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Combination of alcohol and glucose consumption as a risk to induce reactive hypoglycemia

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Keywords
Alcohol, Hypoglycemia, Oral glucose tolerance test

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ABSTRACT

Aims/Introduction: Alcohol consumption has been reported to cause hypoglycemia. However, the mechanism involved has not been unequivocally established. This study comprised healthy volunteers. We carried out a prospective trial to compare the effects of glucose and alcohol consumption, alone or in combination, on glucose and lipid metabolism.

Materials and Methods: A 75-g oral glucose tolerance test (OGTT), a combined 75-g glucose plus 20-g alcohol tolerance test (OGATT) and a 20-g alcohol tolerance test (OATT) were carried out in the participants. Plasma glucose, insulin, triglyceride and ethanol concentrations during each test were compared.

Results: We studied 10 participants. Their plasma glucose concentrations 15 and 30 min after the intake of 75 g of glucose were significantly higher during the OGATT than the OGTT. Hypoglycemia occurred in five participants after the OGATT, which was significantly more frequently than after the OGTT ($P = 0.046$). Hypoglycemia did not occur after the OATT, and the ethanol concentration was significantly lower after the OGATT than the OATT. The changes in triglyceride concentration from 30 min after the consumption of 75 g of glucose were significantly greater during the OGATT than the OGTT. The plasma insulin concentrations peaked after 60 min during both the OGTT and OGATT, and were significantly higher during the OGATT ($P = 0.047$). There were no differences between the two interventions in the Matsuda or disposition indexes.

Conclusions: Hypoglycemia occurred more frequently after the simultaneous consumption of alcohol plus glucose than after the consumption of glucose alone, suggesting that alcohol in the combination of glucose induces reactive hypoglycemia.

INTRODUCTION

Alcohol consumption has been well known to be associated with hypoglycemia[1]. In previous studies, the hypoglycemic mechanism of alcohol has been described as a decline in hepatic gluconeogenesis[2] and/or an increase in insulin secretion[3,4]. Furthermore, some previous studies showed that alcohol consumption increases peripheral insulin resistance[5,6], whereas others have made the seemingly contradictory findings of greater insulin secretion[3,7] or lower insulin resistance[8–12]. Thus, a number of heterogeneous effects of alcohol on carbohydrate metabolism have been hypothesized, presumably because of variations in the study participants, differences in the assessment of hypoglycemia or differences in the food consumed with the alcohol. We speculate that the trend of low-carbohydrate diets is correlated with the increase of people drinking alcohol without carbohydrate intake. Therefore, it is also important to clarify whether simultaneous carbohydrate intake influences the effects of alcohol.

The purpose of the present study was to clarify the relationship between glucose and alcohol metabolism in individuals

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with normal glucose tolerance, by measuring the blood glucose, immunoreactive insulin (IRI) and ethanol concentrations after the intake of glucose and alcohol, alone or in combination.

METHODS

Participants

The present study comprised healthy volunteers who had not been diagnosed with impaired glucose tolerance. The exclusion criteria were severe liver, kidney or heart disease, alcohol intolerance, a history of ill health caused by alcohol or hypersensitivity to alcohol, pregnancy, breast-feeding or a chance of becoming pregnant, and intention to drive on a study day. The participants provided their written informed consent to participate in the study before entry and after explaining the potential risks, such as abdominal symptoms and acute alcohol intoxication. The study was carried out in accordance with the Declaration of Helsinki and with the approval of the Sapporo Medical Association's Ethical Review Board. The study was registered with the University Hospital Information Network Clinical Trials Registry (ID UMIN 000031993).

Methods

This was a prospective trial carried out between March and June 2017. A sweat-patch alcohol test was used to identify alcohol resistance. We genotyped the alcohol dehydrogenase (*ADH*)*1B* and aldehyde dehydrogenase (*ALDH*)*2* loci in saliva samples using real-time polymerase chain reaction (552C Regular Flocked Swab, Nylon Tip; NSD Co., Ltd., Tokyo, Japan). The participants then completed a questionnaire regarding their drinking habits (frequency and amount of alcohol consumption on a single occasion). When we verified that the potential participants were biologically capable of consuming alcohol, using these tests, they were enrolled in the study.

