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Original Article

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Determinants of Glycated Hemoglobin in Subjects With Impaired Glucose Tolerance: Subanalysis of the Japan Diabetes Prevention Program

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Abstract

Background: Limited evidence is available about the relationship of lifestyle factors with glycated hemoglobin (HbA1c) in subjects with impaired glucose tolerance. The aim of study was to identify such determinant factors of HbA1c in subjects with impaired glucose tolerance.

Methods: This cross-sectional study included 121 men and 124 women with impaired glucose tolerance, who were diagnosed based on a 75-g oral glucose tolerance test. Demographic and biochemical parameters, including the body mass index (BMI), fasting plasma glucose (FPG), 2-h post-load glucose (2-h PG), and HbA1c, were measured. The pancreatic β-cell function and insulin resistance were assessed using homeostasis model assessment (HOMA-β). Dietary intake was assessed by a food frequency questionnaire.

Results: The levels of FPG, 2-h PG, and carbohydrate intake were correlated with the HbA1c level in men, while the FPG and 2-h PG levels were correlated with the HbA1c level in women. In multiple regression analyses, BMI, FPG, 2-h PG, and white rice intake were associated with HbA1c levels in men, while BMI, FPG, HOMA-β, and bread intake were associated with HbA1c levels in women.

Conclusions: The present findings suggest that a substantial portion of HbA1c may be composed of not only glycemic but also several lifestyle factors in men with impaired glucose tolerance. These factors can be taken into consideration as modifiable determinants in assessing the HbA1c level for the diagnosis and therapeutic monitoring of the disease course.

Keywords: Bread; Carbohydrate; Diabetes; Glycosylated hemoglobin; White rice

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Introduction

The prevalence of type 2 diabetes is increasing globally, placing a heavy burden on the public health and socioeconomic development of all nations [1]. Type 2 diabetes is a multifactorial disease due to the combination of environmental and genetic risk factors. Many environmental risk factors contribute to the pathogenesis of type 2 diabetes, including lifestyles such as sedentary behavior, unhealthy diet, smoking, and alcohol consumption. Measuring glycated hemoglobin (HbA1c) has long been fundamental to managing patients with diabetes. HbA1c is not only used to monitor long-term glycemic control (representing the average blood glucose concentration over the previous 8 - 12 weeks), but also to adjust therapy, assess the quality of care, and predict the risk for the development of complications in subjects with impaired glucose metabolism [2-6].

Exploring the determinants of HbA1c is thus important. The HbA1c level has been reported to be associated with lifestyle-related factors such as smoking, dietary factors, and alcohol drinking in the general population [7-9]. Carbohydrate intake has

Table 1. Population Characteristics of Men and Women With Impaired Glucose Tolerance in the Japan Diabetes Prevention Study

