Associations of alcohol consumption and alcohol flush reaction with leukocyte telomere length in Korean adults

Hyewon Wang, Hyungjo Kim and Inkyung Baik[§]

Department of Foods and Nutrition, College of Science and Technology, Kookmin University, 77, Jeongnung-ro, Seongbuk-gu, Seoul 02707, Korea

BACKGROUND/OBJECTIVES: Telomere length is a useful biomarker for determining general aging status. Some studies have reported an association between alcohol consumption and telomere length in a general population; however, it is unclear whether the alcohol flush reaction, which is an alcohol-related trait predominantly due to acetaldehyde dehydrogenase deficiency, is associated with telomere length. This cross-sectional study aimed to evaluate the associations of alcohol consumption and alcohol flush reaction with leukocyte telomere length (LTL).

SUBJECTS/METHODS: The study included 1,803 Korean adults. Participants provided blood specimens for LTL measurement assay and reported their alcohol drinking status and the presence of an alcohol flush reaction via a questionnaire-based interview. Relative LTL was determined by using a quantitative polymerase chain reaction. Statistical analysis used multiple linear regression models stratified by sex and age groups, and potential confounding factors were considered.

RESULTS: Age-specific analyses showed that heavy alcohol consumption (> 30 g/day) was strongly associated with a reduced LTL in participants aged $\geq$ 65 years ($P < 0.001$) but not in younger participants. Similarly, the alcohol flush reaction was associated with a reduced LTL only in older participants who consumed > 15 g/day of alcohol ($P < 0.01$). No significant alcohol consumption or alcohol flush reaction associations with LTL were observed in the sex-specific analyses.

CONCLUSIONS: The results suggest that older alcohol drinkers, particularly those with the alcohol flush reaction, may have an accelerated aging process.

INTRODUCTION

Telomeres, which are repetitive deoxyribonucleic acid (DNA) sequences, are found at the ends of chromosomes and have a critical role in protecting against chromosome degradation or end-to-end fusion. Telomeric sequence length shortens during DNA replication due to the end-replication problem; thus, telomere length is considered a marker of biological aging [1,2]. Previous studies have reported that telomere length shortening is associated with age-related diseases such as hypertension, diabetes mellitus, cardiovascular disease, and cancer [3-6]. Telomere length shortening is influenced by genetic and environmental factors including socioeconomic status, psychological conditions, physical activity, and lifestyle factors [7-13]. Among the lifestyle factors, excessive alcohol consumption, particularly alcohol dependence, has been hypothesized to reduce telomere length partly due to oxidative stress related to acetaldehyde accumulation in the body [14]. However, there are few reports showing a significant association between alcohol consumption and telomere length in a general population. Furthermore, to the best of our knowledge, no study has investigated the association between the alcohol flush reaction and telomere length. The alcohol flush reaction is an aversive physiological response that occurs after consuming alcoholic beverages, even after consuming a small amount of alcohol. This reaction is mostly due to an acetaldehyde dehydrogenase (ALDH) deficiency, which leads to the accumulation of acetaldehyde, a metabolite involved in the alcohol metabolism process. ALDH deficiency is caused by a genetic mutation and is predominantly found in East Asians, including Koreans [15]. In addition, because the enzyme activity of ALDH steadily decreases with aging, older people are likely to exhibit an alcohol flush reaction due to their decreased alcoholysis in the liver [16].

The aim of the present study was to evaluate the associations of alcohol consumption and alcohol flush reaction with leukocyte telomere length (LTL). Because alcohol consumption and/or the prevalence of the alcohol flush reaction may differ by sex or age, our evaluations of the associations of alcohol consumption and alcohol flush reaction with LTL were stratified by sex and age.

