10], Stumvoll indices [11, 12], Quicki index [13–16], HOMA index [17,18], and the McAuley index [19]. Considering the close interconnection of insulin resistance/sensitivity with hypertension, cardiovascular diseases, and diabetes as public health problems, it is of great interest to choose an adequate ISI for prevention and treatment of the previously mentioned diseases. Several studies have been devoted to comparison of the ISI with the hyperinsulinemic-euglycemic clamp technique [6,20–22], with the minimal model analysis [23], and eventually with each other [24]. However, because of the occurrence of many borderline values in the comparison and analysis of the correlation coefficients between the evaluated indices and the clamp studies, the presence of high correlation coefficients does not necessarily mean that these indices have the optimal predictive performance for diagnosing insulin resistance [25]. Consequently, according to some authors, the use of the ISI in evaluation of data from OGTT sets forth the following questions: 1) Which formula should be used? 2) What are dimensions of the input and output quantities? 3) What are normal ISI values? 4) How should results be compared that are obtained using different ISI formulas? 5) How should ISI values be compared with parameters of the OGTT model, which takes into account gastric emptying rate [26]?

Taking these questions under consideration, the aims of this study were to compare several ISI formulas from the aspect of point and interval contrast, and to present the properties of formulas for calculating ISI from oral glucose tolerance test (OGTT) data as dimensionless, mutually comparable contrasts within a continuous scale. The study involved comparison of 2 groups of subjects: one group with body mass index (BMI) lower than 25 kg/m^2, and a second group with BMI higher or equal to 25 kg/m^2, under the assumption put forth in the literature that insulin sensitivity is lower in overweight/obese and older individuals [27].

2. Materials and methods

2.1. Subjects

One hundred and twenty-two volunteers (71 males and 51 females, aged 20–52 years) participated in the study. Study subjects were divided to 2 groups according to BMI: the first group (G1) with BMI<25 kg/m^2, and the second group (G2) with BMI≥25 kg/m^2. Table 1 shows clinical characteristics of the study individuals. According to the diagnostic criteria of the American Diabetes Association (ADA), 92 had normal glucose tolerance, 19 had impaired glucose tolerance, 8 had impaired fasting glucose, 2 had impaired glucose regulation, and 1 had diabetes. Exclusion criteria were a previous diabetes diagnosis, use of medication known to alter glucose metabolism, and presence of hepatic or endocrine diseases. The subjects were asked to fast and to restrain from heavy physical activity for 12 hours prior to the examination at the Institute of Experimental Endocrinology. The Ethics Committee of that Institute approved the study; after explanation of the procedures, written voluntary consent was obtained from all subjects.

Table 1 Clinical characteristic of study subjects.

Group	G1 BMI<25 kg/m^2	G2 BMI≥25 kg/m^2
	n=59	n=60
Age (yrs.)	28.20±4.90	32.7±9.30
NGT/IGT/IFG/IGR/DM	50/6/2/0/1	42/13/6/2/0
Body mass index (kg/m^2)	21.80±1.80	30.80±4.10
Fasting plasma glucose (mmol/l)	4.85±0.50	5.13±0.60
2-h Plasma glucose (mmol/l)	6.20±1.60	7.04±1.50

NGT - normal glucose tolerance; IGT - impaired glucose tolerance; IFG - impaired fasting glucose; IGR - impaired glucose regulation; DM - Diabetes mellitus.

2.2. Test protocol

Upon arrival in the laboratory at 8.00 AM, an indwelling catheter was inserted into an antecubital vein and the subjects were asked to rest at least 30 min in a comfortable armchair to avoid the effect of acute stress. After obtaining the fasting samples, the subjects underwent frequent oral glucose tolerance tests: subjects ingested 75 gram of anhydrous glucose diluted in 250 ml water within 1–3 minutes, then blood samples were obtained 15, 30, 45, 60, 90, 105, and 120 minutes after the complete glucose solution had been ingested.

2.3. Analytical techniques

After centrifugation at 4°C and separation, the aliquots of plasma were stored at – 20°C until assayed. Plasma glucose concentration was measured using a glucose oxidase method (Roche Diagnostics Hitachi, Hitachi Ltd., Japan). Plasma insulin concentration was measured using a commercial IRMA kit (Immunotech S.A., Marseille, France)

2.4. Contrast definition

The contrasts formulated by Eqs 1–3 were used in evaluation of the lean (group G1) and obese (group G2) volunteer data sets.

