**ALDH2 polymorphism is associated with fasting blood glucose through alcohol consumption in Japanese men**

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**ABSTRACT**

Associations between alcohol consumption and type 2 diabetes risk are inconsistent in epidemiologic studies. This study investigated the associations of **ADH1B** and **ALDH2** polymorphisms with fasting blood glucose levels, and the impact of the associations of alcohol consumption with fasting blood glucose levels in Japanese individuals. This cross-sectional study included 907 men and 912 women, aged 35–69 years. The subjects were selected from among the Japan Multi-institutional Collaborative Cohort study across six areas of Japan. The **ADH1B** and **ALDH2** polymorphisms were genotyped by Invader Assays. The **ALDH2** Glu504Lys genotypes were associated with different levels of fasting blood glucose in men (P = 0.04). Mean fasting glucose level was positively associated with alcohol consumption in men with the **ALDH2** 504 Lys allele (P_{trend} = 0.02), but not in men with the **ALDH2** 504Glu/Glu genotype (P_{trend} = 0.45), resulting in no statistically significant interaction (P = 0.38). Alcohol consumption was associated with elevated fasting blood glucose levels compared with non-consumers in men (P_{trend} = 0.002). The **ADH1B** Arg48His polymorphism was not associated with FBG levels overall or after stratification for alcohol consumption. These findings suggest that the **ALDH2** polymorphism is associated with different levels of fasting blood glucose through alcohol consumption in Japanese men. The interaction of **ALDH2** polymorphisms in the association between alcohol consumption and fasting blood glucose warrants further investigation.

**Key Words:** **ADH1B** and **ALDH2** polymorphisms, type 2 diabetes, fasting blood glucose, alcohol consumption

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INTRODUCTION

Associations between alcohol consumption and type 2 diabetes risk are inconsistent in epidemiologic studies. In a meta-analysis of 15 prospective cohort studies performed worldwide, moderate alcohol consumption was associated with a decreased risk of type 2 diabetes, whereas high alcohol consumption was not\(^1\). In contrast, a systematic review of five prospective cohort studies in Japan reported that moderate alcohol consumption was associated with an increased risk of type 2 diabetes in subjects with a low body mass index (BMI)\(^3\). These inconsistent results may be due to different genetic susceptibilities to alcohol exposure between different populations. Therefore, it is necessary to investigate the possible associations between fasting blood glucose (FBG) levels and polymorphisms in \textit{ADH1B} or \textit{ALDH2}, taking into account alcohol consumption.

Alcohol is primarily oxidized to acetaldehyde by alcohol dehydrogenase (ADH) enzymes. Acetaldehyde is further oxidized to acetate by aldehyde dehydrogenase (ALDH) enzymes. Functional polymorphisms are found in the genes encoding \textit{ADH1B}, affecting alcohol consumption in humans\(^3, 4\). The \textit{ADH1B} Arg48His polymorphism (rs1229984) greatly affects enzyme activity, as the 48His allele is associated with faster oxidation of ethanol. The \textit{ADH1B} 48His allele is fairly common in Asian populations and rare in Caucasian populations. \textit{ALDH2} is the gene encoding mitochondrial ALDH, which contributes the majority of acetaldehyde oxidation in the human liver, and contains a functional polymorphism of Glu504Lys (rs671), with the minor 504Lys allele resulting in an inactive form. The minor allele of \textit{ALDH2} 504Lys is mainly found in Asian populations\(^5, 6\).

