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Factors responsible for age-related elevation in fasting plasma glucose: a cross-sectional study in Japanese men

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Abstract

To evaluate the factors associated with age-related increase in fasting plasma glucose (FPG) in Japanese men with normal fasting glucose, we measured FPG, fasting immunoreactive insulin, glycated hemoglobin, total cholesterol, triglyceride, and high-density lipoprotein cholesterol levels in health check examinees. Subjects with FPG less than 6.1 mmol/L together with glycated hemoglobin less than 5.6% were enrolled in the study. The homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA-β were used as the indices of insulin sensitivity and insulin secretion, respectively. Fasting plasma glucose increased significantly with age ($r = 0.30$, $P < .0001$), and HOMA-β decreased significantly with age ($r = 0.24$, $P < .0001$). The HOMA-IR had no significant relation with age ($r = 0.06$, not significant), whereas body mass index and serum triglyceride were associated with HOMA-IR ($r = 0.49$, $P < .0001$ and $r = 0.33$, $P < .0001$, respectively). Thus, in Japanese male subjects with normal fasting glucose, it is suggested that the FPG increment with age is associated with decreased β-cell function rather than with insulin resistance. Further analyses were performed by comparing 3 groups: low FPG (FPG <5.0 mmol/L), high FPG (5.0 ≤ FPG < 5.6 mmol/L), and mild impairment of fasting glycemia (mild IFG) (5.6 ≤ FPG < 6.1 mmol/L). The insulin levels in mild IFG and high FPG were significantly higher than in low FPG ($P < .001$), but those in mild IFG were similar to those in high FPG. Analysis of the 3 subgroups revealed that, whereas insulin sensitivity was impaired more in high FPG, there was little compensatory increase in insulin in mild IFG, suggesting that β-cell function is already deteriorated when the FPG level is greater than 5.6 mmol/L.

1. Introduction

Type 2 diabetes mellitus is characterized by both decreasing insulin secretion and insulin sensitivity, partly due to genetic factors [1-3]. Although diabetes is a worldwide health problem [4], it is clear that there are ethnic differences in the pathophysiology of the decreasing glucose tolerance characteristic of its development [5]. Factors responsible for glucose intolerance occur from a prediabetic state: impaired glucose regulation according to the World Health Organization classification. Impaired glucose regulation comprises 2 subgroups: impaired fasting glycemia (IFG) characterized by increasingly impaired fasting plasma glucose (FPG) with 2-hour plasma glucose (2h-PG) within normal limits and impaired glucose tolerance (IGT) characterized by increasingly impaired 2h-PG [6,7]. We previously reported that insulin secretory capacity and insulin sensitivity are both decreased in Japanese subjects with IFG [8-10]. Although β-cell function and insulin sensitivity may well begin to deteriorate earlier, there are few studies of the normal glucose tolerance (NGT) population. Fasting plasma glucose is known to increase with age [11], and both insulin secretory capacity and insulin

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sensitivity are reported to decrease with age [12-14]. We have reported that some subgroups of Japanese NGT subjects show especially decreased β-cell function [15]. However, it is unclear whether deteriorated insulin secretion or insulin sensitivity is the primary factor in the increase in FPG during the period of development from NGT to IFG in Japanese.

In addition, the American Diabetes Association (ADA) lowered the cutoff value of IFG from 6.1 to 5.6 mmol/L [16]. Subjects with FPG from 5.6 to 6.1 mmol/L and with normal postprandial glucose level are categorized as having IFG in the ADA criteria, although they are categorized as having NGT in the criteria of the World Health Organization and the Japanese Diabetes Association. Thus, analysis of these subjects with mild IFG (mild impairment of fasting glucose) in view of insulin secretion and insulin sensitivity is crucial to elucidate the characteristic of subjects with borderline glucose dysregulation. To investigate the pathogenesis of prediabetes in Japanese, we compared insulin secretory capacity and insulin sensitivity in health check examinees exhibiting normal fasting glucose (NFG).

2. Subjects and methods

2.1. Subjects

Among health check examinees between 1993 and 2004 at Kyoto University Hospital, Kansai-Denryoku Hospital, and Kyoto Preventive Medical Center, 657 male subjects with FPG <6.1 mmol/L and glycated hemoglobin (HbA_{1c}) <5.6% were enrolled in the study (Table 1). Subjects with known history or signs of diabetes, previous gastrointestinal operation, liver disease, renal failure, endocrine disease, malignancy, hypertension, frequent heavy exercise, or history of medications before the study were excluded.

