Utility of Homeostasis Model Assessment of β-Cell Function in Predicting Diabetes in 12,924 Healthy Koreans

KI-CHUL SUNG, MD, PHD[1]
GERALD M. REAVEN, MD[2]
SUN H. KIM, MD[2]

OBJECTIVE — It is unclear how well homeostasis model assessment of β-cell function (HOMA-β) predicts diabetes development beyond its components, especially glucose.

RESEARCH DESIGN AND METHODS — We identified 12,924 nondiabetic Koreans who had fasting plasma glucose and insulin concentrations measured in 2003 and again in 2008. To minimize the impact of differences in baseline glucose concentration, individuals were divided into three glucose categories: normal fasting glucose (NFG, glucose <5.6 mmol/l), impaired fasting glucose (IFG-100) (5.6–6.0 mmol/l), and IFG-110 (6.1–6.9 mmol/l).

RESULTS — Diabetes developed in 29% of individuals in the IFG-110 group, compared with 5% in IFG-100 and 0.3% in NFG groups. Within each glucose category, those who progressed to diabetes had higher baseline glucose concentrations ($P \leq 0.04$). Baseline HOMA-β, however, was not lower but higher in individuals who developed diabetes in the NFG group ($P = 0.009$) and similar in the IFG-100 and IFG-110 groups.

CONCLUSIONS — These data question the utility of using HOMA-β to predict the development of diabetes.

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The homeostasis model assessment of β-cell function (HOMA-β) is an index of insulin secretory function derived from fasting plasma glucose and insulin concentrations (1). It has been used to predict diabetes development in nondiabetic individuals in four studies (2–5), and the conclusion in each instance was that a decrease in insulin secretory function, as estimated by HOMA-β, predicted the development of diabetes and/or impaired glucose tolerance. However, because it was also shown in these studies that baseline glucose concentration was higher in individuals who developed diabetes, it could be argued that the lower values for HOMA-β may only be reflecting the difference in glucose concentration. The current analysis was initiated to see if HOMA-β provided a more sensitive assessment of the likelihood of developing type 2 diabetes than did knowledge of individual fasting plasma glucose and insulin concentrations.

RESEARCH DESIGN AND METHODS

— The institutional review board of Kangbuk Samsung Hospital approved this study. Through review of electronic medical records, 12,924 patients were identified who had a general health status evaluation in both 2003 and 2008 at Kangbuk Samsung Hospital located in Seoul, Korea. Patients were divided based on their 2003 glucose concentrations into three groups to reflect normal glucose category (normal fasting glucose [NFG], glucose <5.6 mmol/l or <100 mg/dl), 2003 American Diabetes Association–modified impaired fasting glucose (IFG) category (IFG-100, 5.6–6.0 mmol/l or 100–109 mg/dl), and prior IFG category (IFG-110, 6.1–6.9 mmol/l or 110–125 mg/dl). Development of diabetes was defined as glucose ≥7 mmol/l (≥126 mg/dl) on laboratory examination in 2008 or diagnosis of diabetes and/or initiation of diabetes medications.

Laboratory examinations were collected after at least 12 h of fasting, analyzed in the same core laboratory, and available from the electronic medical records. Glucose was measured using the hexokinase method (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Insulin was measured with an immunoradiometric assay (Biosource, Nivelle, Belgium) with an intra- and interassay coefficient of variation of 2.1–4.5% and 4.7–12.2%, respectively. HOMA-β and HOMA of insulin resistance (HOMA-IR) were calculated using the online calculator (6).

All statistical analysis was performed using SPSS (version 12 for Windows; SPSS, Chicago, IL). Differences in measurements between groups were assessed by independent *t* tests, ANOVA, or χ^2 test for categorical variables.

RESULTS

— Out of the total 12,924 individuals, there were 10,132 (78%) in the NFG group, 2,546 (20%) in the IFG-100 group, and 246 (2%) in the IFG-110 group. During the 5-year interval from 2003 to 2008, 234 individuals (1.8%) developed diabetes. Being in the IFG-110 group conferred the greatest risk to develop diabetes, with 29% converting to diabetes, compared with 5% in the IFG-100 group and 0.3% in the NFG group.

Table 1 compares baseline features of those who developed diabetes (diabetic) compared with those who did not (nondiabetic) by glucose category. Although age was relatively similar between the two subgroups within each glucose category, patients who developed diabetes were heavier at baseline and more likely to be male. They also had higher glucose and

From the [1]Department of Medicine, Division of Cardiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea; and the [2]Department of Medicine, Division of Endocrinology, Stanford University School of Medicine, Stanford, California.
Corresponding author: Ki-Chul Sung, kcmd.sung@samsung.com.
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Table 1—*Baseline characteristics by diabetes status in 2008*

