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ORIGINAL ARTICLE

Alcohol-induced impaired insulin secretion in a Japanese population: 5-year follow up in the Gifu Diabetes Study

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ABSTRACT

Aims/Introduction: Although moderate alcohol consumption lowers the risk of type 2 diabetes in European populations, the same cannot be assumed for Japanese patients with diabetes related to low insulin secretion rather than resistance. We aimed to evaluate the effects of daily alcohol consumption on glucose tolerance and diabetes development risk in Japanese populations.

Materials and methods: This retrospective study randomly enrolled 452 men and 659 women aged 40–78 years in 2005 (Gifu, Japan). The participants completed a 75-g oral glucose tolerance test and medical questionnaire. The homeostasis model assessment of insulin resistance, homeostasis model assessment of β-cell function and insulinogenic index were used to estimate insulin sensitivity and secretion. The relationships between alcohol consumption and these parameters were analyzed using logistic regression after adjusting for potential confounders. The 5-year changes in hemoglobin A1c levels were also evaluated.

Results: The adjusted odds ratios for elevated homeostasis model assessment of β-cell function values (<40%) in the 0–19.9 g/day, 20.0–39.9 g/day and ≥ 40 g/day alcohol consumption groups were 0.98, 1.46 and 2.68, respectively. Alcohol consumption induced a significant decrease in the insulin secretion level among the ≥40 g/day drinkers, especially in men. However, there was no risk of increased insulin resistance based on the homeostasis model assessment of insulin resistance (<2.5) results. The 5-year risk of elevated hemoglobin A1c levels (≥6.5%) was increased according to increase in alcohol consumption in both men and women.

Conclusions: Daily alcohol consumption was associated with reduced insulin secretion and an increased diabetes development risk in Japanese populations.

INTRODUCTION

The effect of moderate alcohol consumption in protecting against type 2 diabetes development has been reported in a systematic review and meta-analysis of studies carried out worldwide (most of them in Europe), and a meta-analysis of 15 prospective observational studies[1,2]. In addition, follow-up studies from Finland[3], England[4] and the USA[5] have confirmed that moderate alcohol consumption lowers the risk of type 2 diabetes. However, a systematic review of seven Japanese studies showed that alcohol intake is a risk factor for diabetes in non-obese Japanese men[6]. Of those seven studies[7-13], only one provided 75-g oral glucose tolerance test (OGTT) data[7], whereas five assessed fasting plasma glucose levels[8-12], and one carried out only a questionnaire-based assessment[13]. No studies to date have evaluated the relationship between alcohol consumption and insulin secretion or resistance in a Japanese population. As Japanese and European individuals have different insulin

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secretion abilities[14], the specific risks for diabetes onset associated with alcohol intake might differ between Japanese and European/North American populations. The present study aimed to evaluate the specific relationship between alcohol consumption and impaired glucose tolerance in Japanese people, using insulin secretion and resistance data.

METHODS

Ethical considerations

All study procedures complied with the ethical requirements of the national and institutional committees that oversee human studies, and with the 1964 Declaration of Helsinki and its later revisions. All participants provided informed consent for inclusion in the Gifu Diabetes Study. The study design was reviewed and approved by the ethical review committee of the Graduate School of Medicine, Gifu University (no. 17-107).

Participants and study procedures

This study used data from the Gifu Diabetes Study, which was carried out in Gifu, Japan. Although the methods used in the study have been described by Oba *et al.*[15] and Nonoyama *et al.*[16], the procedures are briefly described here. In March 2005, we asked the personal information protection committee of Gifu city hall to randomly select 2,260 men and 3,010 women aged 40–78 years from the Gifu residential registry, and to provide information on names and addresses. We requested the selected residents to participate in the Gifu Diabetes Study by mail. All participants who provided informed consent were allowed to select one of 35 participating medical institutions, in which they underwent an examination and completed a questionnaire between November 2005 and May 2007. Finally, a total of 1,097 individuals (449 men and 648 women) participated in the study, and we could collect the data to create the database of the Gifu Diabetes Study. Of the 1,097 individuals, 19 were excluded owing to incomplete or unreliable estimates of daily alcohol consumption and energy intake. Thus, data on 1,078 (441 men and 637 women) individuals were analyzed in the present study. None of the participants had liver cirrhosis.