Parameters	Men (n = 121)	Women (n = 124)	P-value
Demographic parameters			
Age, years	50.0 (46.0 - 56.0)	53.0 (49.5 - 57.0)	< 0.01
Current smoker, %	39.7	5.6	< 0.01
BMI, kg/m^2	24.7 (23.2 - 26.6)	23.2 (21.9 - 26.0)	0.15
Waist circumference, cm	88.4 (83.0 - 92.0)	80.5 (74.3 - 88.0)	< 0.01
Blood pressure			
Systolic blood pressure, mm Hg	130.0 (118.0 - 140.0)	131.5 (120.0 - 140.0)	0.76
Diastolic blood pressure, mm Hg	80.0 (74.0 - 89.0)	80.0 (72.0 - 86.0)	0.24
Metabolic parameters			
Fasting plasma glucose, mmol/L	6.1 (5.8 - 6.5)	5.8 (5.5 - 6.3)	< 0.01
2-h post-load plasma glucose, mmol/L	9.1 (8.4 - 10.0)	8.8 (8.2 - 9.6)	0.03
HbA1c, %	5.7 (5.4 - 6.0)	5.8 (5.6 - 6.0)	< 0.01
HOMA-IR	1.9 (1.4 - 2.6)	1.5 (1.1 - 2.1)	< 0.01
HOMA-β	57.4 (43.3 - 72.0)	51.9 (36.3 - 75.7)	0.68
Triglycerides, mmol/L	3.6 (2.9 - 5.2)	2.4 (1.7 - 3.7)	< 0.01
HDL-cholesterol, mmol/L	1.3 (1.2 - 1.6)	1.5 (1.3 - 1.7)	< 0.01
Dietary factors			
Total energy intake, kcal	2,471.1 (1,857.8 - 3,099.9)	2,123.2 (1,810.1 - 2,542.0)	< 0.01
Protein intake, g	86.7 (67.0 - 118.2)	89.2 (70.8 - 112.3)	0.46
Fat intake, g	67.4 (46.1 - 96.3)	64.4 (55.1 - 87.0)	0.49
Carbohydrate intake, g	305.9 (248.3 - 366.7)	283.8 (241.6 - 331.6)	0.06
Alcohol intake, g	22.5 (4.0 - 51.1)	0.4 (0.0 - 2.9)	< 0.01
Main carbohydrate-containing foods			
White rice, g	111.3 (81.1 - 172.4)	89.0 (65.9 - 109.8)	< 0.01
Bread, g	18.4 (6.7 - 38.1)	18.7 (7.6 - 34.2)	0.96
Noodles, g	19.2 (9.8 - 31.5)	13.0 (7.2 - 22.6)	< 0.01
Fruit, g	8.0 (4.8 - 14.1)	15.1 (9.7 - 25.7)	< 0.01
Milk, g	5.6 (2.4 - 15.5)	12.1 (5.2 - 18.1)	0.01
Snacks, g	9.2 (4.5 - 18.9)	16.8 (10.6 - 30.4)	< 0.01
Energy expenditure, kcal	2,289.9 (2,107.4 - 2,544.5)	2,149.1 (1,879.4 - 2,433.8)	< 0.01

BMI: body mass index; HOMA-IR: homeostasis model assessment-insulin resistance; HOMA-β: homeostasis model assessment-beta-cell function; HDL: high-density lipoprotein. The values are the percentage and median (25th - 75th percentiles).

also been suggested to be one of the factors associated with the HbA1c level and, in fact, there is a report showing that the substitution of fat for carbohydrate was associated with low HbA1c levels in diabetic patients with high-level energy consumption [10]. However, limited evidence is available on the relationship of lifestyle factors with HbA1c in subjects with impaired glucose tolerance. The aim of the study was to examine such factors of HbA1c in subjects with impaired glucose tolerance.

Materials and Methods

Participants

Subjects with impaired glucose tolerance, aged 30 - 60 years, were recruited through health checkups conducted at each collaborative center. Recruitment started in March 1999 and was completed in December 2002. A two-step strategy was adopted for identifying those with impaired glucose tolerance as described previously [11]. Using the data from health checkups, those who met one of the following criteria were extracted: 1) fasting plasma glucose (FPG) concentration ≥ 5.6 mmol/L but < 7.0 mmol/L, 2) casual plasma glucose (PG) concentration ≥ 7.8 mmol/L but < 11.1 mmol/L when blood was drawn within 2 h after a meal, or casual PG concentration ≥ 6.1 mmol/L but < 7.8 mmol/L when blood was drawn 2 h or more after a meal, or 3) impaired glucose tolerance as indicated by a previous 75-g oral glucose tolerance test (OGTT). The subjects were examined by the 75-g OGTT if they fulfilled any one of the above mentioned criteria. The definition of impaired glucose tolerance was based on the WHO's criteria [12, 13]. Those with: 1) a previous diag-