	NFG			IFG-100			IFG-110		
	Nondiabetic	Diabetic	*P**	Nondiabetic	Diabetic	*P**	Nondiabetic	Diabetic	*P**
n	10,097	35		2,419	127		174	72	
Clinical variables									
Age (years)	41 ± 6	40 ± 6	0.83	42 ± 6	43 ± 6	0.02	44 ± 7	43 ± 5	0.18
BMI (kg/m^2)	23.6 ± 2.8	26.0 ± 3.2	<0.001	24.7 ± 2.7	26.9 ± 3.4	<0.001	25.6 ± 2.7	26.3 ± 3.1	0.09
Male (%)	6,918 (69)	32 (91)	0.001	1,964 (81)	114 (90)	0.007	154 (89)	62 (86)	0.37
Laboratory variables									
Glucose (mmol/l)									
Unadjusted	5.0 (5.0–5.0)	5.1 (5.0–5.3)	0.003	5.8 (5.8–5.8)	5.9 (5.9–5.9)	<0.001	6.5 (6.5–6.5)	6.6 (6.6–6.7)	<0.001
Adjusted*	5.0 (5.0–5.0)	5.1 (5.0–5.2)	0.04	5.8 (5.8–5.8)	5.9 (5.9–5.9)	<0.001	6.5 (6.5–6.5)	6.6 (6.6–6.7)	<0.001
Insulin (pmol/l)									
Unadjusted	49 (49–49)	68 (61–74)	<0.001	54 (54–55)	67 (64–71)	<0.001	60 (56–64)	67 (62–73)	0.04
Adjusted*	49 (49–49)	62 (56–68)	<0.001	55 (54–56)	61 (58–65)	<0.001	61 (58–64)	65 (60–71)	0.19
HOMA2-IR									
Unadjusted	1.1 (1.0–1.1)	1.4 (1.3–1.6)	<0.001	1.2 (1.2–1.2)	1.5 (1.4–1.6)	<0.001	1.4 (1.3–1.5)	1.6 (1.4–1.7)	0.03
Adjusted*	1.1 (1.0–1.1)	1.3 (1.2–1.5)	<0.001	1.2 (1.2–1.2)	1.4 (1.3–1.4)	<0.001	1.4 (1.3–1.5)	1.5 (1.4–1.6)	0.17
HOMA2-B									
Unadjusted	99 (98–99)	115 (106–123)	<0.001	80 (79–80)	87 (84–91)	<0.001	68 (65–71)	71 (66–75)	0.28
Adjusted*	99 (98–99)	110 (102–118)	0.009	80 (79–81)	82 (78–85)	0.26	68 (66–71)	69 (65–73)	0.82

Data are means ± SD or means (95% CI). *Data are adjusted for age, sex, and BMI.

insulin concentrations and HOMA2-IR, and this was seen in all three glycemic categories. HOMA-β was also higher in individuals who developed diabetes. These differences were attenuated when adjusted for age, sex, and BMI, especially in the IFG-110 group; however, the trends remained similar. In particular, HOMA-β remained significantly higher in individuals who developed diabetes in the NFG group and were similar in the IFG-100 and IFG-110 groups.

CONCLUSIONS — In contrast to other studies, we did not find a lower HOMA-β to be associated with the development of diabetes when individuals had relatively similar glucose concentrations. Indeed, if anything, individuals who developed diabetes tended to have higher HOMA-β, reflecting the inadequacies of the HOMA-β calculation.

In an attempt to understand this fundamental disparity between the current findings and previous studies, we believe it useful to begin by examining the basis of the HOMA-β calculation. The HOMA calculation is derived from a computer-solved model that assumes certain relationships between basal plasma glucose and insulin concentration (1,6). Although values of both fasting plasma glucose and insulin concentrations are used to solve the equation, the degree of glycemia is often the major determinant. In Table 1, for example, as glucose increases, insulin concentrations also increase, but HOMA-β declines. In fact, for individuals with IFG-110 to have similar HOMA-β as individuals with NFG, insulin concentrations would have to be ~120 pmol/l or double the actual insulin concentration.

When examined in this light, it is easy to see why our results differ from others. There have been four prospective studies that have evaluated the role of HOMA-β in predicting diabetes (2–5). They all concluded that a lower HOMA-β was predictive of future diabetes. In three of the studies that provided results by diabetes status, baseline glucose was also higher in individuals who developed diabetes. In one of the studies, the baseline glucose was only different by 0.5 mmol/l, and the baseline HOMA-β was not significantly different. In a multiple logistic regression analysis, HOMA-β also did not predict the development of diabetes when adjusted for age, sex, BMI, and waist-to-hip ratio (odds ratio 0.93 [95% CI 0.69–1.26]). However, when they added HOMA-IR to the model, HOMA-β became significant (0.34 [0.21–0.55]). The authors therefore concluded that a higher HOMA-β was protective against the development of diabetes and emphasized the importance of adjusting for insulin resistance (HOMA-IR) when evaluating insulin secretion. While this has biological basis, it should be noted that HOMA-IR and insulin concentration were nearly perfectly correlated ($r = 0.98$); therefore, adding HOMA-IR to the model merely adjusts for insulin concentration and isolates the effect of glucose concentration on diabetes risk.

In conclusion, we confirm that baseline glucose concentration is strongly associated with diabetes development, with 29% of individuals meeting the old IFG criteria (IFG-110) progressing to diabetes within 5 years. However, individuals who were at risk to develop diabetes were not characterized by insulin deficiency, as defined by absolute insulin concentration or HOMA-β. As pancreatic β-cell dysfunction has been established as a requisite defect in type 2 diabetes (7), these findings likely highlight the inadequacies of fasting measures as surrogates for pancreatic function (8,9).

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