Several studies in Japan have investigated the associations between these alcohol-related genetic polymorphisms and glucose metabolism and type 2 diabetes. A study has found elevated fasting plasma glucose levels in men with the \textit{ADH1B} 48Arg/Arg genotype who consumed ≥ 10 g of alcohol per day\(^7\). Another study reported that fasting plasma insulin levels are lower in subjects with the \textit{ADH1B} 48Arg allele than in subjects with the 48His/His genotype\(^8\). Our previous study showed that the \textit{ADH1B} His48Arg polymorphism modified the association between alcohol consumption and type 2 diabetes in middle-aged Japanese men\(^9\), but the sample size was small. In terms of the \textit{ALDH2} Glu504Lys polymorphism, the \textit{ALDH2} 504Lys allele was associated with impaired glycemic control, as assessed by hemoglobin A\(_1c\) concentrations, in Japanese patients with type 2 diabetes and habitual light-to-moderate alcohol consumption\(^10\). Another study reported that the \textit{ALDH2} 504Lys allele was associated with elevated levels of fasting plasma glucose in Japanese women who consumed ≥ 5 g of alcohol per day\(^7\). Our previous study reported that the \textit{ALDH2} 504Lys allele is associated with a decreased risk of type 2 diabetes\(^9\). However, the study did not have enough statistical power to assess the interactions.

Two studies mentioned that the association of some gene polymorphisms with type 2 diabetes mellitus was sex-specific in Japanese individuals\(^7, 11\). The present study therefore examined the association of the \textit{ADH1B} and \textit{ALDH2} polymorphisms to FBG levels in a cross-sectional study in Japanese by sex, focusing on effect modifications by gene-environment interactions.

MATERIAL AND METHODS

Study population

The study subjects were among participants in the Japan Multi-institutional Collaborative Cohort (J-MICC) study. The design of the J-MICC study and the characteristics of the participants in the present cross-sectional study are described in more detail elsewhere\(^12, 13\). In brief, the subjects were enrolled across 10 study areas (Chiba, Shizuoka, Okazaki, Aichi Cancer Center,
Takashima, Kyoto, Tokushima, Fukuoka, Saga, and Amami) in Japan between 2004 and 2008. The subjects for the cross-sectional study comprised about 500 participants enrolled consecutively and arbitrarily in each area of the J-MICC study, except in two areas, where fewer participants had been recruited. Of them, individuals aged 35–69 years enrolled across six areas (Shizuoka, Okazaki, Takashima, Kyoto, Tokushima, and Amami) that had collected baseline blood glucose data were included in this analysis.

The present study included 2415 subjects. Of these, 596 subjects were excluded for the following reasons: non-fasting blood samples (individuals had a meal within 3 h of blood sampling, n =180), history of diabetes (n = 83), chronic hepatitis or liver cirrhosis (n = 49), fatty liver (n =186), history of cardiovascular or cerebrovascular disease (n = 78), history of cancer (n = 15), and missing measurements of blood glucose levels (n = 5). Therefore, a total of 1819 subjects (907 men and 912 women) were included in the present analysis.

The protocol for the J-MICC Study was approved by the ethics committees of Nagoya University School of Medicine and at the other participating institutions. All of the study subjects gave written informed consent before participating in this study.

Lifestyle questionnaire and clinical characteristics

Subjects completed a questionnaire to record alcohol consumption, smoking habits, physical activity, diseases under current or previous treatment, family history of selected diseases, and other lifestyle habits. Current alcohol consumers were defined as subjects who reported consuming alcoholic beverages at least once a month. Past and current drinkers were asked to state the age at which they began drinking habitually. Current alcohol consumers also stated the frequency and amount of consumption for six alcoholic beverages (sake, shochu, chuhai, beer, whisky, and wine). The frequency of consumption options was recorded as almost never, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week or daily. The subjects were also asked to state the amount of each beverage consumed. Daily ethanol intake was estimated for current alcohol consumers based on the frequencies and amount of each type of alcoholic beverage consumed over the past year. Regarding smoking status, participants were asked whether they had ever smoked, the age when they started smoking (for ever smokers), and the age when they quit smoking (for former smokers). Weekly and daily frequency of coffee consumption and the number of cups of coffee consumed per day were also recorded.

