Sex difference in the effects of alcohol on gastric emptying in healthy volunteers: A study using the \(^{13}\)C breath test

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ABSTRACT

Several studies on alcohol and gastric emptying using the \(^{13}\)C breath test showed that alcohol consumption delayed gastric emptying of meals in healthy male subjects. However, they did not employ female subjects, and the retention time of alcoholic beverages in the stomach has not been examined, yet. We examined the retention time (= gastric emptying rate) of alcoholic beverages in the stomach in healthy male and female subjects. We also examined whether the congeners (non-alcoholic components) of red wine have any effect on gastric emptying. The retention time of 60 mL of red wine, vodka, congeners of red wine, or mineral water, was measured using a \(^{13}\)C-labeled acetic acid breath test. In male subjects, the retention time of wine and vodka was significantly longer than that of congeners and mineral water. In female subjects, although the \(^{13}\)C content in the breath was slightly but significantly decreased by wine and congeners, but not by vodka, and the parameters for gastric emptying did not differ significantly among the 4 drinks. That is, alcohol hardly influenced the retention time in female subjects. In conclusion, there are sex differences in the gastric emptying rate of alcohol.

Alcohol is known to have the potential to modify food intake (18, 20). Alcohol consumption prior to a meal has been reported to promote greater food intake than non-alcoholic preloads (8, 19). As the rate of gastric emptying and satiety are closely related to each other: delayed gastric emptying reduces hunger sensations (10), we thought that alcohol ingestion might have enhanced gastric emptying of the meal. In 1993, the measurement of the gastric emptying rate of solids using a carbon thirteen-labeled (\(^{13}\)C) octanoic acid breath test was carried out (5), and several studies on alcohol and gastric emptying using the \(^{13}\)C breath test were reported (3, 6, 11). These studies showed that alcohol consumption delayed gastric emptying of meals.

In detail, Hainrich et al. (6) examined the effect of 300 mL of white wine (containing 13% alcohol) followed by 20 mL of schnapps (containing 40% alcohol) on the gastric emptying of cheese fondue, and found that drinking alcoholic beverages prolonged the gastric emptying time of the cheese fondue (6). Franke et al. (2, 3) determined the retention time of various alcohol beverages (500 mL beer, 125 mL whisky etc.) and the effect of alcohol beverages (300 mL) on gastric emptying of solid meals. On the other hand, most of the acetaldehyde generated during alcohol metabolism is eliminated by liver mitochondrial aldehyde dehydrogenase 2 (ALDH2). Although the majority of Caucasians possess the active form of ALDH2 (2*1/2*1), more than 40% of Japanese have the inactive form of ALDH2, encoded either as heterozygous ALDH2*1/2*2 or as homozygous ALDH2*2 (9). These subjects (with an inactive form of ALDH2) experience facial flushing, palpitation and nausea when drinking alcohol. Therefore,
the regimen by Hainrich et al. (6) and by Franke et al. (2, 3) seems to be too much alcohol intake for some of the Japanese population.

Inamori et al. (11) observed that only 50 mL of Japanese plum liqueur (containing 14% alcohol) prolonged the gastric emptying time of a liquid meal in male subjects. However, they did not employ female subjects (2, 3, 6, 11). We previously observed that 60 mL of red wine or vodka significantly inhibited gastric emptying of solids in male subjects but not in female subjects (presented at the meeting of the 40th Japanese Society of Digestion and Absorption in 2009). As the retention time of alcoholic beverages in the stomach has not been examined in female subjects, yet, in the present study, we planned to compare the retention time of alcoholic beverages in the stomach using the $^{13}$C breath test between healthy male and female subjects.