SUBJECTS AND METHODS

Study population

We conducted a cross-sectional study embedded in a 2001-2003 population-based cohort study that enrolled 5,012 men and women aged 40-69 years who were residents of Ansan, South Korea [17]. The cohort members periodically completed questionnaire-based interviews and underwent health examinations performed by trained researchers at Korea University Ansan Hospital. In the interviews, information on sociodemographic characteristics, medical history, and lifestyle factors, including smoking behavior, alcohol consumption, physical activity, and diet was collected. The health examination included standardized measurements of anthropometric characteristics and blood pressure, clinical assessment, and collection of blood samples. Participants took part in biennial follow-up interviews and health examinations and provided written informed consent at every visit. All study procedures were approved by the Human Subjects Review Committee at Korea University Ansan Hospital (ED0624).

Between February 2011 and November 2012 LTL measurement assays were performed by using blood samples from 2,137 participants. After excluding 334 participants who showed an outlier LTL value (n = 1) or reported a diagnosis of cancer or cardiovascular disease (n = 333), data from 1,803 participants were included in the analyses.

Measurement of leukocyte telomere length

The LTL was measured as described previously [18]. Briefly, a QIAamp DNA blood mini kit (Qiagen, Hilden, Germany) was used to extract genomic DNA from leukocytes obtained from peripheral blood samples. Purified DNA samples were diluted and quantified by using a NanoDrop 1000 spectrophotometer. The telomere repeat copy number and the single-copy gene (*36B4*, which encodes acidic ribosomal phosphoprotein) copy number were obtained by using an iQ Multi-Color Real-Time Polymerase Chain Reaction Detection System (Bio-Rad, Hercules, CA, USA). The final concentrations of the components of the polymerase chain reaction mixture were 1× SYBR Green Super Mix (Bio-Rad), 50 ng DNA, 0.2 μM telomere primers, and 0.3 μM *36B4* primers. The reactions were performed with telomere and *36B4* primers in the same 96-well plate, and each plate included a reference DNA sample. Using a four-point standard curve, the cycle threshold was converted into nanograms of DNA. To calculate a relative value of LTL for each sample, the amount of telomeric DNA was divided by the amount of *36B4* DNA. A validity test was applied and its results demonstrated that the Pearson correlation coefficients were 0.78 (intra-assay) and 0.69 (inter-assay) when 25 samples were run in triplicate.

Alcohol consumption

Detailed information on the questionnaire used to determine alcohol consumption is available in a previous study [19]. The questionnaire enquired about alcohol drinking history, as well as amount and frequency of alcohol consumption in the past year according to specific alcoholic beverages and included questions about physical responses (e.g., whether the subject has a flush reaction after consumption of one drink; whether they have different moods after consumption of one drink). The average daily amount of alcohol consumption (g/day) was calculated by adding the beverage-specific alcohol amounts consumed. We classified participants as abstainers (persons who have never consumed alcoholic beverages in their lifetime), past alcohol drinkers (persons who have ever consumed alcoholic beverages but abstained from alcohol drinking), and alcohol drinkers. We further classified alcohol drinkers according to their level of alcohol consumption as follows: very light (1-5 g/day), light (6-15 g/day), moderate (16-30 g/day), and heavy (> 30 g/day).

Confounding factors

Data on potential confounding variables, such as age, sex, body mass index (BMI), physical activity levels denoted as metabolic equivalents (MET-h), average daily sleep duration at night, household monthly income, smoking status, and presence of hypertension or diabetes mellitus, were collected from questionnaires completed between February 2011 and November 2012.

BMI (kg/m^2) was calculated by using body weight (kg) and height (m). Total MET-h was calculated by multiplying hours spent in an activity by a MET value for the specific activity category: 1.0 for sleep or sedentary, 1.5 for very light, 2.4 for light, 5.0 for moderate, and 7.5 for vigorous activity.

Statistical analysis

According to the categories of alcohol consumption, such as abstainers or past alcohol drinkers, light drinkers, moderate drinkers, and heavy drinkers, descriptive statistics were calculated. The significance of the differences among the categories was evaluated by using the chi-squared test and analysis of variance. The associations of alcohol consumption and alcohol flush reaction with LTL, which was transformed using the natural logarithm function to minimize the effect of outliers, were evaluated by using linear regression analysis stratified by sex and age groups (< 65 years, ≥ 65 years). In the multiple linear regression models, age, BMI, physical activity levels, and sleep duration were fitted as continuous variables while sex, household monthly income (< 2,000,000 won, 2,000,000-3,999,999 won, ≥ 4,000,000 won), smoking status (never smokers, former smokers, current smokers), and the presence of hypertension or diabetes mellitus were fitted as categorical variables.

