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A novel disposition index without insulin is an earlier and sensitive predictor of type 2 diabetes than current diagnostic criteria

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ABSTRACT

Aims: Early identification of individuals at risk for type 2 diabetes (T2D) is essential for prevention. We evaluated a novel model-derived disposition index without insulin (mDI-woI), which requires only glucose values from a three time-point oral glucose tolerance test (OGTT: 0, 60, 120 min).

Methods: Among 5,742 healthy Koreans (age 51.2 ± 8.6 years, BMI 24.5 ± 3.1 kg/m^2) followed biennially for up to 14 years with repeated OGTTs, we compared baseline mDI-woI with current diabetes biomarkers and the oral disposition index (oDI) using AUC-ROC analyses.

Results: mDI-woI and mean OGTT glucose (mean G) showed the strongest prediction for incident T2D (AUC = 0.79 each), outperforming fasting plasma glucose (0.67), 1 h-PG (0.77), 2 h-PG (0.72), HbA1c (0.71), and oDI (0.68; all $P < 0.001$). In individuals who progressed to T2D, baseline mDI-woI, mean G, and 1-PG exceeded their thresholds while fasting and 2 h glucose were still below prediabetes cutoffs, indicating earlier risk detection. Moreover, the novel marker mDI-woI is the earliest one, 4 years earlier than mean G and 4.5 years earlier than 1 h-PG, the next two earliest.

Conclusions: Using only three glucose measurements without measuring insulin, mDI-woI provides a simple, sensitive, and clinically practical early marker that outperforms current diabetes criteria for predicting T2D progression, with strong potential for large-scale studies.

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1. Introduction

Prediabetes (PreDM) represents an intermediate state between normal glucose tolerance (NGT) and type 2 diabetes (T2D) defined using hemoglobin A1c, fasting plasma glucose (FPG) or two-hour plasma glucose (2 h-PG) levels during an oral glucose tolerance test (OGTT) [1]. In addition, the International Diabetes Federation (IDF) has endorsed the use of one-hour glucose (1 h-PG) as a diagnostic criterion of prediabetes and type 2 diabetes [2]. Current OGTT-based criteria rely on glucose measurements at a single time point, such as fasting or two-hour glucose (2 h-PG) and do not utilize all available data. Moreover, during the progression from NGT to prediabetes to diabetes, changes in these traditional biomarkers are modest, which makes it challenging to detect subtle changes that indicate disease progression [3]. Thus, an early marker that undergoes large, easily identified changes during the early stage of progression of prediabetes to diabetes is desirable. We describe such a marker in this paper.

We have previously introduced a mathematical model-derived disposition index (mDI)[4] that utilizes sparse data sampling points during an OGTT to estimate β-cell function relative to insulin resistance and does not require insulin measurements. When determined solely from glucose, it is referred to as mDI without insulin (mDI-woI) [4]. We showed in a previous cross-sectional study of ethnically diverse youth in the US that mDI-woI detected prediabetes better than an oral disposition index (oDI) and a clamp-derived disposition index (cDI)[4]. Furthermore, mDI-woI in that study changed more from NGT to PreDM than oDI or cDI, biomarkers of diabetes risk commonly used in clinical trials. This study extends our findings to validate mDI-woI in a large longitudinal data set in adults. In the present study, we evaluated the sensitivity and specificity of mDI-woI to predict progression to T2D from baseline measurements in a Korean population during a 14-year longitudinal study to determine: 1) the optimal cut-point of the novel marker mDI-woI by ROC analysis, 2) performance of mDI-woI as a predictor of T2D and prediabetes compared to standard diabetes risk markers (FPG, 1 h-PG, 2 h-PG, HbA1c) and oDI, and 3) if mDI-woI is a more sensitive or earlier marker than current diabetes criteria.

2. Subjects, materials and methods

2.1. Study population

Data sets of this study were obtained from the Ansung-Ansan Cohort study, which was part of the long-term Korean Genome Epidemiology Study (KoGES), conducted in Korean urban and rural communities. The study population comprises two Korean regional cohorts, Ansung (representing an urban community, N = 5,018) and Ansan (representing a rural community, N = 5,012). KoGES includes longitudinal data, which investigate the risk of major chronic diseases such as T2D, hypertension, and cardiovascular disease. The data were obtained by biannual surveys and biochemical examinations from 2001 to 2002 to 2017–2018. All eligible individuals were between 40–69 years of age at baseline. The cohort underwent a baseline health examination at the Ajou University Medical Center and the Korea University Ansan Hospital from June 2001 to January 2003[5,6]. The Ansan–Ansung study protocol was approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention, and all patients provided written informed consent. The study protocol was approved by the Institutional Review Board of Pusan National University (South Korea) (IRB No. 2101–007-099).

Of 10,030 participants derived from KoGES, we included people with NGT or PreDM at baseline who were observed longitudinally for 14 years. The following data (n = 3,882) were excluded: (1) people without follow-up data, or who had missing OGTT glucose or insulin values (n = 3,355), (2) people with comorbidities including malignancy, diseases or medications affecting glucose levels (n = 513), (3) T2D at baseline (n = 406). In total 5,742 persons (3,111 with NGT and 2631 with PreDM) were eligible for longitudinal analysis. During the 3rd to 8th follow-up periods (year 4 to year 14), 1,279 participants progressed to T2D (Supplementary Fig. 1). To assess which markers rise earliest and quantify longitudinal changes of markers of participants, a subset of 215 participants who progressed from NGT at baseline to PreDM and T2D and underwent at least three OGTTs was selected.

