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Evaluation of proposed oral disposition index measures in relation to the actual disposition index

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Abstract

Aims While the disposition index provides a useful measure of B-cell function, its calculation requires the performance of a frequently sampled intravenous glucose tolerance test (FSIVGTT). Recently, the demonstration of a hyperbolic relationship between indices of insulin secretion and insulin sensitivity derived from the oral glucose tolerance test (OGTT) has led to the introduction of two novel OGTT-based measures of B-cell function analogous to the disposition index: (i) the insulin secretion-sensitivity index-2 (ISSI-2) (defined as the ratio of the area-under-the-insulin-curve to the area-under-the-glucose curve, multiplied by the Matsuda index) and (ii) insulinogenic index (IGI)/fasting insulin. However, neither of these two measures has been directly compared with the disposition index.

Methods Two hundred and thirteen non-diabetic children (122 boys, 91 girls) underwent both OGTT and FSIVGTT, allowing for the calculation of ISSI-2, IGI/fasting insulin and the disposition index.

Results ISS1-2 and IGI/fasting insulin were strongly correlated with each other ($r = 0.82$, $P < 0.0001$). Both measures correlated with the disposition index, with ISSI-2 showing a modestly stronger association (ISSI-2: $r = 0.24$, $P = 0.0003$; IGI/fasting insulin: $r = 0.21$, $P = 0.0022$). Standardized linear regression analyses confirmed that the relationship between log ISSI-2 and the disposition index (standardized regression coefficient = 0.224, $P = 0.001$) was stronger than that between log IGI/fasting insulin and the disposition index (standardized regression coefficient = 0.166, $P = 0.015$).

Conclusions The OGTT-derived measures ISSI-2 and IGI/fasting insulin exhibit modest correlations with the disposition index. These relationships require further assessment in other patient populations.

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Keywords B-cell function, disposition index, oral glucose tolerance test

Abbreviations AIR_g, acute-insulin-response-to-glucose; AUC_{gluc}, area-under-the-glucose-curve; AUC_{ins}, area-under-the-insulin-curve; $AUC_{ins/gluc}$, ratio of the area-under-the-insulin-curve to the area-under-the-glucose-curve; BMI, body mass index; CI, confidence interval; FSIVGTT, frequently sampled intravenous glucose tolerance test; HOMA-B, homeostasis model of assessment of B-cell; HOMA-IR, homeostasis model of assessment for insulin resistance; IGI, insulinogenic index; ISSI-2, insulin secretion–sensitivity index-2; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; S_I, insulin sensitivity index; SOLAR, Study of Latino Adolescents at Risk

Introduction

The physiologic regulation of glucose homeostasis requires that pancreatic B-cells compensate for changes in whole-body insulin sensitivity through a proportionate and reciprocal change in insulin secretion [1,2]. The resultant negative feedback loop has been characterized mathematically as a rectangular hyperbolic function (i.e. y = constant/x) between insulin secretion and insulin sensitivity, as originally postulated by Bergman and colleagues [3]. Kahn *et al.* [4] subsequently confirmed the existence of this hyperbolic relationship in humans, using the acute-insulin-response-to-glucose (AIR_g) and the insulin sensitivity index (S_I), measures of insulin secretion and sensitivity, respectively, obtained during the frequently sampled

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intravenous glucose tolerance test (FSIVGTT). Two key concepts arise from these data. First, for the appropriate assessment of B-cell compensation, insulin secretion must be evaluated in the context of ambient insulin sensitivity [1]. Secondly, the hyperbolic relationship between AIR_g and S_I implies that the product of these two indices, termed the disposition index, should yield a constant for a given degree of glucose tolerance and thereby provide a measure of B-cell function [2–4]. Indeed, the disposition index has since emerged as a valuable tool in clinical research by providing an integrated measure of B-cell compensation, whereby insulin secretion is appropriately assessed in relation to prevailing insulin sensitivity.