Regarding physical activity, participants were asked about work-related activity (including domestic housework) and leisure-time activity. For work-related activity, participants reported the amount of time spent per day in sedentary activity, standing, walking, and performing strenuous labor using one of eight options: never, < 1, 1–2.9, 3–4.9, 5–6.9, 7–8.9, 9–10.9, or ≥11 h. For leisure-time activity, the frequency and amount of time per occasion were ascertained for three categories of exercise intensity (light activity: resulting in no shortness of breath, moderate activity: causing shortness of breath but not preventing speaking, and heavy activity: causing shortness of breath and difficulty in speaking). The frequency was recorded as never, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week or daily. The duration of each activity was recorded as < 30 min, 30–59 minutes, 1–1.9 h, 2–2.9 h, 3–3.9 h, and ≥ 4 h. The intensity of each physical activity was determined in terms of the metabolic equivalent (MET) value (work-related activity: sedentary activity, 0; standing, 0; walking, 3.0; and strenuous labor, 4.5 METs; leisure-time activity: light, 3.4; moderate, 7; and heavy, 10 METs). Work-related and leisure-time physical activities were each expressed as the total number of METs multiplied by the duration of each activity per week (MET-h/week). The subjects also stated whether they had parental history of diabetes mellitus (i.e., yes, no, or unknown).

Clinical data, including height, weight, and blood glucose were measured using routine
methods. BMI (kg/m²) was calculated as weight (kg)/height (m²). Because blood glucose returns to near fasting levels approximately 3 h after a meal, the samples that were collected ≥ 3 h after the last meal were defined as fasting samples in this study.

Genotyping

DNA was extracted from buffy coat fractions using a BioRobot M48 Workstation (Qiagen Group, Tokyo, Japan) at the central office of the J-MICC study. The ADH1B Arg48His and ALDH2 Glu504Lys polymorphisms were genotyped using the multiplex polymerase chain reaction (PCR)-based Invader assay (Third Wave Technologies, Madison, WI) at the Laboratory for Genotyping Development, Center for Genomic Medicine, RIKEN, Japan.

Statistical analysis

Departure of the genotype distribution from the Hardy–Weinberg equilibrium was tested using the χ² test with one degree of freedom. The characteristics of the study subjects according to ADH1B and ALDH2 genotypes were statistically analyzed using χ² tests for proportions, analysis of covariance for means, and the Kruskal–Wallis test for medians. Associations of genetic polymorphisms with FBG levels were evaluated using analysis of variance or covariance. Analyses were adjusted for age, area (Shizuoka and Okazaki = 0, Kyoto and Takashima = 1, Tokushima = 2, Amami = 3), BMI, smoking, alcohol consumption, coffee consumption, physical activity, and parental history of diabetes mellitus (no = 0, unknown = 1, yes = 2). All of the factors included for adjustment were entered as continuous variables, except for area and parental history of diabetes mellitus. Trends for associations were tested by linear regression analysis using an ordinal score for the variable of interest. Alcohol consumption was stratified as never, past consumption, and current consumption. Because 1 go of Japanese sake is equal to about 23 g ethanol, the amount of alcohol consumed was classified as < 23.0, 23.0–45.9, and ≥ 46.0 g/day for men, or as < 11.5, 11.5–22.9, and ≥ 23.0 g/day for women. BMI was stratified for < 22.5, 22.5–24.9, 25.0–27.4, and ≥ 27.5 kg/m². Interactions were evaluated using linear regression analysis (for example: Multiplying the variable that summarizes the drinking and the variable that summarizes the ALDH2 genotypes, put into a linear regression model). Statistical significance was declared if the two-sided P-value was < 0.05. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

The ADH1B Arg48His and ALDH2 Glu504Lys genotypes were not determined in three and one subjects, respectively. The genotype distributions of the ADH1B and ALDH2 polymorphisms in individual subjects were in agreement with the Hardy–Weinberg equilibrium (ADH1B: P = 0.88 for men, P = 0.60 for women; ALDH2: P = 0.18 for men, P = 0.32 for women).

Selected characteristics of the study subjects stratified by ADH1B Arg48His and ALDH2 Glu504Lys genotypes are summarized in Table 1. BMI and alcohol intake were greater in subjects with the ADH1B 48Arg/Arg or ALDH2 504Glu/Glu genotypes compared with each ADH1B 48His allele and ALDH2 504Lys allele, respectively, in men and women. Coffee consumption was higher in men with the ALDH2 504Lys allele, but lower in women with this allele. Parental history of diabetes mellitus was less frequent in women with the ALDH2 504Glu/Lys genotype. Age, smoking, and physical activity did not vary among subjects with these polymorphisms.

