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Predictive Value of Glucose Parameters Obtained From Oral Glucose Tolerance Tests in Identifying Individuals at High Risk for the Development of Diabetes in Korean Population

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Abstract: Previous studies suggest that the future risk for type 2 diabetes is not similar among subjects in the same glucose tolerance category. In this study, we aimed to evaluate simple intuitive indices to identify subjects at high risk for future diabetes development by using 0, 30, 120 minute glucose levels obtained during 75 g OGTTs from participants of a prospective community-based cohort in Korea.

Among subjects enrolled at the Chungju Metabolic disease Cohort, those who performed an OGTT between 2007 and 2010 and repeated the test between 2011 and 2014 were recruited after excluding subjects with diabetes at baseline. Subjects were categorized according to their 30 minute glucose (G_{30}) and the difference between 120 and 0 minute glucose ($G_{(120-0)}$) levels with cutoffs of 9.75 and 2.50 mmol/L, respectively.

Among 1126 subjects, 117 (10.39%) developed type 2 diabetes after 4 years. In diabetes nonconverters, increased insulin resistance was accompanied by compensatory insulin secretion, but this was not observed in converters during 4 years of follow-up. Subjects with $G_{(120-0)} \geq 2.50$ mmol/L or $G_{30} \geq 9.75$ mmol/L demonstrated lower degrees of insulin secretion, higher degrees of insulin resistance, and ~6-fold higher risk of developing future diabetes compared to their lower counterparts after adjustment for possible confounding factors. Moreover, subjects with high $G_{(120-0)}$ and high G_{30} demonstrated 22-fold higher risk for diabetes development compared to subjects with low $G_{(120-0)}$ and low G_{30}.

By using the $G_{(120-0)}$ and G_{30} values obtained during the OGTT, which are less complicated measurements than previously reported methods, we were able to select individuals at risk for future diabetes development. Further studies in different ethnicities are required to validate our results.

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Abbreviations: AUC = area under-the-curve, BMI = body mass index, BP = blood pressure, CGI = combined glucose intolerance, CMC = Chungju Metabolic disease Cohort, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HOMA-IR = homeostasis model assessment estimate of insulin resistance, HOMA-ß = homeostasis model assessment estimate of ß-cell function, hs-CRP = high-sensitivity C-reactive protein, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, MDRD equation = modification of diet in renal disease equation, NGT = normal glucose tolerance, OGTT = oral glucose tolerance test, PG = plasma glucose, ROC = receiver operating characteristic.

INTRODUCTION

Along with the increasing prevalence of diabetes,[1] the mean fasting plasma glucose level has been rising globally by 0.07 mmol/L per decade over the past 30 years.[2] This emphasizes the importance of preventive intervention and detecting individuals at risk for future diabetes.[3] Subjects with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) have an increased risk for type 2 diabetes, with a conversion rate of 5% to 10% per year.[4–6] Although more than half of the subjects who develop type 2 diabetes have IGT or IFG at baseline,[7] prospective epidemiologic studies have demonstrated that ~40% of subjects have normal glucose tolerance (NGT) at baseline.[4,6,8] Among individuals with IGT, only 35% to 50% convert to type 2 diabetes after 10 to 20 years of follow-up.[9] These observations suggest that the future risk for type 2

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diabetes is not similar among subjects in the same glucose tolerance category. Therefore, other than fasting plasma glucose (FPG) and 2-hour postprandial glucose (PG), additional information might help us identify a group of subjects who might benefit from early lifestyle intervention.

A number of models have been proposed to evaluate high-risk subjects based on the risk factors for diabetes, such as age, ethnicity, obesity, lipid profile, blood pressure, and FPG levels.[10–12] Several recent studies have used the shape of the glucose or insulin curve[13–15] or 60 minute glucose[16–18] during an oral glucose tolerance test (OGTT) to identify the potential risk for future diabetes. Tura et al[19] developed a novel index, the WHole-Ogtt-SHape index using 9 time-point measurements during a 3-hour OGTT as an index of β-cell function. Many of these previous indices require risk score calculations, insulin or C-peptide measurements, or complicated equation to identify subjects at high risk for diabetes development.

In this study, we aimed to evaluate simple intuitive indices to identify subjects at high risk for future diabetes development by using 0, 30, and 120 minute glucose levels obtained during 75 g OGTTs from participants of a prospective community-based cohort in Korea.

METHODS

Subjects and Methods

The Chungju Metabolic disease Cohort (CMC) study is a community-based study, which includes participants aged ≥ 40 years who are living in the rural area of Chungju City, Korea (ClinicalTrials.gov ID NCT00707668).[20] The baseline study was performed in 2003 to 2006, and enrolled 11,718 participants from 334 districts selected by stratified random cluster sampling. The subjects were followed-up at 4-year intervals in the second (2007–2010) and the third (2011–2014) phases of the study. During the earlier period of the second phase of the study, OGTT was performed if the FPG level was > 5.6 mmol/L. However, after September 2009, every subject underwent an OGTT, regardless of the FPG level. Subjects who performed a 75 g OGTT in the second phase (baseline) and repeated OGTT in the third phase (follow up) were included in this study. Participants who are lacking data, and those with previously or newly diagnosed diabetes at baseline were excluded. Written informed consents were obtained from all participants. This study was approved by the institutional review board of the Catholic University of Korea (No. KCMC070T076, KC14SISI0335).

Study Protocol

Well-trained interviewers obtained the information on medical histories and lifestyle behaviors of enrolled participants. Weight, height, and waist circumference were measured according to the standardized methods. Blood pressure (BP) was measured after taking a 5-minute rest in a sitting position. The BP was measured twice in each participant and the average values were recorded. Hypertension was defined according to the history of taking antihypertensive medication or according to the Joint National Committee 7 report as $\geq$140 (systolic BP)/90 (diastolic BP) mm Hg.