2.2. Measurements

Physical measurement (body height, body weight) and laboratory measurements (urine test, FPG, fasting immunoreactive insulin [F-IRI], HbA_{1c}, total cholesterol [TC], triglyceride [TG], and high-density lipoprotein cholesterol [HDL-C] level) were taken. The study was designed in compliance with the ethics regulations of the Helsinki Declaration. Blood samples were collected after overnight fasting for 16 hours [8]. Plasma glucose levels were measured by glucose oxidase method using the Hitachi Automatic Clinical Analyzer 7170 (Hitachi, Tokyo, Japan). Serum insulin levels were measured by radioimmunoassay (RIA beads II; Dainabot, Tokyo, Japan), which shows low cross-reaction with C-peptide of less than 0.005% and proinsulin less than 0.5% [8]. Glycated hemoglobin levels were measured by high-performance liquid chromatography methods. Serum TC, TG, and HDL-C levels were measured as reported previously [17]. To evaluate insulin resistance, we used the homeostasis model assessment of insulin resistance index (HOMA-IR) calculated by the formula FPG (in millimoles per liter) × IRI (in microunits per milliliter)/22.5. The HOMA-IR is a reliable measure of insulin resistance, correlating well with values obtained by glucose clamp and minimal model studies [18-20]. To calculate pancreatic β-cell function (HOMA β-cell), we used the formula 20 × IRI (in microunits per milliliter)/[FPG (in millimoles per liter) − 3.5] [18].

Table 1
Clinical characteristics of the subjects with NFG

	Data
n	657
Age (y)	44.9 ± 11.2
BMI (kg/m^2)	23.6 ± 2.8
HbA_{1c} (%)	4.8 ± 0.3
FPG (mmol/L)	5.1 ± 0.4
F-IRI (μU/mL)	5.2 ± 2.9
TC (mmol/L)	5.19 ± 0.88
TG (mmol/L)	1.45 ± 1.01
HDL-C (mmol/L)	1.45 ± 0.35

Data are mean ± SD.

2.3. Statistical analysis

Clinical data are expressed as mean ± SD. Analyses were performed using the STATVIEW 5 system (StatView, Berkeley, CA). Multiple regression analysis was used to compare age and FPG, HOMA-β, HOMA-IR, and body mass index (BMI). The same analysis was performed between HOMA-IR and BMI and TG. The NFG group was divided into low and high FPG and mild IFG, and the metabolic profiles were compared using analysis of variance. The data are expressed as mean ± SE. $P < .05$ is considered significant.

3. Results

3.1. Characteristics of the study population

As shown in Table 1, the mean age of the subjects is 44.9 ± 11.2 years and the mean BMI is 23.6 ± 2.8 kg/m^2. Among them, the number of subjects with BMI more than 30 are 22 (3.4%), concomitant with the representative epidemiologic studies in Japanese [21-23].

3.2. Correlation between age and FPG, HOMA-β, and HOMA-IR

Fig. 1A shows a positive relationship of FPG with age ($r = 0.30$, $P < .0001$; FPG [in millimoles per liter] = 0.011 × age + 4.6). Fig. 1B shows that HOMA-β has a negative correlation with age ($r = 0.24$, $P < .0001$), whereas there is no significant correlation between HOMA-IR and age ($r = 0.06$, not significant).

3.3. Correlation between HOMA-IR and BMI and serum TG levels

Fig. 2A, B shows that BMI and serum TG levels are associated with HOMA-IR ($r = 0.49$, $P < .0001$ and $r = 0.33$,

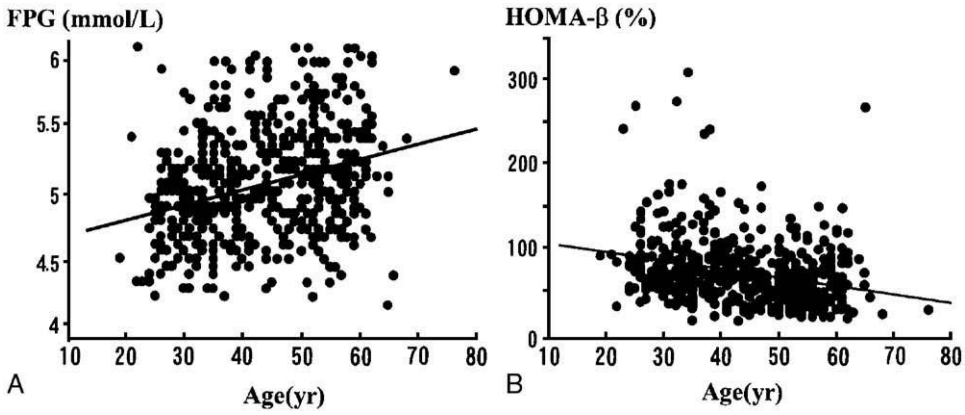

Fig. 1. Distribution of FPG (A) and HOMA-β (B) cell by age. The FPG increases with age (r = 0.30, P < .0001). The HOMA-β cell is negatively correlated with age (r = 0.24, P < .0001).