Point contrast (C_p) is expressed by Eq. 1

$$C_p = \frac{mean\ ISI^{G1}}{mean\ ISI^{G2}} \quad \text{(Eq. 1)}$$

under the condition that

$$mean\ ISI^{G1} > mean\ ISI^{G2}$$

Consequently, comparison of individual subject with the standard can be described by Eq. 2

$$C_i = \frac{ISI^i}{mean\ ISI^{G1}}, \quad \text{(Eq. 2)}$$

where ISI^i is the calculated ISI value of individual subject.

The interval contrast between the groups (C_t) was calculated by Eq. 3

$$C_t = \frac{mean\ ISI^{G1} - mean\ ISI^{G2}}{\sqrt{\frac{SD\ ISI^{G1}}{n_{G1}} + \frac{SD\ ISI^{G2}}{n_{G2}}}}{t(1-\frac{\alpha}{2}, df)}, \quad \text{(Eq. 3)}$$

where $SD\ ISI^{G1}$ is the standard deviation of $mean\ ISI^{G1}$, $SD\ ISI^{G2}$, is the standard deviation of $mean\ ISI^{G2}$, n_{G1}, is the number of G1 group subjects, n_{G2} is the number of G2 group subjects, a is 0.05, and *df* is degrees of freedom, where $df = n_{G1} + n_{G2} - 2$.

Table 2 The individual formulae for calculations of insulin sensitivity indices (ISI).

#	ISI name or autor name	ISI definition
1	Cederholm	$ISI_{CED} = \frac{75000 + (G_0 - G_{120})\ 39.33\ m}{120\ G_{mean} \log I_{mean}}$
2	Gutt	$ISI_{GUT} = \frac{75000 + (G_0 - G_{120})\ 0.19\ m}{120\ G_{mean} \log I_{mean}}$
3	Matsuda	$ISI_{MAT} = \frac{10000}{\sqrt{G_0\ I_0\ G_{mean}\ I_{mean}}}$
4	Belfiore$_b$	$ISI_{BEL_b} = \frac{2}{\frac{AUC_{G,S}(0,60,120)}{AUC_{G,N}(0,60,120)} \cdot \frac{AUC_{I,S}(0,60,120)}{AUC_{I,N}(0,60,120)} + 1}$
5	Belfiore$_a$	$ISI_{BEL_a} = \frac{2}{\frac{AUC_{G,S}(0,120)}{AUC_{G,N}(0,120)} \cdot \frac{AUC_{I,S}(0,120)}{AUC_{I,N}(0,120)} + 1}$
6	Stumvoll$_b$	$ISI_{STU_b} = 0.156 - 0.0000459\ I_{120} - 0.000321\ I_0 - 0.00541\ G_{120}$
7	Stumvoll$_a$	$ISI_{STU_a} = 0.222 - 0.0033\ BMI - 0.0000779\ I_{120} - 0.000422\ Age$
8	Avignon$_c$	$ISI_{AVI_c} = \frac{0.137\ ISI_{AVI_a} + ISI_{AVI_b}}{2}$
9	Avignon$_b$	$ISI_{AVI_b} = \frac{10^8}{G_{120}\ I_{120}\ VD}$
10	Quicki	$ISI_{QUI} = \frac{1}{\log G_0 + \log I_0}$
11	Avignon$_a$	$ISI_{AVI_a} = \frac{10^8}{G_0\ I_0\ VD}$
12	HOMA	$ISI_{HOMA} = \frac{22.5}{G_0\ I_0}$

Table 3 Summary of formulae's parameters used for calculation of individual insulin sensitivity indices.

#	ISI name or name of autor	Time point				Other parameters				Remarks
		0 (min)	30 (min)	60 (min)	120 (min)	m (kg)	Age (year)	AUC_N norm.	BMI (kg/m^2)	
1	Cederholm	Y	Y	Y	Y	Y				Calculated G_{mean}, I_{mean}
2	Gutt	Y			Y	Y				Calculated G_{mean}, I_{mean} G in mg/dl
3	Matsuda	Y		Y	Y					Calculated G_{mean}, I_{mean}
4	Belfiore$_b$	Y		Y	Y			Y		ISI is dimensionless Need $AUC_{G,N}$, $AUC_{I,N}$
5	Belfiore$_a$	Y			Y			Y		ISI is dimensionless Need $AUC_{G,N}$, $AUC_{I,N}$
6	Stumvoll$_b$	Y			Y					Without G_0
7	Stumvoll$_a$				Y		Y		Y	Without G_0
8	Avignon$_c$	Y			Y	Y				Calculated VD = m.150
9	Avignon$_b$				Y	Y				Calculated VD = m.150
10	Quicki	Y								
11	Avignon$_a$	Y				Y				Calculated VD = m.150
12	HOMA	Y								

For statistically significant differences between mean ISI values of groups G1 and G2, values of c_p and c_t above 1 were expected.