All participants visited their chosen facility after an overnight fast. Their height, weight and blood pressure were measured, and blood samples were collected for the laboratory tests including the measurement of hemoglobin A1c (HbA1c), triglyceride (TG) and gamma-glutamyltranspeptidase (γ-GTP) levels. The levels of HbA1c were measured using the latex-enhanced immunoturbidimetry method, which was calibrated using Japanese Clinical Laboratory Use-certified Reference Material and corrected to the National Glycohemoglobin Standardization Program values, based on the recommendation of the Japanese Diabetes Society[17]. To define glucose tolerance levels, a 75-g OGTT was also carried out, with glucose levels at 2h ≥200 mg/dL classified as "diabetic," and ≥140 mg/dL as "impaired glucose tolerance," based on the World Health Organization criteria[18]. The levels of fasting glucose and insulin were used to calculate the homeostasis model assessment for insulin resistance (HOMA-IR) and β-cell function (HOMA-β) values: HOMA-IR = (fasting plasma glucose [mg/dL] × fasting insulin [μU/mL]) / 405; and HOMA-β = (fasting insulin [μU/mL] × 360) / (fasting plasma glucose [mg/dL] − 63)[19]. We also used the insulinogenic index (I/I) to evaluate β-cell function, which was measured as the ratio of incremental insulin (I) and glucose (G) responses over the first 30 min of the OGTT (ΔI_{0-30} / ΔG_{0-30})[20]. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

The Food Frequency Questionnaire (FFQ), which is valid and reproducible in the Japanese population[21], was used to estimate the nutrient intakes including those through alcohol consumption for each individual. In the FFQ, a standard portion size using natural units usually used in Japan for most food items, including alcohol drinks, was adopted. The quantity of alcoholic beverages was assessed using four categories; for example, one can of beer or less, two cans, three cans, or four cans or more. Frequencies of alcoholic beverage intake were assessed using nine response categories ranging from never or hardly ever to four or more times a day. Shimizu *et al.*[21] carried out the FFQ, 3-day dietary recall by dietitian, and 24-h recall by postal mail and call by a dietitian. They analyzed these data, and showed the validity and reproducibility of the FFQ. As portion size information is important for obtaining accurate nutrient intake habits, including those associated with alcohol, they suggested that the FFQ can be used to estimate the nutrient intake of each individual in the cohort. The participants were categorized according to their alcohol consumption level: non-drinkers and drinkers (0–19.9 g/day, 20.0–39.9 g/day or ≥ 40 g/day) according to the criteria of the National Health and Nutrition Survey Japan 2016. According to the National Health and Nutrition Survey, "those who drink alcohol at a level which increased the risk of lifestyle-related diseases" referred to men and women who consumed ≥40 g or ≥20 g pure alcohol, respectively, daily[22].

Of the 1,078 included individuals, 603 (237 men and 366 women) attended the 5-year follow up and HbA1c testing (November 2010 to May 2012). We also evaluated the relationship between alcohol consumption and the 5-year changes in HbA1c levels. To estimate the glucose tolerance level after 5 years of the first survey, we used HbA1c rather than the results of the 75-g OGTT according to the National Health and Nutrition Survey, Japan[22], as recommended by the international expert committees of Japan,[23] the USA[24] and the UK.[25]

Statistical analysis

To assess the associations of alcohol intake and the glucose metabolism parameters, we used logistic regression analyses to calculate the odds ratios (ORs) that were adjusted for potential confounders (e.g., sex, age, daily caloric intake, smoking and BMI).

The logistic regression model was: Log (odds) = intercept + β_1G + β_2A + β_3D + β_4C + β_5S + β_6B (G: gender, A: age, D: daily caloric intake [kcal/day], C: alcohol consumption, S:

smoking, B: BMI). Non-drinkers were included in the reference group. The other reference values were defined as follows: blood glucose levels <140 mg/dL at 2 h after the 75-g OGTT, HOMA-β values ≥40, HOMA-IR values <2.5, I/I ≥0.4, γ-GTP levels ≤68 IU/L (men) and ≤38 IU/L (women), TG levels <150 mg/dL, BMI <25 kg/m^2, BMI change <3.0 kg/m^2, systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg. All statistical analyses were carried out using JMP software (version 11; SAS Institute Inc., Tokyo, Japan).