Each participant made three visits on separated days within 3 months of providing their informed consent. A 75-g oral glucose tolerance test (OGTT) was carried out at visit 1, then a combined 75-g glucose and 20-g alcohol tolerance test (OGATT) was carried out at visit 2. Finally, a 20-g alcohol tolerance test (OATT) was carried out to determine the effects of alcohol alone on blood glucose concentration at visit 3 (Figure 1). A total of 20 g of alcohol was loaded, because this

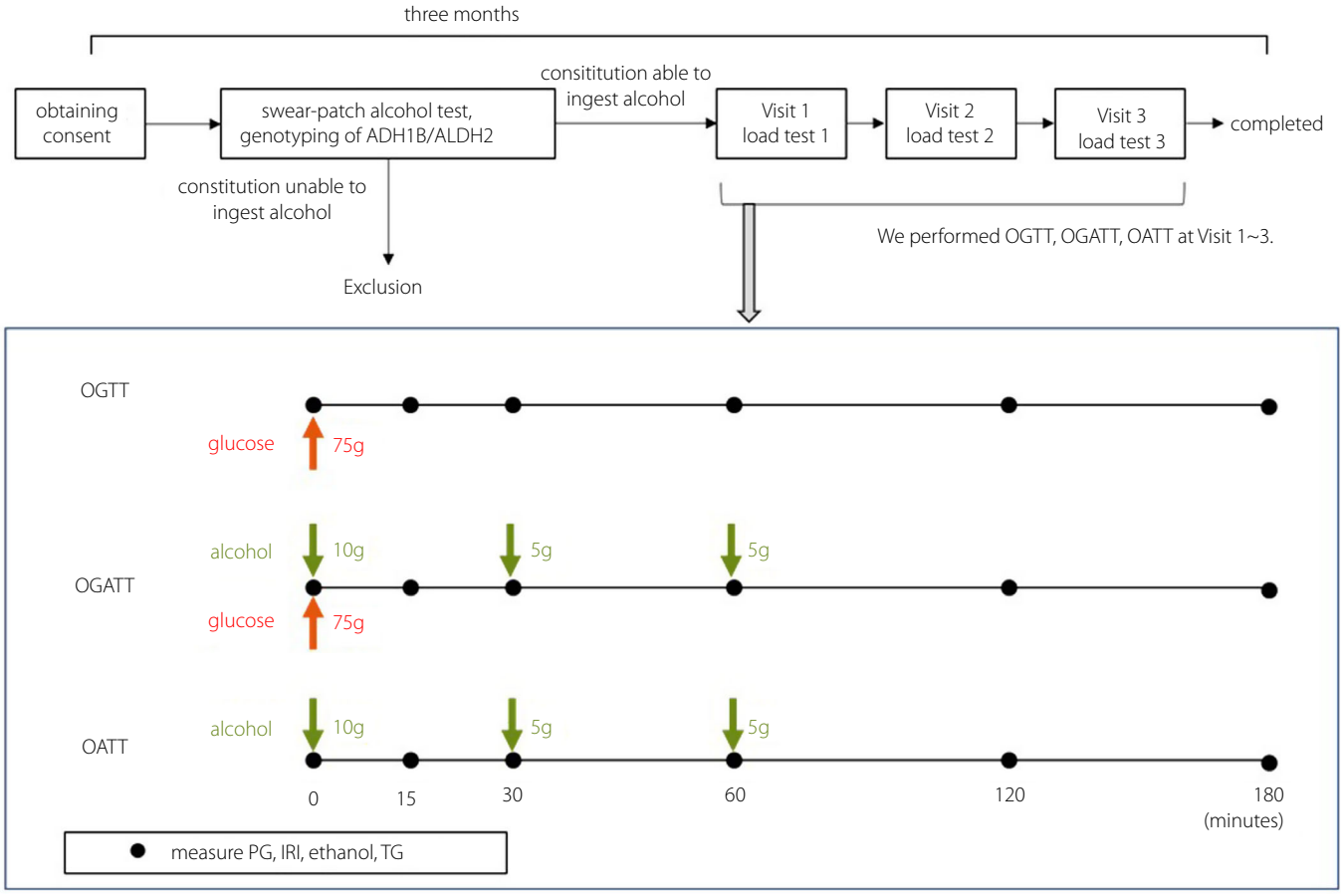


Figure 1 | Flow diagram. We carried out the 75-g oral glucose tolerance test (OGTT), combined 75-g glucose and 20-g alcohol tolerance test (OGATT) and 20-g alcohol tolerance test (OATT) on separate days, early in the morning and after an overnight fast. IRI, immunoreactive insulin; PG, plasma glucose; TG, triglyceride.

