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Clinical Study

Genetic Polymorphisms of Alcohol Dehydrogenase and Aldehyde Dehydrogenase: Alcohol Use and Type 2 Diabetes in Japanese Men

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This study investigated the association of *ADH1B* (rs1229984) and *ALDH2* (rs671) polymorphisms with glucose tolerance status, as determined by a 75-g oral glucose tolerance test, and effect modification of these polymorphisms on the association between alcohol consumption and glucose intolerance in male officials of the Self-Defense Forces. The study subjects included 1520 men with normal glucose tolerance, 553 with prediabetic condition (impaired fasting glucose and impaired glucose tolerance), and 235 men with type 2 diabetes. There was an evident interaction between alcohol consumption and *ADH1B* polymorphism in relation to type 2 diabetes (interaction $P = .03$). The *ALDH2*487Lys* allele was associated with a decreased prevalence odds of type 2 diabetes regardless of alcohol consumption. In conclusion, the *ADH1B* polymorphism modified the association between alcohol consumption and type 2 diabetes. A positive association between alcohol consumption and type 2 diabetes was confounded by *ALDH2* polymorphism.

1. Introduction

Moderate alcohol consumption has generally been associated with decreased risk of type 2 diabetes, as summarized in a meta-analysis of 15 prospective cohort studies [1]. However, the results from these studies are not necessarily consistent, especially regarding high alcohol consumption and diabetes risk. While several studies showed a U-shaped relationship between alcohol and diabetes risk [1], others reported increased risks of type 2 diabetes in alcohol consumption categories of ≥25 g/day [2], >40 g/day [3], and >3 drinks per day [4]. Another study found a progressive decrease in the risk of type 2 diabetes up to a consumption of ≥50 g of alcohol per day [5]. The inconsistent results may be ascribed to differences in ascertainment of alcohol consumption and diabetes mellitus among studies and different genetic susceptibilities to alcohol exposure among study populations.

Ethanol is first oxidized to acetaldehyde by alcohol dehydrogenase (ADH), and acetaldehyde is further metabolized to acetate by aldehyde dehydrogenase (ALDH). Human ADH exhibits several isoenzymes, and functional polymorphisms are known for the *ADH1B* and *ADH1C* genes [6, 7]. The *ADH1B* Arg47His polymorphism (rs1229984) affects the enzyme activity substantially, and the *ADH1B*47His* allele (alternatively *ADH2*2*) is associated with faster oxidation. The *ADH1C* Ile349Val polymorphism (rs698) influences ADH activity to a lesser extent, and the *ADH1C*349Ile* allele (alternatively *ADH3*1*) is associated with moderately faster oxidation [8]. The *ADH1B*47His* allele is the major allele in Asians and is very rare in Caucasians, while the *ADH1C*349Val* allele is rare in Asians and fairly common in Caucasians [7, 9]. The *ALDH2* gene encodes mitochondrial ALDH which contributes to acetaldehyde oxidation in human liver and contains a functional polymorphism

of *ALDH2* Glu487Lys (rs671). The variant *ALDH2*487Lys* allele (alternatively *ALDH2*2*) results in an inactive form and is almost exclusively found in Asian populations [9, 10].

Few studies have addressed the relation of these genetic polymorphisms to glucose metabolism and type 2 diabetes. Cross-sectional studies in Japan reported higher concentrations of fasting plasma glucose in men with *ADH1B*47Arg/Arg* genotype who consumed ≥10 g of alcohol per day [11] and lower concentrations of fasting plasma insulin associated with *ADH1B*47Arg* allele [12]. On the other hand, the *ADH1C*349Val* variant allele was shown to attenuate a decreased risk of type 2 diabetes with alcohol consumption in the United States [13]. As regards *ALDH2* Glu487Lys polymorphism, *ALDH2*487Lys* allele was associated with deterioration in glycemic control assessed by hemoglobin A_{1c} concentrations in Japanese patients with type 2 diabetes who had a habitual light to moderate alcohol consumption [14]. In this paper reported here, we examined the relation of *ADH1B* Arg47His and *ALDH2* Glu487Lys polymorphisms to glucose tolerance status determined by a 75-g oral glucose tolerance test (OGTT) in middle-aged Japanese men, focusing on the effect modification of these genetic polymorphisms on the association between alcohol consumption and glucose intolerance.

2. Methods

2.1. Study Population. Study subjects were male officials in the Self-Defense Forces who received a preretirement health examination at the Self-Defense Forces Fukuoka Hospital (Kasuga, Japan) or Kumamoto Hospital (Kumamoto, Japan) during the period from January 1997 to March 2001. The preretirement health examination is a nationwide program offering comprehensive medical examinations including a 75-g OGTT for those retiring from the Self-Defense Forces. Details of the health examination have been described elsewhere [15, 16]. A sample of 7 mL fasting venous blood was obtained for the purpose of medical research with written informed consent. The study was approved by the ethics committee of Kyushu University Faculty of Medical Sciences.