RESULTS

Characteristics of the study population

The mean LTL was 1.50 (standard deviation: 1.12) and was correlated with chronological age (Spearman's correlation coefficient = -0.07; *P* < 0.01) (data available upon request) in the study participants.

Table 1 shows that heavy alcohol drinkers were younger, current smokers, heavier, more active, and had a higher income and longer sleep duration than abstainers or other drinker types (*P* < 0.001). In addition, heavy alcohol drinkers were more likely to have hypertension or diabetes mellitus than other drinker types (*P* < 0.05). However, LTL was similar among abstainers and the four types of alcohol consumers.

Table 1. Characteristics of 1,803 study participants according to alcohol consumption status

Characteristics	Abstainers or past alcohol drinkers	Alcohol drinkers (average daily amount of alcohol)			P-value
		(1-15 g/day)	(16-30 g/day)	(> 30 g/day)	
Number of participants	906	489	180	228	
Leukocyte telomere length	1.08 ± 0.41	1.08 ± 0.41	1.08 ± 0.38	1.03 ± 0.34	0.42
Age, yrs	59.5 ± 7.7[a]	57.3 ± 7.1[b]	56.7 ± 6.4[bc]	55.1 ± 4.7[c]	< 0.001
Monthly income, %					
< 2,000,000 won	35.9	20.4	20.0	12.7	< 0.001
2,000,000-3,999,999 won	39.4	43.2	36.7	36.0	
≥ 4,000,000 won	24.7	36.4	43.3	51.3	
Smoking status, %					
Never smoker	79.9	55.2	25.0	12.3	< 0.001
Former smoker	14.1	32.7	48.9	50.9	
Current smoker	6.0	12.1	26.1	36.8	
Body mass index, kg/m^2	24.6 ± 3.1[b]	24.6 ± 2.9[b]	24.7 ± 2.7[b]	25.6 ± 2.7[a]	< 0.001
Physical activity, MET-h	40.3 ± 5.4[b]	41.7 ± 7.3[a]	41.8 ± 7.2[a]	41.6 ± 7.4[a,b]	< 0.001
Sleep duration, h/day	5.99 ± 1.25[b]	6.06 ± 1.17[b]	6.24 ± 1.18[a,b]	6.38 ± 1.10[a]	< 0.001
Presence of hypertension	32.9	32.3	41.7	39.9	< 0.05
Presence of diabetes mellitus	18.5	15.8	19.4	24.6	< 0.05

MET-h: metabolic equivalents
Data are presented as mean ± standard deviation or as proportion.
P-value from chi-squared test or analysis of variance
Different letters indicate significant differences between groups (Scheffé *post hoc* test, $P < 0.05$).

Table 2. Association between alcohol consumption and leukocyte telomere length by sex and age group