Instead of the FSIVGTT that is required for calculation of the disposition index, large clinical and epidemiologic studies generally utilize the oral glucose tolerance test (OGTT). As such, several simple indices have been derived such that measurements obtained during the OGTT can be used for estimation of insulin secretion [e.g. insulinogenic index (IGI)], insulin sensitivity (e.g. Matsuda index) and insulin resistance [e.g. homeostasis model of assessment for insulin resistance (HOMA-IR)], respectively [5–7]. To assess B-cell function by OGTT, investigators have typically applied these indices to adjust insulin secretion for ambient insulin sensitivity/resistance, such as with the commonly used construct of IGI/HOMA-IR [1]. Until recently, however, a true OGTT-based measure of B-cell compensation analogous to the disposition index has been lacking, owing to the fact that the derivation of such a measure first requires the rigorous confirmation of a hyperbolic relationship between its component indices of insulin secretion and sensitivity. Importantly, in the past year, the formal mathematical demonstration of this hyperbolic relationship between specific OGTT-based indices of insulin secretion and sensitivity has led to the emergence of two novel OGTT-based measures of B-cell function, conceptually analogous to the disposition index [8,9]. Specifically, we introduced the insulin secretion-sensitivity index-2 (ISSI-2), defined as the product of (i) insulin secretion measured by the ratio of the total area-under-the-insulin-curve (AUC_{ins}) to the area-under-the-glucose curve (AUC_{gluc}) and (ii) insulin sensitivity measured by the Matsuda index [8]. Subsequently, Utzschneider and colleagues [9] demonstrated a similar hyperbolic relationship between IGI and 1/fasting insulin, leading to their proposal of IGI/fasting insulin as a second OGTT-based measure of B-cell function similar to the disposition index. However, neither ISSI-2 nor IGI/fasting insulin has been directly compared with the disposition index. Thus, our objective in the current analysis was to directly evaluate these two measures in relation to the disposition index in subjects undergoing both OGTT and FSIVGTT.

Methods

The current analysis was performed using data from the Study of Latino Adolescents at Risk (SOLAR), which has previously been described in detail [10]. Briefly, in this longitudinal study investigating risk factors for the development of Type 2 diabetes in at-risk youth, a cohort of Latino children completed a 2-h OGTT, followed within 2 weeks by an insulin-modified FSIVGTT, with calculation of S_I, AIR_g and the disposition index, as previously described [10]. All participants and their parents provided written informed consent and the SOLAR study was approved by the institutional review board of the University of Southern California.

For the current analysis, the following four measures of B-cell function were calculated from the OGTT: ISSI-2, IGI/fasting insulin, IGI/HOMA-IR and HOMA-B. To calculate ISSI-2, total AUC_{ins} and AUC_{gluc} were first determined by applying the trapezoidal rule to insulin and glucose measurements, respectively, during the OGTT and then the ratio of these two measures ($AUC_{ins/gluc}$) was multiplied by the Matsuda index [6], as previously described [8]. IGI, calculated as the incremental change in insulin during the first 30 min of the OGTT divided by the incremental change in blood glucose over the same period, was divided by fasting insulin and by HOMA-IR [7] to yield IGI/fasting insulin [9] and IGI/HOMA-IR, respectively. HOMA-IR [7] was calculated using the formula HOMA-IR = (fasting insulin × fasting glucose)/22.5. HOMA-B [7] was calculated using the formula HOMA-B = (20 × fasting insulin)/(fasting glucose – 3.5). For both HOMA-IR and HOMA-B, insulin was measured in μU/ml and glucose was measured in mmol/l.

Statistical analyses

We first determined whether a rectangular hyperbolic relationship could be confirmed between the respective insulin secretion and sensitivity components of ISSI-2 ($AUC_{ins/gluc}$ and Matsuda index, respectively) and IGI/fasting insulin (IGI and 1/fasting insulin, respectively) in the current dataset. To do so, we applied the very same methodology that was previously used to establish this relationship between the component secretion and sensitivity measures that define the disposition index [4], IGI/fasting insulin [9] and ISSI-2 [8]. Specifically, as previously described in detail [8], perfectly weighted (PW) regression was applied to determine the regression coefficient beta relating insulin secretion and insulin sensitivity in the following model: log (insulin secretion measure) = constant + beta × log (insulin sensitivity measure). Using this approach, a rectangular hyperbolic relationship between the insulin secretion measure and insulin sensitivity measure in the model can be established if the following criteria are satisfied: (i) beta is approximately equal to −1, (ii) the 95% confidence interval (CI) of beta contains −1 and (iii) the 95% CI of beta excludes 0 [8,9].