The present study included 553 cases of prediabetic condition, 235 cases of type 2 diabetes, and 1520 controls of normal glucose tolerance. In the consecutive series of 2454 men aged 46–59 years, 121 men were excluded for the following reasons: chronic hepatitis or liver cirrhosis (n = 49), use of steroids (n = 6), past history of gastrectomy (n = 38), history of insulin treatment for type 2 diabetes (n = 11), and undetermined glucose tolerance status (n = 19). Of the remaining 2333 men, 25 men were further excluded due to lack of DNA sample (n = 23) and unsuccessful genotyping for both of the two polymorphisms (n = 2). Thus, a total of 2308 men remained in the analysis.

2.2. Determination of Glucose Tolerance Status. After an overnight fast, a 75-g OGTT was performed. Plasma glucose levels were assayed by the glucose oxidase method using commercial reagents (Shino Test Co. Ltd., Tokyo) at each laboratory of the two hospitals. Subjects were classified as having normal glucose tolerance, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or type 2 diabetes in accordance with the World Health Organization criteria in 1998 [17]. Men under dietary or drug treatment for type 2 diabetes were regarded as having type 2 diabetes, irrespective of their glucose levels. The number of men with normal glucose tolerance, IFG, IGT, and type 2 diabetes were 1520, 137, 416, and 235, respectively. IFG and IGT were combined as prediabetic condition.

2.3. Lifestyle Questionnaire. A self-administered questionnaire was used to ascertain alcohol use, smoking habits, coffee intake, and other lifestyle characteristics. Details have been described previously [15, 16]. In brief, alcohol drinkers were defined as those who had drunk once a week or more over a period of one year or longer. Past alcohol drinkers were separated from lifelong nondrinkers. Daily ethanol intake was estimated for current alcohol drinkers, based on consumption frequencies and amounts of five different types of alcoholic beverages (sake, shochu, beer, whisky/brandy, and wine) on average in the past year. Estimated alcohol intake was highly valid in comparison with the intake derived from 7-day diet records in four seasons [18]. Cumulative exposure to cigarette smoking was expressed as cigarette-years, which were calculated by multiplying the average number of cigarettes per day by total years of smoking. Weekly frequency of coffee consumption was inquired about, and the number of cups of coffee consumed per day was ascertained among daily coffee users. As regards physical activity, men with a regular participation in leisure-time physical activity in the past year (one or more times a week) reported at most three types of physical activities together with frequency per week and time spent per occasion for each activity. Type of physical activity was classified into light, moderate, heavy, or very heavy activity in terms of metabolic equivalent (MET). The time spent in recreational exercise was multiplied by the corresponding MET value (light 2, moderate 4, heavy 6, and very heavy 8) to yield a MET-hour score per week. Parental history of diabetes mellitus was also elicited.

2.4. Genotyping. DNA was extracted from the buffy coat using a commercial kit (QIAGEN GmbH, Hilden, Germany) and genotyping was performed with the polymerase chain reaction (PCR) restriction fragment length polymorphism method. The PCR was performed in a reaction mixture of 10 μL containing 0.5 units of *Taq* and 1 μL of template DNA with a concentration of approximately 50–150 ng/μL. The *ADH1B* Arg47His genotypes were determined according to the method described by Osier et al. [7], and the *ALDH2* Glu487Lys genotypes were determined by the method described by Goedde et al. [19].

2.5. Statistical Analysis. Departure from the Hardy-Weinberg equilibrium of the genotype distribution was tested by χ^2 test with 1 degree of freedom. Associations of the genetic polymorphisms with prediabetic condition and type

Table 1: Characteristics of the study subjects by glucose tolerance status.

Characteristics	Normal glucose tolerance ($n = 1520$)	Prediabetic condition* ($n = 553$)	Type 2 diabetes ($n = 235$)	P-value†
Age, mean (SD)	52.4 (0.9)	52.4 (0.9)	52.4 (0.9)	.91
BMI (kg/m^2), mean (SD)	23.5 (2.4)	24.5 (2.7)	24.4 (3.0)	<.0001
Cigarette-years, median (IQR)	450 (0–660)	440 (0–660)	460 (100–680)	.44
Alcohol use, N (%)				.004
Never	238 (15.6)	60 (10.8)	21 (9.0)	
Former	42 (2.8)	11 (2.0)	9 (3.8)	
Current	1240 (81.6)	482 (87.2)	205 (87.2)	
Alcohol (ml/day), median (IQR)‡	43 (24–68)	47 (26–71)	43 (23–68)	.15
Coffee (cups/day), median (IQR)	2 (0–4)	1 (0–3)	2 (0–3)	.0001
MET-hours/week, median (IQR)	14 (4–25)	12 (4–24)	16 (4–28)	.10
Parental diabetes mellitus, N (%)	108 (7.1)	47 (8.5)	41 (17.5)	<.0001
ADH1B genotype, N (%)§				.99
His/His	851 (56.5)	310 (56.5)	131 (56.5)	
His/Arg	558 (37.1)	204 (37.1)	88 (37.9)	
Arg/Arg	97 (6.4)	35 (6.4)	13 (5.6)	
ALDH2 genotype, N (%)¶				<.0001
Glu/Glu	871 (57.4)	368 (66.7)	172 (73.2)	
Glu/Lys	553 (36.5)	161 (29.1)	61 (26.0)	
Lys/Lys	92 (6.1)	23 (4.2)	2 (0.8)	