The ADH1B Arg48His polymorphism was not associated with FBG levels in either men or women. By contrast, the ALDH2 504Lys allele was associated with lower FBG levels compared
**ALDH2 polymorphism and FBG levels**

**Table 1** Characteristics of the study subjects according to ADH1B and ALDH2 genotype

| Characteristics | ADH1B Arg48His | P-value | ALDH2 Glu504Lys | P-value |
|-----------------|---------------|--------|----------------|---------|
| Men             |               |        |               |         |
| (n = 515)       | His/His       | (n = 338) | His/Arg       | (n = 499) | (n = 337) | (n = 71) |
| Age, mean (SD)  | 54.7 (9.2)    | 55.4 (9.3) | 55.5 (9.4)    | 0.57     | 54.6 (9.1) | 55.4 (9.2) | 56.3 (10.1) | 0.21 |
| BMI (kg/m²), mean (SD) | 23.2 (2.8) | 23.6 (2.9) | 24.4 (3.0) | 0.004 | 23.6 (3.0) | 23.3 (2.8) | 22.8 (2.3) | 0.06 |
| Ever-smoking, N (%) | 362 (70.3) | 238 (70.4) | 41 (75.9) | 0.68 | 340 (68.1) | 252 (74.9) | 49 (69.0) | 0.11 |
| Cigarette-years, median (IQR) | 520 (280-810) | 490 (280-780) | 660 (340-880) | 0.53 | 540 (270-820) | 500 (290-780) | 510 (272-800) | 0.96 |
| Current alcohol consumption, (%) | 400 (77.8) | 263 (77.8) | 46 (85.2) | 0.44 | 460 (92.2) | 245 (72.9) | 4 (5.6) | < 0.0001 |
| Alcohol consumption (g/day), median (IQR) | 25 (12-46) | 25 (12-51) | 35 (12-55) | 0.40 | 31 (15-55) | 17 (7-34) | 6 (2-9) | < 0.0001 |
| Coffee consumption (cups/day), median (IQR) | 1.5 (0.3-2.0) | 1.5 (0.3-3.0) | 1.5 (0.1-1.6) | 0.70 | 1.0 (0.1-1.6) | 1.5 (0.5-3.0) | 1.5 (0.5-3.0) | 0.01 |
| MET-h/week, median (IQR) | 66 (12-42) | 50 (14.8) | 5 (9.3) | 0.42 | 65 (13.0) | 48 (14.2) | 6 (8.8) | 0.42 |
| Parental diabetes mellitus, N (%) | 64 (12.4) | 50 (14.8) | 5 (9.3) | 0.42 | 65 (13.0) | 48 (14.2) | 6 (8.8) | 0.42 |

