Primacy of β-Cell Dysfunction in the Development of Hyperglycemia: A Study in the Japanese General Population

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To elucidate the hierarchy in the evolution of glucose intolerance in the general population, the relationship between plasma glucose (PG), β-cell function (insulinogenic index [II] = $\Delta IRI_{0\text{-}30}/\Delta PG_{0\text{-}30}$ on 75 g oral glucose tolerance test [OGTT], where IRI is immunoreactive insulin), insulin sensitivity (Si; determined by quantitative insulin sensitivity check index [QUICKI]), age, and body mass index (BMI) were analyzed in 504 Japanese health examinees (men/women: 347/157). The mean (±SD) age was 53 (±11) years, BMI 23.6 (±3.2) kg/m^2, fasting PG (FPG) 5.61 (±0.97) mmol/L, 2-hour PG 7.42 (±3.1) mmol/L, II 74.2 (±169.3) [pmol/L] · [mmol/l]$^{-1}$, and QUICKI 0.385 (±0.057) [log (μU/mL) + log (mg/100 mL)]$^{-1}$. Higher FPG and 2-hour PG, respectively, were independently correlated with lower II, lower QUICKI, higher age, and higher BMI; the standardized correlation coefficient was largest for the correlation between PG and II. Based on the multiple linear regression, FPG = 8.565 − 1.201 · log [II] − 5.374 · QUICKI + 0.007 · age + 0.030 · BMI (r^2 = 0.442), and 2-hour PG = 14.239 − 4.206 · log [II] − 0.141 · QUICKI + 0.034 − age + 0.141 · BMI (r^2 = 0.493). Thus, elevation of PG correlated most prominently with β-cell dysfunction and less prominently with decreased Si, higher age, and BMI (especially so in the case of 2-hour PG). In conclusion, the primacy of β-cell dysfunction in the process of developing glucose intolerance was strongly suggested in the Japanese general population.

β-CELL dysfunction and insulin resistance (IR) or decreased insulin sensitivity (Si) (IR and Si are used interchangeably in this communication, ie, "IR" as a synonym for "low Si") are causally related to development of diabetes mellitus (DM).[1] However, the relative importance of these 2 variables and their interaction with other diabetogenic factors are in dispute. In the "two-step theory," IR was proposed as the primary event responsible for conversion from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT), and then transition from IGT to DM was considered to take place when the β-cell fails to adapt to the increased demand caused by IR.[2] Thus, IR was regarded as the initial abnormality and β-cell dysfunction as the secondary phenomenon, ie, adaptation failure.[2] This hypothesis has been widely accepted[3,4]; however, others have placed β-cell dysfunction as a more proximal event.[5] Recently, a longitudinal analysis of the data from Pima Indians revealed that β-cell dysfunction is an important factor for conversion from NGT to IGT too.[6] In another longitudinal study, IR was a poor predictor of development of DM.[7] Aging is associated with worsening of glucose tolerance in humans,[8,9] and in addition to the age-related increase in IR and lowering of insulin secretion, age per se was proposed to be an independent determinant of glucose tolerance.[10] However, this idea was not supported by recent studies.[11,12]

In Japanese, the prevalence of DM has been rapidly rising despite the low prevalence of obesity.[13,14] Yet, a systematic analysis of risk factors for glucose intolerance and DM has not been performed. With this information as background, we performed multivariate correlation analysis between PG and known diabetogenic factors in the Japanese general population to elucidate the hierarchy in the evolution of glucose intolerance.