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amount is the daily intake limit recommended by the Ministry of Health, Labor and Welfare, Japan. Participants were prohibited from drinking alcohol the day before each visit, and visited early in the morning after an overnight fast. Shochu (a Japanese distilled alcoholic beverage) was used in the alcohol-loading test. For the OGTT, Trelan-G75g (AY Pharmaceuticals Co., Ltd., Tokyo, Japan) was used. In the OGATT, each participant consumed 62.5 mL of shochu, equivalent to 10 g of alcohol, with Trelan-G75g, and after 30 and 60 min, they consumed 31.25 mL of straight shochu, (5 g of alcohol each). In the OATT, each participant consumed 62.5 mL of shochu with sugar-free carbonated water, and after 30 and 60 min, they consumed a further 31.25 mL of straight shochu. In consideration of participant safety against acute alcohol poisoning, the protocol was designed to administer alcohol in separate amounts, rather than all at once.

At each visit, we collected blood before loading, and 15, 30, 60, 120 and 180 min after loading, to measure plasma glucose, IRI, triglyceride and ethanol concentrations. We also calculated the Matsuda Index[13] as an indicator of insulin resistance, the insulinogenic index (II) at 15 and 30 min (ΔIRI [15′] / Δplasma glucose [15′], ΔIRI [30′] / Δplasma glucose [30′]) as an indicator of initial insulin secretory capacity, and the disposition index as a combined index of insulin secretion and insulin sensitivity[14]. We measured IRI using an E-test Tosoh II kit (Tosoh, Tokyo, Japan), and whole blood ethanol concentration was measured by gas chromatography at the Specimen Research Laboratory (Tokyo, Japan).

The primary end-points were the changes in plasma glucose and IRI concentrations during glucose loading in the presence/absence of alcohol. The secondary end-points were the changes in serum ethanol concentration during alcohol loading in the presence/absence of glucose. Hypoglycemia was defined as a blood glucose of <54 mg/dL. We express the values as the mean ± standard deviation. We used the Wilcoxon rank sum test and McNemar test for statistical analysis, and accepted $P < 0.05$ as denoting statistical significance. Data were analyzed using Ekuseru-Toukei 2015 software (Social Survey Research Information, Tokyo, Japan).

RESULTS

Characteristics of the participants

A total of 10 participants without diabetes (five women and five men) were included and all completed the study. The participants were aged 36.1 ± 6.5 years, and had a hemoglobin A1c concentration of 5.3 ± 0.4%, a body mass index of 21.7 ± 2.6 kg/m^2, a homeostatic model assessment for β-cell function of 76.6 ± 34.1 and a homeostasis model assessment for insulin resistance of 1.1 ± 0.5. With respect to their alcohol tolerance genotypes, seven had active *ADH1B* and *ALDH2*, and three had active *ADH1B* and inactive *ALDH2* genotypes. Their stated alcohol consumption frequencies were: daily (n = 2), 5–6 times a week (n = 2), 3–4 times a week (n = 1), 1–2 times a week (n = 2), 1–3 times a month (n = 2) and seldom (n = 1). The usual quantity of alcohol consumed per occasion was 80–100 g (n = 1), 60–80 g (n = 1), 40–60 g (n = 1), 20–40 g (n = 5) and <20 g (n = 2; Table 1). There were no differences in the results of glucose and/or alcohol loading between the sexes, participants with differing alcohol metabolism genotypes, or participants with differing alcohol consumption habits.