BMI: body mass index; IQR: interquartile range; SD: standard deviation.
*Impaired fasting glucose and impaired glucose tolerance were combined.
†Based on chi-squared test for proportion, analysis of variance for means, and Kruskal-Wallis test for medians.
‡Among current alcohol drinkers.
§Genotype was not determined for 21 men.
¶Genotype was not determined for 5 men.

2 diabetes were evaluated using logistic regression analysis, with those of normal glucose tolerance as controls. Odds ratio (OR) and 95% confidence interval (CI) were obtained from the logistic regression coefficient and standard error for the corresponding indicator variables. Statistical adjustment was made for age (continuous variable), hospital (Fukuoka or Kumamoto hospital), rank in the Self-Defense Forces (low, middle, or high), body mass index (<22.5, 22.5–24.9, 25.0–27.4, and ≥27.5 kg/m^2), cigaretteyears (0, 1–399, 400–799, and ≥800), alcohol consumption (never, past use, and current use with consumption of <30, 30–59, or ≥60 mL/day), coffee intake (<1, 1-2, 3-4, and ≥5 cups per day), physical activity (categorized at quartiles of MET-hours per week), and parental diabetes. The trend of an association was tested by the Wald statistic, using an ordinal score for a variable of interest. The interaction was evaluated by the likelihood ratio test, comparing models with and without interaction terms. Statistical significance was declared if the two-sided P-value was less than .05 or if the 95% CI did not include unity. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

3. Results

Selected characteristics of the study subjects by glucose tolerance status are summarized in Table 1. Body mass index was greater in men with prediabetic condition and type 2 diabetes, and alcohol intake was greater in the former than in those with normal glucose tolerance. Parental history of diabetes mellitus was more frequent in individuals with type 2 diabetes and showed little difference between normal glucose tolerance and prediabetic condition. Coffee consumption was lower in those with prediabetic condition. Age, smoking, and leisure-time physical activity did not vary much according glucose tolerance status.

The *ADH1B* and *ALDH2* genotypes were not determined in 21 subjects and 5 men, respectively. Genotype distributions of the *ADH1B* Arg47His and *ALDH2* Glu487Lys polymorphisms in individuals of normal glucose tolerance were each in agreement with the Hardy-Weinberg equilibrium ($P = .67$ for *ADH1B* and $P = .73$ for *ALDH2*).

While the *ADH1B* Arg47His polymorphism was not associated with either prediabetic condition or type 2 diabetes, the *ALDH2* polymorphism was associated with a substantial decrease in the prevalence odds of type 2 diabetes and with a modest decrease in the prevalence odds of prediabetic condition (Table 2). The OR of type 2 diabetes decreased stepwise in men heterozygous and homozygous for the *ALDH2*487Lys* allele regardless of adjustment for the covariates.

There was no measurable interaction between the *ADH1B* and *ALDH2* polymorphisms for either prediabetic condition or type 2 diabetes (Table 3). Individuals

Table 2: Association of *ADH1B* and *ALDH2* polymorphisms with prediabetic condition and type 2 diabetes.

Genotype		Prediabetic condition*			Type 2 diabetes		
	No. of Controls	No.	Crude OR (95% CI)	Adjusted OR (95% CI)†	No.	Crude OR (95% CI)	Adjusted OR (95% CI)†
ADH1B Arg47His							
His/His	851	310	1.00 (referent)	1.00 (referent)	131	1.00 (referent)	1.00 (referent)
Arg/His	558	204	1.00 (0.82–1.23)	0.97 (0.78–1.20)	88	1.02 (0.77–1.37)	1.00 (0.74–1.35)
Arg/Arg	97	35	0.99 (0.66–1.49)	0.89 (0.59–1.36)	13	0.87 (0.47–1.60)	0.81 (0.43–1.52)
Arg/His + Arg/Arg	655	239	1.00 (0.82–1.22)	0.96 (0.78–1.18)	101	1.00 (0.76–1.32)	0.97 (0.73–1.30)
ALDH2 Glu487Lys							
Glu/Glu	871	368	1.00 (referent)	1.00 (referent)	172	1.00 (referent)	1.00 (referent)
Glu/Lys	553	161	0.69 (0.56–0.85)	0.79 (0.63–1.01)	61	0.56 (0.41–0.76)	0.54 (0.38–0.77)
Lys/Lys	92	23	0.59 (0.37–0.95)	0.83 (0.48–1.43)	2	0.11 (0.03–0.45)	0.12 (0.03–0.52)
Glu/Lys + Lys/Lys	645	184	0.68 (0.55–0.83)	0.80 (0.63–1.01)	63	0.49 (0.36–0.67)	0.51 (0.36–0.72)

CI: confidence interval; OR: odd ratio.
*Impaired fasting glucose and impaired glucose tolerance were combined.
†Adjusted for age, hospital, rank in the Self Defense Forces, body mass index, smoking, alcohol use, coffee intake, leisure-time physical activity, and parental diabetes mellitus.