Alcohol consumption status (average daily amount)	Number of participants	Coefficient estimates ± SE for LTL (P-value)	
		Model 1	Model 2
Among men			
Abstainers	191	Reference	Reference
Past drinkers	77	-0.09 ± 0.05 (0.06)	-0.09 ± 0.05 (0.06)
Very light drinkers (1-5 g/day)	148	-0.05 ± 0.04 (0.16)	-0.05 ± 0.04 (0.16)
Light drinkers (6-15 g/day)	157	-0.03 ± 0.04 (0.37)	-0.04 ± 0.04 (0.34)
Moderate drinkers (16-30 g/day)	163	-0.02 ± 0.04 (0.50)	-0.03 ± 0.04 (0.46)
Heavy drinkers (> 30 g/day)	215	-0.07 ± 0.03 (0.06)	-0.07 ± 0.04 (0.07)
Among women			
Abstainers	631	Reference	Reference
Past drinkers	7	-0.01 ± 0.13 (0.96)	-0.02 ± 0.13 (0.87)
Very light drinkers (1-5 g/day)	147	0.03 ± 0.03 (0.40)	0.03 ± 0.03 (0.39)
Light drinkers (6-15 g/day)	44	0.06 ± 0.06 (0.25)	0.07 ± 0.06 (0.21)
Moderate drinkers (16-30 g/day)	17	0.02 ± 0.09 (0.84)	0.01 ± 0.09 (0.93)
Heavy drinkers (> 30 g/day)	6	-0.10 ± 0.14 (0.48)	-0.12 ± 0.1 (0.42)
Among participants aged < 65 years			
Abstainers	618	Reference	Reference
Past drinkers	51	-0.05 ± 0.05 (0.33)	-0.05 ± 0.05 (0.36)
Very light drinkers (1-5 g/day)	239	-0.01 ± 0.03 (0.93)	-0.01 ± 0.03 (0.98)
Light drinkers (6-15 g/day)	173	0.02 ± 0.03 (0.44)	0.03 ± 0.03 (0.40)
Moderate drinkers (16-30 g/day)	154	0.01 ± 0.03 (0.99)	-0.01 ± 0.03 (0.98)
Heavy drinkers (> 30 g/day)	209	-0.01 ± 0.03 (0.72)	-0.01 ± 0.03 (0.84)
Among participants aged ≥ 65 years			
Abstainers	204	Reference	Reference
Past drinkers	33	-0.09 ± 0.08 (0.25)	-0.08 ± 0.08 (0.34)
Very light drinkers (1-5 g/day)	56	-0.01 ± 0.06 (0.82)	-0.03 ± 0.06 (0.67)
Light drinkers (6-15 g/day)	28	-0.09 ± 0.09 (0.27)	-0.11 ± 0.09 (0.19)
Moderate drinkers (16-30 g/day)	26	0.03 ± 0.09 (0.74)	0.01 ± 0.09 (0.90)
Heavy drinkers (> 30 g/day)	12	-0.44 ± 0.12 (< 0.001)	-0.46 ± 0.12 (< 0.001)

LTL, leukocyte telomere length; SE, standard error.
Model 1: data are adjusted for age or sex.
Model 2: data are adjusted for age, sex, income status, smoking status, body mass index, physical activity levels, sleep duration, and presence of hypertension or diabetes mellitus.

Table 3. Joint analysis for the association between alcohol consumption and leukocyte telomere length by sex and age in alcohol drinkers

Sex or age groups	Alcohol consumption	Number of participants	Coefficient estimates ± SE for LTL (*P*-value)
Men	1-5 g/day	148	Reference
	> 5 g/day	535	-0.02 ± 0.02 (0.46)
Women	1-5 g/day	147	0.03 ± 0.03 (0.38)
	> 5 g/day	67	0.04 ± 0.04 (0.40)
< 65 yrs	1-5 g/day	239	Reference
	> 5 g/day	536	0.02 ± 0.02 (0.43)
≥ 65 yrs	1-5 g/day	56	-0.02 ± 0.05 (0.72)
	> 5 g/day	66	-0.11 ± 0.05 (< 0.05)

LTL, leukocyte telomere length; SE, standard error.
Data are adjusted for age, sex, income status, smoking status, body mass index, physical activity levels, sleep duration, and presence of hypertension or diabetes mellitus.

Association between alcohol consumption and LTL

Table 2 presents results stratified by sex and age groups for the association between alcohol consumption and LTL. The sex-specific analysis results revealed no significant association. However, age-specific analysis showed that, among those aged 65 years or older, heavy alcohol drinkers had significantly shorter LTL than abstainers ($P < 0.001$), but there was no significant association among younger people, even after adjusting for confounding factors. The interaction term of the age and alcohol consumption groups in the model was significant ($P < 0.05$) (data available upon request).

Table 3 summarizes the results from the joint analysis of sex or age groups with alcohol consumption in alcohol drinkers. For that joint analysis, we classified alcohol consumption by using varied cutoff points (i.e., 5 g/day, 15 g/day, or 30 g/day) to convert consumption into a binary variable. Even when 5 g/day was used as a cutoff point, a significant reduction in LTL was observed among alcohol drinkers aged 65 years or older consuming > 5 g/day compared to the LTL reduction in younger alcohol drinkers consuming 1-5 g/day ($P < 0.05$). However, no significant association was observed in the joint analysis of sex and alcohol consumption.