Analytical Methods

Blood samples were collected after the subjects had fasted for at least 12 hour and were centrifuged within 30 minute. Samples were collected in sodium fluoride tubes for plasma glucose measurement and in serum-separating tubes for others. All of the samples were analyzed at a central laboratory (Seegene Medical Foundation, Seoul, Korea). During the 75 g OGTT, samples were obtained at 0, 30, and 120 minute to measure plasma glucose and insulin levels. The plasma glucose level was measured using a hexokinase method, whereas serum insulin was measured using an immunoradiometric assay kit (Izotope, Budapest, Hungary). Serum creatinine was measured using an enzymatic method, and the estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation (MDRD). Various metabolic profiles were measured using the following methods: serum total cholesterol and triglyceride, enzymatic colorimetric tests; low-density lipoprotein (LDL) cholesterol, calculation using the Friedewald formula;[21] high-density lipoprotein (HDL) cholesterol, selective inhibition method; high-sensitivity C-reactive protein (hs-CRP) level, particle enhanced immunoturbidometric assay. The intra- and inter-assay coefficients of variances of analytical procedures were $< 4.7\%$ and $< 4.5\%$, respectively.

Index Calculation

Plasma glucose and insulin levels were measured from samples obtained during the OGTT, and the insulin-to-glucose (I/G) ratios were calculated for each time point. The areas under the curves (AUCs) from 0 minute to 120 minute ($AUC_{0-120\,min}$), 0 minute to 30 minute ($AUC_{0-30\,min}$), and 30 minute to 120 minute ($AUC_{30-120\,min}$) were calculated separately for glucose, insulin, and I/G ratio curves using the trapezoid method. The early phase insulin secretion was assessed, using the insulinogenic index which was calculated by (30-min insulin [μU/mL]–0-min insulin)/(30-min glucose [mg/dL]–0-min glucose).[22] The first- and second-phase insulin secretion were evaluated using the following equations: first-phase insulin release $= 1283 + 1.829 \times$ 30-minute insulin (μU/mL)$-138.7 \times$ 30-minute glucose (mmol/L) $+ 3.772 \times$ 0-minute insulin (μU/mL); second-phase insulin release $= 287 + 0.4164 \times$ 30-minute insulin (μU/mL)$-26.07 \times$ 30-minute glucose (mmol/L) $+ 0.9226 \times$ 0-minute insulin (μU/mL).[23] The homeostasis model assessment estimate of ß-cell function (HOMA-ß)[24] was calculated as $20 \times$ 0-minute insulin (μU/mL)/(0-min glucose [mmol/L]–3.5), and the homeostasis model assessment estimate of insulin resistance (HOMA-IR)[24] was calculated as 0-minute glucose (mmol/L) $\times$ 0-minute insulin (μU/mL)/22.5. The Matsuda index was calculated as 10,000/square root of (FPG [mg/dL] $\times$ fasting insulin [μU/mL]) $\times$ (mean glucose [mg/dL] $\times$ mean insulin [μU/mL] during an OGTT).[25] The oral disposition index, which is predictive of future diabetes development, was calculated as the combination of the insulinogenic index and 1/fasting insulin level.[22]

Definition of Glucose Tolerance Status

Glucose tolerance status was defined according to the ADA 2010 criteria. NGT was defined as an FPG level < 5.6 mmol/L and a 2-hour plasma glucose (2-h PG) level < 7.8 mmol/L, isolated IFG was defined as an FPG of 5.6 to 6.9 mmol/L and 2-h PG < 7.8 mmol/L, and isolated IGT was defined as FPG $<$ 5.6 mmol/L and a 2-h PG of 7.8 to 11.0 mmol/L.[26] Subjects with combined IFG and IGT were defined as having combined glucose intolerance (CGI). Subjects with FPG ≥ 7.0 mmol/L or 2-h PG $\geq$ 11.1 mmol/L were defined as having diabetes. Those who developed diabetes in the third phase of the study were considered diabetes converters, whereas those who did not develop diabetes were considered diabetes nonconverters.

Predictive Variables for Development of Diabetes

To analyze the power to predict the development of diabetes, receiver operating characteristic (ROC) curves were evaluated for various parameters obtained during the OGTT. The diagnostic properties of the cutoff values of each parameter were evaluated with the Youden index, defined as (sensitivity + specificity −1).[27] The area under the ROC curve (95% CI) of 30 minute glucose (G_{30}) was 0.790 (0.752–0.828) which was comparable to the area under the ROC curve of 120 minute glucose (0.795 [0.751–0.839], $P = 0.73$ vs G_{30}) and higher than that of 0 minute glucose (0.680 [0.630–0.730], $P < 0.001$ vs G_{30}). The difference between 120 and 0 minute glucose level ($G_{(120-0)}$) demonstrated area under the ROC curve of 0.760 (0.712–0.809) ($P = 0.157$ vs G_{30}). Other variables such as 0, 30, and 120 minute insulin values and insulinogenic index, first- and second-phase Stumvoll indices, HOMA–β, HOMA-IR, Matsuda index, and disposition index were insignificant or demonstrated lesser power to predict the development of diabetes compared to G_{30} or $G_{(120-0)}$ values (Table 1). Therefore, the G_{30} and $G_{(120-0)}$ were selected for further analysis. The cutoff value of 9.75 mmol/L was selected as the optimal value for G_{30} with the highest Youden index. The sensitivity and specificity for $G_{30} \geq 9.75$ mmol/L were 0.744 and 0.707, respectively. The cutoff value of 2.50 was selected for $G_{(120-0)}$ and the sensitivity and specificity were 0.735 and 0.695, respectively.

Statistical Analysis

The data are presented as the mean ± standard error (SE), as medians (25–75 percentiles) or as proportions. Differences in the baseline characteristics between converters and nonconverters were determined using *t* tests or Mann–Whitney tests for continuous variables and the chi-square test for categorical variables. Paired *t* test or Wilcoxon signed-rank test was used to evaluate the changes in insulin sensitivity and secretion indices at baseline and at follow-up in each individual. Subjects were categorized into 2 groups according to the $G_{(120-0)}$ or G_{30} values obtained from the baseline OGTTs with cutoff values of 2.50 and 9.75 mmol/L, respectively. Further categorization into 4 groups according to the combination of the $G_{(120-0)}$ and G_{30} values was performed. Multivariable logistic regression analysis was used to determine whether the $G_{(120-0)}$, G_{30} level or their combination is a predictor for development of diabetes. Age, sex, and BMI were adjusted in Model 1, and further adjustment for the variables that differed between converters and nonconverters were performed in Model 2. SPSS for Windows was used for statistical analysis (version 18.0; SPSS, Chicago, IL), and $P < 0.05$ was considered to be statistically significant.