Comparison of changes in the plasma glucose and IRI concentrations during glucose loading in the presence/absence of alcohol

The plasma glucose concentrations 15 and 30 min after a 75-g glucose load were significantly higher during the OGATT than during the OGTT (P = 0.047 and P = 0.037, respectively). The plasma glucose concentrations peaked at 30 min during both the OGTT and OGATT (Figure 2; Table 2). We identified hypoglycemia in one participant after the OGTT and five

Table 1 | Characteristics of the participants

	Person with normal glucose tolerance
n	10
Sex (women/men)	5/5
Age (years)	36.1 ± 6.5
BMI (kg/m^2)	21.7 ± 2.6
Cre (mg/dL)	0.76 ± 0.11
AST (U/L)	23.7 ± 7.1
ALT (U/L)	23.4 ± 12.8
γGTP (U/L)	26.1 ± 15.0
T-Cho (mg/dL)	210.5 ± 27.7
TG (mg/dL)	94.0 ± 38.5
HDL-Cho (mg/dL)	75.7 ± 11.6
LDL-Cho (mg/dL)	116.9 ± 26.0
HbA1c (%)	5.3 ± 0.4
GA (%)	14.8 ± 2.0
HOMA-β	76.6 ± 34.1
HOMA-IR	1.1 ± 0.5
Genotyping of ADH1B/ALDH2 (active ADH1B and ALDH2/active ADH1B and inactive ALDH2)	7/3
Alcohol consumption frequency (daily/5–6 times a week/3–4 times a week/1–2 times a week/1–3 times a month/seldom drank)	2/2/1/2/2/1
Amount of one-time alcohol consumption† (80–100/60–80/40–60/20–40/<20 g)	1/1/1/5/2

γGTP, gamma-glutamyl transpeptidase; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Cre, creatinine; GA, glycated albumin; HbA1c, hemoglobin A1c; HDL-Cho, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; HOMA-β, homeostatic model assessment for β-cell function; LDL-Cho, low-density lipoprotein cholesterol; T-Cho, total cholesterol; TG, triglyceride. †Values are expressed as the mean ± standard deviation. Converted to the amount of ingested alcohol.

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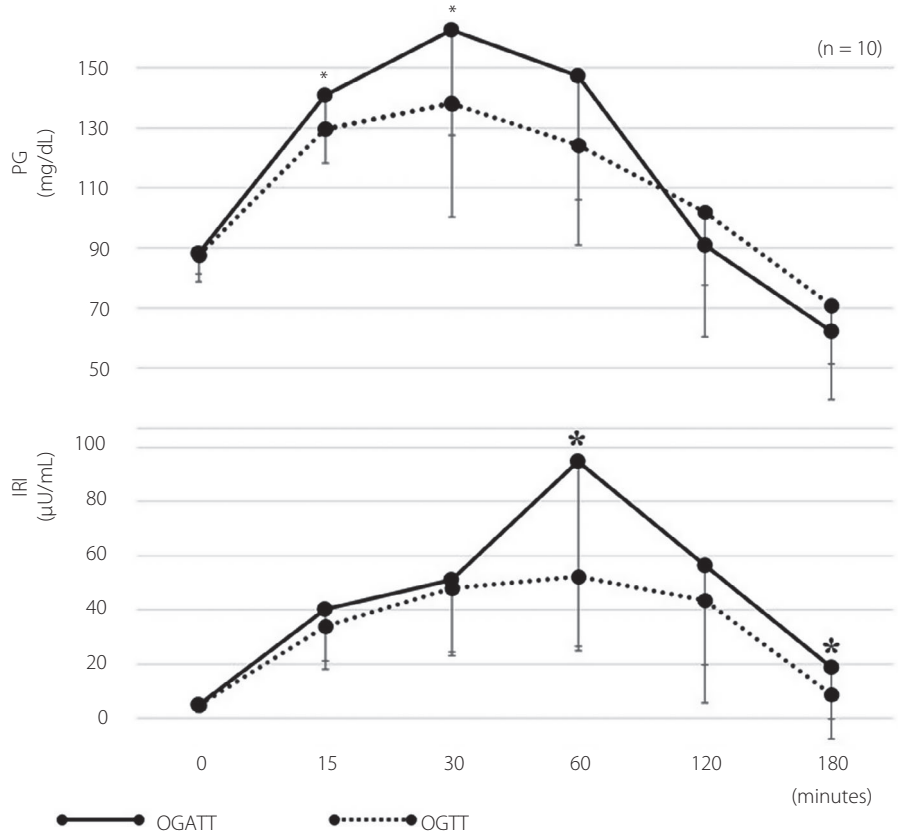