MATERIALS AND METHODS

The study population consisted of 504 consecutive Japanese health examinees (Table 1). Those with known DM and abdominal surgery were excluded. The subjects were not selected from any particular group of people, and included businessmen, housewives, industry workers, and farmers. Thus, the study population can be regarded as representative of the Japanese adult population. In support of this contention, the mean body mass index (BMI) (23.6 kg/m^2) and prevalence of morbid obesity (BMI ≥ 30 kg/m^2, 3.8%) in the study population were similar to the corresponding values in the general Japanese population.[14] The result of an oral glucose tolerance test (OGTT) was classified as NGT, impaired fasting glucose (IFG), IGT, and DM based on the current criterion.[15] The new American Diabetes Association (ADA) criteria for IFG[16] was not adopted in this study because we completed the data analysis before its publication. IFG and IGT were collectively categorized as nondiabetic hyperglycemia (NDH). The OGTT was performed after an overnight fast in the morning. Plasma immunoreactive insulin (IRI) was measured in 0- and 30-minute blood samples at OGTT by insulin-specific enzyme-linked immunoassay.[17] Changes in IRI from 0 to 30 minutes during OGTT ($\Delta IRI_{0\text{-}30}$) and PG during the same period ($\Delta PG_{0\text{-}30}$) were calculated, and the ratio of the 2 ($\Delta IRI_{0\text{-}30}/\Delta PG_{0\text{-}30}$), the insulinogenic index (II), was obtained as an index of β-cell function.[18,19] Low II indicates diminished β cell function, and II is highly correlated (r = 0.88) with acute insulin release (AIR) upon intravenous glucose challenge over the wide range of glucose tolerance.[20] As an index of IR, homeostasis model assessment of insulin resistance (HOMA-R)[21] was calculated: HOMA-R = [fasting IRI (FIRI) (pmol/L) · FPG (mmol/L)]/3.75. As indices of Si, 1/FIRI[22] and quantitative insulin sensitivity check index (QUICKI)[23] were calculated: 1/FIRI is simply a reciprocal of FIRI and QUICKI = [log FIRI (μU/mL) · log FPG (mg/100 mL)]$^{-1}$. QUICKI was adopted in the correlation analysis because it correlated with the glucose clamp–based Si better (r = 0.78) than the other 2 indices.[23] In the current study population, QUICKI correlated with both FPG and 2-hour PG slightly stronger than 1/FIRI and HOMA-R (data not shown). II values were logarithmically transformed in the statistical

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Table 1. Characteristics of the Study Population

Variable	All	NGT	NDH	DM
n	504	320	118	66
Men/women	347/157	223/98	81/37†	43/22†
Age (yr)	53 ± 11 (22-83)	51 ± 11	56 ± 11¶	57 ± 10¶
BMI (kg/m^2)	23.6 ± 3.2 (14.7-36.0)	23.1 ± 3.0	24.0 ± 3.2‡	25.3 ± 3.5¶
FPG (mmol/L)	5.61 ± 0.97 (4.0-10.9)	5.17 ± 0.43	5.82 ± 0.63	7.36 ± 1.23
2-h PG (mmol/L)	7.42 ± 3.1 (3.11-22.9)	5.80 ± 1.03	8.22 ± 1.50	13.8 ± 3.37
II [(pmol/L) · (mmol/L)$^{-1}$]	74.26 ± 169.3 (0.52-339)	96.3 ± 207.8	46.0 ± 38.6¶	18.1 ± 17.2¶
1/FIRI [(pmol/L)$^{-1}$]	0.051 ± 0.083 (0.008-1.67)	0.057 ± 0.100	0.040 ± 0.032§	0.043 ± 0.037§
HOMA-R ([(pmol/L) · (mmol/L)]/3.75)	1.40 ± 1.07 (0.022-6.75)	1.15 ± 0.76	1.61 ± 1.05¶	2.27 ± 1.72¶
QUICKI ([log(μU/mL) · log(mg/100 mL)]$^{-1}$)	0.385 ± 0.057 (0.291-1.048)	0.395 ± 0.061	0.371 ± 0.040¶	0.358 ± 0.047¶
SBP* (mm Hg)	119 ± 18 (79-192)	117 ± 17	125 ± 19§	129 ± 16§
DBP* (mm Hg)	73 ± 12 (48-110)	71 ± 12	76 ± 11‡	82 ± 10¶
TC* (mmol/L)	5.10 ± 0.93 (3.08-9.91)	5.04 ± 0.91	5.12 ± 0.80	5.54 ± 1.22‡
TG* (mmol/L)	1.80 ± 1.27 (0.29-8.93)	1.67 ± 1.18	1.91 ± 1.22	2.99 ± 1.84¶

NOTE. Values are means ± SD (range).

Abbreviations: NGT, normal glucose tolerance; NDH, nondiabetic hyperglycemia; DM, diabetes mellitus; BMI, body mass index; FPG, fasting plasma glucose; 2-h PG, 2-hour PG at OGTT; II, insulinogenic index; FIRI, fasting immunoreacitive insulin; HOMA-R, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; log, logarithm; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides.

*Blood pressure and serum lipids data were obtained in 301 subjects.