RESULTS

Baseline Characteristics

The mean age and BMI of the study subjects were 65.3 ± 0.3 years and 24.29 ± 0.10 kg/m^2, respectively. Among 1126 subjects, the number of subjects showing NGT, isolated IFG, isolated IGT, and CGI were 588 (52.2%), 152 (13.5%), 199 (17.7%), and 187 (16.6%), respectively. At follow-up, 117 (10.4%) subjects developed diabetes. Subjects who developed diabetes demonstrated higher baseline systolic BP, BMI, waist circumference, total cholesterol, triglyceride, and hs-CRP levels compared to nonconverters (Table 2). The percentage of women and the prevalence of hypertension were higher in converters than in nonconverters. The baseline glucose tolerance differed ($P < 0.001$), demonstrating 56.6% and 14.5% of NGT in nonconverters and converters, respectively.

Glucose, Insulin, and Insulin-to-Glucose Ratio Curves During OGTT at Baseline

During a baseline 75 g OGTT, glucose levels at 0, 30, and 120 minute were higher in converters compared to nonconverters (Figure 1A). The 30 minute insulin level was lower, and the 120 minute insulin level was higher in converters versus nonconverters. Although the I/G ratio was comparable between the 2 groups at 0 and 120 minute, the value at 30 minute was lower in converters compared to nonconverters.

TABLE 1. Area Under the ROC Curve for Various Predictive Models for Future Development of Type 2 Diabetes

Parameters	AUC (95% CI)	*P*	*P* vs G_{30}
0 min glucose	0.680 (0.630–0.730)	<0.001	<0.001
30 min glucose	0.790 (0.752–0.828)	<0.001	–
120 min glucose	0.795 (0.751–0.839)	<0.001	0.73
120 min glucose–0 min glucose	0.760 (0.712–0.809)	<0.001	0.16
0 min insulin	0.540 (0.486–0.594)	0.16	<0.001
30 min insulin	0.451 (0.399–0.503)	0.08	<0.001
120 min insulin	0.658 (0.612–0.704)	<0.001	<0.001
120 min insulin–0 min insulin	0.659 (0.614–0.705)	<0.001	<0.001
Insulinogenic index	0.330 (0.284–0.376)	<0.001	<0.001
Stumvoll index			
First-phase insulin release	0.205 (0.167–0.243)	<0.001	<0.001
Second-phase insulin release	0.206 (0.167–0.244)	<0.001	<0.001
HOMA-β	0.467 (0.509–0.617)	0.24	<0.001
HOMA-IR	0.563 (0.509–0.617)	0.026	<0.001
Matsuda index	0.387 (0.335–0.440)	<0.001	<0.001
Disposition index	0.207 (0.277–0.376)	<0.001	<0.001

AUC = area under-the-curve, CI = confidence interval, G_{30} = 30 min glucose, HOMA-IR = homeostasis model assessment of insulin resistance, HOMA-ß = homeostasis model assessment of beta-cell function.

TABLE 2. Baseline Characteristics of Subjects According to Diabetes Status at Follow-Up

	Diabetes Nonconverters	Diabetes Converters	*P*
Number	1009	117	
Age (y)	65.1 ± 0.3	66.6 ± 0.8	0.11
Men (%)	39.7	27.4	0.01
Systolic blood pressure (mm Hg)	141.5 ± 0.6	145.6 ± 1.6	0.04
Diastolic blood pressure (mm Hg)	84.2 ± 0.3	84.8 ± 0.9	0.51
BMI (kg/m^2)	24.2 ± 0.1	25.5 ± 0.3	<0.001
Waist circumference (cm)	88.0 ± 0.3	91.8 ± 0.8	<0.001
Serum creatinine (μmol/L)	65.78 ± 0.50	63.47 ± 1.27	0.13
eGFR	99.10 ± 0.66	98.34 ± 1.87	0.71
Total cholesterol (mmol/L)	4.83 ± 0.03	5.05 ± 0.09	0.02
Triglyceride (mmol/L)	1.29 (0.92–1.95)	1.62 (1.11–2.31)	0.001
HDL-cholesterol (mmol/L)	1.26 ± 0.01	1.24 ± 0.03	0.32
LDL-cholesterol (mmol/L)	2.86 ± 0.02	2.99 ± 0.08	0.10
hs-CRP (mg/dL)	0.09 (0.06–0.17)	0.13 (0.08–0.27)	<0.001
Hypertension (%)	43.3	59.0	0.001
Current or exsmoker (%)	34.3	26.5	0.09
Glucose tolerance status (%)			
Normal glucose tolerance	56.6	14.5	<0.001
Isolated IFG	14.1	8.5	
Isolated IGT	15.5	36.8	
Combined glucose intolerance	13.9	40.2	

Data are expressed as the means ± standard errors, median (25th–75th percentiles) or %.

BMI = body mass index, hs-CRP = high-sensitivity C-reactive protein, eGFR = estimated glomerular filtration rate according to Modification of Diet in Renal Disease equation, HDL = high-density lipoprotein, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, LDL = low-density lipoprotein.

Insulin Sensitivity and Secretion Indices of Converters and Nonconverters at Baseline

The $AUC_{0-120\,min}$, $AUC_{0-30\,min}$, and $AUC_{30-120\,min}$ values for glucose were significantly higher in converters compared to nonconverters (Table 3). The $AUC_{0-120\,min}$ and $AUC_{30-120\,min}$ values for insulin were higher in converters versus nonconverters, and the $AUC_{0-30\,min}$ of insulin was similar between the 2 groups. Regarding the I/G ratio curves, the $AUC_{0-120\,min}$ and $AUC_{30-120\,min}$ were similar between 2 groups, whereas the $AUC_{0-30\,min}$ was lower in converters than nonconverters. The insulinogenic index and the first- and second-phase Stumvoll indices were lower in converters compared to nonconverters. The HOMA-ß value was similar between 2 groups, but the HOMA-IR value was higher and the Matsuda index was lower in converters. The disposition index of converters was less than half of that in nonconverters.