2.2. Anthropometric and biochemical measurements

Participants answered a self-administered questionnaire including medical history and sociodemographic information. Laboratory measurements, such as FPG, fasting insulin, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and HbA_{1c} were measured in a central laboratory after an overnight fast of at least 8 hours. At the baseline and all biennial visits, plasma glucose and insulin concentrations during a 75 g OGTT were obtained at 0 min, 60 min, and 120 min. Plasma glucose, TG, total cholesterol and HDL cholesterol were measured by Automatic Chemistry Analyzer (Hitachi 7600; Hitachi, Tokyo, Japan). HbA1c levels were measured by high-performance liquid chromatography (Variant II; BioRad Laboratories, Hercules, CA, USA). Plasma insulin concentrations were measured by radioimmunoassay (LINCO kit, St Charles, MO, USA)[7]. Serum LDL concentrations were calculated with the Friedewald formula: serum total cholesterol – serum HDL – serum TG/5[8].

2.3. Outcomes and definitions of PreDM and T2D

The main outcome assessed was the development of T2D or PreDM evaluated at study years 4, 6, 8, 10, 12, and 14. PreDM was diagnosed if participants met at least one of the following criteria: (1) $100 \leq \text{FPG} < 126$ mg/dL ($5.6 \leq \text{FPG} < 7.0$ mmol/L); (2) $5.7\% \leq \text{HbA1c} < 6.5\%$ (48 mmol/mol); (3) $140 \leq 2\text{ h-PG} < 200$ mg/dL ($7.8 \leq 2\text{ h-PG} < 11.1$ mmol/L). T2D was defined as: (1) FPG $\geq$ 126 mg/dL (7.0 mmol/L) or (2) HbA1c $\geq$ 6.5% (48 mmol/mol) or (3) 2 h-PG $\geq$ 200 mg/dL (11.1 mmol/L) or (4) current treatment with insulin, oral antidiabetic drugs, or injectable GLP-1 agonists or (5) clinical diagnosis of T2D. Individuals who did not meet any of these conditions were classified as having non-diabetes.

2.4. OGTT-derived calculations

Glucose area under the curve (G-AUC) and insulin area under the curve (I-AUC) were calculated by the trapezoidal method[9]. OGTT-derived oDI was calculated using the product of the Matsuda insulin sensitivity index (ISI) 10,000/sqrt ($G0 \times I0 \times mG \times mI$),[10] and the 60-min insulinogenic index (IGI), calculated as (plasma insulin at 60 min – plasma insulin at 0 min)/ (plasma glucose at 60 min – plasma glucose at 0 min)[11]. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as 405/(fasting insulin (μU/ml) × fasting glucose (mg/dL), and homeostasis model assessment of β-cell function (HOMA-β) was calculated as 360 × fasting insulin (μU/ml)/(fasting glucose (mg/dL) – 63) [12].

2.5. Mathematical model-derived parameters

The Insulin Sensitivity and Secretion (ISS) model was fitted to OGTT glucose from each biennial OGTT using Matlab (v.9.5.0 (R2021b), Natick, MA: The MathWorks Inc) to estimate insulin sensitivity mSI and β-cell function (mBCF). The product of mSI and mBCF gives the disposition index, mDI-woI, as described in [13]. Matlab code and instructions for its use are available at https://doi.org/10.6084/m9.figshare.25326055.

In brief, the core of the model consists of two differential equations. The first is for glucose balance,

$$\frac{dG}{dt} = OGTT(t) + HGP(mS_I, I) - (E_{GO} + mS_I I)G. \quad (1)$$

$OGTT(t)$ is the influx rate of glucose, G, during the OGTT. $HGP(mS_I, I)$ is the rate of hepatic glucose production, which depends on the insulin concentration I and insulin sensitivity, mS_I. Glucose uptake has an insulin-dependent component, $mS_I IG$, and an insulin-independent component, $E_{G0}G$. This equation is closely related to the glucose equation in the Minimal Model [14] , with modifications introduced by Topp et al [15].

The second equation is for insulin balance,

$$\frac{dI}{dt} = \frac{\beta}{V} ISR(\sigma, G) - kI. \quad (2)$$

The rate of change of insulin, I, is the net of insulin secretion rate ISR, which depends on beta-cell mass, β, BCF, represented by the parameter σ, glucose and the volume of distribution, V, and insulin clearance kI.

As described in [13], the glucose data from the OGTTs is fitted to Eq. (1), to yield estimates for mS_I and σ, which are multiplied to give mDI-woI. Because insulin is not fitted to Eq. (2), the estimates for mS_I and σ are not meaningful, but the product is a good estimate of the disposition index. In [13], it was shown that mDI-woI is a better cross-sectional marker for PreDM and T2D than other commonly used disposition indices derived from OGTTs as well as a disposition index derived from glucose and insulin clamps. Here we evaluated the performance of mDI-woI at baseline in predicting T2D during the longitudinal KoGES study.

It was further shown that mDI-woI is logarithmically related to mean glucose during the OGTT, which captures the fact that the percentage change is greater during the transition from NGT to PreDM compared to the percentage change of mean glucose. Here, we relate this feature to the timing of when markers cross their thresholds.

