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ORIGINAL ARTICLE

The oral disposition index is a strong predictor of incident diabetes in Asian Indian prediabetic men

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Abstract
Aims In this analysis, we sought to examine the prospective association of the disposition index (DIo) derived from oral glucose tolerance test with incident diabetes in Asian Indian men with impaired glucose tolerance (IGT).
Methods These post hoc analyses used data from a 2-year prospective study in primary prevention of diabetes using lifestyle intervention among 517 men with IGT. All the participants received standard lifestyle advice at baseline. The surrogate insulin sensitivity and insulin secretion measures were tested for their hyperbolic relationship. Predictive associations of various surrogate measures with incident diabetes were determined using receiver operating characteristic curves.
Results The combination of total area under the curve of insulin-to-glucose ratio (AUCinsulin/glucose) and Matsuda's insulin sensitivity index was the best equation to depict DIo [β: −0.954 (95 % CI −1.015 to −0.893)] compared to other measures tested in this cohort. There was an inverse association between change in DIo at the final follow-up and development of incident diabetes. Among the surrogate insulin measures studied, DIo [AUC (0.717 (95 % CI 0.675–0.756))] as a composite measure was superior than other surrogate indices.
Conclusions Among the surrogate indices studied, DIo was the best measure associated with incident diabetes.

Keywords Oral disposition index · Asian Indians · Prediabetes · Predictor of diabetes · Lifestyle modification

Abbreviations

ANOVA	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
HOMA-IR	Homeostasis model assessment-estimated insulin resistance
IVGTT	Intravenous glucose tolerance test
IGT	Impaired glucose tolerance
NGT	Normoglycemia
OGTT	Oral glucose tolerance test
SMS	Short message service
T2DM	Type 2 diabetes

Introduction

Adaptation of insulin secretion to prevailing insulin sensitivity is a tightly regulated mechanism, and deterioration of both functions is associated with the development of type 2 diabetes (T2DM) [1]. As originally postulated by Bergman and associates [2], there is a strict reciprocal compensatory mechanism between insulin secretion and

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insulin action, and the product of these approximates a constant, termed the "disposition index (DIo)" [3]. Subsequently, Kahn et al. [4] established the existence of a hyperbolic relationship in humans, using the acute insulin response to glucose (AIRg) and the insulin sensitivity index (ISI), measures of insulin secretion and sensitivity, respectively, obtained during the frequently sampled intravenous glucose tolerance test (FSIVGTT). T2DM occurs only if this beta-cell function is inadequate to compensate for the compounding insulin resistance [3].

The FSIVGTT in a large-scale epidemiological setting is not practical owing to the laborious procedure of multisampling, it requires expertize and is an expensive procedure [2, 5]. Therefore, a variety of surrogate mathematical "paradigm" models derived from fasting or oral glucose tolerance test (OGTT), glucose and insulin measurements such as homeostasis model of assessment for insulin resistance (HOMA-IR) [6], Matsuda's insulin sensitivity index [7], and the insulinogenic index (IGI) [8, 9] has been validated as an alternate measures to evaluate insulin sensitivity and secretion. Indeed, these measures have been shown to perform reasonably well for the discrimination of individuals with differing levels of insulin resistance and impaired beta-cell function. Various versions of the DIo derived from OGTT such as $\Delta I_{0-120}/\Delta G_{0-120}$ * ISI [10], IGI/HOMA-IR, IGI/fasting insulin, and area under the curve of insulin-to-glucose ratio ($AUC_{ins/glu}$) * ISI (ISSI2) have been proposed as analogous to the DIo derived from the FSIVGTT. These indices exhibit moderate associations with the reference methods (standardized β coefficient: 0.166–0.221) [11, 12].