Changes in Insulin Sensitivity and Secretion Indices in Converters and Nonconverters

Compared to the baseline values, the BMI level significantly increased both in converters (25.5 ± 0.3 kg/m^2 at baseline to 25.7 ± 0.3 kg/m^2 at follow-up) and nonconverters (24.2 ± 0.1 kg/m^2 to 24.3 ± 0.1 kg/m^2 at follow-up) after 4 years of follow-up (Table 3). In nonconverters, the $AUC_{0-120\,min}$, $AUC_{0-30\,min}$, and $AUC_{30-120\,min}$ for glucose demonstrated minimal changes between baseline and follow-up, whereas those for insulin and the I/G ratio all increased at follow-up compared to baseline. However, in converters, the $AUC_{0-120\,min}$, $AUC_{0-30\,min}$, and $AUC_{30-120\,min}$ for glucose significantly increased at follow-up, whereas those for the I/G ratio did not demonstrate any significant changes. In converters, the increase in the $AUC_{0-120\,min}$ for insulin was accompanied by an increase in the $AUC_{30-120\,min}$ but the changes in the $AUC_{0-30\,min}$ values were insignificant.

The insulinogenic index and first- and second-phase Stumvoll indices remained unchanged in converters, whereas these indices were improved in nonconverters (Table 3). There were no significant changes in HOMA-ß, but HOMA-IR increased in both groups after 4 years with greater changes occurring in converters. A decrease in the disposition index was significant in nonconverters, but not in converters. However, the disposition index of nonconverters at follow-up was about 2 times higher than that of converters at baseline.

Glucose, Insulin, and Insulin-to-Glucose Ratio Curves According to the $G_{(120-0)}$ and G_{30} Values

Among total of 1126 participants, 731 and 395 subjects were categorized as having low $G_{(120-0)}$ (< 2.50 mmol/L) and high $G_{(120-0)}$ (≥ 2.50 mmol/L) values, respectively. Also, 743 and 383 subjects were categorized as having low G_{30} (< 9.75 mmol/L) and high G_{30} (≥ 9.75 mmol/L) values, respectively. The glucose levels at 0, 30, and 120 minute were higher in subjects with high $G_{(120-0)}$ and high G_{30} compared to their lower counterpart (Figure 1B and C). Although 30 minute insulin values were similar between 2 groups, 0 and 120 minute insulin values were higher in subjects with high $G_{(120-0)}$ and high G_{30} compared to their lower counterparts. The 30 minute I/G ratio values were lower in subjects with high $G_{(120-0)}$