| Women (n = 514) | (n = 343) | (n = 52) | (n = 499) | (n = 337) | (n = 71) |
|-----------------|-----------|---------|-----------|-----------|---------|
| Age, mean (SD)  | 55.2 (9.2) | 55.0 (9.6) | 55.3 (9.4) | 0.93 | 55.4 (9.8) | 54.9 (9.0) | 54.8 (9.4) | 0.62 |
| BMI (kg/m²), mean (SD) | 22.8 (3.3) | 22.7 (3.2) | 23.9 (3.5) | 0.03 | 23.6 (3.3) | 23.6 (3.3) | 22.8 (2.3) | 0.06 |
| Ever-smoking, N (%) | 22 (4.3) | 14 (4.1) | 2 (3.8) | 0.38 | 24 (4.7) | 16 (4.8) | 2 (3.8) | 0.38 |
| Cigarette-years, median (IQR) | 1.5 (0.3-1.6) | 1.5 (0.3-1.6) | 1.5 (0.3-3.0) | 0.53 | 1.5 (0.3-3.0) | 1.5 (0.5-3.0) | 1.5 (0.5-3.0) | 0.01 |
| Current alcohol consumption, (%) | 40 (7.8) | 22 (6.4) | 4 (7.7) | 0.75 | 35 (6.4) | 28 (9.0) | 3 (5.7) | 0.33 |
| Alcohol consumption (g/day), median (IQR) | 174 (33.9) | 128 (37.3) | 25 (48.1) | 0.10 | 260 (47.5) | 66 (21.2) | 2 (3.8) | < 0.0001 |
| Coffee consumption (cups/day), median (IQR) | 40 (7.8) | 22 (6.4) | 4 (7.7) | 0.75 | 35 (6.4) | 28 (9.0) | 3 (5.7) | 0.33 |
| MET-h/week, median (IQR) | 10 (5-21) | 9 (5-20) | 12 (4-22) | 0.50 | 10 (5-21) | 9 (4-20.5) | 12 (6-23) | 0.19 |
| Parental diabetes mellitus, N (%) | 79 (15.4) | 59 (17.2) | 5 (9.6) | 0.35 | 100 (18.3) | 33 (10.6) | 11 (20.8) | 0.007 |

BMI, body mass index; IQR, interquartile range; SD, standard deviation; N, number; TC, total cholesterol; HDL, high-density lipoprotein.

a) The genotype was not determined for three subjects for ADH1B and one subject for ALDH2.

b) χ² tests for proportions, analysis of variance for means, and the Kruskal–Wallis test for medians.

c) Among ever-smokers.

d) Among current alcohol consumers (current alcohol consumers were defined as subjects who reported consuming alcoholic beverages at least once a month).

**Table 2** Associations of ADH1B and ALDH2 polymorphisms with fasting blood glucose levels in men and women

| Genotype | ADH1B Arg48His | P-value | ALDH2 Glu504Lys | P-value |
|----------|---------------|--------|----------------|---------|
| Men      |               |        |               |         |
| N        | 515           | 338    | 54            | 514     |
| Crude mean (SE) | 98.2 (0.5) | 98.3 (0.5) | 98.2 (0.5) | 92.4 (0.5) |
| Adjusted mean (SE) | 98.3 (0.5) | 98.3 (0.5) | 98.3 (0.5) | 92.7 (0.4) |
| p-value  | 0.51          | 0.51   | 0.54          | 0.51    |

| Women    |               |        |               |         |
| N        | 514           | 337    | 71            | 547     |
| Crude mean (SE) | 99.9 (0.5) | 99.2 (0.5) | 99.1 (0.5) | 93.6 (0.5) |
| Adjusted mean (SE) | 99.2 (0.5) | 99.2 (0.5) | 99.2 (0.5) | 92.9 (0.4) |
| p-value  | < 0.0001      | 0.04   | 0.04          | 0.06    |

N, number; SE, standard error.

a) The genotype was not determined for three subjects for ADH1B and one subject for ALDH2.

b) Adjusted for age, area, body mass index, smoking, coffee consumption, physical activity, and parental diabetes mellitus.

c) Adjusted for age, area, body mass index, smoking, alcohol consumption, coffee consumption, physical activity, and parental diabetes mellitus.

d) Analysis of variance or covariance for means.
Fig. 1  Fasting blood glucose (FBG) levels in men (panel A) and women (panel B) according to alcohol consumption. FBG levels were adjusted for age, area, BMI, smoking, coffee consumption, physical activity, and parental diabetes mellitus. The values shown at the top of each bar are FBG levels (mean). The error bar shows the standard error (SE). The $P$ for trend was 0.002 in men and 0.11 in women. The $P$ for trend was determined by linear regression analysis, with ordinal numbers assigned to each category of alcohol consumption (0 = never, 1 = light, 2 = moderate, and 3 = heavy).
ALDH2 polymorphism and FBG levels