It is now well established that healthy diet and improvement in physical activity and weight reduction improve insulin sensitivity in individuals with high risk for diabetes [13–15]. The US diabetes prevention program [13] and Finnish Diabetes Prevention study [14] show that higher insulin secretion and sensitivity at baseline and improvements in response to lifestyle intervention such as healthy dietary and physical activity practices were associated with lower incidence of diabetes among prediabetic individuals. Earlier, we had noted that the presence of good beta-cell function (as measured by IGI) at baseline along with the improvement in insulin sensitivity facilitated the reversal of prediabetes to normoglycemia, whereas deterioration in both resulted in progression to diabetes in Asian Indian populations [8]. Ancillary analysis of the same cohort described in this paper asserted the same finding when beta-cell function was assessed by DIo [15]. However, information is sparse on the pathogenic mechanisms responsible for progression to diabetes in Asian Indians. Moreover, no study has assessed the association of healthy lifestyle changes on the improvement of beta-cell function in this population. Asian Indians have a strong predisposition for T2DM and have several peculiar pathophysiological features including young age of onset of diabetes, high rates of insulin resistance with relatively lower body mass index (BMI), and lower thresholds for the risk factors for diabetes [16] compared with Caucasians.

The objectives of this analysis were to assess the predictive association of baseline DIo with subsequent incidence of T2DM. We hypothesize that adequate beta-cell compensation at baseline and improvement of the function during intervention will be associated with decreased incidence of diabetes.

Materials and methods

Study participants

These ancillary analyses used data in a cohort of men with impaired glucose tolerance (IGT) who were followed up for 2 years in a previously published, randomized controlled trial on primary prevention of diabetes in India [17]. A total of 537 men were randomized into two groups: (a) control group, which received standard care advice only at baseline and (b) an intervention group, which received automated, customized text messages (SMS) about healthy lifestyle habits in addition to standard care advice. At baseline, both the control and intervention groups received one-to-one, identical, lifestyle advice. The groups being distinguished solely by whether they received reinforcement of lifestyle advice by text messages. We, therefore, considered the cohort as a single group for this analysis, to explore the association of DIo with the incidence of diabetes. The study showed for the first time that mobile phone-based text messaging reminder is an effective and acceptable tool to deliver and support lifestyle modification to prevent T2DM in Asian Indian men with IGT [17]. Of the 537 participants recruited for the study, 517 continued participation to the final follow-up visit (response rate 96.3 %); among them, 123 developed T2DM. The present analyses were limited to those who completed the final follow-up.

The study was approved by the Institutional Ethics Committee of India Diabetes Research Foundation, India, and the participants gave informed consent (ClinicalTrial.Gov No: NCT00819455).

The primary outcome was the incidence of diabetes. OGTT was done at baseline, 12, and 24 months and was assessed by World Health Organization (WHO) recommendations [18]: a plasma glucose of a value of 7.0 mmol/l or higher in the fasting state or 11.1 mmol/l or higher 2 h after a 75-g oral glucose load. To minimize discomfort and inconvenience, at 6 and 18 months, a capillary blood sample was taken 2 h after oral glucose was given in the

fasting state. If this value was ≥11.1 mmol/l, a 2-h OGTT was done within 1 week with venous plasma sampling in the fasting state, and at 30 min and 2 h after glucose consumption.

Anthropometric and laboratory measures

Height, weight, and waist circumference were measured, and BMI was calculated. Blood pressure (average of two readings) was measured using a standard mercury sphygmomanometer after a 5-min' rest. A standard OGTT was performed after a 10- to 12-h fast with venous plasma sampling in the fasting state, and at 30 min and at 2 h after glucose consumption. Plasma glucose was measured by hexokinase method with appropriate quality control measures using auto-analyzer (COBAS—Integra, Germany). Plasma insulin was measured using an electrochemiluminescence assay in an Elesys Cobas e411 auto-analyzer (Roche diagnostics, Mannheim, Germany; CV <3 %; detection range 1.39–6,945 pmol/l).

The habitual nutrient intakes of the participants were recorded by a trained dietician by interview using a single 24-h dietary recall method at baseline and at the 6 monthly reviews. The total energy intake (kcal) and components of individual food constituents [carbohydrates, proteins, and fat (in grams)] consumed by the participants were calculated with an in-house dietary analysis program (visual basic programing tool) using the National Institute of Nutrition guidelines for India [19]. A physical activity questionnaire used for South Asians in a UK epidemiological survey [20] was slightly modified to suit the Indian environment. Self-reported activity for one week was captured using a validated questionnaire and was quantified on a score of 7–70. Information about adherence to recommendations for dietary intake and physical activity was recorded at the six monthly reviews [17, 21].