Table 3: Association of combined genotypes of *ADH1B* and *ALDH2* polymorphisms with prediabetic condition and type 2 diabetes.

ADH1B	*ALDH2*	No.*	Crude OR (95% CI)	Adjusted OR (95% CI)†	Interaction
Prediabetic condition					$P = .36$
His/His	*Glu/Glu*	200/486	1.00 (referent)	1.00 (referent)	
His/His	*Glu/Lys + Lys/Lys*	110/363	0.74 (0.56–0.96)	0.86 (0.64–1.16)	
Arg/His	*Glu/Glu*	140/319	1.07 (0.82–1.38)	1.03 (0.79–1.34)	
Arg/His	*Glu/Lys + Lys/Lys*	63/237	0.65 (0.47–0.89)	0.74 (0.53–1.05)	
Arg/Arg	*Glu/Glu*	25/55	1.10 (0.67–1.82)	1.00 (0.59–1.67)	
Arg/Arg	*Glu/Lys + Lys/Lys*	10/42	0.58 (0.28–1.18)	0.65 (0.31–1.34)	
Type 2 diabetes					$P = .29$
His/His	*Glu/Glu*	98/486	1.00 (referent)	1.00 (referent)	
His/His	*Glu/Lys + Lys/Lys*	33/363	0.45 (0.30–0.68)	0.46 (0.29–0.72)	
Arg/His	*Glu/Glu*	65/319	1.01 (0.72–1.43)	0.99 (0.69–1.42)	
Arg/His	*Glu/Lys + Lys/Lys*	23/237	0.48 (0.30–0.79)	0.48 (0.28–0.80)	
Arg/Arg	*Glu/Glu*	7/55	0.63 (0.28–1.43)	0.61 (0.27–1.41)	
Arg/Arg	*Glu/Lys + Lys/Lys*	6/42	0.71 (0.29–1.71)	0.73 (0.29–1.81)	

CI: confidence interval; OR: odd ratio.
*Numbers of cases/controls.
†Adjusted for age, hospital, rank in the Self Defense Forces, body mass index, smoking, alcohol use, coffee intake, leisure-time physical activity, and parental diabetes mellitus.

homozygous for *ALDH2*487Lys* allele were relatively few, and they were combined with those heterozygous for the polymorphism. The *ALDH2*487Lys* allele was associated with a statistically significant decrease in the prevalence odds of type 2 diabetes in the *ADH1B*47His/His* and **47Arg/His* genotypes, while such a decrease was not clear in the *ADH1B*47Arg/Arg* genotype. Decreases in the prevalence odds of prediabetic condition associated with the *ALDH2*487Lys* allele were modest across the *ADH1B* genotypes.

Alcohol drinking differed substantially by *ALDH2* genotype and slightly so with respect to the *ADH1B* polymorphism (Figure 1). Both current alcohol drinkers (hatched bar) and heavy alcohol drinkers (black bar) were less frequent with increasing numbers of the *ALDH2*487Lys* allele and were slightly more frequent with increasing numbers of the *ADH1B*47Arg* allele. High alcohol consumption was associated with increased prevalence odds of prediabetic condition and type 2 diabetes (Table 4). There was a dose-dependent increase in the OR of prediabetic condition, but no such increase in the OR was noted for type 2 diabetes.

In the analysis on the interaction of alcohol and genotype, past alcohol drinkers ($n = 62$) were excluded, and men homozygous for the *ALDH2*487Lys* allele ($n = 117$) were also excluded in the interaction analysis on *ALDH2* genotypes because their alcohol consumption was markedly low. There was a statistically significant interaction between alcohol use and *ADH1B* polymorphism in relation to type 2 diabetes while a positive association between alcohol consumption and prediabetic condition did not