Table 3  Associations of ADH1B and ALDH2 polymorphisms with fasting blood glucose levels according to alcohol consumption status in men and women

| Alcohol consumption (g/day) | ADH1B Arg48His * | P for trend | ALDH2 Glu504Lys * | P for differences |
|----------------------------|-----------------|-------------|------------------|------------------|
|                            | N | Adjusted mean (SE) | N | Adjusted mean (SE) | N | Adjusted mean (SE) | N | Adjusted mean (SE) |
| Men                        |    |                 |    |                 |    |                 |    |                 |
| Never use                  | 105 | 96.3 (1.0) | 70 | 95.5 (1.2) | 7 | 97.5 (3.8) | 0.83 | 28 | 97.2 (2.0) | 154 | 95.8 (0.8) | 0.45 |
| < 23.0                     | 172 | 98.6 (0.8) | 109 | 98.6 (1.0) | 16 | 99.9 (2.8) | 0.96 | 155 | 99.1 (0.8) | 142 | 98.2 (0.8) | 0.60 |
| 23.0–45.9                  | 108 | 99.7 (1.0) | 60 | 97.7 (1.3) | 11 | 99.8 (3.2) | 0.49 | 122 | 99.6 (1.0) | 57 | 97.9 (1.4) | 0.18 |
| ≥ 46.0                     | 94 | 98.3 (1.1) | 70 | 101.2 (1.3) | 15 | 101.1 (2.8) | 0.28 | 142 | 99.7 (0.9) | 37 | 99.6 (1.8) | 0.63 |
| P for trend                |     | P = 0.06 |     | P = 0.03 |     | P = 0.62 |     | P = 0.45 |     | P = 0.02 |
| Interaction P = 0.35       |     |           |     |           |     |           |     |           |     |           |
| Women                      |    |                 |    |                 |    |                 |    |                 |
| Never use                  | 334 | 92.8 (0.5) | 211 | 92.6 (0.6) | 27 | 93.9 (1.7) | 0.77 | 279 | 93.0 (0.5) | 294 | 92.9 (0.5) | 0.93 |
| < 11.5                     | 104 | 91.1 (0.9) | 82 | 93.4 (1.0) | 15 | 92.1 (2.3) | 0.10 | 155 | 92.3 (0.7) | 47 | 91.3 (1.3) | 0.30 |
| 11.5–22.9                  | 20 | 94.4 (2.0) | 15 | 92.0 (2.2) | 4 | 92.3 (4.2) | 0.42 | 36 | 93.5 (1.5) | 3 | 90.5 (4.9) | 0.57 |
| ≥ 23.0                     | 25 | 96.6 (1.8) | 11 | 99.8 (2.7) | 5 | 92.7 (4.3) | 0.65 | 34 | 96.8 (1.5) | 7 | 98.6 (3.5) | 0.16 |
| P for trend                |     | P = 0.21 |     | P = 0.16 |     | P = 0.25 |     | P = 0.13 |     | P = 0.47 |
| Interaction P = 0.66       |     |           |     |           |     |           |     |           |     |           |

N, number; SE, standard error.

a) The genotype was not determined for three subjects for ADH1B and one subject for ALDH2.

b) Adjusted for age, area, body mass index, smoking, coffee consumption, physical activity, and parental diabetes mellitus.

c) Linear regression analysis with ordinal numbers (0, 1, and 2) assigned to each genotype.

with the 504Glu/Glu genotype in men, but not in women (Table 2). FBG levels were also lower in individuals with the ALDH2 504Lys allele, even after adjusting for covariates including alcohol consumption.

Alcohol consumption was associated with elevated FBG levels compared with non-consumers in men (Fig. 1A). By contrast, light to moderate alcohol consumption was not associated with increased FBG levels compared with non-consumers in women (Fig. 1B). Former alcohol drinkers (n =25) were excluded from this analysis. The distribution of alcohol consumption in men was 182 (21.7%), 297 (35.5%), 179 (21.4%), and 179 (21.4%) for non-consumers, < 23.0, 23.0–45.9, and ≥ 46.0 g/day, respectively. That in women was 574 (67.1%), 198 (23.1%), 43 (5.0%), and 41 (4.8%) for non-consumers, < 11.5, 11.5–22.9, and ≥ 23.0 g/day, respectively.