RESULTS

The participants were categorized into four groups according to their alcohol consumption levels, comprising 387 non-drinkers, 453 drinkers who consumed 0–19.9 g/day, 109 drinkers who consumed 20–39.9 g/day and 129 drinkers who consumed ≥40.0 g/day. The non-drinker and 0–19.9 g/day groups predominantly comprised women (77.3% and 63.4%, respectively), and the 20–39.9 g/day and ≥40 g/day groups predominantly comprised men (70.6% and 85.3%, respectively). The participants' average age was 59.6 ± 9.9 years (men 60.3 ± 10.0 years, women 59.0 ± 9.8 years), and the average daily caloric intake was 2,111.3 ± 735.7 kcal/day (men 2,199.9 ± 720.7 kcal/day; women 2,050.0 ± 740.3 kcal/day). Alcohol consumption was positively correlated with the average caloric intake, BMI, TG and γ-GTP values. There were significant differences between the men and women in their average values for age, caloric intake, BMI, plasma glucose levels at 2 h after the OGTT and HOMA-IR. However, there were no significant sex-related differences in the average values for HOMA-β, I/I and HbA1c (Table 1).

The ORs for the normal ranges of variables being exceeded after adjusting for age, sex, daily caloric intake, smoking and BMI are shown in Table 2. The adjusted ORs for elevated blood glucose levels at 2 h after the OGTT (≥140 mg/dL) were not significantly different across the alcohol consumption subgroups (0.49, 0.70 and 0.85 for the 0–19.9 g/day, 20–39.9 g/day and ≥ 40 g/day groups, respectively). The adjusted ORs for elevated HOMA-IR (≥2.5) and decreased I/I (<0.4) values were also not significantly different between the alcohol consumption subgroups. However, the ≥40.0 g/day group showed a significantly higher adjusted OR for decreased HOMA-β values (<40) compared with the non-drinkers (OR 2.68, 95% CI 1.27–5.74). Among men, the adjusted OR for decreased HOMA-β values (<40) was significantly higher in the ≥40 g/day group compared with the non-drinkers (OR 3.11, 95% CI 1.30–7.78).

The adjusted ORs for elevated γ-GTP levels (>68 for men, >38 for women) increased with increasing alcohol consumption levels and was significantly elevated in the ≥40 g/day group (OR 3.24, 95% CI 1.38–7.95), especially in men (OR 4.56, 95% CI 1.73–13.42). There were no significant increases in the adjusted ORs for elevated TG (≥150 mg/dL) and HbA1c (≥6.5 %) values according to alcohol consumption (Table 2).

The adjusted ORs for HbA1c levels ≥6.5% after 5 years were 1.65 (95% CI 0.53–5.61), 3.42 (95% CI 0.62–16.29) and 4.01 (95% CI 0.51–15.63) in the 0–19.9 g/day, 20–39.9 g/day and ≥ 40 g/day groups, respectively. In the sex-specific subanalyses, these ORs were also elevated in the 20–39.9 g/day group (men OR 3.36, 95% CI 0.30–75.55; women OR 3.76, 95% CI 0.18–29.53) and in the ≥40.0 g/day group (men OR 4.81, 95% CI 0.50–109.34; women, no participants; Table 3).

DISCUSSION

The present study is the first to provide evidence on the alcohol-induced reduction in the degree of insulin secretion in a randomly selected Japanese population, after adjusting for sex, age, daily caloric intake, smoking and BMI. Our analyses showed that the risk of reduced insulin secretion, as demonstrated by the adjusted ORs for lower HOMA-β values, was positively associated with alcohol intake and significantly increased in the group with high alcohol consumption levels (≥40 g/day). The risk of increased insulin resistance (i.e., adjusted OR for higher HOMA-IR values) was not related to alcohol consumption.

Several recent studies have examined the relationship between daily alcohol consumption and type 2 diabetes risk in the Japanese population[7-13]. Tsumura *et al.*[9] showed that lean men with high ethanol consumption levels (≥50.1 mL/day) had an increased risk of type 2 diabetes. Watanabe *et al.*[10] also showed that alcohol consumption was a risk factor for diabetes development among Japanese men and women with a low BMI. Although those studies both evaluated prospective cohorts with >1,000 Japanese participants and had an observation period >5 years, neither evaluated the participants' insulin secretion and resistance capabilities.