Table 4 displays results stratified by sex and age groups for the association between the alcohol flush reaction and LTL. The sex-specific analysis revealed no significant association ($R^2 = 0.01$). However, the age-specific analysis showed that, among those aged 65 years or older, moderate-to-heavy alcohol drinkers with a flush reaction had significantly shorter LTL than

Table 4. Association between alcohol flush reaction and leukocyte telomere length by sex and age

Alcohol consumption and flush reaction status	Number of participants	Coefficient estimates ± SE for LTL (*P*-value)	
		Model 1	Model 2
Among men			
Abstainers and past drinkers	268	Reference	Reference
Alcohol drinkers			
No flush reaction (1-15 g/day)	160	-0.01 ± 0.03 (0.70)	-0.01 ± 0.04 (0.67)
No flush reaction (> 15 g/day)	289	-0.01 ± 0.03 (0.69)	-0.01 ± 0.03 (0.70)
Flush reaction (1-15 g/day)	112	-0.03 ± 0.04 (0.48)	-0.03 ± 0.04 (0.46)
Flush reaction (> 15 g/day)	62	-0.09 ± 0.05 (0.06)	-0.09 ± 0.05 (0.06)
Among women			
Abstainers and past drinkers	638	Reference	Reference
Alcohol drinkers			
No flush reaction (1-15 g/day)	136	0.04 ± 0.03 (0.29)	0.04 ± 0.03 (0.25)
No flush reaction (> 15 g/day)	17	0.02 ± 0.09 (0.86)	0.01 ± 0.09 (0.98)
Flush reaction (1-15 g/day)	39	0.01 ± 0.06 (0.98)	-0.01 ± 0.06 (0.92)
Flush reaction (> 15 g/day)	4	-0.02 ± 0.18 (0.90)	-0.03 ± 0.18 (0.86)
Among participants aged < 65 years			
Abstainers and past drinkers	669	Reference	Reference
Alcohol drinkers			
No flush reaction (1-15 g/day)	247	0.02 ± 0.03 (0.52)	0.02 ± 0.03 (0.40)
No flush reaction (> 15 g/day)	282	0.01 ± 0.03 (0.90)	0.01 ± 0.03 (0.83)
Flush reaction (1-15 g/day)	122	-0.01 ± 0.03 (0.79)	-0.01 ± 0.03 (0.73)
Flush reaction (> 15 g/day)	54	-0.02 ± 0.05 (0.70)	-0.02 ± 0.05 (0.69)
Among participants aged ≥ 65 years			
Abstainers and past drinkers	237	Reference	Reference
Alcohol drinkers			
No flush reaction (1-15 g/day)	49	0.01 ± 0.06 (0.96)	-0.01 ± 0.06 (0.86)
No flush reaction (> 15 g/day)	24	0.02 ± 0.09 (0.83)	0.01 ± 0.09 (0.95)
Flush reaction (1-15 g/day)	29	-0.02 ± 0.08 (0.78)	-0.05 ± 0.08 (0.51)
Flush reaction (> 15 g/day)	12	-0.33 ± 0.12 (< 0.01)	-0.35 ± 0.12 (< 0.01)

SE: standard error
Model 1: data are adjusted for age or sex.
Model 2: data are adjusted for age, sex, income status, smoking status, body mass index, physical activity levels, sleep duration, and presence of hypertension or diabetes mellitus.

abstainers, but there was no such association among younger people, even after adjusting for confounding factors ($R^2 = 0.05$; $P < 0.01$). When we conducted similar analyses excluding past alcohol drinkers from the analysis, the results were similar (data available upon request).