In analyses stratified by alcohol consumption status, the homozygous ALDH2 504Lys allele was combined with the heterozygous ALDH2 504Lys allele, because the rates of alcohol consumption were very low in these subjects. Also, former alcohol drinkers (n =25) were excluded from this analysis. Alcohol consumption was associated with a dose-dependent increase in FBG levels in men with the ALDH2 504Lys allele (P_trend = 0.02), but not in men with the ALDH2 504Glu/ Glu genotype (P_trend = 0.45). However, the greater decreases in FBG with increasing alcohol consumption identified in men with the ALDH2 504Lys allele than in men with the ALDH2 Glu/ Glu genotype were not apparent, as the interaction was not statistically significant (P = 0.38).

There was no measurable interaction between ADH1B polymorphisms and alcohol consumption in either men or women (Table 3).

**DISCUSSION**

The present study showed that FBG levels were lower in men, but not in women, in those with the ALDH2 504Lys allele than in those without. Alcohol consumption was associated with
a dose-dependent increase in FBG levels in men with the ALDH2 504Lys allele but not in men with the ALDH2 504Glu/Glu genotype. The ADH1B Arg48His polymorphism was not associated with FBG levels in either men or women.

The ALDH2 504Lys allele was associated with higher fasting plasma glucose levels in women with high alcohol consumption (≥ 5 g/day)\(^7\). However, unlike this earlier observation, the present study showed that men with the ALDH2 504Lys allele may have lower FBG levels, whereas no change was observed in women. It is possible that individuals with the ALDH2 504Lys allele may follow more favorable lifestyle factors, such as abstaining from alcohol consumption. For example, in the present study, men with the ALDH2 504Lys allele reported greater coffee consumption, which is associated with decreased risk of type 2 diabetes\(^16\). It was reported that BMI is a risk factor for type 2 diabetes\(^17\), and individuals with the ALDH2 504Lys allele had lower BMI compared with individuals with the ALDH2 504Glu/Glu genotype in this study. Nevertheless, even when adjusting the potential confounders including alcohol consumption, the level of FBG was lower in the ALDH2 504Lys/Lys genotype. However, we also found that alcohol consumption was associated with a dose-dependent increase in FBG levels in men with the ALDH2 504Lys allele. This finding supports the results of a previous study in Japan in which the ALDH2 504Lys allele was associated with impaired glycemic control in patients with type 2 diabetes reporting habitual light-to-moderate alcohol consumption\(^10\). This result is particularly important in the context of diabetes prevention, because individuals with the ALDH2 504Lys allele should be encouraged to abstain from alcohol.

Alcohol consumption was associated with a dose-dependent increase in FBG levels in men. In contrast, light-to-moderate alcohol consumption was associated with lower FBG levels in women. Therefore, the association between alcohol consumption and risk of type 2 diabetes may differ between men and women in Japan. Several studies in Japanese men also reported that alcohol consumption was associated with an increased risk of type 2 diabetes\(^9, 18, 19\), but not in women.

The mechanisms for an association between ALDH2 polymorphism and FBG levels, as well as an association between alcohol consumption and FBG levels, are still unknown. Because type 2 diabetes is associated with both insufficient insulin secretion and high insulin resistance, it appears likely that the alcohol-induced increase in blood glucose levels has adverse effects on one or both of those variables. Several studies have shown that ethanol causes insulin resistance in the liver and skeletal muscle by interfering with insulin signaling\(^20-22\). In addition, several experimental studies have reported that chronic ethanol feeding in rodents causes pancreatic β-cell apoptosis\(^23, 24\) and decreases β-cell mass\(^20, 25\). One recent study reported that ethanol causes endoplasmic reticulum stress and impairment of insulin secretion in pancreatic β-cells\(^26\). However, one study reported that moderate alcohol consumption is associated with improved insulin sensitivity, reduced basal insulin secretion rate and a lower fasting glucagon concentration in women, but not men\(^27\). Clearly, further studies in this area are needed.