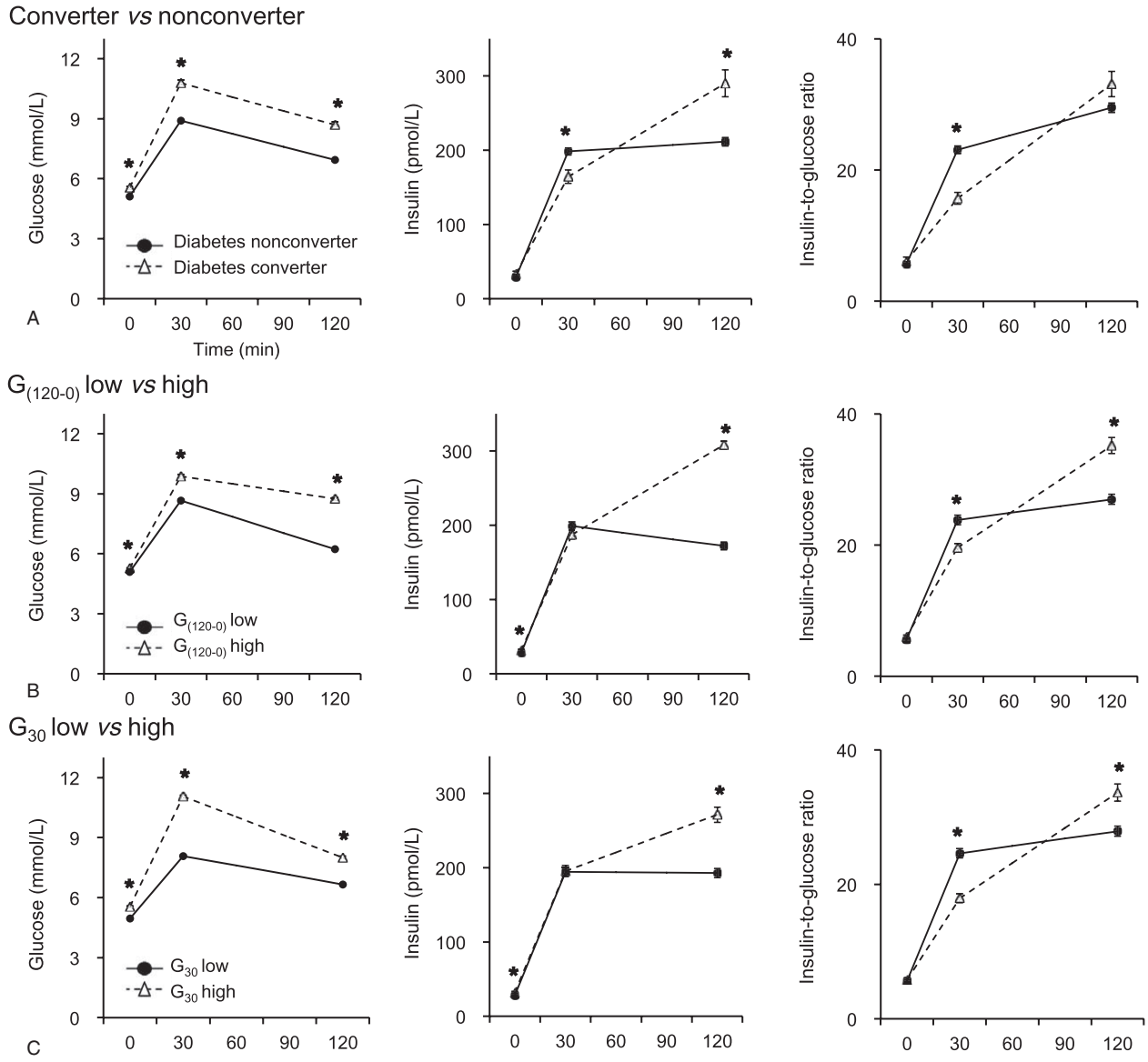

FIGURE 1. The 75 g oral glucose tolerance test at baseline. The baseline profiles of glucose, insulin, and insulin-to-glucose ratio during a 75 g oral glucose tolerance test in diabetes converters and nonconverters (A), and in subjects with low and high $G_{(120-0)}$ (B) and with low and high G_{30} (C). $G_{(120-30)}$, difference between 0 min and 120 min glucose; G_{30}, 30 min glucose. Values are presented as the means ± standard errors, *, $P < 0.05$ between 2 groups at each time point.

and high G_{30}, but the 120 minute I/G ratio values were higher compared to their lower counterparts.

Future Risk of Diabetes Development According to the $G_{(120-0)}$ and G_{30} Values and Their Combination

Logistic regression analysis was performed to determine the risk of developing diabetes according to the $G_{(120-0)}$ and G_{30} values and their combination (Table 4). A significantly higher OR was observed among subjects with $G_{(120-0)} \geq 2.50$ mmol/L than among subjects with $G_{(120-0)} < 2.50$ mmol/L in the crude analysis. Adjustment for age, sex, BMI, systolic BP, total cholesterol, triglyceride and hs-CRP levels (Model 1) demonstrated that the risk for diabetes development was 5.31 times higher among the individuals with high $G_{(120-0)}$ compared to subjects with low $G_{(120-0)}$ values. Further adjustment for family history of diabetes and smoking status (Model 2) slightly attenuated this association.

Similarly, the crude odds ratio for diabetes development was 6.99 among subjects showing $G_{30} \geq 9.75$ mmol/L compared to those with $G_{30} < 9.75$ mmol/L. Adjustment for possible confounding factors in Models 1 and 2 slightly attenuated the association, and these models demonstrated ORs of 6.65 and 6.78, respectively.

Participants were then categorized into 4 groups according to the combination of the $G_{(120-0)}$ and G_{30} values. Compared to subjects with low $G_{(120-0)}$ and low G_{30}, those with high $G_{(120-0)}$

TABLE 3. Changes in Insulin Sensitivity and Secretion Indices Between Baseline and Follow-Up

	Diabetes Nonconverters (n = 1009)				Diabetes Converters (n = 117)			
	Baseline	Follow-Up	Mean Change (95% CI)	*P*	Baseline	Follow-Up	Mean Change (95% CI)	*P*
Body mass index	24.2 ± 0.1	24.3 ± 0.1	0.10 (0.03, 0.18)	0.01	25.5 ± 0.3*	25.7 ± 0.3	0.26 (0.07, 0.44)	0.01
AUC of glucose curve								
0–120 min	919 (828–1031)	915 (823–1013)	0.22 (−8.80, 9.27)	0.95	1112 (1017–1219)*	1293 (1203–1425)	203 (163, 243)#	<0.001
0–30 min	208 (189–233)	208 (189–228)	0.06 (−1.85, 1.97)	0.92	246 (223–265)*	253 (228–277)	12 (4, 20)#	0.01
30–120 min	708 (635–795)	705 (628–788)	0.17 (−7.31, 7.64)	1.00	868 (793–961)*	1033 (969–1149)	192 (158, 225)#	<0.001
AUC of insulin curve								
0–120 min	18281 (12310–28080)	21901 (14784–31709)	3754 (2722, 4787)	<0.001	20715 (14816–29867)*	23692 (18106–37298)	6333 (3581, 9085)	<0.001
0–30 min	2726 (1866–4398)	3192 (2105–5062)	553 (376, 730)	<0.001	2573 (1747–3877)	2823 (1867–4334)	354 (−0.3, 708)	0.11
30–120 min	15395 (10304–23981)	18234 (12529–26695)	3201 (2320, 4083)	<0.001	18073 (12952–25860)*	21677 (16502–32470)	5979 (3460, 8498)	<0.001
AUC of I/G curve								
0–120 min	2383 (1590–3569)	2853 (1937–4057)	475 (353, 596)	<0.001	2255 (1588–3112)	2138 (1543–3238)	66 (−176, 308)#	0.77
0–30 min	347 (230–546)	402 (266–624)	65 (43, 86)	<0.001	286 (182–426)*	317 (197–476)	26 (−13, 66)	0.24
30–120 min	2021 (1332–3030)	2441 (1641–3426)	410 (306, 514)	<0.001	1987 (1416–2699)	1850 (1376–2759)	40 (−181, 261)#	0.55
Insulinogenic index	0.35 (0.20–0.61)	0.43 (0.24–0.74)	0.12 (0.05, 0.2)	<0.001	0.20 (0.14–0.33)*	0.21 (0.13–0.35)	0.05 (−0.09, 0.19)#	0.68
Stumvoll index								
First-phase insulin release	137.94 (−26.44–290.28)	167.56 (12.52–305.72)	23.65 (9.01, 38.29)	0.004	−112.12 (−308.69–16.73)*	−134.23 (−289.87–7.33)	−9.56 (−63.01, 43.9)	0.91
Second-phase insulin release	74.89 (43.63–103.82)	80.38 (51.65–107.11)	4.95 (2.17, 7.72)	0.001	28.43 (−9.14–51.71)*	22.86 (−6.85–54.1)	−1.26 (−11.29, 8.76)	0.95
HOMA-β	49.96 (26.07–81.80)	52.57 (8.81–93.14)	−5.17 (−14.08, 3.73)	0.31	44.26 (25.24–75.06)	48.67 (17.26–77.97)	−2.70 (−17.74, 12.34)	0.97
HOMA-IR	0.93 (0.47–1.49)	1.01 (0.15–1.75)	0.1 (0.003, 0.2)	0.04	1.10 (0.59–1.68)*	1.75 (0.36–2.58)	0.72 (0.20, 1.24)#	<0.001
Matsuda index	9.16 (5.97–14.87)	8.32 (5.15–20.24)	0.24 (−1.27, 1.76)	0.36	6.77 (4.79–10.38)*	4.4 (3.01–11.00)	−0.54 (−2.80, 1.71)	0.02
Disposition index	0.098 (0.048–0.221)	0.096 (0.040–0.336)	−0.406 (−1.460, 0.647)	<0.001	0.047 (0.028–0.082)*	0.036 (0.021–0.102)	0.013 (−0.055, 0.080)	0.15