A few studies have also evaluated the relationship between insulin sensitivity and alcohol consumption in Western populations[4,26-29]. Wannamethee *et al.*[4] showed that the adjusted OR for hyperinsulinemia increased with increasing alcohol consumption levels in a British population (up to >60 g/day). Mayer *et al.*[26] evaluated American twins, and found significantly low serum insulin levels before and 2 h after a 75-g OGTT in the group with ≥10 g/day of alcohol consumption, compared with non-drinkers. Lazarus *et al.*[27] evaluated a population of American military veterans, and found that the lowest fasting insulin levels were observed in the 10.0–29.9 g/day alcohol consumption group, compared with the other groups (non-drinkers 0.1–9.9 g/day, and ≥30 g/day). Kiechl *et al.*[28] evaluated an Italian population, and found significant decreases in the fasting and post-OGTT insulin concentrations according to increasing alcohol consumption level (from 0 g/day to ≥100 g/day). The aforementioned four reports show that alcohol consumption might induce reductions in serum insulin levels through improvements in insulin sensitivity in European and American populations. This relationship might be explained by the findings of Sierksma *et al.*[29] and Ley *et al.*[30], who showed that an ethanol consumption level of 40 g/day induced increases in the levels of adiponectin and fetuin-A, and decreases in the degree of insulin resistance in Dutch and American populations. It is possible that moderate

Table 1 | Characteristics of the participants according to alcohol consumption

	Total	Alcohol consumption (g of ethanol/day)			
		Non-drinker	0–19.9 g	20.0–39.9 g	≥40.0 g
No. participants	1078	387	453	109	129
Male	441 (40.9)	88 (22.7)	166 (36.6)	77 (70.6)	110 (85.3)
Female	637 (59.1)	299 (77.3)	287 (63.4)	32 (29.4)	19 (14.7)
Age (years)	59.6 ± 9.9	60.1 ± 10.1	60.0 ± 9.9	58.1 ± 10.2	57.7 ± 9.0
Male	60.3 ± 10.0*	62.2 ± 10.1	60.7 ± 10.3	60.3 ± 10.3	58.4 ± 9.1
Female	59.0 ± 9.8	59.5 ± 10.0	59.6 ± 9.6	52.9 ± 7.9	54.1 ± 8.3
Calorie intake (kcal/day)	2111.3 ± 735.7	1946.6 ± 699.0	2097.6 ± 722.0	2124.1 ± 625.2	2642.7 ± 737.0
Male	2199.9 ± 720.7*	1943.3 ± 634.3	2072.5 ± 650.9	2110.6 ± 635.5	2659.8 ± 745.6
Female	2050.0 ± 740.3	1947.5 ± 717.9	2112.1 ± 760.8	2156.7 ± 608.2	2543.7 ± 696.2
BMI (kg/m^2)	23.0 ± 3.2	22.8 ± 3.4	23.0 ± 3.1	22.9 ± 3.3	23.8 ± 3.0
Male	23.8 ± 3.1	23.9 ± 3.3	23.8 ± 3.2	23.5 ± 3.3	24.1 ± 2.8
Female	22.4 ± 3.1	22.4 ± 3.3	22.5 ± 2.9	21.7 ± 3.0	22.0 ± 3.4
Blood glucose level at 2 h of OGTT (mg/dL)	126.0 ± 47.2	124.4 ± 46.4	122.7 ± 42.2	127.2 ± 46.9	141.3 ± 61.3
Male	136.3 ± 56.2***	139.1 ± 59.9	129.6 ± 48.6	135.0 ± 52.5	144.9 ± 64.8
Female	118.9 ± 38.2	120.0 ± 40.7	118.8 ± 37.6	109.0 ± 21.8	121.4 ± 30.7
HOMA-β	78.7 ± 61.2	77.3 ± 47.7	82.6 ± 61.6	71.4 ± 59.0	75.1 ± 90.2
Male	76.7 ± 67.7	78.3 ± 54.8	80.0 ± 51.2	70.9 ± 64.0	74.8 ± 95.7
Female	80.0 ± 56.4	77.0 ± 45.5	84.2 ± 66.9	72.5 ± 45.7	77.3 ± 48.8
HOMA-IR	1.5 ± 1.3	1.4 ± 1.1	1.6 ± 1.4	1.4 ± 1.4	1.6 ± 1.6
Male	1.6 ± 1.4*	1.7 ± 1.4	1.6 ± 1.0	1.6 ± 1.6	1.7 ± 1.7
Female	1.4 ± 1.3	1.4 ± 1.0	1.5 ± 1.6	1.1 ± 0.7	1.1 ± 0.8
I/I	0.9 ± 4.3	0.7 ± 6.3	1.2 ± 3.1	0.7 ± 1.6	0.6 ± 0.6
Male	0.9 ± 2.4	0.9 ± 0.9	1.3 ± 3.8	0.7 ± 1.0	0.6 ± 0.6
Female	0.9 ± 5.2	0.6 ± 7.2	1.2 ± 2.6	0.7 ± 2.5	0.7 ± 0.6
HbA1c	5.8 ± 0.7s	5.8 ± 0.7	5.9 ± 0.8	5.8 ± 0.5	5.8 ± 0.6
Male	5.9 ± 0.6	5.8 ± 0.6	5.9 ± 0.7	5.8 ± 0.5	5.8 ± 0.6
Female	5.8 ± 0.8	5.8 ± 0.7	5.9 ± 0.8	5.6 ± 0.5	5.7 ± 0.5
TG (mg/dL)	109.7 ± 69.8	102.3 ± 50.8	108.6 ± 73.6	113.1 ± 61.7	132.7 ± 100.7
Male	124.7 ± 73.7***	115.0 ± 52.7	116.5 ± 58.4	128.5 ± 65.6	142.2 ± 105.1
Female	99.3 ± 65.1	98.6 ± 49.7	104.1 ± 80.9	75.8 ± 26.4	78.3 ± 40.6
γ-GTP (IU/L)	33.0 ± 35.4	25.6 ± 26.7	30.1 ± 27.4	41.5 ± 40.4	57.5 ± 58.9
Male	45.3 ± 43.6***	33.5 ± 24.4	39.7 ± 31.3	46.9 ± 44.3	62.0 ± 62.4
Female	24.4 ± 24.9	23.2 ± 26.9	24.7 ± 23.2	28.4 ± 25.0	31.7 ± 15.9