The lack of an association between ADH1B Arg48His polymorphisms and FBG in the present study is consistent with an earlier cross-sectional study in Japan\(^8\). That study found no differences in fasting plasma glucose or hemoglobin A\(_1c\) concentrations among ADH1B genotypes. However, fasting plasma insulin concentrations were lower in men and women with the ADH1B 48His/Arg genotype than in those with the 48His/His genotype, although there was no difference in alcohol consumption between the 48His/His and 48His/Arg genotypes. In the present study, we could not analyze the possible associations of these polymorphisms with hemoglobin A\(_1c\) or plasma insulin concentrations, because these parameters were not measured in a sufficient number of subjects. Another study reported that fasting plasma glucose concentrations were higher in men with the ADH1B 48Arg/Arg genotype than in those with the His/His or His/Arg genotype, when alcohol consumption was high (≥ 10 g/day)\(^7\). However, the sample size of that study was small.
The ADH1C 349Ile allele, which is associated with fast oxidation of ethanol, was reported to decrease the risk of type 2 diabetes associated with alcohol consumption in the United States\textsuperscript{28}. Those results suggest that acetate, the end product of alcohol oxidation, is involved in the protective association between alcohol and type 2 diabetes. The ADH1C Ile349Val polymorphism was not assessed in the present study because the ADH1C 349Val allele is extremely rare in Japanese individuals\textsuperscript{5}. The ADH1B Arg48His polymorphism is in linkage disequilibrium with the ADH1C Ile349Val polymorphism in Asian and Caucasian individuals\textsuperscript{29, 30}. Therefore, the present results do not fully support the hypothesis that fast alcohol oxidation confers protection against the risk of type 2 diabetes associated with alcohol consumption.

There are several advantages and limitations of this study. The study subjects were representative of Japanese men and women in the general population. The frequencies of ADH1B 48Arg (25\%) and ALDH2 504Lys (25\%) alleles were similar to those reported in other general Japanese populations\textsuperscript{31, 32}. However, an attrition bias is possible in cross-sectional studies. It is desirable that we should evaluate the association of these polymorphisms with hemoglobin A\textsubscript{1c} or C-peptide, because those biomarkers are more stable than either FBG levels or insulin. However, the study only assessed the association between FBG levels and alcohol-related polymorphisms, because those other biomarkers were not measured in a sufficient number of subjects.

Blood samples obtained equal to and more than 3 h after the last meal were defined as fasting samples in this study. Nevertheless, similar results were obtained when we restricted the analysis to subjects (1546 total; men 794, women 752) with blood samples obtained 8 h after a meal and subjects (1405 total; men 726, women 679) with blood samples obtained 12 h after a meal. For the 8 h after a meal group, FBG levels (mg/dL) (SE) were 99.5 (0.6), 97.8 (0.6), and 95.1 (1.4) for the ALDH2 genotypes of Glu/GLu, Glu/Lys and Lys/Lys, respectively ($P$-value was 0.02). For the 12 h after a meal group, FBG levels (SE) were 99.4 (0.6), 97.8 (0.7), and 95.1 (1.4) mg/dL for the ALDH2 genotypes of Glu/GLu, Glu/Lys, and Lys/Lys, respectively. It was also statistically significant ($P = 0.01$).

Taken together, the present findings suggest that ALDH2 genotypes are associated with different FBG levels through alcohol consumption in Japanese men. The interaction of ALDH2 polymorphisms in the association between alcohol consumption and FBG levels warrants further investigation.

ACKNOWLEDGMENTS

This study was supported in part by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Nos. 17015018 and 221S0001), and Grants-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (No. 15K08718). The authors thank Mr. Kyota Ashikawa, Ms. Tomomi Aoi, and the other members of the Laboratory for Genotyping Development, Center for Genomic Medicine, RIKEN, for support with genotyping. The authors also thank Ms. Yoko Mitsuda, Ms. Keiko Shibata, and Ms. Etsuko Kimura at the Department of Preventive Medicine, Nagoya University Graduate School of Medicine.

CONFLICT OF INTEREST

The authors declare that there is no duality of interest.
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