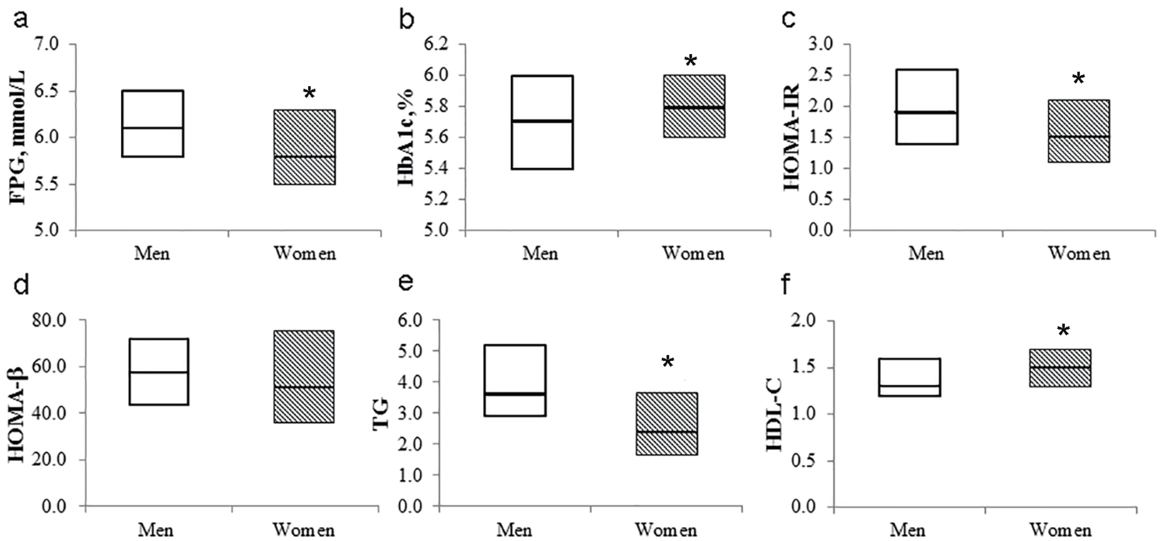

Figure 1. Box plot of metabolic parameters according to sex. The bold horizontal line represents the median, and the box represents the bounds of the 25th and 75th percentiles. FPG: fasting plasma glucose; HOMA-IR: homeostasis model assessment-insulin resistance; HOMA-β: homeostasis model assessment-beta-cell function; TG: triglycerides; HDL: high-density lipoprotein. *P < 0.05 (vs. men).

nosis of any type of diabetes or gestational diabetes, 2) a history of gastrectomy, 3) a physical condition such as ischemic heart disease, heart failure, exercise-induced asthma, or orthopedic problems where exercise was not allowed by a doctor, 4) definitive liver and kidney diseases, 5) autoimmune diseases (including hemolytic anemia), and 6) drinking heavily (69 g or more of ethanol per day [14] were excluded.

Measurements

All participants underwent a complete physical examination, including measurements of height, weight, waist circumference (WC), and blood pressure (BP). The body mass index (BMI) was calculated as the weight divided by the height squared. WC was measured at the umbilical level. Biochemical studies, including a 75-g OGTT, were conducted biannually during the first year and annually thereafter. Blood total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, HbA1c, plasma glucose, and insulin levels were measured at a central laboratory (SRL Co., Ltd, Tokyo, Japan). The pancreatic β-cell function and insulin resistance were assessed using homeostasis model assessment (HOMA-β and HOMA-IR) [15]. The dietary intake of each participant was assessed using a semiquantitative food frequency questionnaire (FFQ) [16] with photographs of 122 varieties of dishes and foods. Each item was shown with the actual portion size. Self-reported levels of physical energy expenditure were assessed using a physical activities questionnaire [17]. Current smoking was self-reportedly defined as a smoker.