The contrasts were applied according to Eqs 1 and 3, and calculated for twelve of the most applicable ISI formulas from Table 2. A description of the parameters of each formula is shown in Table 3.

2.5. Statistical analysis

A two-sided t-test [28–30] was used to compare differences between mean ISI values calculated for group G1 and group G2. The value $P<0.001$ was considered statistically significant.

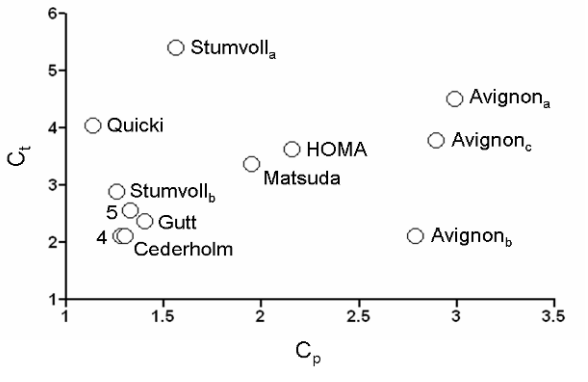
3. Results

3.1. Contrasts C_p, C_t

The individual ISIs were calculated by formulas listed in Table 2. A statistically significant difference was observed between the mean ISI values of G1 and G2. The formulas for ISI calculation were analyzed according to C_p and C_t contrast by Eq. 1 and Eq. 3; point and interval contrast above 1 (Figure 1) was reached for all twelve ISI formulas. The results are illustrated on Figure 1 as the position of the individual ISI formulas. Figure 1 reveals the properties of the formulas in reference to the the C_t and C_p data in this study. (Because of crowding in the figure, the numbers of individual ISI formulas are used in place of names in Figure 1,and relate to those shown in the first column of Tables 2 and 3).

According to the analysis, the highest C_p was observed for the Avignon$_a$ index and the least C_p for the Quicki index, with values of 2.99 and 1.14, respectively. The highest C_t was observed for the Stumvoll$_a$ index C_t = 5.40 and the least C_t for the Avignon$_b$ index with values of 5.40 and 2.09, respectively (Figure 1).

Figure 1 Point C_p and interval C_t contrast of insulin sensitivity indices calculated from OGTT data of subjects. 4 – Belfiore$_b$; 5 – Belfiore$_a$.



3.2. Individual contrast C_i

On the basis of Eq. 2, individual contrasts C_i of the all twelve ISI formulae were calculated for both groups. For the groups separately, the percentage of subjects with $C_i > 1$ indicated that these subjects had the normal insulin sensitivity. The values for individual ISI formulae show that the greatest percentage for group G1 had the Stumvoll$_b$ index and the least percentage for group G2 was detected at the Stumvoll$_a$ index (Figure 2).

To illustrate the individual contrasts in detail, Figures 3–5 display C_i calculated for the Avignon$_a$, Quicki, and Stumvoll$_b$ indices according to BMI. The subjects in group G1 are indicated by circles and group G2 by squares. Individual contrast was analyzed by linear regression lines in form $C_i = a + b.BMI$ in relation to groups G1 and G2.

The results of the analysis, with the percentage of the subjects whose individual contrast C_i exceeds the mean value (C_i = 1), are shown in Table 4. It is apparent that the intercept with the most rapid decrease by BMI was detected by the Avignon$_a$ index, and the least intercept and decrease were detected by the Quicki index for both groups. The percentage of $C_i > 1$ characterizes the properties of ISI formulas demonstrating the normal insulin sensitivity in humans. This study showed that differences between ISI formulae are evaluated not only from the aspect of having an identical scale, but also from the aspect of their properties for the purpose of assigning subjects to groups with normal or impaired insulin sensitivity.

4. Discussion

To assess insulin sensitivity using an oral glucose tolerance test, the open question is, which formula should

Figure 2 The percentage overview of individual contrasts for $C_i > 1$ by the groups G1 and G2. Empty bars – group G1; Full bars – group G2; ISI formulas – No. 1-12 according to Table 2.