Data are expressed as the means ± standard errors or median (25th–75th percentiles).

AUC = area-under-the curve, CI = confidence interval, HOMA-IR = homeostasis model assessment of insulin resistance, HOMA-ß = homeostasis model assessment of beta-cell function, I/G = insulin-to-glucose ratio.

P = changes between baseline and follow-up determined by paired *t* test or Wilcoxon signed-rank test.

*$P < 0.05$ between nonconverters vs converters at baseline.

#$P < 0.05$ comparison of mean changes of each variables between nonconverters vs converters.

TABLE 4. Future Risk of Diabetes Development According to the 30-Min Glucose Level and the Difference of 0-Min and 120-Min Glucose Levels

	Number of Converter/ Total Population (%)	Crude	Model 1	Model 2
Difference of 0-min and 120-min glucose				
$G_{(120-0)}$–Low (< 2.5 mmol/L)	31/731 (4.2%)	1 (reference)	1 (reference)	1 (reference)
$G_{(120-0)}$–High (≥ 2.5 mmol/L)	86/395 (21.8%)	6.31 (4.09–9.71)	5.31 (3.40–8.29)	5.12 (3.26–8.05)
30-min glucose				
G_{30}– Low (<9.75 mmol/L)	30/743 (4.0%)	1 (reference)	1 (reference)	1 (reference)
G_{30}–High (≥ 9.75 mmol/L)	87/383 (22.7%)	6.99 (4.51–10.81)	6.65 (4.25–10.38)	6.78 (4.30–10.70)
Combination				
$G_{(120-0)}$–Low, G_{30}–Low	10/541 (1.85%)	1 (reference)	1 (reference)	1 (reference)
$G_{(120-0)}$–Low, G_{30}–High	21/190 (11.05%)	6.60 (3.05–14.29)	6.70 (3.08–14.61)	6.93 (3.17–15.16)
$G_{(120-0)}$–High, G_{30}–Low	20/202 (9.9%)	5.87 (2.70–12.77)	5.09 (2.32–11.19)	4.94 (2.23–10.97)
$G_{(120-0)}$–High, G_{30}–High	66/193 (34.2%)	27.60 (13.80–55.17)	23.11 (11.41–46.78)	22.45 (11.03–45.70)

$G_{(120-30)}$ = difference between 0 min and 120 min glucose, G_{30} = 30 min glucose.
Model 1: adjusted for age, sex, body mass index, systolic blood pressure, total cholesterol, triglyceride and hs-CRP level.
Model 2: adjusted for age, sex, body mass index, systolic blood pressure, total cholesterol, triglyceride and hs-CRP level, family history of diabetes and smoking status.

and high G_{30} demonstrated 27.60 times higher risk for diabetes development in the crude analysis. Adjustment for possible confounding factors in Models 1 and 2 demonstrated ORs of 23.11 and 22.45, respectively.

Characteristics of Subjects According to the Combination of the $G_{(120-0)}$ and G_{30} Values

Baseline characteristics of subjects categorized into 4 groups according to the combination of the $G_{(120-0)}$ and G_{30} values were evaluated (Table 5). Age, gender, systolic BP, BMI, waist circumference, triglyceride, HDL-cholesterol and hs-CRP levels and the prevalence of hypertension differed among 4 groups.

The insulinogenic index, first- and second-phase Stumvoll indices, and HOMA-ß were lower in subjects with high $G_{(120-0)}$ and high G_{30} compared to the individuals with low $G_{(120-0)}$ and low G_{30}, suggesting an impaired insulin secretory capacity. Compared to subjects with low $G_{(120-0)}$ and low G_{30} values, participants with high $G_{(120-0)}$ and high G_{30} values demonstrated higher insulin resistance, as determined by HOMA-IR and Matsuda indices. Of note, the disposition index of those with high $G_{(120-0)}$ and high G_{30} was less than half of that in subjects with low $G_{(120-0)}$ and low G_{30} values.

Future Risk of Diabetes Development According to the Pattern of Insulin and I/G Ratio Curves

Apart from glucose levels during OGTT, the pattern of insulin or I/G ratio curves differed, showing steeper slope between 30 and 120 minute insulin level or I/G ratio in converters versus nonconverters (Figure 1A). We categorized subjects into 2 groups according to the pattern of insulin curve during the OGTT; those showing a downward (30-min insulin ≥ 120-min insulin, n = 482) or upward (30-min insulin < 120-min insulin, n = 644)-sloping insulin curve. A significantly higher ORs (4.37 [2.64–7.26]) for diabetes development was observed among subjects showing upward-sloping insulin curves versus downward-sloping insulin curves in the crude analysis. Further adjustment (Model 2) demonstrated ORs of 3.51 (2.08–5.90) (Supplementary Table 1, http://links.lww.com/MD/A758). Participants with upward-sloping insulin curves demonstrated lower levels of insulin secretory function and higher degree of insulin resistance compared to those with down-sloping insulin curves (Supplementary Table 2, http://links.lww.com/MD/A758). Similar finding was observed when subjects were categorized according to the pattern of I/G ratio curves determined by the 30 and 120 minute I/G ratio levels (Supplementary Table 1, 3, http://links.lww.com/MD/A758).