Surrogate insulin measures calculations

HOMA-IR [6] was calculated using the formula: [fasting insulin (μU/ml) * fasting glucose (mmol/l)/22.5], since it is a measure of insulin resistance, the inverse of which (i.e., 1/HOMA-IR) was used to express insulin sensitivity. ISI was calculated by the following formula: (10^4/square root of [fasting glucose (mg/dl) * insulin (μU/ml)] * [mean OGTT glucose (mg/dl) * mean OGTT insulin (μU/ml)], with mean glucose and insulin calculated from values at fasting, 30, and 120 min of the OGTT test [7]. IGI was calculated as the ratio of the change in insulin (pmol/l) to the change in glucose (mmol/l) from 0 to 30 min following the oral glucose load ($\Delta I_{0-30}/\Delta G_{0-30}$) [8]. Total area under the curve (AUC) for insulin (pmol/l) and for glucose (mmol/l) was calculated using the trapezoidal rule, and a ratio of the two was calculated ($AUC_{ins/glu}$) [9]. For the present analysis, the following combinations of DIo was calculated from the OGTT: (a) IGI/HOMA-IR; (b) IGI/fasting insulin;

Table 1 Baseline characteristics of study participants based on the glycemic outcomes at the end of second year

Variables	IGT to NGT (n = 170)	IGT to IGT (n = 224)	IGT to T2DM (n = 123)	P value
Age (years)	46.1 ± 4.8	46.1 ± 4.7	46.1 ± 4.5	0.951
Body mass index (kg/m^2)	25.9 ± 3.2	25.5 ± 2.9	26.1 ± 3.6	0.206
Waist circumference (cm)	93.0 ± 7.4	91.9 ± 6.8	93.0 ± 8.0	0.229
Blood pressure (mmHg)				
Systolic	123.8 ± 12.8	122.0 ± 14.0	124.0 ± 14.4	0.274
Diastolic	80.1 ± 8.0	79.6 ± 8.4	81.2 ± 9.0	0.207
Family history of diabetes, [n (%)][a]	82 (48.2)	122 (54.5)	69 (56.1)	0.332
Smoking, [n (%)][a]	37 (21.8)	44 (19.6)	36 (29.3)	0.116
Drinking habits, [n (%)][a]	60 (35.3)	84 (37.5)	47 (38.2)	0.855
Glucose (mmol/l)				
Fasting	5.5 ± 0.5	5.6 ± 0.5	5.8 ± 0.5$^{\dagger, \P}$	<0.0001
2 h	8.5 ± 0.7	8.7 ± 0.8*	9.2 ± 0.9$^{\dagger, \P}$	<0.0001
Insulin (pmol/l)[b]				
Fasting	81.3 (57.8–102.6)	80.0 (58.3–99.7)	93.2 (72.2–118.1)$^{*, \ddagger}$	0.001
30 min	620.2 (425.4–957.7)	531.8 (350.3–809.3)	468.0 (338.9–832.7)$^{*, \ddagger}$	0.006
2 h	848.0 (581.9–1,389.2)	857.4 (583.6–1,255.4)	847.3 (604.4–1,286.0)	0.666

Data are mean ± SD (for normally distributed variables) and analyzed by one-way ANOVA

* $P < 0.05$ versus NGT; † $P < 0.001$ versus NGT; ‡ $P < 0.05$ versus IGT; ¶ $P < 0.001$ versus IGT

[a] Expressed as counts (percentage) for categorical measures—analyzed by χ test

[b] Expressed as median (interquartile range) for skewed variables—analyzed by Kruskal–Wallis test

(c) IGI * ISI; (d) $AUC_{ins/glu}$ from 0 to 120 min/HOMA-IR; and (e) $AUC_{ins/glu}$ from 0 to 120 min * ISI (ISSI-2).