Data are the mean ± standard deviation. Statistically significant difference to female by *t*-tests *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. γ-GTP, gamma-glutamyltranspeptidase; BMI, body mass index; HbA1c, hemoglobin A1c; HOMA-β homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; I/I, insulinogenic index; OGTT, oral glucose tolerance test; TG, triglycerides.

alcohol consumption levels (approximately ≤50 g/day) can improve glucose tolerance through the suppression of insulin resistance among European and North American individuals, explaining the relationship between moderate alcohol intake and a lower incidence of type 2 diabetes among various European populations[31-34].

In contrast, we observed two conflicting findings in the present Japanese population. The first is that β-cell function (HOMA-β) was suppressed by moderate alcohol consumption (20–39.9 g/day and ≤40 g/day); however, this level of consumption did not affect insulin resistance (HOMA-IR). The second is that even a low alcohol consumption level (≤20.0 g/day) increased the risk of diabetes development in both men and women. To the best of our knowledge, this is the first study to show the presence of a relationship between alcohol-induced impaired β-cell function and an increased risk of diabetes in a Japanese population.

A recent study found that low (≤28 g/day) and high (≥29 g/day) alcohol consumption levels were associated with an increased risk of impaired β-cell function in Chinese men,[35] which supports the present findings and suggests that ethnicity-related differences should be considered in the evaluation of the relationship between alcohol consumption and diabetes risk. The presence of ethnicity-related differences has been confirmed in terms of insulin sensitivity and β-cell function among non-diabetic individuals, with Torréns *et al.*[36] reporting that Japanese Americans show weaker insulin sensitivity and β-cell function than non-Hispanic, non-African, non-Chinese and

Table 2 | Adjusted odds ratios for insulin secretion, resistance and associated factors according to alcohol consumption