Figure 2 | Changes in plasma glucose (PG) and immunoreactive insulin (IRI) during the combined 75-g glucose and 20-g alcohol tolerance test (OGATT) and 75-g oral glucose tolerance test (OGTT). The PG concentrations 15 and 30 min after the start of each test were significantly higher during the OGATT than during the OGTT. The IRI concentrations 60 min after the start of the test were significantly higher during the OGATT. Values are expressed as the mean ± standard deviation. The Wilcoxon rank-sum test was used for statistical analysis. *$P < 0.05$.

participants after the OGATT, and there was a significant difference ($P = 0.046$, Table 3). Although almost all participants experienced hypoglycemia at 180 min, one participant had hypoglycemia at 120 min (plasma glucose level of 33 mg/dL). Therefore, the missing values at 180 min in this participant were complemented using a single imputation method. IRI concentrations peaked after 60 min during the OGTT and OGATT, with significantly different changes of 52.3 ± 27.2 and 94.7 ± 68.2 μU/mL, respectively ($P = 0.013$). The changes in triglyceride 30, 60, 120 and 180 min after a 75-g glucose load were significantly higher during the OGATT than during the OGTT ($P = 0.028$, $P = 0.019$, $P = 0.022$ and $P = 0.017$, respectively). There were no differences between the two interventions in the Matsuda Index, II or disposition Index (Table 3).

Comparison of changes in serum ethanol concentration during alcohol loading in the presence/absence of glucose

The ethanol concentrations peaked 120 min after loading during both the OGATT and OATT (0.14 ± 0.07 and 0.24 ± 0.16 mg/dL, respectively). The ethanol concentration was significantly lower during the OGATT than during the OATT 15, 30, 60 and 120 min after a 20-g ethanol load (Table 4).

Plasma glucose and insulin concentrations did not change during the OATT, and hypoglycemia was not identified (Table S1). There were no differences in plasma glucose or ethanol fluctuations between the sexes, participants with differing alcohol-metabolism genotypes, or participants with differing alcohol consumption habits. We observed no adverse events after alcohol consumption.

DISCUSSION

This was the first trial in which both OGTTs and OGATTs were carried out in individuals with normal glucose tolerance since 1975. Two studies were carried out in white volunteers at that time[3,15], but none have been carried out in Asian volunteers. We have shown three important findings in the present prospective pilot study. First, hypoglycemia did not occur after an alcohol load alone (OATT was not carried out in the previous two studies). Second, simultaneous consumption of glucose and alcohol was associated with lower ethanol concentrations than the consumption of alcohol alone. Third, simultaneous

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Table 2 | Changes in the measured values during the 75-g oral glucose tolerance test and combined 75-g glucose and 20-g alcohol tolerance test

	OGTT	OGATT	*P*
Glucose (mg/dL)			
0′	87.7 ± 8.8	88.2 ± 6.7	0.760
15′	129.7 ± 11.4	140.9 ± 22.8	0.047
30′	138.2 ± 37.9	162.5 ± 34.9	0.037
60′	124.2 ± 33.2	147.3 ± 41.2	0.241
120′	101.9 ± 24.4	90.8 ± 30.3	0.260
180′	70.8 ± 19.5	62.2 ± 22.7	0.067
IRI (μU/mL)			
0′	4.8 ± 1.7	5.0 ± 2.7	0.721
15′	34.1 ± 15.9	40.2 ± 19.0	0.445
30′	48.0 ± 23.7	51.0 ± 27.7	0.721
60′	52.3 ± 27.2	94.7 ± 68.2	0.013
120′	43.6 ± 23.8	56.4 ± 50.8	0.386
180′	8.9 ± 9.0	18.5 ± 26.3	0.028
ΔTG (mg/dL)			
0′	0.0 ± 0.0	0.0 ± 0.0	NA
15′	−2.5 ± 3.2	0.6 ± 6.4	0.169
30′	−1.8 ± 4.2	13.6 ± 14.6	0.028
60′	−1.1 ± 7.0	16.6 ± 15.5	0.019
120′	−6.7 ± 11.7	5.1 ± 10.9	0.022
180′	−10.3 ± 16.0	4.9 ± 11.9	0.017

Values are expressed as the mean ± standard deviation. IRI, immunoreactive insulin; NA, data not available; OGATT, combined 75-g glucose and 20-g alcohol tolerance test; OGTT, 75-g oral glucose tolerance test; TG, triglyceride.