Statistical analysis

A relationship between insulin sensitivity and insulin secretion is thought to be a "rectangular hyperbola" wherein the product of the two measures approximates a constant. The validity of the DIo was assessed by demonstrating a hyperbolic relationship between the measure of insulin secretion and insulin sensitivity derived from the OGTT. Regression coefficient "β" for the following models was calculated as ln(insulin secretion) = constant + β * ln(insulin sensitivity). In this context, the product of OGTT-based surrogate insulin measures obeys a hyperbolic relationship if the following criteria are satisfied: regression coefficient (β) is $\cong -1$, and the 95 % confidence interval (CI) of β includes -1 and excludes 0 [11, 22].

Results of the OGTT were used to designate a participant's glucose tolerance status as regressors (IGT to NGT), unchangers (IGT to IGT), and progressors (IGT to T2DM). Normally distributed variables were compared across glycemic categories using one-way ANOVA after Bonferroni post hoc corrections. For nonparametric variables, Kruskal–Wallis test with Dunn's post hoc corrections was used. Changes from baseline to follow-up were compared between groups by the "t" test when variables were normally distributed and by Wilcoxon's test for variables nonnormally distributed. The power of DIo and other surrogate insulin measures to predict the progression to diabetes was assessed using ROC curve [23, 24]. All analyses were performed using SPSS software (IBM SPSS Statistics for Windows, version 19.0. Armonk, NY: IBM Corp).

Results

Table 1 shows the baseline anthropometric and metabolic risk factors, according to the OGTT status at the end of the study. Participants who developed T2DM had higher baseline fasting and 2-h plasma glucose compared with regressors (IGT to NGT). The mean fasting plasma insulin was higher, and 30-min plasma insulin was lower in the progressors (IGT to T2DM) compared with the regressors (IGT to NGT).

Demonstration of hyperbolic relationship

Using OGTT data, the two measures of insulin secretion and three measures of insulin sensitivity were tested for the existence of a hyperbolic relationship. As shown in the electronic supplementary material, the only pairing that satisfied both of the hyperbolic criteria is the ISSI-2 [β: -0.954 (95 % CI -1.015 to -0.893)]. Importantly, ISSI-2 yielded distinct hyperbolae for each glucose tolerance group [NGT: β: -0.946 (95 % CI -1.048 to -0.842); IGT: β: -1.000 (95 % CI -1.085 to -0.915); T2DM: β: -1.063 (95 % CI -1.202 to -0.923)], consistent with the existence of a hyperbolic relationship (electronic supplementary material). There was a gradient deterioration in the values of ISSI-2 from NGT to T2DM (IGT to NGT:

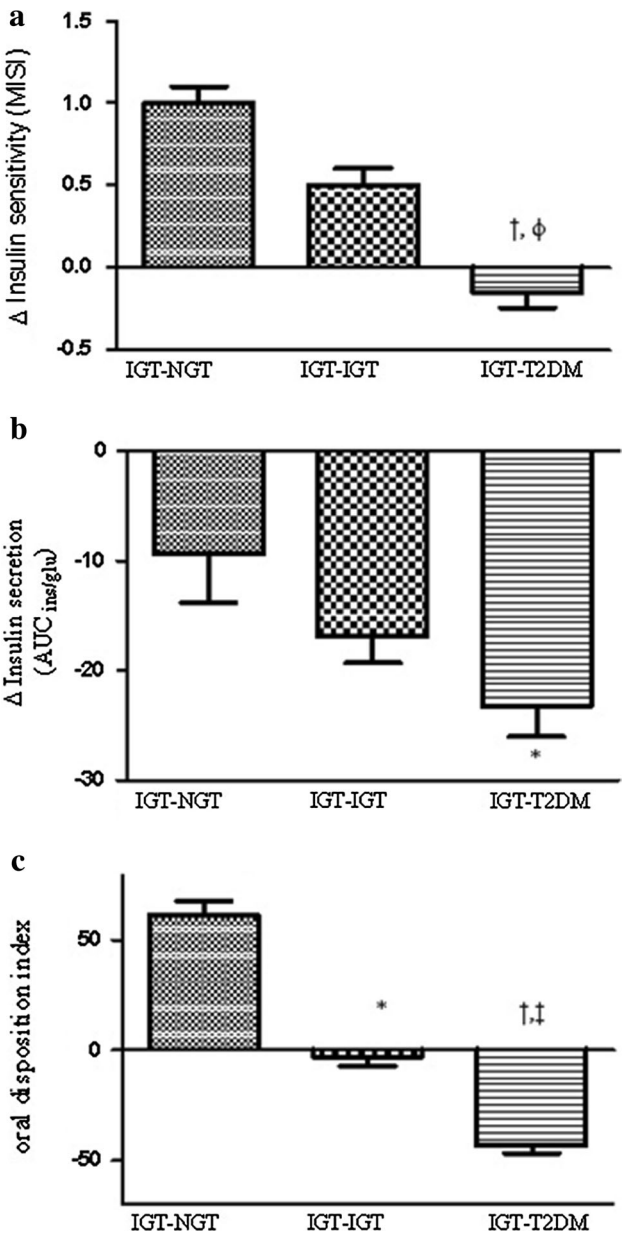

Fig. 1 **a** Changes in Matsuda's insulin index, **b** AUCins/glu ratio, and **c** oral disposition index throughout the study. Individuals were all IGT at baseline, and groups were distinguished by glycemic status at the end of the study. * $P < 0.05$ vs. NGT; † $P < 0.001$ vs. NGT; ‡ $P < 0.05$ vs. IGT; ϕ $P < 0.001$ vs. IGT

Table 2 Baseline and final levels of insulin sensitivity, insulin secretion, and oral disposition index according to glucose tolerance categories

	Baseline	Follow-up	% change	*P* value
IGT to NGT				
Insulin sensitivity index	2.4 ± 1.4	3.4 ± 1.3	41.7	<0.0001
Total $AUC_{ins/glu}$	81.2 (51.5–110.7)	68.6 (52.8–92.2)	−15.5	0.003
Oral disposition index	168.8 (136.3–203.8)	217.5 (179.3–281.0)	28.9	<0.0001
IGT to IGT				
Insulin sensitivity index	2.6 ± 1.5	3.0 ± 1.7	15.4	<0.0001
Total $AUC_{ins/glu}$	71.2 (48.3–99.1)	54.8 (38.9–74.7)	−23.0	<0.0001
Oral disposition index	154.8 (125.3–184.1)	146.1 (113.9–180.3)	−5.6	0.115
IGT to T2DM				
Insulin sensitivity index	2.1 ± 1.0	2.0 ± 0.8	−4.8	<0.0001
Total $AUC_{ins/glu}$	62.6 (43.9–94.3)	45.0 (34.3–60.1)	−28.1	<0.0001
Oral disposition index	124.1 (101.3–155.8)	81.2 (69.6–100.8)	−34.6	<0.0001

Data are mean ± SD for normally distributed variables and median (interquartile range) for skewed variables

IGT impaired glucose tolerance, *NGT* normal glucose tolerance, *T2DM* diabetes, *total* $AUC_{ins/glu}$ ratio of total area under the curve between insulin and glucose

% change is calculated by (final values−baseline values/baseline values) * 100

175.5 ± 56.1; IGT to IGT: 159.3 ± 49.3; IGT to T2DM: 130.5 ± 52.5); $P < 0.0001$). Therefore, ISSI-2 was considered as the measure of DIo in this cohort.

Characteristics of the improvement in DIo

Overall, the transition from IGT to NGT was associated with an improvement in insulin sensitivity and DIo, and a reduction in insulin secretion (Fig. 1, Panels a–c; Table 2). Among the individuals who progressed to diabetes (IGT to T2DM group), there were reductions in ISI (−4.8 %), total $AUC_{ins/glu}$ (−28.1 %), and deterioration of DIo (−34.6 %). Conversely, ISI and DIo improved significantly among those who regressed to NGT (IGT to NGT group). Among individuals who continued to have IGT, there was a slight improvement in insulin sensitivity and a decrease in insulin secretion. No change in the DIo was noted.