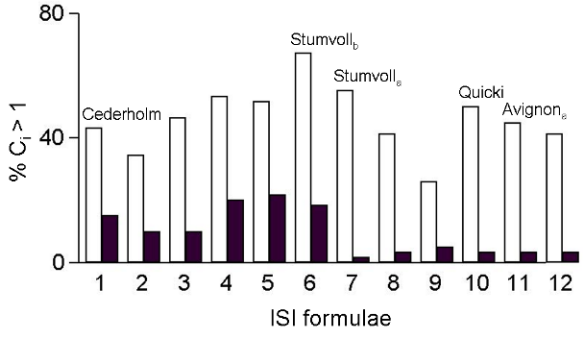


Figure 3 Individual contrast C_i of $Avignon_a$ index in groups G1 and G2. Circles – subjects of group G1; squares – subjects of group G2; thin regression line – group G1; thick regression line – group G2; broken line – limit value of C_i.

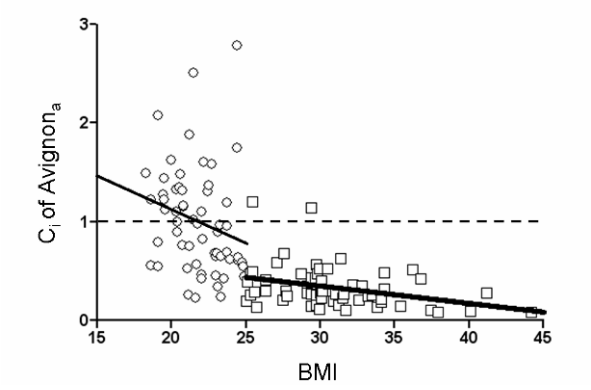


Figure 4 Individual contrast C_i of Quicki index in subjects of groups G1 and G2. Circles – group G1; squares – group G2; thin regression line – group G1; thick regression line – group G2; broken line – limit value of C_i.

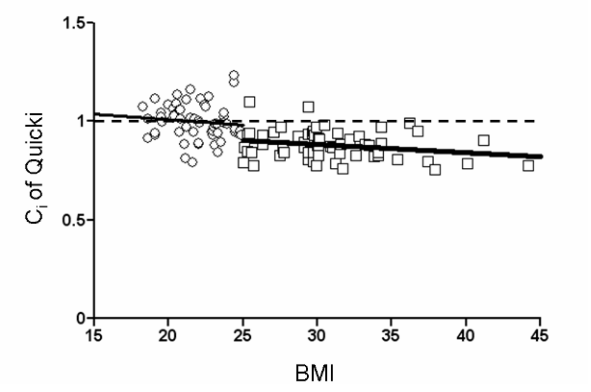


Figure 5 Individual contrast C_i of $Stumvoll_b$ index in subjects of groups G1 and G2. Circles – group G1; squares – group G2; thin regression line – group G1; thick regression line – group G2; broken line – limit value of C_i.

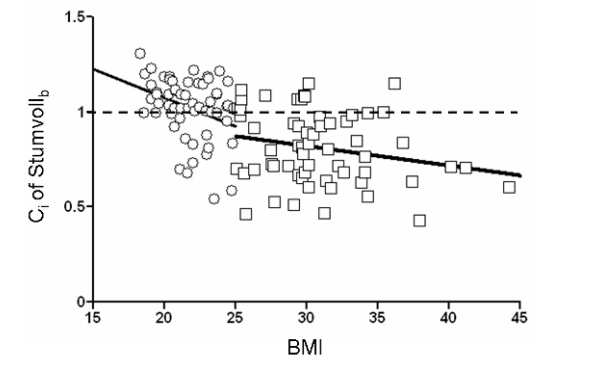


Table 4 The analysis results of individual contrasts properties of selected ISI

#	Individual contrasts of ISI	No. of Figs	Group	*intercept* a	*slope* b	% $C_i > 1$
11	$Avignon_a$	2	G1	2.480	-0.068	44.8
			G2	0.878	-0.017	3.3
10	Quicki	3	G1	1.120	-0.005	50
			G2	1	-0.004	3.3
6	$Stumvoll_b$	4	G1	1.677	-0.030	67.2
			G2	1.128	-0.006	18.3

be used to distinguish between subjects with normal and those with impaired insulin sensitivity. Following the determination of point and interval contrast between individual ISI formulae calculated from OGTT, it is possible to observe their applicability for comparison of individuals or groups of individuals with different insulin sensitivity levels.

Our results show the significant properties of ISI formulae as dimensionless, mutually comparable contrasts within a continuous scale. Within the evaluation of the properties of the individual ISI formulas, it is not possible to start only from the results illustrated in Figure 1, i.e., from the view of point and interval contrast.