Table 3 | Comparisons of the 75-g oral glucose tolerance test and combined 75-g glucose and 20-g alcohol tolerance test data

	OGTT	OGATT	*P*-value
PG-AUC (mg/dL)	19,540 ± 3663	20,374 ± 4189	0.415†
IRI-AUC (μU/mL)	6,863 ± 3137	9,987 ± 7004	0.047†
Hypoglycemia (*n* (%))	1 (10%)	5 (50%)	0.046‡
Matsuda Index	9.00 ± 3.91	8.47 ± 4.57	0.575†
15 min II	0.732 ± 0.468	0.725 ± 0.369	0.799†
30 min II	1.127 ± 0.928	0.848 ± 0.919	0.139†
15 min Disposition Index	0.107 ± 0.120	0.137 ± 0.130	0.386†
30 min Disposition Index	0.150 ± 0.134	0.145 ± 0.123	0.441†

Hypoglycemia was defined as a plasma glucose (PG) <54 mg/dL. 15-min II, ΔIRI(15′) / ΔPG(15′); 30-min II, ΔIRI(30′) / ΔPG(30′); 15-min Disposition Index, 15-min II / Matsuda Index; 30-min Disposition Index, 30-min II / Matsuda Index; AUC, area under the curve; II, insulinogenic index; IRI, immunoreactive insulin; OGATT, 75-g glucose and 20-g alcohol tolerance test; OGTT, 75-g oral glucose tolerance test; PG, plasma glucose. †Values are expressed as the mean ± standard deviation. Wilcoxon signed-rank test. ‡McNemar test.

consumption of alcohol and glucose led to significantly higher plasma glucose concentrations 15–30 min after loading, and significantly greater insulin secretion 60 min after loading, than glucose consumption alone. Reactive hypoglycemia was more likely after a combined alcohol and glucose load than after a glucose load alone.

Table 4 | Changes in the ethanol values during the 75-g glucose and 20-g alcohol tolerance test and 75-g oral glucose tolerance test

ΔEthanol (mg/mL)	OGATT	OATT	*P*
0′	0.00 ± 0.00	0.00 ± 0.00	NA
15′	0.04 ± 0.05	0.16 ± 0.12	0.043
30′	0.06 ± 0.07	0.18 ± 0.08	0.012
60′	0.09 ± 0.07	0.22 ± 0.10	0.008
120′	0.14 ± 0.07	0.24 ± 0.16	0.028
180′	0.03 ± 0.05	0.11 ± 0.13	0.068

Values are expressed as the mean ± standard deviation. NA, data not available; OATT, 20-g alcohol tolerance test; OGATT, combined 75-g glucose and 20-g alcohol tolerance test.

These data have confirmed the very early increase in plasma glucose after glucose and alcohol consumption, which is followed by an increase in insulin secretion. In the previous two studies carried out with white participants without diabetes, the plasma glucose concentrations were slightly higher[15] or lower[3] at the 15- or 30-min time points. Plasma insulin concentrations were also higher 15 or 30 min[3,15] after loading with glucose and ethanol than after glucose alone. The authors speculated that the mechanism for the increase in insulin secretion might have been an ethanol-induced increase in glucose absorption from the gut[15] or an increase in gastrointestinal secretagogue secretion[3]. These glucose and insulin responses were different from those in the present study. There was an initial ethanol-induced glucose disappearance in healthy participants, but not in participants who were obese or had diabetes, in one previous study[15]. This suggests that the response to ethanol consumption might differ, depending on the individual's insulin secretory ability or degree of insulin resistance, as well as between white and Asian individuals.

On the basis of previous findings made not only in healthy individuals[3,15], but also in patients with type 1 or type 2 diabetes, several mechanisms for alcohol-induced hypoglycemia have been proposed. Namely, a reduction in glucose production in the liver as a result of a reduction in hepatic gluconeogenesis[2] and/or glycogenolysis[16], an increase in insulin secretion[3,4], a reduction in intestinal glucose absorption[3,17,18], and a suppression of growth hormone secretion[19]. Although insulin resistance in peripheral tissues is increased by long-term alcohol intake[20,21], no significant differences were identified at the 15- or 30-min time points in the II, Matsuda Index or the disposition index between the OGTT and OGATT in the present study, which suggests that insulin secretion and resistance do not change in the first 30 min after alcohol loading. Therefore, changes in insulin secretion or peripheral insulin resistance during the first 30 min do not represent a likely mechanism for the hypoglycemic events identified in the present study.