Statistical analysis

Variables were presented as the median (25th - 75th percentiles). Pearson's correlation coefficient analysis and regression analysis were used to determine the correlation between HbA1c and interest parameters. Main carbohydrate-containing foods included white rice, bread, noodles, fruit, milk, and snacks. To clarify the relationship of HbA1c and other parameters, we performed stepwise multiple linear regression analysis. We set it at P < 0.05 for univariate analysis and then selected FPG, 2-h PG, BMI, HOMA-β, white rice intake, and bread intake.

The Statistical Package for the Social Sciences (SPSS 20.0, IBM Corp., New York, USA) program was used. A two-tailed P-value < 0.05 was considered significant. Those cases with missing data were omitted in the relevant analysis.

Ethics

The study protocol was approved by the Ethics Committee of the National Hospital Organization Kyoto Medical Center, and all subjects gave their written informed consents before the start of the study.

Results

Men had significantly higher WC (88.4 (83.0 - 92.0) vs. 80.5 (74.3 - 88.0) mmol/L; P < 0.01), FPG (6.1 (5.8 - 6.5) vs. 5.8 (5.5 - 6.3) mmol/L; P < 0.01), 2-h PG (9.1 (8.4 - 10.0) vs. 8.8 (8.2 - 9.6) mmol/L; P < 0.05), HOMA-IR (1.9 (1.4 - 2.6) vs. 1.5 (1.1 - 2.1); P < 0.01), triglycerides (3.6 (2.9 - 5.2) vs. 2.4 (1.7 - 3.7) mmol/L; P < 0.01), total energy intake (2,471.1 (1,857.8 - 3,099.9) vs. 2,132.2 (1,810.1 - 2,542.0) kcal; P < 0.01), alcohol intake (22.5 (4.0 - 51.1) vs. 0.4 (0.0 - 2.9) g; P < 0.01), and energy expenditure (2,289.9 (2,107.4 - 2,544.5) vs. 2,149.1 (1,879.4 - 2,433.8) kcal; P < 0.01) than women,

Table 2. Correlation Between HbA1c Levels and Respective Interest Parameters

Parameters	Men		Women	
	r	P-value	r	P-value
Demographic parameters				
Age, years	0.02	0.82	0.08	0.38
Current smoking, yes	0.02	0.81	0.07	0.42
BMI, kg/m^2	0.29	< 0.01	0.08	0.40
Waist circumference, cm	0.26	< 0.01	0.05	0.57
Metabolic parameters				
Fasting plasma glucose, mmol/L	0.33	< 0.01	0.46	< 0.01
2-h post-load glucose, mmol/L	0.27	< 0.01	0.22	0.02
HOMA-IR	0.11	0.23	0.05	0.59
HOMA-β	-0.06	0.52	-0.27	< 0.01
Dietary factors				
Total energy intake, kcal	0.09	0.35	0.03	0.71
Protein intake, g	0.07	0.42	0.01	0.90
Fat intake, g	0.07	0.42	0.02	0.82
Carbohydrate intake, g	0.24	0.01	0.05	0.61
Alcohol intake, g	-0.17	0.06	-0.14	0.12
Main carbohydrate-containing foods				
White rice, g	0.34	< 0.01	-0.06	0.56
Bread, g	-0.07	0.48	0.25	0.01
Noodles, g	-0.09	0.34	0.16	0.11
Fruit, g	0.14	0.14	-0.05	0.65
Milk, g	0.18	0.07	-0.19	0.06
Snacks, g	0.06	0.53	0.15	0.13
Energy expenditure, kcal	0.18	0.046	0.07	0.42

BMI: body mass index; HOMA-IR: homeostasis model assessment-insulin resistance; HOMA-β: homeostasis model assessment-beta-cell function. "r" is a correlation coefficients.

while women had a significantly higher age (50.0 (46.0 - 56.0) vs. 53.0 (49.5 - 57.0) years; P < 0.01) as well as HbA1c (5.7 (5.4 - 6.0) vs. 5.8 (5.6 - 6.0)%; P < 0.01) and HDL-cholesterol levels (1.3 (1.2 - 1.6) vs. 1.5 (1.3 - 1.7) mmol/L; P < 0.01) than men (Table 1, Fig. 1a-f). The proportion of current smokers was higher in men than women. There was no difference in the levels of BMI or BP between men and women. BMI, WC, FPG, 2-h PG, carbohydrate intake, and white rice intake were correlated with the HbA1c level in men, while FPG, 2-h PG, HOMA-β, and bread intake were correlated with the HbA1c level in women (Table 2).