DISCUSSION

In our study using a community-based cohort, nearly 10% of subjects developed diabetes after 4 years of follow-up. Diabetes converters demonstrated a lower degree of insulin secretion, a higher degree of insulin resistance, and a lower disposition index compared to nonconverters. Participants were categorized according to the $G_{(120-0)}$ and G_{30} values obtained from the baseline 75 g OGTTs. Subjects with high $G_{(120-0)}$ and high G_{30} values demonstrated a lower degree of insulin secretion, a higher degree of insulin resistance and ~22-fold higher risk of developing future diabetes compared to those with low $G_{(120-0)}$ and low G_{30} values, after adjusting for possible confounding variables. By using 30 and 120 minute glucose levels during the OGTT, which is less complicated and does not require any special calculations, we were able to select individuals at risk for future diabetes development.

Various indices obtained from OGTT have been suggested to predict future development of diabetes. Abdul-Ghani et al[18,28] have proposed that 60 minute glucose level during the OGTT is a better predictor for diabetes than fasting or 120 minute glucose. Previous reports have established that the shape of the glucose curve during an OGTT is associated with type 2 diabetes risk factors.[13,14,19] Generally, subjects with a more complex shape of the glucose curve were known to have lower BMI, better glucose tolerance status, better insulin sensitivity, and β-cell function compared to subjects with monophasic shaped curves.[13,19] Most recently, Alyass et al[29] assessed

TABLE 5. Comparison of Baseline Characteristics and Indices Obtained During Oral Glucose Tolerance Tests According to the 30-Min Glucose Level and the Difference of 0-Min and 120-Min Glucose Levels

	$G_{(120-0)}$ < 2.5 mmol/L, G_{30} <9.75 mmol/L	$G_{(120-0)}$ < 2.5 mmol/L, $G_{30} \geq$ 9.75 mmol/L	$G_{(120-0)} \geq$ 2.5 mmol/L, G_{30} < 9.75 mmol/L	$G_{(120-0)} \geq$ 2.5 mmol/L, $G_{30} \geq$ 9.75 mmol/L	*P*
Number	541	190	202	193	
Age (y)	64.4 ± 0.4	65.3 ± 0.6	66.1 ± 0.6*	66.7 ± 0.6*	0.01
Men (%)	40.9	47.9	31.7*	29.5*	0.001
Systolic blood pressure (mm Hg)	139.5 ± 0.8	142.6 ± 1.5	143.1 ± 1.4	147.1 ± 1.3*	<0.001
Diastolic blood pressure (mm Hg)	83.8 ± 0.4	84.0 ± 0.8	84.7 ± 0.7	85.3 ± 0.8	0.30
BMI (kg/m^2)	24.0 ± 0.1	23.9 ± 0.2	24.9 ± 0.2*	24.9 ± 0.3*	<0.001
Waist circumference (cm)	87.5 ± 0.4	88.6 ± 0.7	89.5 ± 0.6*	89.7 ± 0.6*	0.004
Serum creatinine (μmol/L)	65.54 ± 0.64	66.25 ± 1.10	65.25 ± 1.09	65.15 ± 1.21	0.90
eGFR	99.68 ± 0.85	100.74 ± 1.67	97.29 ± 1.35	97.19 ± 1.58	0.21
Total cholesterol (mmol/L)	4.83 ± 0.04	4.87 ± 0.06	4.82 ± 0.06	4.94 ± 0.07	0.37
Triglyceride (mmol/L)	1.24 (0.92–1.85)	1.28 (0.80–1.79)	1.47 (1.05–2.20)*	1.57 (1.03–2.42)*	<0.001
HDL-cholesterol (mmol/L)	1.27 ± 0.01	1.30 ± 0.02	1.22 ± 0.02*	1.24 ± 0.02	0.02
LDL-cholesterol (mmol/L)	2.87 ± 0.03	2.91 ± 0.06	2.81 ± 0.05	2.90 ± 0.06	0.50
hs-CRP (mg/dL)	0.09 (0.05–0.15)	0.11 (0.06–0.18)*	0.10 (0.07–0.19)*	0.12 (0.06–0.25)*	<0.001
Hypertension (%)	37.9	45.8	48.0*	60.6*	<0.001
Current or exsmoker (%)	34.8	42.6	26.7	28.0	0.003
AUC of glucose curve					
0–120 min	831 (752–890)	1038 (972–1091)*	961 (923–1010)*	1154 (1106–1228)*	<0.001
0–30 min	193 (177–208)	247 (234–261)*	207 (197–214)*	247 (237–263)*	<0.001
30–120 min	638 (575–680)	790 (737–841)*	753 (727–795)*	905 (868–964)*	<0.001
AUC of insulin curve					
0–120 min	15805 (10970–24176)	19201 (13027–28999)*	21838 (14665–31852)	22256 (15314–32579)*	<0.001
0–30 min	2583 (1797–4165)	3028 (1937–4666)	2867 (1768–4609)	2750 (1856–4095)	0.15
30–120 min	13159 (8845–19818)	16262 (11136–24706)*	19189 (12590–27181)	19616 (13296–28011)*	<0.001
AUC of I/G curve					
0–120 min	2282 (1552–3354)	2331 (1518–3529)	2565 (1850–3729)*	2269 (1558–3290)	0.02
0–30 min	362 (247–558)	308 (195–484)*	369 (231–556)*	293 (188–447)*	<0.001
30–120 min	1905 (1294–2885)	1997 (1301–2973)	2212 (1550–3221)*	1985 (1317–2823)	0.01
Insulinogenic index	0.42 (0.24–0.76)	0.24 (0.15–0.41)*	0.37 (0.22–0.6)*	0.21 (0.11–0.35)*	<0.001
Stumvoll index					
First-phase insulin release	259.85 (139.44–379.87)	-123.05 (-234.46–-45.22)*	145.11 (82.95–222.67)*	-141.93 (-274.11–-74.3)*	<0.001
Second-phase insulin release	98.29 (74.99–120.7)	25.75 (4.23–40.64)*	75.76 (65.01–90.4)*	22.08 (-2.57–35.59)*	<0.001
HOMA-β	51.26 (28.06–88.46)	44.82 (21.08–68.18)*	54.49 (29.63–90.75)*	42.09 (24.43–70.27)*	0.001
HOMA-IR	0.88 (0.43–1.42)	1.06 (0.56–1.66)*	0.95 (0.45–1.43)*	1.17 (0.54–1.83)*	<0.001
Matsuda index	10.83 (6.98–16.61)	7.53 (5.34–12.19)*	8.23 (5.61–13.33)*	6.50 (4.43–10.16)*	<0.001
Disposition index	0.123 (0.056–0.267)	0.062 (0.038–0.126)*	0.101 (0.056–0.176)*	0.049 (0.028–0.087)*	<0.001

Data are expressed as the means ± standard errors, median (25th–75th percentiles) or %.