Fermented alcoholic beverages contain several materials (so called congeners) in addition to alcohol. Oral administration of beer congeners has been shown to enhance the gastric emptying of a semisolids meal via muscarinic receptor in mice (4), and N-methyltyramine, one of the beer congeners, stimulated pancreatic exocrine secretion in conscious rats (16). Teyssen et al. (15) reported in humans that alcoholic beverages produced by fermentation (including white wine), stimulated gastric acid output and release of gastrin. The congeners of red wine have been proposed to have various biological activities; resveratrol, one of the congeners of red wine, has been proposed to have anti-cancer and anti-aging activities, as well as beneficial effects on the cardiovascular system, inflammation, and the central nervous system (12). As the effect of congeners of red wine on gastric emptying has not been reported, we also examined the retention time of the congeners of red wine. Thus, we compared the retention times of vodka (a distilled alcoholic beverage), red wine (a fermented alcoholic beverage), congeners of red wine, and mineral water in the stomach were compared.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Tokyo Kasei University. All subjects provided their written informed consent.

Subjects and materials. Twenty-seven healthy volunteers (10 males and 17 females) were employed. They were 20–23 years of age, with a body mass index (BMI) ranging from 19.4 to 27.2 (22.5 ± 0.7, mean ± SE) in males and 16.3 to 23.4 (20.3 ± 0.5) in females. All of the male subjects had a drinking habit (more than 5 g alcohol at least 1–2 times per week), and one of the male subjects had a smoking habit. None of the female subjects had either a drinking or a smoking habit. ALDH2 genotype was not determined because of no permission by the Ethics Committee. As one female subject declared to possess homozygous ALDH2*2, she did not participate the experiment of vodka and red wine. Others are considered to be ALDH2 (2*1/2*1) or heterozygous ALDH2*1/2*2 according to personal statement.

No subject had a history of, or symptoms referable to, gastrointestinal or pulmonary disease, had any chronic medical problem, or was receiving any medication at the time of the study.

Mineral water and red wine containing 14% alcohol were purchased at a store. The vodka was a generous gift from the Suntory Co. (Osaka, Japan). The congeners of red wine were prepared as follows: red wine was warmed overnight to evaporate alcohol, and was reconstituted to the primary volume with mineral water. Vodka was diluted to 14% alcohol with mineral water.

Experimental protocols. The protocol was that of a randomized crossover study at intervals of 1 week. The participants were prohibited from eating from 9:00 PM to 9:00 AM. The experiment started at 9:00 AM without eating breakfast.

One hundred mg $^{13}$C-acetic acid was dissolved in each drink. After the first collection of breath, the participants ingested either of 60 mL of red wine, 60 mL of congeners of red wine, 60 mL of vodka, or 60 mL of mineral water. Breath samples were collected at 5-min intervals for 2 h, and then at 15-min intervals for an additional 1 h.

Breath test. Breath $^{13}$CO$_2$ isotopic enrichment was determined using non-dispersive infrared isotope spectrometry (UbiT-1R300; Otsuka Electronics, Osaka, Japan) (11). The changes in $^{13}$C content in the breath samples with respect to time are shown in the figures and compared. The $^{13}$C-labeled compound is hardly absorbed in the stomach, mainly absorbed in the upper small intestine, and metabolized in the liver, then $^{13}$C appears in the breath. The representative pattern is shown in Fig. 1: in the case of rapid gastric emptying, the initial slope is steeper and the peak value is higher, compared to the case of delayed gastric emptying (13).

According to the report by Ghoos et al. (5), T1/2 (the emptying time for 50% of labeled drinks), and
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Tlag (the emptying time for 5% of labeled drinks) were evaluated by using analysis software (Microsoft Office Excel 2003; Microsoft Japan, Tokyo, Japan) from a calculated $^{13}$C breath excretion curve (11). The values of Tmax (the time point of maximum concentration of $^{13}$C in the sampled breath) were also estimated from the results shown in Figs. 2 and 3. The values of Tmax and Tlag should be close to each other (13). Lower values of these parameters represent a faster gastric emptying time.

Statistical analysis. All results were expressed as means ± SE. Results were analyzed by multiple analysis and/or one-way analysis of variance (MANOVA and/or ANOVA), followed by Fisher’s protected least significant difference test. Values of $P < 0.05$ were considered to be statistically significant.