In multiple regression analyses, BMI, FPG, 2-h PG, and white rice intake were associated with HbA1c levels in men, while BMI, FPG, HOMA-β, and bread intake were associated

Table 3. Results of Stepwise Multiple Linear Regression Analysis to Evaluate the Effect of Independent Variables on HbA1c

Model by sex	Independent parameters	Beta	P-value	F	P -value	R^2	Adjusted R^2
Men	BMI	0.27	< 0.01	14.68	< 0.01	0.36	0.34
	Fasting plasma glucose	0.28	< 0.01				
	2-h post-load glucose	0.23	< 0.01				
	White rice intake	0.33	< 0.01				
Women	BMI	0.22	0.03	11.37	< 0.01	0.32	0.29
	Fasting plasma glucose	0.37	< 0.001				
	HOMA-β	-0.28	0.01				
	Bread intake	0.21	0.02				

HOMA-β: homeostasis model assessment-beta-cell function; BMI: body mass index.

with HbA1c levels in women (Table 3).

Discussion

In multiple regression analyses, BMI, FPG, 2-h PG, and white rice intake were associated with HbA1c levels in men, while BMI, FPG, HOMA-β, and bread intake were associated with HbA1c levels in women. The FPG has been established as a glycemic determinant factor of HbA1c [18]. In recent-onset diabetic subjects, the β-cell function, as defined by HOMA-β, was correlated with the HbA1c level [19]. In addition, the BMI was found to be correlated with higher HbA1c [20]. These dietary determinants of HbA1c are relevant when considering the importance of HbA1c as a diagnostic marker of diabetes [2-4], and that these factors are modifiable. This may be applied when using HbA1c for the diagnosis and therapeutic monitoring of diabetes in men with impaired glucose tolerance in particular.

The total amount of carbohydrate consumed strongly predicts the glycemic response [21]. A dietary pattern featuring a frequent intake of white rice, which is one of the main carbohydrate foods in Japan, may deteriorate glucose metabolism in Japanese [22]. A higher intake of white rice is correlated with a significantly increased risk of type 2 diabetes, especially in Asian populations [23]. Therefore, an intake of white rice might increase HbA1c levels in male subjects with impaired glucose tolerance. The reason for the correlation between white rice intake and HbA1c levels in men, but not in women, is unknown. Men tended to have a higher white rice intake than women in the current study. White rice intake may affect the sex differences in the determinants of HbA1c. Bread is another one of the main carbohydrate foods. The consumption of white bread (≥ 2 portions/day) showed a significant correlation with the risk of becoming overweight/obese in Spanish populations [24]. A dietary pattern featuring intake of bread might increase HbA1c levels in female subjects with impaired glucose tolerance. Further examinations including larger samples are needed to clarify these issues.

The strengths of our investigation include a sample of Japanese adults evaluated using both HbA1c and OGTT. However, this study has several limitations. Firstly, the sample size was small. Secondly, causation cannot be determined because our analysis was cross-sectional. Thirdly, dietary intake was assessed only once, and thus may not have reflected the long-term intake. These limitations should be addressed in future research.

Conclusions

In conclusion, HbA1c was influenced by not only residual β-cell function but also several lifestyle factors, such as carbohydrate intake and alcohol drinking, in subjects with impaired glucose tolerance. These factors can be taken into consideration as modifiable determinants in assessing the HbA1c level for the diagnosis and therapeutic monitoring of the disease course.

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Competing Interests

The authors declare that they have no competing interests.

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