†Not significantly different from the ratio in the NGT group.

‡$P < .05$, §$P < .01$, and ¶ $P < .001$, respectively, compared with the corresponding value in NGT group by analysis of variance with post hoc pairwise comparison by Fisher's protected least significant difference. FPG and 2-h PG, respectively, of NDH and DM group were significantly different ($P < .001$) from those in NGT group by definition.

analysis. Data on total cholesterol (TC), triglycerides (TG), and blood pressure (BP) of 301 subjects were also obtained.

Student's t test, Spearman's rank correlation, partial correlation, analysis of variance, and multiple linear regression analysis were performed as needed, and $P < .05$ was considered significant. Locally weighted scattered smoother (LOWESS)[24] with a tension value 0.66 was employed to draw a best-fit line in the scatterplots, which avoids making an a priori judgment about the relationship.

RESULTS

Characteristics of the Study Population

Sex, age, BMI, FPG, 2-hour PG, II, 1/FIRI, HOMA-R, QUICKI, BP, and serum lipids of the entire study population and the subgroups (NGT, NDH, and DM) are shown in Table 1. As reported for the general Japanese population,[14] a majority of the subjects were non-obese, normotensive, and normolipidemic. Based on the current diagnostic criterion, 329 (62%) had NGT, 31 (6%) isolated IFG, 64 (13%) isolated IGT, 23 (5%) IFG/IGT, and 65 (13%) DM. The distribution was comparable to that in many other populations.[25] A recent proposal, that the lower limit for IFG be reduced to100 mg/100 mL,[16] was not adopted in this study.

As a group, age, BMI, BP, and serum lipids were progressively higher and II and Si progressively lower in subjects with NGT, NDH, and DM in this order. The ratio of men to women ratio was not significantly different among the 3 groups (Table 1).

Correlation Between PG and β-Cell Function, Si, Age, Body Weight, and Gender: Univariate Analysis

Elevation of FPG as well as 2-hour PG was significantly correlated with lower II (Fig 1A) and QUICKI (Fig 1B), and higher age (Fig 1C) and BMI (Fig 1D) ($P < .0001$, Spearman's rank correlation). The correlation was most strong between PG and II as indexed by the largest Spearman's ρ values: ρ values for FPG were -0.465 (v II), -0.378 (v QUICKI), 0.185 (v age), and 0.251 (v BMI), and those for 2-hour PG were -0.453 (v II), -0.354 (v QUICKI), 0.299 (v age), and 0.282 (v BMI). PG was not significantly different based on gender (FPG, 5.66 ± 0.95 mmol/L in men and 5.50 ± 1.00 mmol/L in women, $P = 0.0847$ by Student's t test; 2-hour PG, 7.29 ± 3.11 mmol/L in men and 7.68 ± 3.17 mmol/L in women, $P = 0.1983$). Results of the univariate analyses were similar when obtained in those with NGT (n = 320), or in those with NGT and NDH combined (n = 438) (data not shown).

Identification of Independent Correlation by Multivariate Analysis

To identify the variables independently correlated with PG, partial correlation analysis was performed. FPG and 2-hour PG were not incorporated into a single correlation matrix to avoid multiple colinearity. As shown, each of lower II (β-cell dysfunction), lower QUICKI (lower Si), higher age, and higher BMI were significantly correlated with elevation of FPG (Table 2) and 2-hour PG (Table 3). For elevation of both FPG and 2-hour PG, β-cell dysfunction correlated most strongly (as indexed by the largest standardized correlation coefficient), which was followed by Si; age and BMI correlated weakly with elevation of PG (Tables 2 and 3). Age was not significantly correlated with Si, II, or BMI. Lower Si was correlated with higher BMI and higher II, as expected (Tables 2 and 3).