2.6. Statistical analysis

Data are presented as number (%), mean (SD) or median [interquartile ranges] as appropriate. Between-group comparisons were made by the Wilcoxon rank-sum or chi-squared tests. We compared the performance of FPG, 2 h-PG, HbA1c, and oDI to mDI-woI to predict T2D using area under the receiver operating characteristic (AUC-ROC). ROC curves were compared using the method by DeLong et al [16]. The optimal cutoff value was obtained as the maximum Youden index using R (http://cran.r-project.org) version 4.0.5 and additional packages (pROC, plotROC, ggplot2, tableone). A linear mixed effect model was used to estimate time at baseline since thresholds were passed and compare the trajectories followed by individuals to the group average. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of study participants

Baseline characteristics of all participants are shown in Table 1. Among the 5,742 participants, 22.3% (N = 1,279) developed T2D during the 3rd to 8th follow-up period (year 4 to year 14). The average time to develop diabetes was 11.5 (3.7) years. The follow-up duration and the number of follow-ups were 12.6 (2.9) years and 6.0 (1.5), respectively. The OGTT intervals were 2.7 (0.7) years.

3.2. mDI-woI and mean G best predict progression to T2D

The AUC-ROC of mDI-woI and mean G (0.79) were higher compared to FPG, 1 h-PG, 2 h-PG, HbA1c, and oDI, $P < 0.001$ (Fig. 1). The AUC-ROC for mDI-woI was not different from mean G ($P = 0.6$). Thus, based on AUC-ROC, mDI-woI and mean G were both better predictors of T2D than the current measures, FPG, 1 h-PG, 2 h-PG, and HbA1c. The AUC-ROC of 1 h-PG was almost the same as those of mDI-woI and mean G (0.77). The ROC curve for mDI with insulin (not shown) was almost identical to that of mDI-woI.

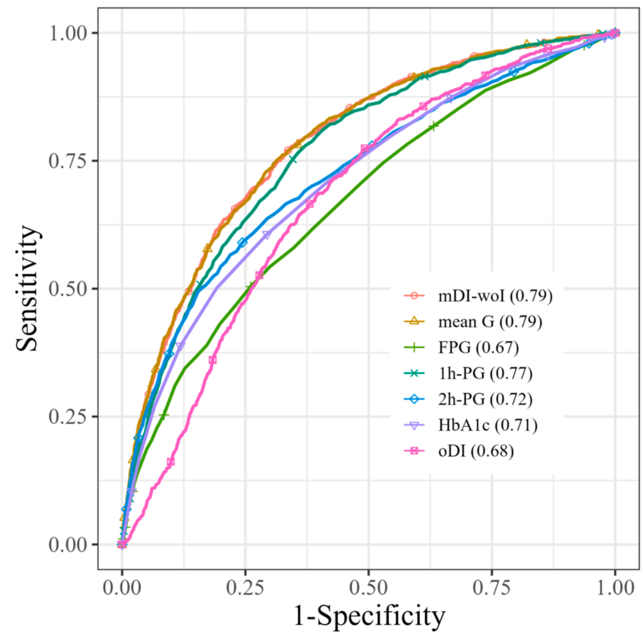

Fig. 1. ROC analysis of baseline metabolic markers for predicting the risk of progression to T2D (N = 5,742 individuals without diabetes at baseline). AUC-ROC values: mDI-woI (0.79), mean G (0.79), FPG (0.67), 1 h-PG (0.77), 2 h-PG (0.72), HbA1c (0.71), and oDI (0.68). mDI-woI and mean G best predicted future T2D, $P < 0.001$ for all markers vs mDI-woI; mDI-woI vs. mean G, $P = 0.6$.

The optimal baseline cut point (Youden index) of mDI-woI was 1.59 for predicting diabetes. Participant characteristics stratified by Youden index are given in Table 1. See Supplementary Table S1 for the AUC confidence intervals, cut-points, sensitivity and specificity of the markers. Participants above the cut point had significantly lower FPG, 1 h-PG, 2 h-PG, HbA1c, and HOMA-IR than participants below the cut point (Table 1). The high mDI-woI group was also younger and had lower waist circumference, BMI, LDL, HDL, TG, and total cholesterol concentrations ($P < 0.001$). oDI was higher in the high mDI-woI group.

3.3. mDI-woI detects small changes in glucose

Fig. 2 shows the population medians of mean OGTT glucose, FPG, 1 h-PG, 2 h-PG and HbA1c at each follow-up visit vs. mDI-woI for progressors to T2D, progressors to preDM, and non-progressors. The shaded regions show the distributions of the data for each marker for all the participants over the entire study. It is striking that the mean G values are clustered more closely around the mean values than those of the standard diabetes risk markers. As we will show later (Sup. Fig. S3), the individuals in each sub-group closely follow the same trajectory as the group medians over time.

In Fig. 2B – E, the horizontal lines represent the current diagnostic thresholds for PreDM for FPG, 1 h-PG, 2 h-PG and HbA1c, respectively. The horizontal and vertical lines for mean G and mDI-woI, which do not have established diagnostic thresholds, represent the cut point values estimated from the ROC analysis (Fig. 1, Sup. Table S1). We can view these as provisional diagnostic cut points for further study.

To illustrate the sensitivity of mDI-woI to changes in glycemia, a subset of participants (N = 215) who progressed from NGT at baseline to PreDM and T2D was analyzed. Each individual's trajectory was tracked, and the percentage changes of each of the markers from NGT to PreDM and from NGT to T2D were estimated. As shown in Fig. 3A, the median percentage changes of mDI-woI, mean G, FPG, 1 h-PG, 2 h-PG, HbA1c, and oDI from NGT to PreDM at baseline were 73%, 26%, 16%, 26.5%,

Table 1
Baseline characteristics of study subjects (N = 5,742).