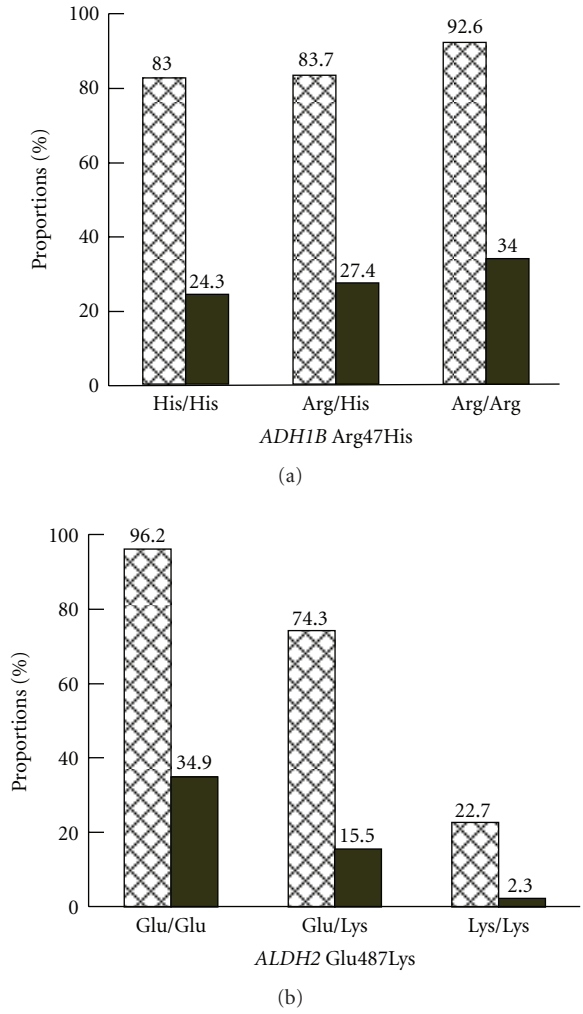

Figure 1: Proportions (%) of current alcohol drinkers (hatched bar) and heavy alcohol drinkers (≥60 mL/day, black bar) according to *ADH1B* Arg47His (a) and *ALDH2* Glu487Lys (b) polymorphisms in the control group. Values shown at the top of each bar are percentages of alcohol drinkers.

appreciably vary according to *ADH1B* genotypes (Table 5). A positive association between alcohol consumption and type 2 diabetes was observed in the *ADH1B* 47His/His* genotype, and the association was in an inverse direction in the *ADH1B* 47Arg/Arg* genotype, which was associated with an increased prevalence odds of type 2 diabetes in nondrinkers.

When stratified by *ALDH2* genotype, alcohol consumption showed no clear positive association with type 2 diabetes although a suggestive, positive association between alcohol consumption and prediabetic condition was noted in the *ALDH2* 487Glu/Glu* genotype. Decreases in the OR of type 2 diabetes associated with *ALDH2* 487Lys* allele were observed regardless of alcohol consumption although such decreases were less notable for prediabetic condition (Table 6). With further adjustment for *ALDH2* 487Glu/Lys* and *Lys/Lys* genotypes, adjusted OR (95% CI) of prediabetic condition for lifelong nondrinkers, past drinkers, and current drinkers consuming <30, 30–59, or ≥60 mL alcohol per day were

Table 4: Association of alcohol use with prediabetic condition and type 2 diabetes.

Alcohol use (mL/day)	No.		OR (95% CI)*
	Cases	Controls	
Prediabetic condition†			
Never use	60	238	1.00 (referent)
Past use	11	42	1.06 (0.51–2.23)
<30	137	405	1.38 (0.97–1.96)
30–59	178	451	1.56 (1.11–2.20)
≥60	167	384	1.74 (1.23–2.46)
Type 2 diabetes			
Never use	21	238	1.00 (referent)
Past use	9	42	2.15 (0.89–5.15)
<30	71	405	2.05 (1.21–3.49)
30–59	70	451	1.70 (1.01–2.89)
≥60	64	384	1.81 (1.06–3.10)

CI: confidence interval; OR: odd ratio.
*Adjusted for age, hospital, rank in the Self Defense Forces, body mass index, smoking, alcohol use, coffee intake, leisure-time physical activity, and parental diabetes mellitus.
† Including impaired fasting glucose and impaired glucose tolerance.

1.00 (referent), 0.99 (0.47–2.09), 1.28 (0.87–1.88), 1.38 (0.94–2.04), and 1.52 (1.02–2.27), respectively, and the corresponding values for type 2 diabetes were 1.00 (referent), 1.40 (0.57–3.44), 1.32 (0.75–2.32), 0.95 (0.53–1.69), and 0.99 (0.54–1.77), respectively.

4. Discussion

The present study showed an effect modification of *ADH1B* Arg47His polymorphism on the association between alcohol consumption and type 2 diabetes. Alcohol consumption was positively associated with type 2 diabetes in individuals harboring the *ADH1B* 47His/His* genotype, but inversely in those with *ADH1B* 47Arg/Arg* genotype. The latter genotype was associated with an increased prevalence odd of type 2 diabetes in the absence of alcohol exposure. *ALDH2* 487Lys* allele was associated with a substantial decrease in the prevalence odds of type 2 diabetes, and a positive association between alcohol consumption and type 2 diabetes disappeared with stratification by *ALDH2* genotype.