In Table 1, continuous variables are presented as mean followed by standard deviation in parentheses. Relationships amongst ISSI-2, IGI/fasting insulin and clinical/metabolic parameters were evaluated in the full dataset (Table 2) and within gender strata (Table 3). Standardized regression was used to compare the respective relationships of log ISSI-2 and log IGI/fasting insulin with the disposition index. Specifically, each

Table 1 Demographic and metabolic characteristics of study population

	n = 213
Age (years)	11.1 (1.7)
Sex (male/female)	122/91
Tanner stage	
1 (*n*)	87
2 (*n*)	63
3 (*n*)	18
4 (*n*)	27
5 (*n*)	18
BMI (kg/m^2)	28.2 (5.5)
Total body fat mass (kg)	24.7 (10.3)
Fasting glucose (mmol/l)	5.0 (0.3)
2-h glucose (mmol/l)	6.8 (0.9)
FSIGTT	
S_I [$\times 10^{-4}$ min^{-1}/(μU/ml)]	2.16 (1.46)
AIR_g (μU/ml)	1723 (1264)
Disposition index	2585 (1164)
OGTT	
IS_{OGTT}	8.0 (4.7)
$AUC_{ins/gluc}$	153.2 (96.8)
ISSI-2	926 (279)
Insulinogenic index/fasting insulin	0.60 (0.36)
Insulinogenic index/HOMA-IR	19.8 (12.2)
HOMA-B	227 (147)

Continuous variables are presented as mean followed by standard deviation in parentheses.
AIR_g, acute-insulin-response-to-glucose; $AUC_{ins/gluc}$, ratio of the area-under-the-insulin-curve to the area-under-the-glucose-curve; BMI, body mass index; FSIGTT, frequently sampled intravenous glucose tolerance test; HOMA-B, homeostasis model of assessment of B-cell; HOMA-IR, homeostasis model of assessment for insulin resistance; IS_{OGTT}, Matsuda index; ISSI-2, insulin secretion–sensitivity index-2; OGTT, oral glucose tolerance test; S_I, insulin sensitivity index.

Table 3 Spearman correlations of OGTT-based measures of B-cell function (ISSI-2, insulinogenic index/fasting insulin, insulinogenic index/HOMA-IR, and HOMA-B) with the disposition index in girls and boys

	Girls (*n* = 91)		Boys (*n* = 122)	
	r	*P*	*r*	*P*
ISSI-2	0.32	0.002	0.25	0.005
Insulinogenic index/fasting insulin	0.25	0.018	0.19	0.038
Insulinogenic index/HOMA-IR	0.28	0.007	0.21	0.019
HOMA-B	−0.11	0.338	−0.03	0.764

HOMA-B, homeostasis model of assessment of B-cell; HOMA-IR, homeostasis model of assessment for insulin resistance; ISSI-2, insulin secretion–sensitivity index-2; OGTT, oral glucose tolerance test.

of these measures (log ISSI-2, log IGI/fasting insulin, disposition index) was standardized (by subtracting each value from the mean and then dividing by the standard deviation) in order to yield a distribution with mean of 0 and standard deviation of 1. Simple linear regression was then performed relating the standardized disposition index to (i) standardized log ISSI-2 and (ii) standardized log IGI/fasting insulin, respectively, such that the standardized regression coefficients would represent the changes in (i) log ISSI-2 and (ii) log IGI/fasting insulin, respectively, that would correspond to a change of 1 standard deviation in the disposition index. Direct comparison of the standardized regression coefficient estimates from the two models thus enabled determination of the relative strength of the relationships between the disposition index and (i) ISSI-2 and (ii) IGI/fasting insulin, respectively. Figure 2 shows the plots of the fitted regression lines relating the standardized disposition