To illustrate the changes in the DIo associated with the three different transitions during the course of the study, insulin secretion was plotted against sensitivity in each of the three groups at baseline and at the end of the study. Thus, six hyperbolic curves were generated, and the point on each curve denoting the mean insulin secretion and mean insulin sensitivity represented the DIo (Fig. 2; Panel a). In the group that underwent the IGT to NGT transition, there was a rightward shift from the baseline toward higher insulin sensitivity and improved DIo, whereas in the group showing IGT to T2DM transition, there was a shift toward the origin of the plot, with lower insulin secretion and sensitivity and lower DIo. In the IGT group, no significant changes were seen. When the change in the DIo from baseline was divided in quintiles, a strong inverse association ($r = 0.9997$; $P < 0.0001$) was observed between the change and the incidence of diabetes. Prediabetic individuals with ≥50 % improvement in β-cell function during the follow-up showed reduced risk of developing diabetes, whereas those who had <50 % improvement in the DIo exhibited an increased risk of diabetes (2 vs. 30 %) (Fig. 2; Panel b).

Table 3 shows the predictive ability of the different baseline measures of insulin sensitivity and beta-cell function explored in this analysis and their corresponding optimal cutoff points in predicting incident diabetes. The area under the ROC curve was the highest for DIo [AUC: 0.717 (95 % CI 0.675–0.756)] followed by HOMA-IR [AUC: 0.642 (95 % CI 0.598–0.685)], 1/fasting insulin [AUC: 0.615 (95 % CI 0.570–0.658)], Matsuda's insulin sensitivity index [AUC: 0.598 (95 % CI 0.554–0.642)], and IGI [AUC: 0.599 [95 % CI 0.554–0.642)], respectively. In this cohort, total $AUC_{ins/glu}$ was not a predictive factor [$P = 0.0728$ (NS)]. The optimal cutoff value for predicting incident diabetes for the DIo was ≤144.7 [sensitivity: 70.0 (95 % CI 61.0–78.0); specificity: 64.1 (95 % CI 59.0–68.9)].

Discussion

Among Asian Indian men with prediabetes, OGTT-based ISSI-2 index was the best equation to depict beta-cell function. The participants with good beta-cell function at baseline were the least likely to develop diabetes. Previously, the ACT NOW study [10, 25] in multiethnic population showed that surrogate measure of beta-cell