	Alcohol consumption (g of ethanol/day)		
	0–19.9 g OR (95% CI)	20.0–39.9 g OR (95% CI)	≥40.0 g OR (95% CI)
Blood glucose level after 120 min	0.49 (0.29–0.82)	0.70 (0.35–1.40)	0.85 (0.45–1.62)
Male	0.52 (0.27–1.00)*	0.79 (0.35–1.72)	0.88 (0.42–1.84)
Female	0.52 (0.22–1.19)	0.44 (0.02–2.97)	0.44 (0.02–2.90)
HOMA-β	0.98 (0.52–1.84)	1.46 (0.65–3.21)	2.68 (1.27–5.74)*
Male	1.20 (0.54–2.75)	1.48 (0.59–3.77)	3.11 (1.30–7.78)*
Female	0.73 (0.22–2.26)	8.33 (0.91–66.73)	-
I/I	0.72 (0.43–1.19)	1.07 (0.54–2.08)	1.04 (0.55–1.96)
Male	1.04 (0.55–1.99)	1.61 (0.76–3.45)	1.51 (0.73–3.16)
Female	0.43 (0.17–1.02)	-	-
HOMA-IR	0.96 (0.48–1.95)	0.88 (0.28–2.48)	1.09 (0.43–2.73)
Male	1.03 (0.40–2.77)	1.23 (0.35–4.18)	1.24 (0.42–3.78)
Female	0.69 (0.21–2.19)	–	3.56 (0.38–26.43)
TG	1.58 (0.87–2.93)	1.97 (0.91–4.29)	1.60 (0.78–3.33)
Male	1.32 (0.64–2.80)	2.04 (0.88–4.84)	1.61 (0.73–3.63)
Female	2.54 (0.87–8.11)	–	–
γ-GTP	0.94 (0.42–2.16)	1.84 (0.69–4.85)	3.24 (1.38–7.95)*
Male	1.13 (0.43–3.22)	2.44 (0.83–7.61)	4.56 (1.73–13.42)*
Female	0.87 (0.22–3.22)	-	-
Blood pressure	1.49 (0.93–2.42)	1.59 (0.81–3.10)	1.84 (0.99-2.42)
Male	1.23 (0.66–2.32)	1.50 (0.71–3.22)	1.93 (0.95–3.99)
Female	2.35 (1.09–5.22)*	2.10 (0.21–15.40)	-
HbA1c	1.09 (0.51–2.43)	1.38 (0.50–3.68)	0.54 (0.17–1.55)
Male	1.02 (0.42–2.68)	1.35 (0.46–4.00)	0.43 (0.12–1.42)
Female	1.33 (0.28–6.66)	–	3.47 (0.14–38.45)

Adjusted for sex (female as reference), age, calorie intake per day, smoking and body mass index. Alcohol consumption per day was categorized as non-drinker (the reference group), 0–19.9 g/day, 20.0–39.9 g/day and ≥40.0 g/day. Normal levels are as follows: blood glucose level <140 mg/dL, homeostasis model assessment of β-cell function (HOMA-β) ≥40, I/I ≥0.4, homeostasis model assessment of insulin resistance (HOMA-IR) <2.5, triglycerides (TG) <150 mg/dL, hemoglobin A1c (HbA1c) <6.5%, gamma-glutamyltranspeptidase (γ-GTP) ≤68 IU/L (male) and ≤38 IU/L (female), blood pressure <90 mmHg (diastolic) and <140 mmHg (systolic). CI, confidence interval; OR, odds ratio. *Statistically significant ($P < 0.05$).

Table 3 | Adjusted odds ratios for developing hemoglobin A1c levels of ≥6.5% at 5 years according to alcohol consumption

	n	Alcohol consumption (g of ethanol/day)		
		0–19.9 g OR (95% CI)	20.0–39.9 g OR (95% CI)	≥40.0 g OR (95% CI)
HbA1c at first survey	603	1.07 (0.52–2.22)	0.91 (0.27–2.62)	1.10 (0.37–3.06)
Male	237	1.07 (0.37–3.37)	0.82 (0.19–3.11)	0.93 (0.24–3.52)
Female	366	0.99 (0.37–2.65)	1.04 (0.05–6.41)	2.82 (0.39–13.37)
HbA1c at 5 years later	603	1.65 (0.53–5.61)	3.42 (0.62–16.29)	4.01 (0.51–15.63)
Male	237	1.37 (0.13–30.10)	3.36 (0.30–75.55)	4.81 (0.50–109.34)
Female	366	1.75 (0.48–7.10)	3.76 (0.18–29.53)	

Adjust for sex (female as reference), age and calorie intake per day. Alcohol consumption per day was categorized non-drinker (the reference group), 0–19.9 g/day, 20.0–39.9 g/day and ≥40.0 g/day. CI, confidence interval; HbA1c, hemoglobin A1c; OR, odds ratio.

non-Mexican American women. The present results, which show that even lower alcohol consumption levels can reduce the degree of insulin secretion and increase the risk of diabetes onset in Japanese people, are acceptable; however, they are different from those observed in studies carried out in European populations.