Table 2 (a) Spearman correlations between (i) ISSI-2, IGI/fasting insulin, IGI/HOMA-IR, HOMA-B and disposition index and (ii) clinical and metabolic parameters and (b) levels of B-cell measures by Tanner stage (presented as mean followed by standard error in parentheses)

(a)

	ISSI-2		IGI/fasting insulin		IGI/HOMA-IR		HOMA-B		Disposition index	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age	−0.26	0.0002	−0.07	0.302	−0.09	0.172	0.29	< 0.0001	−0.34	< 0.0001
BMI	−0.16	0.024	−0.01	0.860	−0.01	0.840	0.60	< 0.0001	−0.27	< 0.0001
Total body fat mass	−0.13	0.058	0.02	0.777	0.02	0.799	0.61	< 0.0001	−0.29	< 0.0001

(b)

	Tanner 1	Tanner 2	Tanner 3 or higher	*P*
ISSI-2	975 (30)	896 (35)	888 (35)	0.099
IGI/fasting insulin	0.64 (0.04)	0.58 (0.05)	0.55 (0.05)	0.318
IGI/HOMA-IR	21.1 (1.3)	19.0 (1.5)	18.6 (1.5)	0.389
HOMA-B	168 (15)	239 (17)	299 (17)	< 0.0001
Disposition index	3017 (119)	2446 (139)	2130 (139)	< 0.0001

BMI, body mass index; HOMA-B, homeostasis model of assessment of B-cell; HOMA-IR, homeostasis model of assessment for insulin resistance; IGI, insulinogenic index; ISSI-2, insulin secretion–sensitivity index-2.

index to standardized log ISSI-2 (a) and standardized log IGI/fasting insulin (b), respectively. All analyses were conducted using the SAS version 9.1 (SAS Institute, Cary, NC, USA). Plots were prepared using R version 2.7.2.

Results

Table 1 shows the demographic and metabolic characteristics of the study population, which consisted of 213 non-diabetic children (122 boys, 91 girls) with mean age 11.1 ± 1.7 years and body mass index (BMI) 28.2 ± 5.5 kg/m^2. On univariate correlation analysis, AIR_g and S_I were significantly related ($r = -0.62$, $P < 0.0001$). Similarly, $AUC_{ins/gluc}$ was correlated with the Matsuda index ($r = -0.65$, $P < 0.0001$) and insulinogenic index correlated with both 1/fasting insulin ($r = -0.49$, $P < 0.0001$) and 1/HOMA-IR ($r = -0.48$, $P < 0.0001$).

Using the model of log (insulin secretion) = constant + beta × log (insulin sensitivity), the coefficient beta relating $AUC_{ins/gluc}$ and Matsuda index (i.e. the component insulin secretion and sensitivity measures of ISSI-2) indeed satisfied hyperbolic criteria in this dataset [beta = −0.95, 95% CI (−1.48,−0.42)] (Fig. 1). For IGI and 1/fasting insulin (i.e. the component insulin secretion and sensitivity measures of IGI/fasting insulin), however, hyperbolic criteria were not fully satisfied as the 95% CI of beta included 0 [beta = −0.90, 95% CI (−1.83, 0.03)]. A hyperbolic relationship was confirmed between the disposition index components AIR_g and S_I [beta = −1.05, 95% CI (−2.02, −0.08)].

As expected, ISS1-2 and IGI/fasting insulin were highly correlated ($r = 0.82$, $P < 0.0001$). Importantly, both ISSI-2 and IGI/fasting insulin also correlated significantly with the disposition index, with ISSI-2 showing a modestly stronger association (ISSI-2: $r = 0.24$, $P = 0.0003$; IGI/fasting insulin: $r = 0.21$, $P = 0.0022$). IGI/HOMA-IR also correlated with the disposition index ($r = 0.23$, $P = 0.0009$) while HOMA-B was not significantly associated ($r = -0.09$, $P = 0.195$).