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In the present study, the circulating ethanol concentration decreased, and the plasma glucose and serum triglyceride concentrations increased during the early phase of the OGATT, relative to those during the OATT or OGTT. Similar results have been previously reported for simultaneous fructose consumption[22–25], which were ascribed to a reduction in intestinal alcohol absorption[22,23] or an increase in the rate of alcohol metabolism in the liver. This might occur because fructose metabolism generates nicotinamide adenine dinucleotide, which is required for the oxidation of ethanol by ADH[24,25]. However, these findings could also be explained by the increase in triglyceride identified in the present study, which was probably the result of hepatic insulin resistance. Hepatic insulin resistance might be marked when glucose is consumed with alcohol, compared with the consumption of alcohol or glucose alone. Furthermore, intestinal glucose absorption might be increased under the same circumstances[15,17]. Those two mechanisms would be associated with increases in glucose and triglyceride concentrations early in an OGATT, resulting in hyperinsulinemia at 60 min and reactive hypoglycemia toward the end of the OGATT in healthy individuals. To confirm the speculated mechanisms underlying the glucose and lipid metabolic changes, *in vitro* studies using hepatic cells or insulinoma cell lines loaded with glucose and ethanol, alone or in combination, are required in the future.

Considering the possibility that inactive ALDH2 genotypes might influence the results, additional analyses were carried out in the subgroup of participants with both active ADH1B and ALDH2 genotypes. The OGTT, OGATT and OATT in this subgroup showed similar patterns and tendencies to those in all participants, although the differences did not reach statistical significance because of the smaller sample size (Tables S2–S5). It is necessary to confirm these findings by accumulating more cases in the future.

The present study had some limitations. The first was the small number of participants and the lack of randomization of the order of each test. The second was the divided administration of the alcohol load and its volume containing 20 g; differences in the loading methods might have affected carbohydrate metabolism and alcohol-induced hypoglycemia differently. In addition, other nutrient loads, such as a complex carbohydrate- or protein-rich meal, could have induced different effects. The third limitation was that the study was only of participants without diabetes. The results might have been different for patients with diabetes, who have a lower insulin secretory capacity. The fourth limitation was that the study used the Matsuda Index as the only indicator of insulin resistance. More detailed data might be obtained through the use of methods such as the glucose clamp technique. Finally, we did not measure the concentrations of hormones, such as growth hormone, cortisol and incretins, or free fatty acids. Such measurements might have assisted understanding of the mechanisms of the effects of glucose and alcohol consumption on blood glucose fluctuations.

We have shown that hypoglycemia occurs more frequently after the simultaneous consumption of alcohol and glucose than the consumption of glucose alone. The concurrent carbohydrate intake might be the principal reason for the sensation of hunger after alcohol consumption in the non-diabetic participants. Although we did not study the effects of simultaneous protein or fat consumption in the present study, intake of these nutrients with alcohol might be able to prevent the reactive hypoglycemia. We speculate on the basis of the present and previous findings that alcohol-induced hypoglycemia might represent reactive hypoglycemia caused by hepatic insulin resistance, an increase in intestinal glucose absorption or altered lipid metabolism. Further studies are required to confirm the mechanisms of this reactive hypoglycemia.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Changes in the measured values during the 20-g alcohol tolerance test.
Table S2 | Changes in measured values during the 20-g alcohol tolerance test in the subgroup of the participants with both active alcohol dehydrogenase 1B and aldehyde dehydrogenase 2 genotypes.
Table S3 | Changes in measured values during the 75-g oral glucose tolerance test and the combined 75-g glucose plus 20-g alcohol tolerance test in the subgroup of the participants with both active alcohol dehydrogenase 1B and aldehyde dehydrogenase 2 genotypes.
Table S4 | Comparisons of the 75-g oral glucose tolerance test and the combined 75-g glucose plus 20-g alcohol tolerance test data in the subgroup of the participants with both active alcohol dehydrogenase 1B and aldehyde dehydrogenase 2 genotypes.
Table S5 | Changes in ethanol values during the combined 75-g glucose plus 20-g alcohol tolerance test and the 20-g alcohol tolerance test in the subgroup of the participants with both active alcohol dehydrogenase 1B and aldehyde dehydrogenase 2 genotypes.

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