Characteristics	mDI without Insulin			*P* value
	Overall (5,742)	Low (≤ 1.59) (2,476)	High (> 1.59) (3,266)	
Diabetes status				<0.001
NGT	3,111 (54.2)	749 (30.4)	2,362 (72.2)	
PreDM	2,631 (45.8)	1,723 (69.6)	908 (27.8)	
Age, years	51.2 (8.6)	52.0 (8.7)	50.5 (8.4)	<0.001
Sex				0.011
Male	2,849 (49.6)	1,274 (51.6)	1,575 (48.1)	
BMI, kg/m^2	24.5 (3.1)	24.9 (3.1)	24.1 (2.9)	<0.001
Waist circumference, cm	82.1 (8.6)	83.5 (8.8)	81.1 (8.4)	<0.001
SBP	115.9 (17.2)	118.2 (17.4)	114.1 (16.7)	<0.001
DBP	74.6 (11.2)	75.9 (11.2)	75.6 (11.1)	<0.001
Laboratory findings				
HbA1c, %	5.5 (0.3)	5.6 (0.4)	5.5 (0.3)	<0.001
Creatinine, mg/dL	0.8 (0.2)	0.9 (0.2)	0.8 (0.2)	<0.001
Total cholesterol, mg/dL	189.5 (33.9)	195.3 (34.4)	185.1 (32.8)	<0.001
LDL, mg/dL	115.7 (32.0)	118.4 (33.2)	113.7 (31.0)	<0.001
HDL, mg/dL	44.9 (9.9)	45.2 (10.3)	44.7 (9.6)	0.083
TG, mg/dL	144.6 (100.2)	158.7 (109.1)	133.9 (91.5)	<0.001
OGTT measures				
Glucose (0-min), mg/dL	82.8 (8.5)	86.3 (9.2)	80.2 (6.8)	<0.001
Glucose (60-min), mg/dL	140.5 (39.5)	174.6 (28.2)	114.7 (24.3)	<0.001
Glucose (120-min), mg/dL	113.2 (29.5)	135.4 (25.9)	96.3 (19.2)	<0.001
Insulin (0 min), mU/mL	7.5 (4.6)	7.7 (4.8)	7.4 (4.4)	0.012
Insulin (60 min), mU/mL	32.9 (31.9)	37.1 (34.1)	29.7 (29.8)	<0.001
Insulin (120 min), mU/mL	28.1 (26.9)	36.1 (32.7)	22.0 (19.4)	<0.001
Follow-up duration, years	12.6 (2.9)	12.6 (2.9)	12.7 (2.9)	0.246
Number of follow-ups	6.0 (1.5)	6.0 (1.5)	6.0 (1.5)	0.417
OGTT interval, years	2.7 (0.7)	2.8 (0.7)	2.7 (0.7)	0.263
HOMA-IR	1.5 (1.0)	1.7 (1.0)	1.5 (0.9)	<0.001
HOMA-β	164.9 (156.0)	139.2 (121.0)	184.3 (175.5)	<0.001
oDI	3.5 [1.8, 7.0]	2.3 [1.3, 3.5]	5.9 [3.2, 10.6]	<0.001
mDI-woI, 1/μU/ml/min	2.5 (2.0)	0.8 (0.4)	3.8 (1.7)	<0.001

Variables are showed as number (%), mean (SD) or median [interquartile ranges]. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; LDL, low density lipoprotein; HDL, high density lipoprotein; Triglyceride, TG; HOMA-IR, homeostatic Model Assessment for Insulin Resistance; HOMA-β, homeostatic Model Assessment for beta cell function; oDI, oral disposition index; mDI-woI, model disposition index without insulin; NGT, normal glucose tolerance; PDM, prediabetes; OGTT, oral glucose tolerance test.

37%, 1.8%, and 44%, respectively (All $P < 0.001$ vs mDI-woI). The change in mDI-woI was by far the largest. Thus, mDI-woI, by this measure, was the most sensitive to early changes in glycemia.

The percentage changes of the six markers from NGT to T2D were larger, with values for the six markers 91%, 54%, 22%, 49%, 88%, 7.5%, and 68%, respectively, as shown in Fig. 3B. The change for mDI-woI was again the largest but more similar to the other markers.

3.4. mDI-woI is an earlier marker of T2D risk than the standard PreDM markers and 1 h-PG

Fig. 2 also shows that mDI-woI, mean G, and 1 h-PG are earlier markers of T2D risk than the standard PreDM markers. The baseline values of mDI-woI and mean G of progressors to T2D were already past the cut points determined by the ROC analysis of Figs. 1, and 1h-PG was past its IDF prediabetes cut point. In contrast, the baseline values of FPG (Fig. 2B) and 2 h-PG (Fig. 2D) for the progressors to T2D were below their diagnostic cut points (the horizontal lines) for PreDM. The baseline value of HbA1c was slightly above its diagnostic cut point at baseline but then dipped below it at year 4, so this case is ambiguous (Fig. 2E).