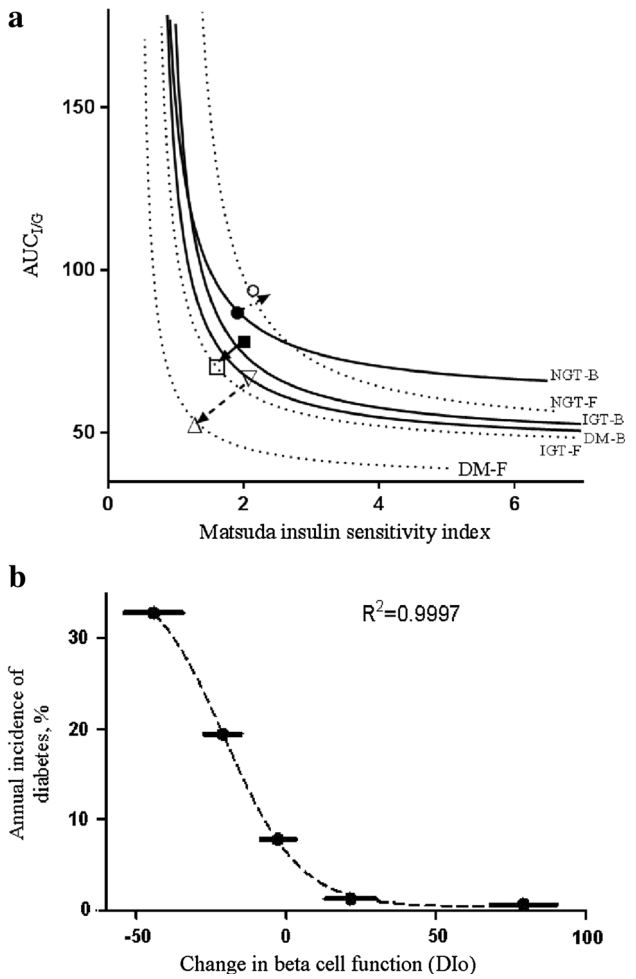

Fig. 2 **a** Change in oral disposition index in relation to the final glycemic outcomes and **b** the relationship between the annual diabetes incidence rate and change in the disposition index divided into quintiles in study participants. **a** The means for baseline and final year oral disposition index are plotted for individuals with NGT, IGT, and T2DM relative to the hyperbolic curves; individuals deteriorated to diabetes had decreased beta-cell function at baseline. Those who regressed to normoglycemia showed an improvement in beta-cell function at the end of follow-up (**a**). *filled circle*: NGT baseline; *open circle* : NGT final; *filled square*: IGT baseline; *open square*: IGT final; *inverted triangle*: T2DM baseline; *triangle*: T2DM final; **b** means±SD of each quintile are represented by *solid circles*. A nonlinear association between the incidence of diabetes and change in beta-cell function is observed

function ($\Delta I_{0-120}/\Delta G_{0-120}$ * Matsuda's insulin sensitivity index) was most closely associated with the glucose tolerance at the end of the study. An observational study of 10 years in Japanese American individuals showed a strong association of oral disposition index ($\Delta I_{0-30}/\Delta G_{0-30}$ * 1/fasting insulin) with incident diabetes [22]. A recent cross-sectional analysis in 1,264 individuals conducted in Asian Indians also found early reductions in beta-cell function ($\Delta I_{0-30}/\Delta G_{0-30}$ * 1/fasting insulin) as the primary etiological factor for the development of diabetes [25, 26].

In this cohort, ISSI-2 yielded distinct hyperbolae (significant difference in the intercept values) for different degrees of glucose tolerance. Besides, these hyperbolae exhibited a shift toward the origin as glucose tolerance worsened, in a manner analogous to the DIo curves measured by euglycemic clamp and IVGTT methods [27]. This shift in hyperbola position is a hallmark of T2DM pathophysiology and is considered as one of the earliest indicators of beta-cell dysfunction [28].

Among the surrogate insulin measures studied, the DIo as a composite measure was superior than that of individual measures such as HOMA-IR, 1/fasting insulin, ISI, and IGI. In this cohort, total $AUC_{ins/glu}$ did not show an association with T2DM. This discordant observation noted in the present study could be due to the fact that IGT itself was a compromized beta-cell responsive state, so total $AUC_{ins/glu}$ per se might have offered less potential for T2DM risk discrimination. $AUC_{ins/glu}$ ratio may not be a surrogate measure to depict insulin secretion in this cohort [29].

The utility of DIo for assessing the beta-cell functional capacity has been reported in varied populations [30–32]. Although insulin resistance is a core pathophysiologic abnormality in the conversion of NGT to diabetes, overt diabetes will occur only if pancreatic beta-cells fail to compensate for chronic insulin resistance [31]. As reported by Petersen et al. [33], beta-cell compensation for a given level of insulin resistance was around 60 % lower in healthy Asian Indians compared with white populations matched for age, sex, BMI, and lifestyle factors. These observations suggest the possibility of ethnic differences in the optimal relationship between insulin sensitivity and insulin response [34]. For a given BMI and waist circumference, Asian Indians have a lower beta-cell reserve and insulin sensitivity when compared with white populations [35]. Therefore, declining beta-cell compensation may be the primary etiological precursor for glycemic deterioration from NGT to diabetes [36].