DISCUSSION

Our study results showed that, among subjects aged 65 years or older, heavy alcohol drinkers consuming > 30 g/day of alcohol had significantly reduced LTL compared with abstainers. Furthermore, older people consuming > 5 g/day of alcohol exhibited a significant reduction in LTL when compared with younger alcohol drinkers consuming 1-5 g/day. We also observed that the alcohol flush reaction was associated with a reduced LTL in subjects aged 65 years or older but not in younger people. These results suggest that even a low level of alcohol consumption may contribute to a reduction in LTL among older people, particularly in those with the alcohol flush reaction.

Some previous studies have shown that higher income, moderate physical activity levels, lower BMI, tobacco abstinence, and higher consumption of fruits and vegetables are positively associated with LTL, while other studies have reported that lower education or income levels, as well as psychological factors such as stress or depression, short sleep duration, and smoking, are inversely associated with LTL [7-13]. Several studies have investigated the association between alcohol consumption and LTL [13,18,20-23], and most reported no significant association of alcohol consumption and LTL [13,21-23], but two did report a significant association [18,20]. One of those latter studies showed a significant association between alcoholism and LTL [20], while the other showed a significant association between heavy alcohol consumption and LTL among carriers of a particular genetic polymorphism that reflected an *ALDH2* mutation [18].

In the primary pathway of alcohol metabolism, alcohol is oxidized by alcohol dehydrogenase to acetaldehyde, which is then oxidized by ALDH to form acetate. The activity of ALDH is critical in eliminating acetaldehyde, which is a toxic substance, from the liver, and the activity level of ALDH is varied among East Asians, including Koreans, who have a high prevalence of an *ALDH2* mutation. People with an *ALDH2* mutation have decreased alcoholysis due to low or no oxidizing activity by ALDH, and they exhibit some aversive physical responses, including the alcohol flush reaction, even to a small amount of consumed alcohol. In addition, because the activity of this enzyme steadily decreases with aging, older people exhibit decreased alcoholysis and are more likely to display an alcohol flush. The accumulation of acetaldehyde and NADH, which is produced from the oxidation process of acetaldehyde, is known to increase the generation of reactive oxygen species (ROS), which are a source of oxidative stress. It is known that ROS can damage protein molecules, DNA, and cells, and ROS can promote adduct formation [15,16]. Telomere length naturally shortens with every cell division; however, the telomere shortening rate is accelerated by elevations in oxidative stress and ROS production [14]. On the basis of our results, we postulate that excessive or even moderate alcohol consumption

in older people, particularly in those with alcohol flush reaction, may accelerate telomere shortening partly due to the production of acetaldehyde and leading to elevated oxidative stress. In a previous study, an inverse association between heavy alcohol consumption and LTL was observed in carriers of mutant genotypes of rs2074356, which is a surrogate of an *ALDH2* mutation [18]. Furthermore, there are data showing an association between low ALDH activity or an *ALDH2* polymorphism and cancer risk as well as indicating an inverse association between cancer risk and LTL [6,24]. These previous reports appear to support our results suggesting that older people with an alcohol flush reaction have delayed clearance of acetaldehyde due to reduced ALDH activity and are likely to be exposed to a higher oxidative stress state, resulting in reduced LTL.

The strengths of this study include its large sample size from a general population, the use of a wide range of information on confounding factors, and analyses that were stratified by sex and age. However, there are some limitations that should be considered when interpreting our findings. First, this study was a cross-sectional study; thus, a causal relationship between alcohol consumption or alcohol flush reaction and telomere length remains undetermined. Second, we measured the relative telomere length of leukocytes, which is generally shorter than that of somatic cells. However, LTL is considered a useful and representative biomarker for indicating the general telomere length because the rates of telomere shortening are similar in somatic cells and leukocytes [25]. Third, limited generalizability is another weakness of our study because the alcohol flush reaction is mainly found in East Asians, not in individuals of European or African descent.

In conclusion, in this cross-sectional study, we observed that heavy alcohol consumption (> 30 g/day) is associated with a shortened LTL in people aged 65 years or older, and that a lower level of alcohol consumption is associated with shorter LTL in those with the alcohol flush reaction. On the basis of these findings, we recommend that older people with alcohol flush reaction may need to avoid alcohol consumption to delay the biological aging process.

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