To assess how long before baseline mDI-woI, mean G, and 1 h-PG had crossed their cut points, a subset of the population (n = 215) who progressed from NGT to PreDM and T2D, was analyzed by a linear mixed effect model (LME), where each individual's trajectory was tracked, and the time of passing the threshold of markers was estimated in Sup. Fig. S2. Thus, times at baseline since thresholds were passed are shown in Fig. 4. The three earlier markers showed positive values, meaning that the markers had already passed their thresholds, while FPG, 2 h-PG, and HbA1c had not passed their thresholds yet in Fig. 4. Importantly, the novel marker mDI-woI is the earliest one, 4 years earlier than mean G and 4.5 years earlier than 1 h-PG, the next two earliest. Baseline characteristics and follow-up information for the subset of the population (n = 215) were presented in Sup. Table S2, indicating no major differences compared with the overall population.

3.5. Individuals follow the same trajectories as the group

Sup. Fig. S3A shows the trajectories of sub-groups in the mDI-mean G plane, but we can go further and describe the trajectories of individuals. To track individual trajectories, we applied a linear mixed effect model (LME) to log(mDI-woI) vs. mean G, then transformed back to mDI-woI and mean G. Four participants were randomly selected to show the population and individual mixed model fitted curves in Sup. Fig. S3A. In each case, the curves overlapped visually, and the confidence intervals (see legend) confirm that the population and individual regression lines statistically coincide. Sup. Fig. S3B shows the strong correlation between the individual values and the LME fit of mDI-woI vs. mean G at baseline ($R = 0.98$, $P < 0.001$). The corresponding fits at all follow-up times showed the same strong correlations and again overlapped visually (not shown). The population curve in Sup. Fig. S3A that was longitudinally fitted and the baseline fitted curve in Sup. Fig. S3B are overlaid in Sup. Fig. S3C and coincide. Taken together, these figures show that all individuals followed nearly identical trajectories when mean G was plotted vs mDI-woI. Individuals differed only in where they started at baseline and how far they progressed during the study. In contrast, oDI does not have this property (Sup. Fig. S4).

4. Discussion

We have longitudinally validated mDI-woI, a recently introduced disposition index[4], as a robust biomarker to predict future T2D. The baseline measurement of mDI-woI outperformed baseline measurements of the standard diabetes risk markers, FPG, 1 h-PG, 2 h-PG and HbA1c, in predicting diabetes. The mDI-woI index also demonstrated superior predictive ability compared to oDI, another disposition index derived from OGTT. Importantly, mDI-woI required glucose at only three time points, 0, 60, and 120 min, during OGTTs and did not require insulin. We suggest 1.59 (1/IU/ml/min) as a threshold for mDI-woI as a novel marker to predict T2D in Koreans. Longitudinal studies are called for to test the generalizability of this cut point in other populations.