The overall lack of an association of the *ADH1B* Arg47His polymorphism with prediabetic condition or type 2 diabetes in the present study is in agreement with the previous cross-sectional observation regarding type 2 diabetes in Japan [12]. The effect modification of the *ADH1B* Arg47His polymorphism on the association between alcohol consumption and type 2 diabetes is a notable finding. However, the inverse association between alcohol consumption and type 2 diabetes in men with the *ADH1B* 47Arg/Arg* genotype is in disagreement with previous findings [11, 12]. A cross-sectional study reported that fasting plasma glucose concentrations were higher in men, but not in women, with *ADH1B* 47Arg/Arg* genotype than those with the *His/His* and *His/Arg* genotype combined when alcohol

Table 5: Interaction between alcohol use and *ADH1B* Arg47His polymorphism in relation to prediabetic condition and type 2 diabetes.

ADH1B Genotype		Alcohol intake (mL/day)				Trend
		Never use	<30	30–59	≥60	
Prediabetic condition						
His/His	No.*	36/141	90/242	98/245	79/202	
	OR (95% CI)†	1.00 (referent)	1.44 (0.92–2.27)	1.52 (0.97–2.37)	1.48 (0.93–2.35)	$P = .16$
Arg/His	No.*	23/88	37/136	68/169	72/148	
	OR (95% CI)†	0.93 (0.51–1.69)	1.07 (0.63–1.81)	1.49 (0.93–2.40)	1.85 (1.15–2.98)	$P = .004$
Arg/Arg	No.*	1/7	8/21	11/34	15/32	
	OR (95% CI)†	0.61 (0.07–5.25)	1.45 (0.58–3.60)	1.20 (0.54–2.66)	1.64 (0.78–3.44)	$P = .50$
Trend		$P = .73$	$P = .31$	$P = .77$	$P = .29$	
		Interaction $P = .27$				
Type 2 diabetes						
His/His	No.*	9/141	41/242	42/245	36/202	
	OR (95% CI)†	1:00 (referent)	2.74 (1.26–5.95)	2.56 (1.19–5.53)	2.88 (1.32–6.31)	$P = .04$
Arg/His	No.*	9/88	27/136	22/169	25/148	
	OR (95% CI)†	1.64 (0.61–4.39)	3.29 (1.46–7.40)	2.09 (0.91–4.79)	2.46 (1.09–5.57)	$P = .66$
Arg/Arg	No.*	2/7	3/21	4/34	3/32	
	OR (95% CI)†	5.74 (1.01–32.66)	2.63 (0.64–10.87)	1.66 (0.46–5.94)	1.23 (0.31–4.95)	$P = .03$
Trend		$P = .04$	$P = .73$	$P = .27$	$P = .17$	
		Interaction $P = .03$				

CI: interval confidence; OR: odd ratio.
*Numbers of cases/controls.
†Adjusted for age, hospital, rank in the Self Defense Forces, body mass index, smoking, coffee intake, leisure–time physical activity, and parental diabetes mellitus.

Table 6: Interaction between alcohol use and *ALDH2* Glu487Lys polymorphism in relation to prediabetic condition and type 2 diabetes.

ALDH2 Genotype		Alcohol intake (mL/day)				Trend
		Never use	<30	30–59	≥60	
Prediabetic condition						
Glu/Glu	No.*	11/32	70/199	133/322	149/296	
	OR (95% CI)†	1:00 (referent)	1.11 (0.52–2.37)	1.25 (0.60–2.62)	1.56 (0.75–3.27)	$P = .07$
Glu/Lys	No.*	30/138	64/192	44/124	18/83	
	OR (95% CI)†	0.66 (0.29–1.49)	1.07 (0.50–2.30)	1.19 (0.54–2.62)	0.73 (0.30–1.76)	$P = .37$
Difference		$P = .47$	$P = .95$	$P = .79$	$P = .009$	
		Interaction $P = .42$				
Type 2 diabetes						
Glu/Glu	No.*	6/32	45/199	58/322	57/296	
	OR (95% CI)†	1:00 (referent)	0.98 (0.37–2.56)	0.73 (0.28–1.87)	0.78 (0.30–2.02)	$P = .29$
Glu/Lys	No.*	14/138	25/192	12/124	7/83	
	OR (95% CI)†	0.40 (0.14–1.15)	0.59 (0.22–1.60)	0.42 (0.14–1.24)	0.35 (0.10–1.15)	$P = .59$
Difference		$P = .09$	$P = .08$	$P = .13$	$P = .03$	
		Interaction $P = .83$				

CI: interval confidence; OR: odd ratio.
*Numbers of cases/controls.
†Adjusted for age, hospital, rank in the Self Defense Forces, body mass index, smoking, coffee intake, leisure–time physical activity, and parental diabetes mellitus.

intake was high (≥10 g/day) [11] whereas another study found no difference in fasting plasma glucose or hemoglobin A_{1c} concentrations according to *ADH1B* genotypes [12]. In the latter, fasting plasma insulin concentrations were lower in both men and women with *ADH1B*47His/Arg* genotype than those with the *His/His* genotype while there was no difference in alcohol consumption between the *His/His* and *His/Arg* genotypes [12]. None of these studies have suggested adverse effects of *ADH1B*47Arg* allele on glucose metabolism in the absence of alcohol exposure. It

should be noted that the estimated OR associated with *ADH1B*47Arg/Arg* genotype among neveralcohol drinkers was unstable because of very small numbers (2 cases and 7 controls).