From the aspect of users of ISI calculated from OGTT data, rational selection should be motivated only by the high point contrast C_p because of the practically clear range for the marked difference of ISI in groups G1 and G2 with minimal risk of error. In the present study, the highest point contrast C_p (Eq. 1) was detected at the $Avignon_a$ index [10] with C_i values within the interval 2.8–91. In contrast, the least C_p contrasts were observed at the Quicki [13] and $Stumvoll_b$ indices [12] with C_i values within the intervals 0.3–0.5 and 0.04–0.2, respectively.

However, it should also be taken into consideration that the results in Figure 2 show the separate properties of the ISIs we studied in reference to BMI.

1) From the operational and economic points of view, it is significant that a reasonable evaluation of insulin sensitivity by the Quicki index, $Avignon_a$ index and HOMA index can be obtained because of their calculation using only fasting values of glucose G_0 and insulin I_0, and therefore it was not necessary to perform an OGTT. In cases where the 120 min-OGTT is used, regardless of economic and operational options, it is reasonable to use a 4-point OGTT with sample collections at 0, 30, 60 and 120 min by the Cederholm index (Figure 2). A compromise is offered by the other ISI formulas, in

which another 1 or 2 time points of measurements are also used in addition to G_0 and I_0, (see Table 3).

2) The other issue is the separate properties of ISI formulas included the separation of the subjects with potential normal and impaired insulin sensitivity from tested groups G1 and G2. The results in Figure 2 show that in the case of ISI formulas 1 through 6, more subjects with BMI≥25 kg/m^2 (full bars) to subjects with normal insulin sensitivity compared with ISI formulas 7 to 12 showing low subjects of presented group.

The individual contrast C_i of the Avignon$_a$, Quicki, and Stumvoll$_b$ indices according to BMI calculated by Eq. 2 is demonstrated in Figures 3 to 5. Another interpretation of the results in Table 4, other than that found in the Results section, is that according to the Avignon$_a$ index, individual contrast of 55.2% individuals of group G1 and 96.7% individuals of group G2 obtained C_i values are under the limit 1. In terms of the Quicki index, the proportion of individuals in the G1 group represented 50% and 96.7% of individuals in group G2. According to the Stumvoll$_b$ index, the percentage was 32.8% (group G1) and 81.7% (group G2). These results indicate the high variability in selected properties of these ISI formulas. The different range of individual contrast = C_i of Avignon$_a$ index, Quicki index and Stumvoll$_b$ index by BMI (Figs. 3–5) is the results of different number of time points for the measurement of glucose, insulin and other parameters, which are used in ISI formulas. The Quicki index formula was calculated using only logarithmic values of fasting glucose G_0 and fasting insulin I_0; consequently the C_i range was relatively narrow (Figure 4). However, other parameters of the Avignon$_a$ index formula, besides G_0 and I_0, were also enhanced by apparent glucose distribution *VD* (Table 3); therefore, the C_i range of this index was markedly much broader and clearer (Figure 3). Whereas the Stumvoll$_b$ index formula was calculated using I_0 and I_{120}, G_{120}, the C_i range was also notably clear (Figure 5). In the study of Penesova and Radikova [31], the highest correlation with the *M* value from a hyperinsulinemic euglycemic clamp was observed by the Matsuda [6] in comparison with Cederholm index [7]. The Matsuda index of insulin sensitivity therefore provides greater objectivity in assessing insulin sensitivity than Cederholm index [31]. This finding agrees with our results in Figure 1 that show a higher point and interval contrast of Matsuda index in comparison with that of the Cederholm index. On the other hand, in a large prospective study of Hanley et al. [32], it was found that the Gutt index [8] best predicted type 2 diabetes mellitus. These results do not contradict our results, because the Gutt index has similar results in point and interval contrast as the Cederholm index.

In conclusion, as seen in Figure 1 and Table 3, the individual formulas for ISI calculations differ not only in the number of points used for the measurement of glucose and insulin, but also in their properties from the viewpoint of point C_p and interval C_t contrast. The similar conclusion is valid also for individual contrast C_i as shown in Figure 2.

To compare subject groups, we recommend selecting the formula of Stumvoll$_a$ index as the index with high interval contrast C_t. To compare an individual subject with the standard, we recommend use of the Avignon$_a$ index formula as the index with high point contrast C_p by using Eq. 2.

Generally, all our conclusions related to properties of individual formulas for calculating of insulin sensitivity from OGTT are exactly valid only for our analyzed study in terms of BMI. Presented analyses can be performing also for optional ISI formulae as well as for method of study group selection, e.g. in terms of glucose tolerance.

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