4.1. A readily discernible marker

The gradual, insidious increase in FPG, 1 h-PG, 2 h-PG, mean G, and

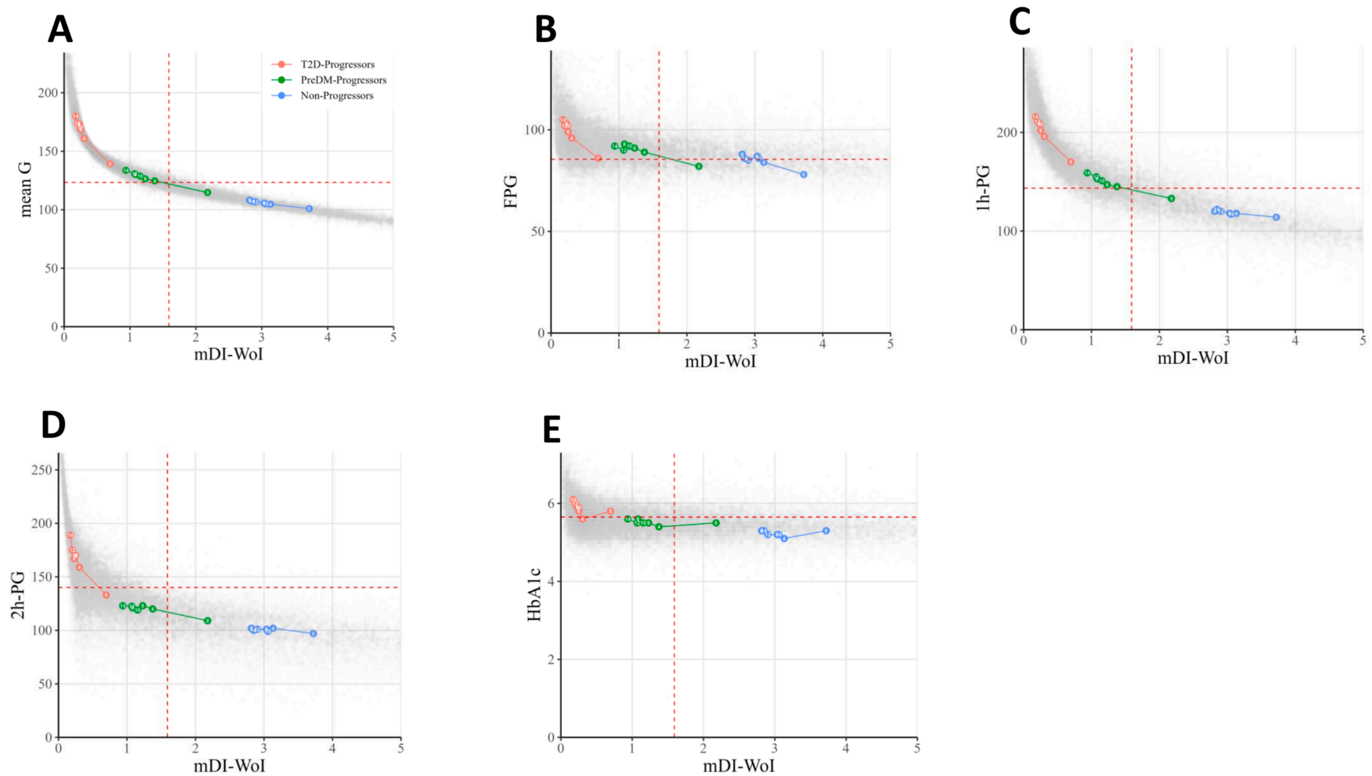

Fig. 2. Sensitivity of mDI-woI to small, early changes in glycemia. Median values of metabolic markers are plotted vs. mDI-woI in progressors to T2D (red), progressors to PreDM (green), and non-progressors (blue) at each follow-up visit. The right most dot of each group is for baseline, and the subsequent dots move up and to the left. The shaded regions show distributions of data over the entire study. (A) mean G vs. mDI-woI; The vertical and horizontal dashed lines represent the cut points of mDI-woI and mean G from the ROC analysis of Fig. 1. (B – E): the horizontal dashed lines represent the diagnostic cut points for pre-diabetes of each marker. Only mDI-woI and mean G are beyond their cut points for progressors to T2D at baseline.

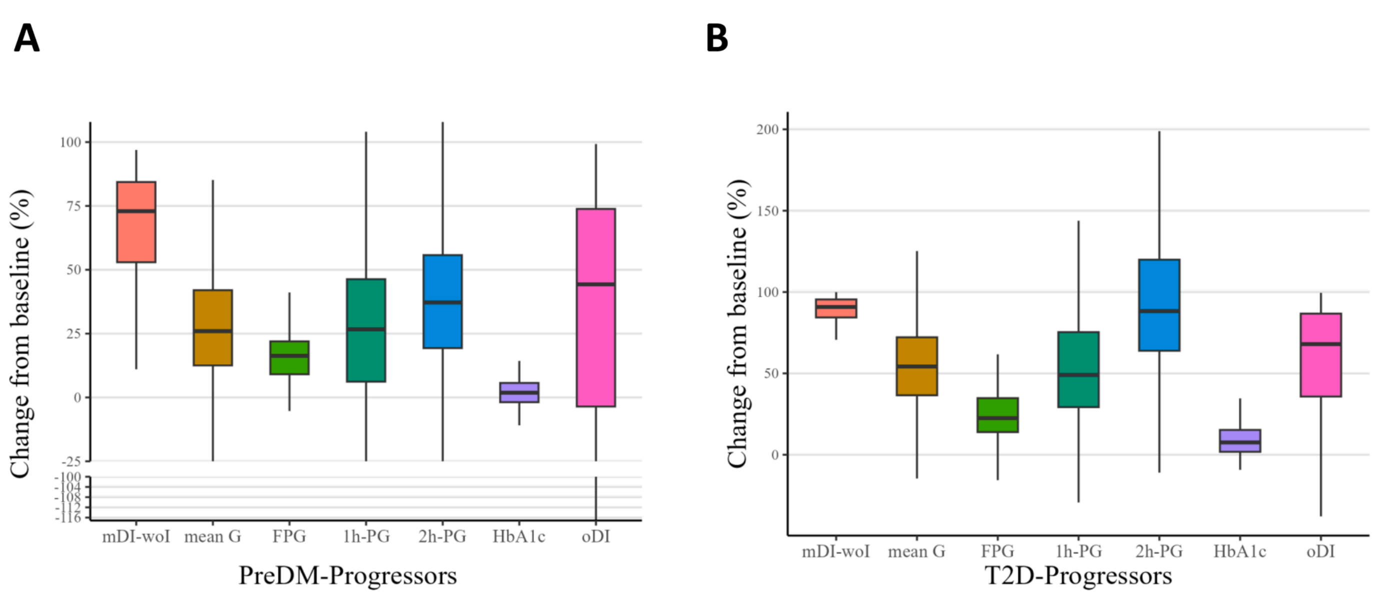

Fig. 3. Percentage changes of 6 metabolic markers from NGT to PDM and from NGT to T2D. (A) The median percentage changes of mDI-woI, mean G, FPG, 1 h-PG, 2 h-PG, HbA1c, oDI from NGT to PreDM were 73%, 26%, 16%, 26.5%, 37%, 1.8%, and 44%, respectively. (B) The percentage changes of HbA1c, FPG, mean G, 1 h-PG, 2 h-PG, oDI, mDI-woI from NGT to T2D were 91%, 54%, 22%, 49%, 88%, 7.5%, and 68%, respectively. mDI-woI changed the most in both panels.

HbA1c during the transition from NGT to dysglycemia can lead to missing the optimal time point for intervention to prevent progression to T2D. Thus, a good marker requires discernible and early change in glycemia before disease progression.