The *ADH1C*349Ile* allele associated with fast oxidation was shown to be related to greater decrease in the risk of type 2 diabetes associated with alcohol consumption in the United States, suggesting an involvement of acetate, the end product of alcohol oxidation, in the protective association between alcohol and type 2 diabetes [13]. The *ADH1C* Ile349Val polymorphism was not assessed in the present study because the **349Val* allele is extremely rare in the Japanese [9]. The *ADH1B* Arg47His polymorphisms are in linkage disequilibrium with the *ADH1C* Ile349val polymorphism in Asian and Caucasian [20, 21]. The present findings do not support the hypothesis that fast alcohol oxidation confers a greater decrease in the risk of type 2 diabetes associated with alcohol consumption. We do not have a prompt explanation for the discrepancy in the role of fast alcohol oxidation in the effect of alcohol on glucose metabolism.

Previously the *ALDH2*487Lys* allele was associated with deterioration in glycemic control in patients with type 2 diabetes who had a habitual light to moderate alcohol consumption [14], and the *ALDH2*487Lys* allele was associated with higher concentrations of fasting plasma glucose when alcohol consumption was high (>5 g/day) [11]. Contrary to these observations, the present study suggests that individuals with the *ALDH2*487Lys* may have a lower risk of type 2 diabetes. It should be noted that a decreased risk of type 2 diabetes associated with *ALDH2*487Lys* allele was observed even in lifelong nondrinkers of alcohol. It is possible that individuals with *ALDH2*487Lys* allele may have had favorable ways of living in addition to abstinence from alcohol use. In the present study population, men with *ALDH2*487Lys* allele had a higher consumption of coffee, which has been related to decreased risk of type 2 diabetes [22], although they had a lower physical activity in leisure time (data not shown). A positive association between alcohol consumption and type 2 diabetes was totally ascribed to a confounding effect of the *ALDH2* genotype. The present study does not support either a decreased risk of type 2 diabetes with moderate alcohol consumption or an increased risk associated with heavy alcohol consumption.

The effect modification of the *ADH1B* genotype on the association with alcohol consumption as well as the association with *ALDH2* genotype was evident for type 2 diabetes, but not for prediabetic condition. We have no clear explanation for these differential effects. Further studies are needed to confirm the present findings.

This is the first large study regarding the *ADH1B Arg47His* or *ALDH2 Glu487Lys* polymorphism and glucose tolerance status, which was determined by the standard 75-g OGTT. However, there were several weaknesses to be discussed. The study subjects were not representative of Japanese men in the general population, but selection bias was unlikely to exist as to the genetic polymorphisms under study. The frequencies of *ADH1B*47Arg* (25%) and *ALDH2*487Lys* (24%) alleles were similar to those reported in Japanese populations elsewhere [9, 23]. An attrition bias is always possible in cross-sectional studies. A decreased risk of type 2 diabetes associated with *ALDH2*487Lys* allele would be observed if men carrying *ALDH2*487Lys* allele were more likely to leave the Self-Defense Forces earlier than the age of retirement when they developed type 2 diabetes.

5. Conclusions

In a cross-sectional study of middle-aged Japanese men, the *ADH1B* Arg47His polymorphism modified the association between alcohol consumption and type 2 diabetes. A positive association between alcohol consumption and type 2 diabetes was confounded by *ALDH2* polymorphism.

Abbreviations

ADH: alcohol dehydrogenase
ALDH: aldehyde dehydrogenase.

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References

[1] L. L. J. Koppes, J. M. Dekker, H. F. J. Hendriks, L. M. Bouter, and R. J. Heine, "Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies," *Diabetes Care*, vol. 28, no. 3, pp. 719–725, 2005.

[2] T. L. Holbrook, E. Barrett-Connor, and D. L. Wingard, "A prospective population-based study of alcohol use and non-insulin-dependent diabetes mellitus," *American Journal of Epidemiology*, vol. 132, no. 5, pp. 902–909, 1990.

[3] M. Wei, L. W. Gibbons, T. L. Mitchell, J. B. Kampert, and S. N. Blair, "Alcohol intake and incidence of type 2 diabetes in men," *Diabetes Care*, vol. 23, no. 1, pp. 18–22, 2000.

[4] W. H. L. Kao, I. B. Puddey, L. L. Boland, R. L. Watson, and F. L. Brancati, "Alcohol consumption and the risk of type 2 diabetes mellitus: atherosclerosis risk in communities study," *American Journal of Epidemiology*, vol. 154, no. 8, pp. 748–757, 2001.

[5] K. M. Conigrave, B. F. Hu, C. A. Camargo Jr., M. J. Stampfer, W. C. Willett, and E. B. Rimm, "A prospective study of drinking patterns in relation to risk of type 2 diabetes among men," *Diabetes*, vol. 50, no. 10, pp. 2390–2395, 2001.