P < .0001, respectively). Multiple regression analysis shows that both BMI and TG are independently associated with HOMA-IR (standardized β = 0.41 and 0.15, respectively). Body mass index was the strongest determinant of HOMA-IR, and BMI did not increase with age significantly in Japanese men (r = 0.07, not significant).

3.4. Analysis of 3 subgroups of NFG subjects

To evaluate the factors involved in increasing FPG in Japanese NFG and the ADA recommendation of lowering the threshold of upper limit of normal FPG from 6.1 to 5.6 mmol/L [16], we divided our NFG subjects into 3 subgroups: low FPG (FPG <5.0 mmol/L), high FPG (5.0 ≤ FPG < 5.6 mmol/L), and mild impairment of fasting glucose (mild IFG) (5.6 ≤ FPG < 6.1 mmol/L); and age, BMI, TG, and insulin secretion and sensitivity were compared. As shown in Table 2, high FPG and mild IFG have higher age and BMI than low FPG (both P < .0001). Insulin in high FPG and mild IFG is increased compared with that in low FPG (P < .001); insulin in mild IFG is similar to that in high FPG. The HOMA-IR in high FPG and mild IFG is increased compared with that in low FPG (P < .0001). The HOMA-β in high FPG and mild IFG is decreased compared with that in low FPG (P < .0001); the HOMA-β in mild IFG is decreased compared with that in high FPG (P < .001).

4. Discussion

In this study, we analyzed the factors responsible for age-related elevation of FPG in Japanese men with NFG. Fasting plasma glucose was found to increase with age primarily because of reduced β-cell function rather than increased insulin resistance. In addition, we have elucidated that there was no compensatory increase in insulin secretion in mild IFG (FPG 5.6-6.1 mmol/L).

Our study subjects were composed only of men because the number of female subjects was 158, which is not comparable with male subjects. Some reports showed a difference between men and women in the elevation of FPG [24-26], and another showed similar results between men and women in the elevation of FPG [27]. We analyzed the results from our 158 female subjects, and we could not find

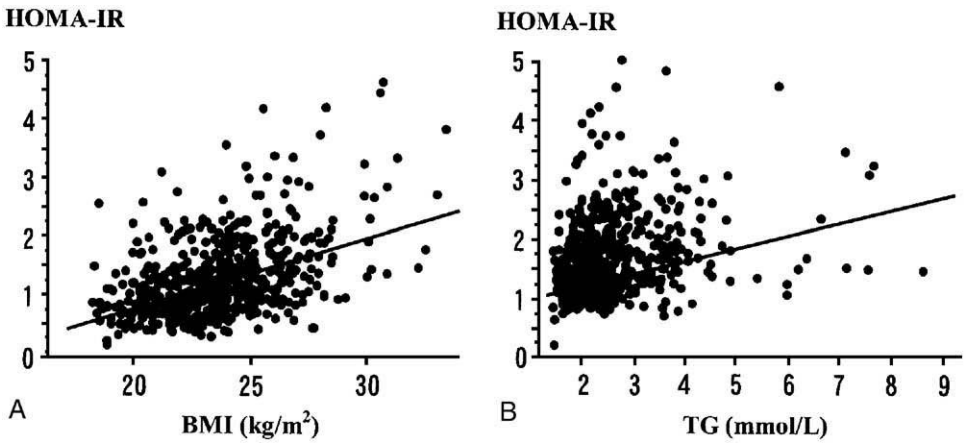

Fig. 2. Distribution of HOMA-IR by BMI (A) and TG (B). Both BMI and TG are associated with HOMA-IR (BMI: r = 0.49, P < .0001; TG: r = 0.33, P < .0001).

Table 2
Comparison of 3 FPG subgroups of NFG subjects

	Low FPG (FPG <5.0 mmol/L)	High FPG (5.0 ≤ FPG < 5.6 mmol/L)	Mild IFG (5.6 ≤ FPG < 6.1 mmol/L)
n	268	288	101
Age (y)	42.0 ± 0.7	45.7 ± 0.6 [a]	49.8 ± 1.0 [a, b]
BMI (kg/m^2)	23.0 ± 0.2	23.9 ± 0.1 [a]	24.3 ± 0.3 [a]
TC (mmol/L)	5.07 ± 0.05	5.23 ± 0.05 [c]	5.35 ± 0.08 [d]
TG (mmol/L)	1.30 ± 0.05	1.55 ± 0.06 [d]	1.56 ± 0.09 [c]
HDL-C (mmol/L)	1.45 ± 0.02	1.44 ± 0.02	1.45 ± 0.03
F-IRI (μU/mL)	4.6 ± 0.2	5.7 ± 0.2 [a]	5.6 ± 0.3 [e]
HOMA-IR	0.96 ± 0.04	1.31 ± 0.04 [a]	1.44 ± 0.07 [a]
HOMA-β (%)	78.5 ± 3.1	65.2 ± 1.9 [a]	49.2 ± 2.4 [a, b]