We propose mDI-woI as an ideal candidate to fill this unmet need in epidemiological studies. The changes in mDI-woI were large and evident, with a decrease from baseline to PreDM in those who progressed to T2D of 73%, much larger than the changes in the standard markers (Fig. 3). Mean G, highly correlated with mDI-woI, had equivalent performance to mDI-woI by AUC-ROC but changed much less than

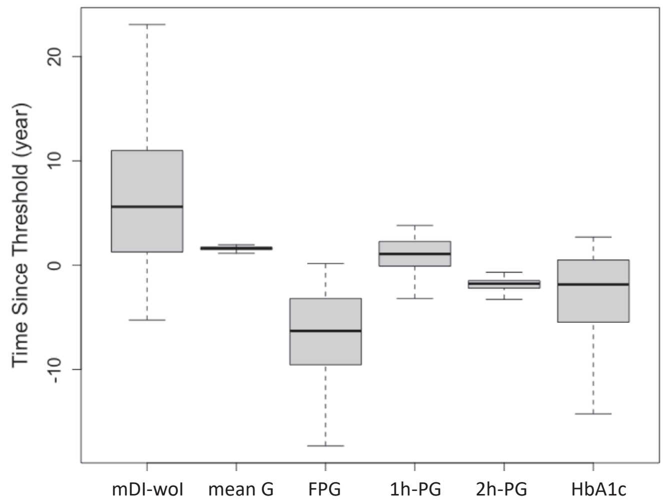

Fig. 4. Times since thresholds were passed. The median times (IQR) of mDI-woI, mean G, FPG, 1 h-PG, 2 h-PG, HbA1c after the thresholds were passed in Supplemental Fig. 2 were 5.6 years (9.7), 1.6 years (0.2), −6.3 years (6.3), 1.0 year (2.3), −1.8 years (0.7), and −1.8 years (6.0), respectively. Respective thresholds are 1.59, 123.3 mg/dl/min, 100 mg/dl, 155 mg/dl, 140 mg/dl, 5.7%.

mDI-woI from baseline to PreDM.

4.2. An early marker

We also found mDI-woI to be an early marker for identifying risk of progression to T2D. At baseline, persons who progressed to T2D were already past (below) its cut point at baseline. PreDM has been defined to serve as an early sign of risk for progression to T2D. However, we found that the baseline values of FPG and 2 h-PG for progressors to T2D were below their PreDM cut points, indicating that the current PreDM criteria are late predictors of T2D. HbA1c was initially slightly above its PreDM threshold but then went below and did not go back above it until six years into the study. Mean G and 1h-PG were also past (above) their cut points at baseline in progressors, suggesting that the two markers also are earlier than FPG and 2 h-PG. For further validation, the direct estimation of time since thresholds passed also showed that mDI-woI, mean G, and 1 h-PG are earlier markers and mDI-woI is the earliest, 4-year and 4.5-year earlier than mean G and 1 h-PG, respectively in Fig. 4 and Sup. Fig. S2.

In contrast, the changes from baseline in T2D progressors of 2 h-PG and mDI-woI were comparable (Fig. 3). However, the large change in 2 h-PG occured too late to signal T2D risk. The large decrease in mDI-woI between NGT and PreDM makes it a preferable marker for T2D risk assessment and early intervention. When mDI-woI is low (for example, < 0.5), small further decreases result in large increases in glycemia, as shown by the sharp upturns in the plots of all measures of glycemia vs. mDI-woI in Fig. 2. Therefore, interventions should be initiated when mDI is close to its cut point of 1.59 and can pick up small changes in glycemia.

4.3. mDI-woI is superior to oDI

The desirable properties of mDI-woI we have highlighted so far stem from its physiology as a disposition index that captures decreases in insulin sensitivity and β-cell function before these become manifest as large increases in glycemia. The other disposition index we considered, oDI, also has this property, but it had worse performance in the ROC analysis. Although oDI exhibited larger changes from baseline than FPG and 2 h-PG during progression to PreDM, they were not as large as those of mDI-woI. In addition, mDI-woI has the unique advantage (over all disposition indices) that it requires only glucose measurements.

4.4. 1 h-PG is superior to FPG, 2 h-PG, and HbA1c

As a recently published work showed the superiority of detection of 1 h-PG to all current criteria with diverse ethnic groups [17], the current study investigated whether the outperformance is valid in a longitudinal study. The predictive power of 1 h-PG is close to mDI-woI (ROC AUC 0.77 vs. 0.79) and higher than FPG, 2 h-PG and HbA1c in this cohort. Furthermore, 1 h-PG is an earlier marker than FPG, 2 h-PG, and HbA1c, as we previously showed in this cohort [18]. Thus, of all the markers considered that require only a single measurement, 1 h-PG is the best and earliest. Importantly, we also here conjecture why 1 h-PG outperforms 2 h-PG: it is more closely correlated with mean glucose than 2 h-PG (Sup. Fig. S5), and, because mean glucose is logarithmically related to mDI-woI, 1 h-PG is more closely related to a disposition index.

4.5. A universal path to PreDM and T2D

Another fundamental and striking feature of mDI-woI is that the curve of mean G vs mDI is the same for all participants. We showed this by fitting LME regression curves for the individual longitudinal and population cross-sectional trajectories, which very nearly overlapped. This extends our previous finding that the cross-sectional curves were nearly identical for three diverse ethnic groups[4]. Moreover, a mathematical analysis in that study of the model showed that the mean G vs. mDI curve is universal. This does not hold for oDI (Sup. Fig. S4), which is an ad hoc, albeit reasonable, algebraic combination of the data values, not a quantity derived from a mathematical model that integrates the physiology of glucose homeostasis.