RESULTS AND DISCUSSION

Retention time of water in the stomach between male and female subjects

As reported by Sanaka et al. (14), the curves obtained from water ingestion differed between male (Fig. 2, closed squares) and female subjects (Fig. 3, closed squares) $[F(1,28) = 681.66, P = 0.000]$, with the peak value in female subjects $[66.2 ± 2.9$ per mil $(1$ per mil $= 0.1\%$, mean ± SE, observed at 30 min] being significantly higher than that in male subjects $[40.4 ± 11.9$ per mil observed at 25 min ($P = 0.0001$).

When the parameters for gastric emptying rate proposed by Ghoos et al. (5) were compared, Tmax,
significant \[F(3,81) = 1.87, \ P = 0.000\]. The curves of water and congeners were close to each other, while the values of wine and vodka were significantly lower than the corresponding values of water and/or congeners during the first 35 min periods.

The parameters for determination of the gastric emptying rate as proposed by Ghoos et al. (5) are summarized in Table 1. The \(T_{\text{max}}\) values were significantly different for the different drinks \[F(3,36) = 4.18, \ P = 0.014\], and the values of vodka and wine were significantly higher than the value of water by the multiple comparison test. \(T_{\text{lag}}\) was also significantly different with respect to drinks \[F(3,36) = 5.64, \ P = 0.003\], and the values of vodka and wine were again significantly higher than the values of both water and congeners. Although the ranking of the mean values of \(T_{1/2}\) was water < congeners < vodka < wine, none of these differences were statistically significant \[F(3,81) = 1.87, \ P = 0.000\]. The curves of water and congeners were close to each other, while the values of wine and vodka were significantly lower than the corresponding values of water and/or congeners during the first 35 min periods.

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did not reach the significant level. Therefore, it is concluded in male subjects that alcohol remained in the stomach longer than (non-alcoholic) congeners and water. In other words, alcohol inhibited gastric emptying.

**Retention time in the stomach of 4 drinks in female subjects**

The changes in $^{13}$C in the breath samples obtained from 17 female subjects are shown in Fig. 2. Changes in $^{13}$C in the breath were found to be significantly different with respect to drinks \( F(3,62) = 24.57, P = 0.000 \) and to time \( F(3,27) = 298.40, P = 0.000 \), but the interaction of drinks and time was not significant \( F(3,81) = 1.15, P = 0.170 \). The values of wine and congeners were similar to each other, and were slightly but significantly lower than the corresponding values of water at 15 min, 20 min, and 25 min by the multiple comparison test, however, the significant levels produced by red wine were less powerful \((0.01 < P < 0.05 \text{ in Fig. 3})\) than those in male subjects \((P < 0.01 \text{ in Fig. 2})\). Moreover, the values of vodka were not significantly different from other values. The values of Tmax, Tlag, and T1/2 were not significantly influenced by ingestion of congeners, vodka, or wine (Table 1).

Therefore, it is concluded that in female subjects, vodka did not inhibit gastric emptying rate, and that wine and/or congeners hardly influenced gastric emptying rate. The reason why red wine and congeners showed weak inhibitory effects on $^{13}$C expiration and vodka did not, is unknown. As it is reported (17) that gastrointestinal transit time was significantly prolonged in the luteal phase when progesterone levels were increased, we speculate the involvement of the menstrual cycle, and plan to conduct the following study.

Ely et al. (1) reported that female subjects were more likely than males to reveal drink problems (such as liver damage and alcoholic dependence) at the same level of alcohol consumption and that this gender difference was largely accounted for individual differences in the weight of body water. However, as most alcohol ingested is absorbed through the upper small intestine, the faster passage (= no or less inhibition of gastric emptying rate) of alcohol through the stomach in female subjects might partly explain their greater susceptibility to the effects of alcohol, yielding the higher blood alcohol concentration, although we did not determine the changes in plasma alcohol concentrations in this study. Although all of the male subjects had a drinking habit but none of the female subjects had either a drinking or a smoking habit, it is not conclusive that presence or absence of a drinking habit affected the retention time of alcohol in the stomach.

In conclusion, the retention time of alcohol (red wine and vodka) in the stomach was significantly elongated compared to that of water and congeners in male subjects. However, vodka did not show any significant effect on gastric emptying in female subjects. Our results suggested that the effect of alcoholic beverages on gastric emptying differs between male and female subjects.

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