The partial correlation matrix was also obtained by using the data set from subjects with NGT (n = 320) (Tables 4 and 5). As in the entire population, independent correlation between ele-

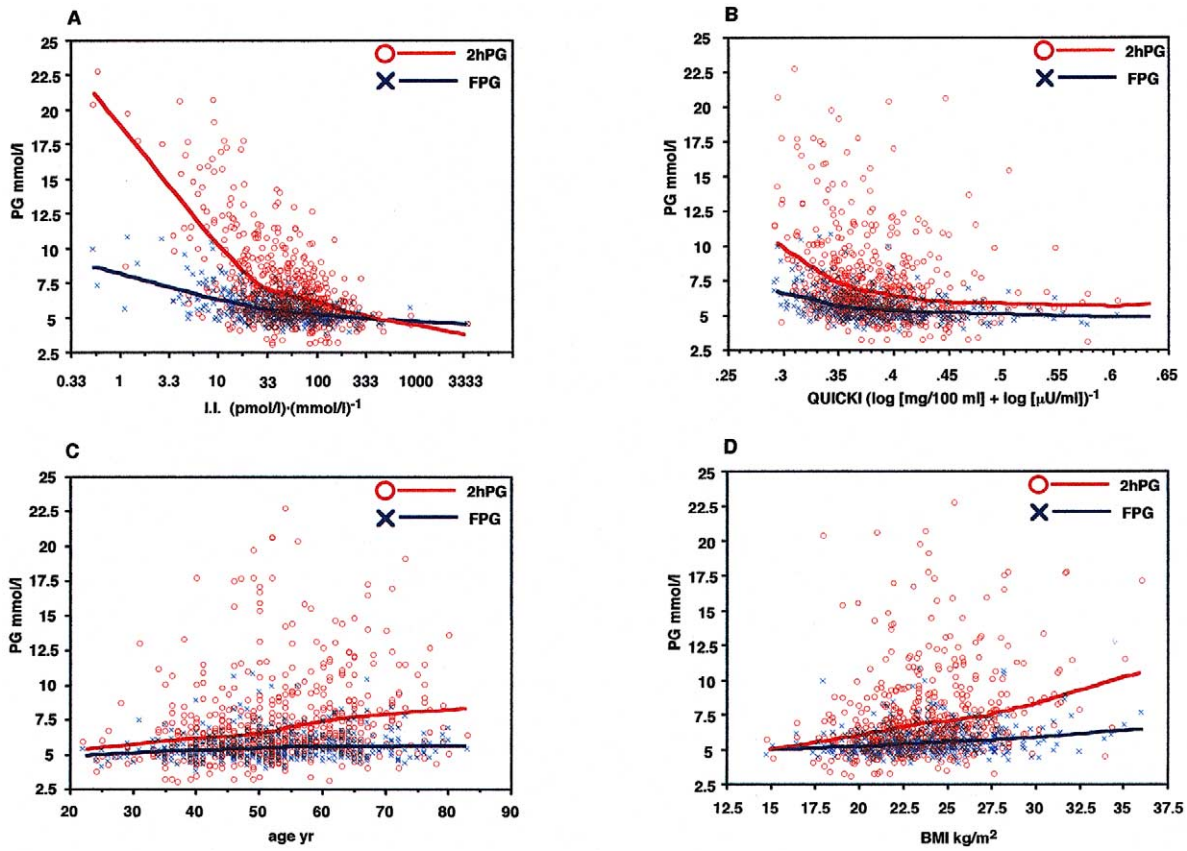

Fig 1. FPG (crosses) and 2-hour PG (circles) plotted as a function of (A) insulinogenic index (II), (B) QUICKI, (C) age, and (D) BMI. Scattered plots with the best-fit line obtained by locally weighted scattered smoother (LOWESS) are shown. By Spearman's rank correlation, correlation between FPG and the 4 variables, and 2-hour PG and the 4 variables, respectively, were significant ($P < .0001$). For ρ value, see text.

vation of PG (both FPG and 2-hour PG) and β-cell dysfunction, low Si, age, and BMI was present; age was more strongly correlated with both FPG and 2-hour PG than weight gain in this population.

By multiple linear regression, the equation for FPG and 2-hour PG were obtained. Based on the correlation shown in Tables 2 and 3, II, Si, age, and BMI were employed as predictor variables. The regression was as follows: FPG (mmol/L) = 8.565 − 1.201 · log II ([pmol/L] · [mmol/L]$^{-1}$) − 5.374 · QUICKI ([log (μU/mL) + log (mg/100 mL)]$^{-1}$) + 0.007 − age (yr) + 0.030 − BMI (kg/m^2) (r^2 = 0.442); 2-hour PG (mmol/L) = 13.931 − 4.099 · log II ([pmol/L] · [mmol/L]$^{-1}$) − 0.143 · QUICKI ([log (μU/mL) + log (mg/100 mL)]$^{-1}$) + 0.039 · age (yr) + 0.143 · BMI (kg/m^2) (r^2=0.482). Thus, β-cell dysfunction contributed most significantly for elevation of PG, especially for elevation of 2-hour PG. Lower Si contributed little to elevation of 2-hour PG. (Note that the mean value of log II was 1.87 and that of QUICKI 0.385 as shown in Table 1, and the standardized correlation coefficient of the former was approximately twice that of the latter as shown in Tables 2 through 5.) The contributions of age per se for elevation of FPG and 2-hour PG were 0.07 mmol/L and 0.39 mmol/L per decade, respectively.