To compare the relative strengths of their relationships with the disposition index, we performed linear regression analyses relating the standardized disposition index to standardized log ISSI-2 and log IGI/fasting insulin, respectively. As shown in Fig. 2(a,b), the standardized coefficient estimates from these analyses confirmed that the relationship between log ISSI-2 and the disposition index (standardized regression coefficient = 0.224, $P = 0.001$) was stronger than that between log IGI/fasting insulin and the disposition index (standardized regression coefficient = 0.166, $P = 0.015$).

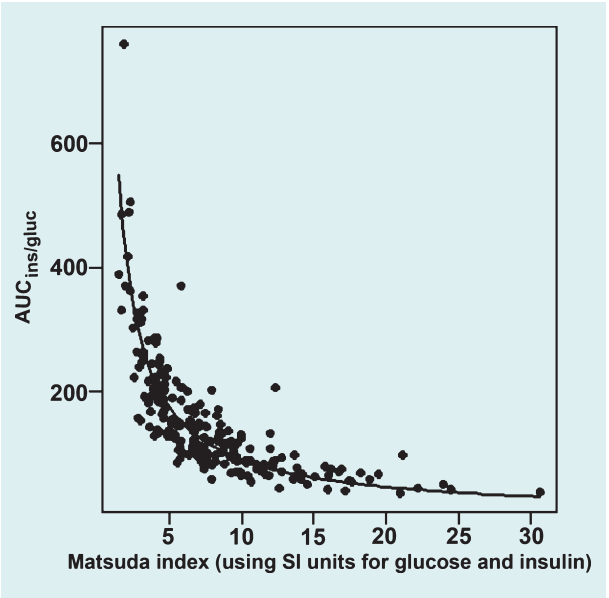

FIGURE 1 Plot of hyperbolic relationship between the ratio of the area-under-the-insulin-curve to the area-under-the-glucose-curve ($AUC_{ins/gluc}$) (insulin secretion) and Matsuda index (insulin sensitivity), the component measures of the insulin secretion–sensitivity index-2 (ISSI-2).

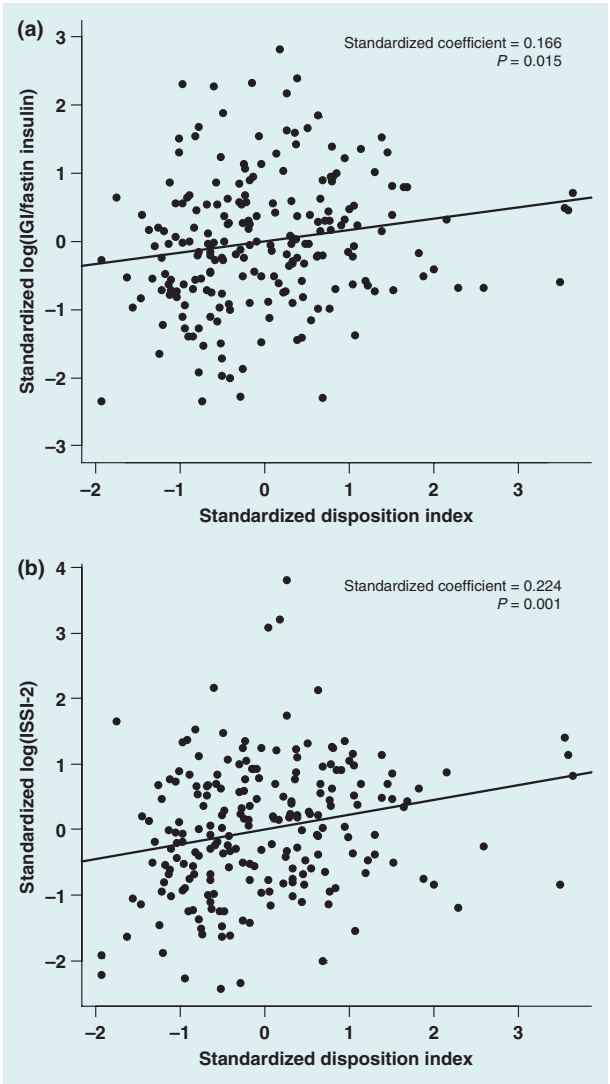

FIGURE 2 Plots of the fitted regression lines relating the standardized disposition index to standardized log insulin secretion–sensitivity index-2 (ISSI-2) (a) and standardized log insulinogenic index (IGI)/fasting insulin (b), respectively.