AUC = area-under-the curve, BMI = body mass index, eGFR = estimated glomerular filtration rate according to Modification of Diet in Renal Disease equation, $G_{(120-30)}$ = difference between 0 min and 120 min glucose, G_{30} = 30 min glucose, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, HOMA-ß = homeostasis model assessment of beta-cell function, hs-CRP = high-sensitivity C-reactive protein, I/G = insulin-to-glucose ratio, LDL = low-density lipoprotein.

P = comparison among 4 groups.

*$P < 0.05$ vs subjects with $G_{(120-0)} < 2.5$ mmol/L and $G_{30} < 9.75$ mmol/L.

14 OGTT glucose trait obtained from the Europeans of Botnia study and Malmö Prevention Project cohorts, and demonstrated that 1 hour PG is a valuable prediction tool for identifying adults at risk for future type 2 diabetes. Among Korean population, Kim et al[30] demonstrated that among subjects who visited a single tertiary referral hospital, those with high glucose (≥ 9.17 mmol/L) and low C-peptide (< 5 ng/mL) levels at 30 minute during OGTTs showed 8.83 times greater risk for diabetes development. Compared to this study, our study enrolled larger number of participants from community-based cohort. The cutoff value for 30 minute glucose was higher in our study compared to the study conducted by Kim et al.[30] As the enrolled subjects of both studies were not representative of general Korean population, further studies are warranted. However, to the best of our knowledge, this is the first demonstration that a combination of $G_{(120-0)}$ and G_{30} values could be a good predictor in detecting high-risk subjects for diabetes development.

Increased insulin resistance and impaired insulin secretion are the main pathophysiological components of type 2 diabetes development,[31] and the contributions of 2 factors are thought to differ in Asians and the Western population. In a cross-sectional study conducted in Korea, a defect in early phase insulin secretion has been suggested as the initial abnormality in the development of type 2 diabetes.[32] Insulin secretion in Japanese individuals has been reported to be less than half of that in Whites.[33,34] However, few studies have investigated longitudinal changes in insulin secretory function and resistance in the course of diabetes development among Asian populations.[30,35–37] Similar to our cohort, the Saku study is a 4-year community-based cohort study that included 3059 Japanese participants without diabetes at baseline. In this study population, isolated impaired insulin secretion at baseline had a greater impact on the incidence of type 2 diabetes than insulin resistance.[38] Among subjects with isolated impaired insulin secretion, greater increase in HOMA-IR had a strong impact on the development of type 2 diabetes.[39] In our study cohort, diabetes converters demonstrated impaired insulin secretion and increased insulin resistance compared to nonconverters at baseline. During 4 years of follow-up, HOMA-IR increased in both converters and nonconverters, but increased insulin secretion was observed only in nonconverters. Therefore, defects in compensatory insulin secretion might be associated with development of type 2 diabetes in converters. However, relative contributions of baseline β-cell dysfunction versus insulin resistance to the diabetes development remain to be elucidated in further analysis.

There are several other limitations of this study. The study participants were mostly elderly subjects living in rural areas, and the proportion of women was relatively high. During a 2-hour OGTT, laboratory values were obtained only at 0, 30, and 120 minute, whereas many of the previous reports obtained 5 time-point measurements. However, by simply using 3 time point values, we were still able to select subjects at high risk for developing diabetes in the future. Moreover, from the 0 and 30 minute values, we could calculate the insulinogenic index, which strongly correlates with the acute insulin response on the intravenous glucose tolerance test,[40] and has been used as an early phase insulin secretion index in clinical studies.[41] Although the HbA1c test have several advantages to OGTT, including greater convenience (fasting not required), greater analytical stability and less day-to-day variation, several conditions such as age, ethnicity, presence of anemia, or hemoglobinopathies should be taken into account.[42] Furthermore, HbA1c alone have been shown to be insufficient to identify individuals at risk for the development of diabetes.[43,44] Therefore, the $G_{(120-0)}$ and G_{30} values can be used to provide additional information to detect subjects who are at high risk for incident diabetes. Finally, as the pathogenesis of impaired fasting glucose and impaired glucose tolerance is thought to be different,[41] the $G_{(120-0)}$ and G_{30} values might demonstrate different predictive values among subjects with normal glucose tolerance, isolated IFG, isolated IGT and CGI. However, in our study population, the number of subjects in each group was relatively small to perform a separate analysis.

In conclusion, diabetes converters demonstrated impaired insulin secretion and a higher degree of insulin resistance compared to nonconverters at baseline. During 4 years of follow-up, increased insulin resistance was not accompanied by compensatory insulin secretion in converters, which was observed in nonconverters. When subjects were categorized according to the $G_{(120-0)}$ and G_{30} values during the OGTT, those with $G_{(120-0)} \geq 2.50$ mmol/L and $G_{30} \geq 9.75$ mmol/L demonstrated impaired insulin secretion and a higher degree of insulin resistance, leading to increased risk of diabetes development compared to those with low $G_{(120-0)}$ and low G_{30}. Moreover, when insulin levels are obtained in addition to glucose levels during OGTT, the pattern of insulin or I/G ratio curve might provide additional information to detect subjects at high risk for diabetes development. Further studies with a larger number of subjects and different ethnicities are needed to validate our results.

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