In this cohort, decreased dietary intake and minimal weight reduction were associated with significantly improved beta-cell function. The beneficial effects of lifestyle interventions appear to be associated with improvement in insulin sensitivity and preservation of pancreatic beta-cell function. Previous post hoc analyses of the same cohort found that good compliance to lifestyle recommendations such as improvement in diet in occupationally active individuals resulted in the beneficial outcome of lower incidence of T2DM in the intervention group in comparison with the control group [37]. Compliance to the good lifestyle habits resulted in improved insulin sensitivity and beta-cell function as shown by enhanced DIo in this cohort independent of group allocation [37]. We did not observe any improvement in physical activity in this cohort owing

Table 3 Area under the receiver operating characteristics and predictabilities of surrogate insulin indices for progression of diabetes[a]

Indices baseline values	AUC (95 % CI)	*P* value[b]	Optimal cutoff point	Sensitivity % (95 % CI)	Specificity % (95 % CI)	Positive likelihood ratio	Incremental AUC (95 % CI)	*P* value[c]
Oral disposition index	0.717 (0.675–0.756)	<0.0001	≤144.7	70.0 (61.0–78.0)	64.1 (59.0–68.9)	1.95	–	–
HOMA-IR	0.642 (0.598–0.685)	<0.0001	≥3.1	59.2 (49.8–68.0)	62.7 (57.6–67.6)	1.58	0.08 (0.01–0.14)	0.0295
1/Fasting insulin	0.615 (0.570–0.658)	0.001	≤0.013	73.3 (64.5–81.0)	43.7 (38.6–48.9)	1.30	0.10 (0.03–0.18)	0.0053
Insulin sensitivity index	0.598 (0.554–0.642)	0.0005	≤2.0	61.7 (52.4–70.4)	53.9 (48.7–59.0)	1.34	0.12 (0.04–0.20)	0.0036
Insulinogenic index	0.599 (0.554–0.642)	0.0013	≤33.8	45.0 (35.9–54.3)	72.5 (67.7–77.0)	1.64	0.12 (0.08–0.16)	<0.0001
Total $AUC_{ins/glu}$	0.554 (0.509–0.599)	0.0728	≤73.6	60.0 (50.7–68.8)	50.4 (45.2–55.6)	1.19	0.16 (0.11–0.21)	<0.0001
HOMA-beta	0.530 (0.485–0.575)	0.3104	≥76.9	85.8 (78.3–91.5)	23.7 (19.5–28.4)	1.13	0.19 (0.11–0.27)	<0.0001

The indices used here were calculated using baseline variables

[a] Diabetes was diagnosed based on WHO recommendations [18]

[b] Significance level *P* (area = 0.5)

[c] *P* value computed from pair-wise comparisons against disposition index

to the fact that 64 % of the study participants were occupationally active at baseline. Hence, further improvement in physical activity could not be achieved. Recently, Bakker et al. [38] showed that the South Asian populations exposed to energy dense food have an inherent inability to adapt metabolically to the high-calorie diet, thereby contributing to the reduced insulin-stimulated glucose disposal when compared with the white populations.

The short duration of 2-year follow-up was one of the limitations of this study. Longer prospective studies are warranted to affirm the role of DIo in the pathogenesis of diabetes. Diet information was captured by a single 24-h recall every 6 months, which was not the ideal method to assess the dietary intake. Also, we did not have a quantitative assessment of the saturated fat intake and micronutrient levels taken by the participants. But, in a community setting, methods used in this study are feasible and cost-effective to collect dietary information. Information on physical activity was also collected by a self-reported questionnaire, a method that could have missed small changes in its improvement.

We infer that an OGTT-derived measure of DIo could be used as an alternate surrogate measure to identify high-risk individuals.

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Conflict of interest DGJ is supported by the UK National Institute for Health Research (NIHR). Imperial College, London, is grateful for support from the NIHR Collaboration for Leadership in Applied Health Research and Care and the Imperial NIHR Biomedical Research Centre. We declare that we have no conflicts of interest.

Ethical standard This study was approved by the Institutional Ethics Committee of the India Diabetes Research Foundation, Chennai, India [Dated 6th July 2007].

Human and animal rights disclosure All human rights were observed in keeping with Declaration of Helsinki 2008 (ICH GCP) and the Indian Council of Medical Research (ICMR) guidelines. There are no animal rights issues as this is a clinical study.

Informed consent disclosure Written informed consent was obtained from all participants before being included in the study.

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