Table 2. Partial Correlation Matrix in the Entire Population With Incorporation of FPG

Variable	FPG	II	QUICKI	BMI
Age	r = 0.103	r = −0.078	r = 0.065	r = −0.022
	P = .0208	P = .0807	.1460	.6289
FPG		r = −0.592	r = −0.350	r = 0.117
		P < .0001	P < .0001	P = .0090
II			r = −0.261	r = −0.052
			P < .0001	P = .2498
QUICKI				r = −0.392
				P < .0001

Table 3. Partial Correlation Matrix in the Entire Population With Incorporation of 2-Hour

Variable	2-h PG	II	QUICKI	BMI
Age	r = 0.185	r = −0.017	r = 0.083	r = −0.042
	P < .0001	P = .7077	P = .0636	P = .3501
2-h PG		r = −0.627	r = −0.290	r = 0.175
		P < .0001	P < .0001	P < .0001
II			r = −0.235	r = 0.093
			P < .0001	P = .0377
QUICKI				r = −0.388
				P < .0001

Table 4. Partial Correlation Matrix in Subjets With NGT With Incorporation of FPG

Variable	FPG	II	QUICKI	BMI
Age	$r = 0.149$	$r = -0.017$	$r = 0.085$	$r = 0.016$
	$P = .0081$	$P = .7668$	$P = .1332$	$P = .7700$
FPG		$r = -0.290$	$r = -0.234$	$r = 0.138$
		$P < .0001$	$P < .0001$	$P = .0143$
II			$r = -0.237$	$r = -0.038$
			$P < .0001$	$P = .4947$
QUICKI				$r = -0.368$
				$P < .0001$

Additive Effect of Lower II and Si, and Higher Age and BMI on PG

The lower third of II ($\leq$30.6 [pmol/L] · [mmol/L]$^{-1}$) and Si ($\leq$0.358 [log (μU/mL) · log (mg/100 mL)]$^{-1}$), and the upper third of age ($\geq$58 years) and BMI ($\geq$24.9 kg/m^2), were defined as risk factors, and the mean PGs of the subjects without and with 1 to 4 risk factors were compared (Fig 2). As shown, the mean FPG and 2-hour PG values were progressively higher with an accumulation of risk factors, with a statistically significant difference up to those with 3 risk factors. The mean FPG and 2-hour PG values of the subjects with 3 risk factors were 6.52 and 10.8 mmol/L, respectively (Fig 2). This 2-hour PG was at the higher end of NDH. Thus, an additive effect of each risk factor for elevation of PG, especially up to the upper end of NDH, was strongly suggested.

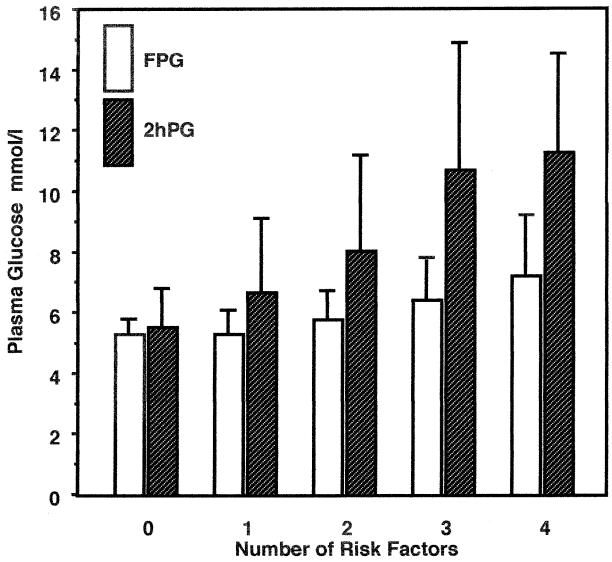

Fig 2. Effect of accumulation of risk factors on PG. A lower third of II and Si, and an upper third of age and BMI, were defined as risk factors, and the entire population was divided into 5 groups based on the number of the risk factors, as shown on the abscissa. See text for details. Acquisition of 1 risk factor was associated with statistically significant ($P < .01$ by analysis of variance with post hoc pairwise comparison with Fisher's protected least significant difference) elevation of FPG and 2-hour PG, respectively, up to 3 risk factors. Differences in FPG and 2-hour PG, respectively, between subjects with 3 and 4 risk factors were not statistically significant.