We next compared the relationships of ISSI-2 and IGI/fasting insulin with clinical and metabolic parameters to those of the disposition index. As shown in Table 2a, the disposition index was inversely correlated with each of age, BMI, and total body fat mass. Similarly, ISSI-2 was also inversely related to each of these parameters (at borderline significance for total body fat mass), although not as strongly as the disposition index. In contrast, IGI/fasting insulin and IGI/HOMA-IR were not significantly related to these measures. Thus, the relationships of ISSI-2 with these clinical and metabolic parameters were much more similar to those of the disposition index than were the analogous relationships of IGI/fasting insulin and IGI/HOMA-IR. HOMA-B was positively and significantly associated with age, BMI and total body fat mass. With respect to pubertal status (Table 2b), the disposition index declined with increasing Tanner stage, while HOMA-B showed the opposite relationship (i.e. increased with Tanner stage). ISSI-2, IGI/fasting insulin and IGI/HOMA-IR were not significantly related to pubertal status (Table 2b).

On gender-stratified analyses (Table 3), the correlation with the disposition index was again stronger for ISSI-2 than for IGI/fasting insulin in both girls (ISSI-2: $r = 0.32$, $P = 0.002$; IGI/fasting insulin: $r = 0.25$, $P = 0.018$) and boys (ISSI-2: $r = 0.25$, $P = 0.005$; IGI/fasting insulin: $r = 0.19$, $P = 0.038$). Furthermore, ISSI-2 was also more strongly associated with the disposition index than was either IGI/HOMA-IR or HOMA-B in both girls and boys (Table 3).

In addition to gender, we also evaluated other subgroups. In participants below the median BMI (27.2 kg/m^2), both ISSI-2 and IGI/fasting insulin were significantly correlated with the disposition index ($r = 0.26$, $P = 0.007$ and $r = 0.31$, $P = 0.001$, respectively). In those above the median BMI, neither ISSI-2 nor IGI/fasting insulin achieved significance in its respective relationship with the disposition index ($r = 0.17$, $P = 0.09$ and $r = 0.12$, $P = 0.24$, respectively). In pubertal children (Tanner 2 or higher), both ISSI-2 and IGI/fasting insulin were significantly correlated with the disposition index ($r = 0.23$ $P = 0.0095$ and $r = 0.22$, $P = 0.012$, respectively). These relationships were not significant in the 87 pre-pubertal children (ISSI-2: $r = 0.17$, $P = 0.13$; IGI/fasting insulin: $r = 0.06$, $P = 0.55$).

Discussion

In the past year, ISSI-2 and IGI/fasting insulin have been proposed as OGTT-derived measures of B-cell function analogous to the disposition index, on the basis of the confirmed hyperbolic relationship between their respective component insulin secretion and sensitivity indices [8,9]. In the current report, we now extend this literature by demonstrating that ISSI-2 and IGI/fasting insulin indeed both correlate significantly with the disposition index, supporting their validity as measures of B-cell compensation. Interestingly, their correlations with the disposition index, although clearly significant, were relatively modest. Likewise, IGI/HOMA-IR, a well-established OGTT-derived measure of B-cell function that has been used in large clinical studies such as the Diabetes Prevention Program (DPP) [1,11], also showed similarly modest associations with the disposition index, while HOMA-B was not significantly associated. It thus emerges that, amongst OGTT-derived measures of B-cell function, both established measures (IGI/HOMA-IR and HOMA-B) and the recently proposed indices (ISSI-2 and IGI/fasting insulin) show modest correlation with the disposition index.