Although we showed that alcohol-induced impaired insulin secretion measured by HOMA-β, I/I – a marker for early phase

of insulin secretion – was not affected significantly by the increase in alcohol consumption. No studies thus far show the relationship between the I/I and daily alcohol consumption, not only in the Japanese population[7-13], but also worldwide[1-5]. Although seven reports have shown alcohol-induced increases in diabetes in Japanese people,[7-13] the present study is the first to report that there were no significant alcohol effects on the I/I level in the Japanese population.

According to one systematic review and meta-analysis of insulin response to glucose in an intravenous glucose tolerance test[37], insulin resistance indicated by HOMA-IR is generally higher in people of white European descent, whereas β-cell response to glucose stimuli measured by HOMA-β and I/I is lower in Japanese patients. Additionally, cross-sectional studies of Japanese individuals showed that I/I and HOMA-β are lower in Japanese patients with normal glucose tolerance, impaired glucose tolerance and type 2 diabetes in comparison with that of European individuals, as discussed in the Botnia Study[38,39]. One possible reason why the I/I level might not have been affected by the amount of alcohol consumption is because the I/I level in Japanese patients is low compared with that in of European individuals (the average level is approximately one-third). In addition, alcohol-induced impaired insulin secretion in the early phase was not significant, although the insulin secretion level measured by HOMA-β was significantly affected by the amount of alcohol intake.

We also found that moderate alcohol consumption (levels >20 g/day) increased the risk of diabetes onset within 5 years in a randomly selected Japanese population. Although several reports from Western countries[1-5,31-34] have found that moderate alcohol intake might reduce the risk of type 2 diabetes development, few have focused on the differences in the effect of alcohol consumption on glucose metabolism between Western and Japanese populations.

We should recognize that the alcohol intake volume categorization in most Japanese studies is different from those involving Western countries. Studies in most Western countries categorize alcohol intake as 0 g/day (non-drinker), <50 g/day (a couple of glasses of wine/day), 50–100 g/day (a bottle of wine) and >100 g/day (more than a bottle of wine)[1-5]. However, most Japanese studies, including the present study, categorized alcohol intake into 0 g/day (non-drinker), <20 g/day (less than a glass of wine/day), 20–40 g/day (one or two glasses of wine) and ≥40 g/day (more than a few glasses of wine)[6], as most Japanese individuals do not drink as much alcohol as Western individuals because of acetaldehyde dehydrogenase deficiencies.

We showed an increase in diabetes onset risk according to daily alcohol intake in Japanese patients, which was adjusted for sex, age, daily energy intake, smoking and BMI. We understand the alcohol-induced increase in type 2 diabetes risk shown in the present study is similar to habitual risks for diabetes, such as overeating or less exercise. We suspect the participants who developed diabetes after 5 years might have gone through a prediabetes period with relatively low I/I, and alcohol consumption accelerated the onset of diabetes reducing the HOMA-β levels without depletion of I/I.

It is possible that Japanese and European individuals have different alcohol-related risks of diabetes, based on their differences in the pathophysiology of type 2 diabetes; Japanese individuals are less obese and have greater β-cell dysfunction, whereas European individuals have greater insulin resistance[14].

As the strength of the present study is that we randomly selected participants from the Japanese population, and evaluated both insulin secretion and resistance using 75-g OGTT, our findings show the characteristic pathological mechanisms of alcohol-induced type 2 diabetes in the Japanese population.

The present study had two limitations. As no clear mechanism was established for the alcohol-induced impairment of human β-cell function, further intracellular or animal studies are required to evaluate the direct effects of alcohol on β-cell function and insulin resistance. Additionally, alcohol consumption was estimated using a self-administered questionnaire, as a result we were unable to identify ex-drinkers or evaluate drinking patterns. Additional studies are required to evaluate whether the present findings can be replicated in non-Japanese Asian populations. Nevertheless, patients with impaired insulin secretion might benefit from lifestyle guidance with recommendations for appropriate alcohol consumption.

In conclusion, the present findings show that an alcohol consumption level >20 g/day is associated with impaired insulin secretion and might increase the risk of diabetes onset in Japanese people.

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DISCLOSURE

The authors declare no conflict of interest.

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