DISCUSSION

Primacy of the β-cell dysfunction in the development of hyperglycemia in the general population was strongly implicated in this study because PG correlated so prominently with II compared to other diabetogenic factors. In addition to β-cell dysfunction and reduced Si, quantitative contribution of age and high body weight cannot be neglected if one considers deviation of PG on a long-term basis: a combination of 30 years of aging and a 5-kg/m^2 increase in the BMI is expected to be associated with a 1.9-mmol/L elevation of 2-hourPG, even if there is no change in β-cell function and Si. This finding at least partly explains why future development of DM could not reliably be predicted by the baseline measurements of β-cell function and Si alone.[7] Taken together, it is most likely that β-cell dysfunction, decreased Si, aging, and weight gain independently contribute to the development of diabetes.

Table 5. Partial Correlation Matrix in Subjects With NGT With Incorporation of 2-Hour PG

Variable	2-h PG	II	QUICKI	BMI
Age	$r = 0.224$	$r = -0.005$	$r = 0.092$	$r = -0.034$
	$P < .0001$	$P = .9237$	$P = .1004$	$P = .5421$
2-h PG		$r = -0.242$	$r = -0.192$	$r = 0.170$
		$P < .0001$	$P = .0006$	$P = .0023$
II			$r = -0.220$	$r = 0.040$
			$P < .0001$	$P = .4797$
QUICKI				$r = -0.370$
				$P < .0001$

A significant contribution of aging per se for glucose intolerance is suggested by simple but concrete evidence that aging is associated with worsening of glucose tolerance and an increase in the prevalence of NDH and DM in human across various ethnic groups.[8,9,26] Progressive worsening of glucose tolerance with age despite intensive treatment/management of DM in patients with type 2 DM[27] also supports this notion. As the underlying mechanism(s) for age- and weight-related elevation of PG after adjustment for β-cell dysfunction and decreased Si, lowering of non–insulin-mediated glucose entry into the cells ("glucose effect") can be considered. Attenuated glucose effect is a well-established abnormality, in addition to decreased Si, in patients with DM.[28] Another possible mechanism would be insufficient suppression of hepatic glucose output by insulin upon nutrient challenge. This could not be detected unless specific measurements are performed.[29] Age-related attenuation of these processes was reported in some studies.[8] Age-related accumulation of visceral fat might also contribute to hepatic IR.

In this study, we evaluated Si by QUICKI, an index derived from FPG and FIRI. This may be a drawback of the study. Namely, a substantial number of subjects had β-cell dysfunction in this population, and QUICKI might underestimate the decrease in Si in such individuals. If the age-related reduction in Si was more accentuated than currently depicted, the seemingly independent correlation between PG and age and body weight, respectively, might be fully explained by reduced Si.

Due to the cross-sectional nature of this study, dissection of the cause-result relationship is impossible by the current data

alone. Although it is logical to consider β-cell dysfunction as the cause of elevation of PG, a part of it may be a result of glucose toxicity. Deranged insulin secretion can be found with elevation of glucose levels that are difficult to distinguish from normal in the rodent models.[30] Thus, elevation of PG within the range of NDH, or even a minimal elevation of it within the range of NGT, could be a cause of β-cell dysfunction, especially in susceptible subjects. Deconvolution of the question might be accomplished by a longitudinal study.

The underlying mechanism for development of type 2 DM in humans may be highly variable as previously proposed.[5] Overwhelming correlation of PG with II compared to other diabetogenic factors was found in the Japanese general population. For prevention of DM, preservation, or restoration if possible, of β-cell function may be as important as, or even more important than, amelioration of IR in a population like Japanese. Improvement of insulin secretion is not easy, but it is possible as reported in some studies.[31,32]

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