Data are mean ± SE.
[a] $P < .0001$ vs low FPG.
[b] $P < .001$ vs high FPG.
[c] $P < .05$ vs low FPG.
[d] $P < .005$ vs low FPG.
[e] $P < .0005$ vs low FPG.

remarkable differences with male subjects (data not shown). Further studies are necessary to elucidate the sex difference of the factors responsible for elevation of FPG. Although some reports showed an increase in insulin resistance in subjects older than 70 years, our male subjects were younger than 70 years. Insulin resistance in subjects older than 70 years was reported mainly because of the change in abdominal adiposity [28,29]; and in representative epidemiologic studies such as the Funagata study and the Hisayama study, the mean age of developing glucose intolerance is around 50 years in Japanese [21-23]. For these reasons, our subjects being around the age of 50 years was enough for our purpose in this study of elucidating the factors responsible for FPG elevation from normal to borderline glucose dysregulation.

Fasting plasma glucose increased by 0.011 mmol/L per year, in accord with previous reports [30]. The HOMA-β decreased by 0.85% per year, clearly indicating reduced basal insulin secretion. Although previous studies in whites and in other populations have found that insulin resistance is closely associated with age-related FPG elevation [12,31], HOMA-IR did not increase with age significantly in our subjects. To characterize the insulin resistance of our study population, we performed both simple and multiple regression analyses between HOMA-IR and the other measured factors. The BMI and serum TG levels were strongly associated with HOMA-IR ($P < .0001$), in accord with our previous results in Japanese diabetic patients [32]. Although BMI was the strongest determinant of HOMA-IR, it did not increase with age; the mean BMI of 23.6 kg/m^2 is in accord with Japanese statistical data [21-23] and is much lower than in whites [33,34]. The BMI of Asians in other studies is also reported to be lower, suggesting a common metabolic profile [35]. The leaner Japanese subjects in this study might therefore be expected to be less influenced by insulin resistance in comparison with whites.

Impaired fasting glycemia is a prediabetic state characterized by FPG elevation without increased 2h-PG. We previously reported that insulin secretory capacity and insulin sensitivity are both already decreased in IFG [8-10], suggesting the clinical importance of early deterioration of β-cell function and insulin sensitivity in developing prediabetes. In addition, we regarded the PG level of 5.6 mmol/L as an important FPG threshold value according to ADA recommendation [16]. Therefore, we compared insulin secretion and insulin sensitivity in 3 subgroups of NFG subjects: low FPG (FPG <5.0 mmol/L), high FPG (5.0 ≤ FPG < 5.6 mmol/L), and mild IFG (5.6 ≤ FPG < 6.1 mmol/L). Insulin secretion in mild IFG was not increased compared with that in high FPG, indicating impaired compensatory insulin secretion against increasing insulin resistance. Some reports have found that early-phase insulin secretion and insulin sensitivity are both decreased in NGT at a higher range of FPG (FPG >5.1-5.3 mmol/L) [36-38]. Fortunately, we could analyze 56 subjects during the 8-year follow-up period using oral glucose tolerance test results [39]. The subjects who developed from NFG to IFG showed decreasing insulin sensitivity and insulin secretory capacity, and those who developed from NFG to IGT showed decreased early insulin secretory response. These follow-up data were compatible with our previous data of IFG and IGT [5,8,10,39]. Taken together, these data indicate that insulin secretory capacity is already decreased in NGT at the higher range of FPG and that a lack of compensatory insulin secretion appears at greater than 5.6 mmol/L in FPG.

We find in Japanese NFG subjects that age-related FPG elevation is mainly due to decreased β-cell function rather than to increasing insulin resistance as in white subjects. In addition, analysis of 3 degrees of increasing FPG indicates that failure of compensatory insulin secretion is responsible for the elevation in FPG in these subjects. Thus, these data could be helpful in reconsideration of the threshold FPG for prediabetes to be recommended by the ADA [16]. However, decreasing the upper threshold of FPG entails increasing the IFG population, a costly social health problem [40]. Further studies are required to clarify the ethnic differences in the development of diabetes and diabetic complications and the value of clinical interventions in newly diagnosed IFG patients.

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