5. Strengths and Limitations

We had access to data on thousands of participants from a relatively homogeneous population, who were systematically followed up over a long period of time, and a substantial percentage of whom developed T2D during the study. A limitation is that a single OGTT was used so mDI-woI and further studies of reproducibility and reliability with diverse populations are needed to determine if mDI-woI is suitable for use in clinical practice. Despite a mean cohort BMI of 24.5, some individuals met the criteria for overweight. The current study used only three glucose measurements, and a future study may require five standard measurements to avoid potential biases. However, mDI-woI uses all data points during the OGTT, which reduces variability and is expected to increase its reproducibility.

5.1. Conclusion

In conclusion, the novel disposition index calculated by the mathematical model (mDI-woI) predicts progression to T2D better than current pre-diabetes criteria and oDI. mDI-woI requires only three glucose data points and does not need insulin measurements, rendering it suitable for large-scale epidemiological studies.

Author Contributions

S.R., J.K., A.S., S.S.K., and J.H. designed the study. S.S.K., J.K., A.S., and J.H. contributed to the specification of the analyses data. S.R., J.K., M.K., M.I., D.K., Y.J.K., H.K., Y.J.K., I.J.K., S.T.C., M.B., A.S., S.S.K., and J.H. contributed to interpretation of data. S.R., S.S.K., and J.H. wrote the initial draft of manuscript. S.R., J.K., M.B., A.S., S.T.C., S.S.K. and J.H. contributed with a critical revision of the first and subsequent manuscript versions. S.R., J.M., M.K., M.I., D.K., Y.J.K., H.K., Y.J.K., I.J.K., S. T.C., M.B., A.S., S.S.K., and J.H. approved the final manuscript. S.S.K., and J.H. are guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CRediT authorship contribution statement

Soree Ryang: Writing – original draft, Resources, Investigation, Formal analysis. **Jinmi Kim:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation. **Minsoo Kim:** Resources, Formal analysis, Data curation. **Myungsoo Im:** Formal analysis, Data curation. **Doohwa Kim:** Formal analysis, Data curation. **Yeong Jin Kim:** Software, Resources, Formal analysis, Data curation. **Hyuk Kang:** Formal analysis, Data curation. **Young Jin Kim:** Software, Resources, Formal analysis, Data curation. **In Joo Kim:** Formal analysis, Data curation. **Stephane T. Chung:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Michael Bergman:** Writing – review & editing, Formal analysis, Data curation. **Arthur Sherman:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Sang Soo Kim:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation. **Joon Ha:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2026.113131.

References

[1] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. Diabetes Care 2023;46:S19–40.
[2] Bergman M, Manco M, Satman I, Chan J, Schmidt MI, Sesti G, et al. International Diabetes Federation Position Statement on the 1-hour post-load plasma glucose for the diagnosis of intermediate hyperglycaemia and type 2 diabetes. Diabetes Res Clin Pract 2024;209:111589.
[3] Golden SH, Yajnik C, Phatak S, Hanson RL, Knowler WC. Racial/ethnic differences in the burden of type 2 diabetes over the life course: a focus on the USA and India. Diabetologia 2019;62:1751–60.
[4] Ha J, Kim JY, Springer M, Chhabra A, Chung ST, Sumner AE, et al. A Mathematical Model-Derived Disposition Index without Insulin Validated in Youth with Obesity. J Clin Endocrinol Metab 2024.
[5] Kim Y, Han BG. Cohort Profile: the Korean Genome and Epidemiology Study (KoGES) Consortium. Int J Epidemiol 2017;46:1350.
[6] Ohn JH, Kwak SH, Cho YM, Lim S, Jang HC, Park KS, et al. 10-year trajectory of β-cell function and insulin sensitivity in the development of type 2 diabetes: a community-based prospective cohort study. Lancet Diabetes Endocrinol 2016;4:27–34.
[7] Lee HA, An H, Lee E. Dietary patterns related to cardiovascular disease based on reduced rank regression analysis of healthy middle-aged Koreans: data from the community-based Korean Genome and Epidemiology Study (KoGES) cohort. Am J Clin Nutr 2020;111:1159–69.
[8] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
[9] Allison DB, Paultre F, Maggio C, Mezzitis N, Pi-Sunyer FX. The use of areas under curves in diabetes research. Diabetes Care 1995;18:245–50.
[10] Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–70.
[11] Seltzer HS, Allen EW, Herron Jr AL, Brennan MT. Insulin secretion in response to glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus. J Clin Invest 1967;46:323–35.
[12] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
[13] Ha J, Kim JY, Springer M, Chhabra A, Chung ST, Sumner AE, et al. A Mathematical Model-Derived Disposition Index without Insulin Validated in Youth with Obesity. J Clin Endocrinol Metab 2025;110:706–14.
[14] Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. Am J Phys Anthropol 1979;236:E667–77.
[15] Topp B, Promislow K, deVries G, Miura RM, Finegood DT. A model of beta-cell mass, insulin, and glucose kinetics: pathways to diabetes. J Theor Biol 2000;206:605–19.
[16] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.
[17] Wang Y, Ram J, Bianchi C, Fiorentino TV, Kim SS, Kim J, et al. Superiority of 1 h plasma glucose vs fasting plasma glucose, 2 h plasma glucose and HbA(1c) for the diagnosis of type 2 diabetes. Diabetologia 2025.
[18] Im M, Kim J, Ryang S, Kim D, Yi W, Mi Kim J, et al. High one-hour plasma glucose is an intermediate risk state and an early predictor of type 2 diabetes in a longitudinal Korean cohort. Diabetes Res Clin Pract 2025;219:111938.