[6] A. Yoshida, L. C. Hsu, and M. Yasunami, "Genetics of human alcohol-metabolizing enzymes," *Progress in Nucleic Acid Research and Molecular Biology*, vol. 40, pp. 255–287, 1991.

[7] M. V. Osier, A. J. Pakstis, H. Soodyall et al., "A global perspective on genetic variation at the ADH genes reveals unusual patterns of linkage disequilibrium and diversity," *American Journal of Human Genetics*, vol. 71, no. 1, pp. 84–99, 2002.

[8] W. F. Bosron and T.-K. Li, "Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism," *Hepatology*, vol. 6, no. 3, pp. 502–510, 1986.

[9] P. Brennan, S. Lewis, M. Hashibe et al., "Pooled analysis of alcohol dehydrogenase genotype and head and neck cancer: a HuGE review," *American Journal of Epidemiology*, vol. 159, no. 1, pp. 1–16, 2004.

[10] T. Takeshita, K. Morimoto, X. Q. Mao, T. Hashimoto, and J. Furuyama, "Characterization of the three genotypes of low K(m) aldehyde dehydrogenase in a Japanese population," *Human Genetics*, vol. 94, no. 3, pp. 217–223, 1994.

[11] M. Dakeishi, K. Murata, M. Sasaki, A. Tamura, and T. Iwata, "Association of alcohol dehydrogenase 2 and aldehyde dehydrogenase 2 genotypes with fasting plasma glucose levels in Japanese male and female workers," *Alcohol and Alcoholism*, vol. 43, no. 2, pp. 143–147, 2008.

[12] Y. Suzuki, F. Ando, I. Ohsawa, H. Shimokata, and S. Ohta, "Association of alcohol dehydrogenase 2∗1 allele with liver damage and insulin concentration in the Japanese," *Journal of Human Genetics*, vol. 51, no. 1, pp. 31–37, 2006.

[13] J. W. J. Beulens, E. B. Rimm, H. F. J. Hendriks et al., "Alcohol consumption and type 2 diabetes: influence of genetic variation in alcohol dehydrogenase," *Diabetes*, vol. 56, no. 9, pp. 2388–2394, 2007.

[14] C. Murata, Y. Suzuki, T. Muramatsu et al., "Inactive aldehyde dehydrogenase 2 worsens glycemic control in patients with type 2 diabetes mellitus who drink low to moderate amounts of alcohol," *Alcoholism: Clinical and Experimental Research*, vol. 24, no. 4, supplement, pp. 5S–11S, 2000.

[15] S. Kono, K. Shinchi, N. Ikeda, F. Yanai, and K. Imanishi, "Physical activity, dietary habits and adenomatous polyps of the sigmoid colon: a study of self-defense officials in Japan," *Journal of Clinical Epidemiology*, vol. 44, no. 11, pp. 1255–1261, 1991.

[16] Y. Miyake, H. Eguchi, K. Shinchi, T. Oda, S. Sasazuki, and S. Kono, "Glucose intolerance and serum aminotransferase activities in Japanese men," *Journal of Hepatology*, vol. 38, no. 1, pp. 18–23, 2003.

[17] K. G. M. M. Alberti and P. Z. Zimmet, "Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation," *Diabetic Medicine*, vol. 15, no. 7, pp. 539–553, 1998.

[18] K.-Y. Lee, K. Uchida, T. Shirota, and S. Kono, "Validity of a self-administered food frequency questionnaire against 7-day dietary records in four seasons," *Journal of Nutritional Science and Vitaminology*, vol. 48, no. 6, pp. 467–476, 2002.

[19] H. W. Goedde, S. Singh, D. P. Agarwal, G. Fritze, K. Stapel, and Y. K. Paik, "Genotyping of mitochondrial aldehyde dehydrogenase in blood samples using allele-specific oligonucleotides: comparison with phenotyping in hair roots," *Human Genetics*, vol. 81, no. 4, pp. 305–307, 1989.

[20] M. Osier, A. J. Pakstis, J. R. Kidd et al., "Linkage disequilibrium at the *ADH2* and *ADH3* loci and risk of alcoholism," *American Journal of Human Genetics*, vol. 64, no. 4, pp. 1147–1157, 1999.

[21] E. Borràs, C. Coutelle, A. Rosell et al., "Genetic polymorphism of alcohol dehydrogenase in Europeans: the ADH2*2 allele decreases the risk for alcoholism and is associated with ADH3*1," *Hepatology*, vol. 31, no. 4, pp. 984–989, 2000.

[22] R. M. Van Dam and F. B. Hu, "Coffee consumption and risk of type 2 diabetes: a systematic review," *Journal of the American Medical Association*, vol. 294, no. 1, pp. 97–104, 2005.

[23] G. Yin, S. Kono, K. Toyomura et al., "Alcohol dehydrogenase and aldehyde dehydrogenase polymorphisms and colorectal cancer: the Fukuoka Colorectal Cancer Study," *Cancer Science*, vol. 98, no. 8, pp. 1248–1253, 2007.