This observation is important on several levels. Firstly, these data highlight the fact that there are distinct differences in the B-cell response to oral as compared with intravenous glucose (i.e. such as the effects of incretin hormones in the former case). Whether these differences underlie the limited correlation between the OGTT-based measures and the disposition index is not clear. Secondly, it should be recognized that the disposition index concept itself has been criticized previously insofar as the appropriateness of a hyperbolic function for relating insulin secretion and insulin sensitivity may depend on the way in which these parameters are expressed (i.e. the appropriate mathematical function may vary with the variables used to measure insulin secretion and insulin sensitivity) [12]. Indeed, there are modes of B-cell function that may be independent of insulin action [12]. While the current analysis cannot address these issues, these findings nevertheless emphasize that further study is needed for informed interpretation of the OGTT-derived surrogate measures of B-cell function commonly used in clinical studies. Moreover, as the current data are from a single patient group of at-risk children, further study should be performed in other patient populations.

In the current study, ISSI-2 was more closely related to the disposition index than was IGI/fasting insulin on the basis of both (i) the standardized regression analyses (Fig. 2) and (ii) the comparative relationship profiles with clinical and metabolic characteristics (Table 2). In addition, although the associations were modest, ISSI-2 consistently exhibited stronger correlations with the disposition index than did IGI/fasting insulin (or IGI/HOMA-IR). This finding is likely because of limitations associated with the IGI component of the latter two measures. One factor is that IGI sometimes cannot be calculated as a result of a paradoxical fall in insulin levels during the first 30 min of the OGTT, thereby confounding the use of IGI-associated measures for assessing B-cell function [13] (although there were no such cases in this dataset). Secondly, and perhaps more importantly, IGI is characterized by marked within-subject variability, ranging from 40.6 to 57.1% in previous reports [8,9,14]. Indeed, it is this considerable variability that likely precluded the satisfaction of hyperbolic criteria in the relationship between IGI and 1/fasting insulin in the current dataset, by causing a wide confidence interval for beta that included 0, despite the estimate for beta being near −1. Similarly, in our earlier report [8], the same pattern (wide confidence interval that crossed 0) repeatedly precluded the confirmation of hyperbolic relationships between IGI and other insulin sensitivity measures (1/HOMA-IR and Matsuda index). Of note,

despite a coefficient of variation of 57.1% for IGI, Utzschneider and colleagues [9] succeeded in demonstrating a hyperbolic function between IGI and 1/fasting insulin in subjects with normal glucose tolerance (NGT) (n = 244), pre-diabetes (n = 254) and diabetes (n = 115), although some influential outliers were eliminated in their analyses. In contrast, without any elimination of outliers, the hyperbolic relationship between $AUC_{ins/gluc}$ and the Matsuda index has been formally demonstrated (i) in seven different analyses in four datasets (including the current), (ii) in different glucose tolerance groups (NGT, impaired glucose tolerance, diabetes), (iii) in adults and now in children and (iv) in subsets as small as 43 and 53 subjects [8]. Overall, in concert with the current findings, these data suggest that, while both ISSI-2 and IGI/fasting insulin provide OGTT-derived measures of B-cell function and correlate strongly with each other, ISSI-2 may be the more robust measure (possibly because of the lesser variability of its component indices [8]) and hence may be particularly preferable in smaller datasets (where the variability of IGI may be especially problematic).

One limitation that relates to both ISSI-2 and IGI/fasting insulin is that circulating insulin levels during the OGTT may be affected by other factors apart from B-cell function, such as incretin hormones and hepatic extraction. Secondly, the current analysis was performed in a single cohort consisting of at-risk children. These findings thus warrant evaluation in different patient groups before they can be applied to other populations. Finally, while both the disposition index and IGI/fasting insulin can predict incident diabetes (as negative predictors [9,15]), such a longitudinal analysis has not yet been reported for ISSI-2. In this context, however, it is encouraging that ISSI-2 correlates strongly with IGI/fasting insulin and shows better correlation than the latter with the disposition index.

In summary, we have demonstrated that both ISSI-2 and IGI/fasting insulin correlate significantly with the disposition index, although the relationships are modest. While ISSI-2 was more closely related to the disposition index than was IGI/fasting insulin and may provide the more robust OGTT-derived measure, these data highlight that considerable differences potentially exist between measures of B-cell function obtained on OGTT and the disposition index derived on FSIVGTT, despite their conceptual similarity. Further study of the relationships between OGTT- and FSIVGTT-based indices of B-cell function is thus needed.

Competing interests

Nothing to declare.

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