Effects of Coffee Consumption against the Development of Liver Dysfunction: A 4-Year Follow-Up Study of Middle-Aged Japanese Male Office Workers

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Abstract: The association of coffee consumption with the development of increased serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) activities over 4 years was studied in 1221 liver dysfunction-free (serum AST and ALT ≤39 IU/l and no medical care for or no past history of liver disease) Japanese male office workers aged 35 to 56 years. From the analysis using the Kaplan-Meier method, the estimated incidence of serum AST and/or ALT ≥40 IU/l, ≥50 IU/l, and ≥60 IU/l decreased with an increase in coffee consumption. From the Cox proportional hazards model, coffee drinking was independently inversely associated with the development of serum AST and/or ALT ≥40 IU/l (p=0.019 by test for tendency), ≥50 IU/l (p=0.002), and ≥60 IU/l (p=0.007), controlling for age, body mass index, alcohol intake, and cigarette smoking. These results suggest that coffee may be protectively against the liver dysfunction in middle-aged Japanese men.

Key words: Coffee, Follow-up study, Liver dysfunction, Aspartate aminotransferase, Alanine aminotransferase

Recent epidemiological studies have suggested possibly beneficial effects of coffee consumption on the occurrence of alcoholic cirrhosis[1] and on serum liver enzymes, particularly serum gamma-glutamyltransferase activity[2–9]. Many cross-sectional studies investigated the association between coffee consumption and serum liver enzyme levels in various populations, but few longitudinal studies have been completed[3]. In this report on a longitudinal population study based on annual health examinations at the workplace, we investigated the association between coffee consumption and the development of increased serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities in middle-aged Japanese men.

The surveillance population consisted of 1464 Japanese male office workers aged 35 to 56 years in May 1994 in T Corporation, Osaka. During the initial and serial annual examinations, fasting blood samples were drawn from an antecubital vein for the determination of serum liver enzyme levels. Serum AST and ALT concentrations were assayed at the Nihon Clinical Laboratories Inc. (Tokyo, Japan), based on the methods recommended by the Japan Society of Clinical Chemistry[10], with an Olympus AU-5000 in 1994 and an Olympus AU-5200 in 1995-1998 (Olympus Japan Co., Ltd., Tokyo, Japan). The cut-off values for serum AST and ALT were set at ≤39 IU/l. Quality control of the laboratory was maintained by internal method, and the inter- and intraassay coefficients of variation for serum AST and ALT were within 3% from 1994 to 1998. Of a total of 1464 subjects, 182 (12.4%) were identified to have increased levels of serum AST and/or ALT ≥40 IU/l at the initial examinations. We

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excluded these 182 subjects to avoid a possible bias, suggested by Klatsky and Armstrong[1], that men with liver disease or liver dysfunction might have reduced coffee consumption because of impaired caffeine clearance[11]. The 32 subjects who had medical care for or past history of liver disease showed normal AST and ALT values. Among the 1250 liver dysfunction-free (serum AST and ALT (39 IU/l and no medical care for or no past history of liver disease) subjects, 29 were taking medication for digestive disease. We excluded these 29 subjects, since those with digestive disease might have reduced coffee consumption. The remaining 1221 constituted the study cohort and were followed up for four years with annual examinations until May 1998. Subjects who were found to have increased levels of AST and/or ALT ≥40 IU/l during repeat surveys were defined to be incidental cases of liver dysfunction, but no one started medication for liver dysfunction or disease during the observation period. Follow-up until May 1998 could be completed for only 1124 subjects (92.1%).

The health examinations at entry included a questionnaire on lifestyle and physical examinations. Data on lifestyle were obtained by interview and selected items of lifestyle for this study were alcohol intake, cigarette smoking, and coffee drinking. As for alcohol intake, the subjects were asked to quantify their consumption of alcohol in respect of how much sake (Japanese rice wine) they drank per day. Alcohol intake was then converted into the equivalent number of go, a traditional Japanese unit of volume for sake (1 go=180 ml and contains 23 g of ethanol). A question queried about smoking habits (never, past or current smokers), with subsequent inquiry to past or current smokers about the number of cigarettes smoked per day. In this study, past and never smokers were combined, and the current amount of cigarettes smoked was used in the analysis. As for coffee drinking, examinees were asked their usual daily intake in cups. Information on the brewing method of coffee was not collected. Data on alcohol intake, cigarette smoking, and coffee drinking were subdivided into terciles and distributions of these variables were as follows: alcohol intake (448 for none, 569 for ≤45.9 g/day of ethanol, and 204 for ≥46.0 g/day of ethanol), cigarette smoking (610 for none, 301 for ≤29 cigarettes/day, and 310 for ≥30 cigarettes/day), and coffee drinking (160 for none, 677 for 1-2 cups/day, and 384 for ≥3 cups/day). Body mass index (BMI) was used as a measure of overall obesity. Weight and height were measured with the subjects wearing typical indoor clothing but with shoes off. BMI was calculated as weight/height^2 (kg/m^2), and its mean value was 23.2 kg/m^2 (SD 2.6

kg/m^2). With respect to age, BMI, alcohol intake, smoking habits, and coffee drinking at entry, the 97 cases which could not be followed up until May 1998 did not differ significantly from the 1124 cases which could.

As for analytic procedures, the observation times were calculated by using the date of the initial examination and the date of the incidence of liver dysfunction or the date of follow-up (the fifth examination), or the date of last registration in T Corporation, Osaka. Those who had been transferred to another locality or had resigned during the follow-up period have censored observation times as do those members of the cohort who were still in T Corporation, Osaka, at the end of the follow-up. The mean observation period of this cohort was 3.7 years with SD of 0.02 years, and the mean (SD) number of times of the measurement of serum AST and ALT, including the initial examination, was 4.8 (0.02). The Kaplan-Meier method was used to estimate the cumulative incidence of increased serum AST and/or ALT levels according to coffee drinking, and the log-rank test was used to assess the significance of the unadjusted differences among the incidence curves. The Cox proportional hazards model was used to evaluate the multivariate relation between coffee drinking and the development of increased serum AST and/or ALT levels, controlling for age (exact values), BMI (exact values), alcohol intake, and cigarette smoking. As for alcohol intake, cigarette smoking, and coffee drinking, hazard ratio (HR) estimates compared to the reference level of each subclass were calculated by creating two dummy variables for each variable as follows: $x1=0$, $x2=0$ for the reference level; $x1=1$, $x2=0$ for the second level; and $x1=0$, $x2=1$ for the third level. Tests for heterogeneity tendency of the HR estimates were also performed. All reported p-values are two-tailed and the level of significance is $p<0.05$.

Table 1 shows the cumulative rates of and multivariate hazard ratios for the incidence of liver dysfunction over 4 years according to coffee drinking. From the univariate analysis using the Kaplan-Meier method, the estimated incidence of serum AST and/or ALT ≥40 IU/l, ≥50 IU/l, and ≥60 IU/l decreased with an increase in coffee consumption. The incidence curves of serum AST and/or ALT ≥40 IU/l did not differ significantly among the three subclasses of coffee drinking on the basis of the log-rank test (p=0.147), but the incidence curves of serum AST and/or ALT ≥50 IU/l and ≥60 IU/l attained statistical significance (p=0.020 and p=0.014, respectively). From the multivariate analysis using the Cox proportional hazards model, coffee drinking had an independently inverse parameter-response

Table 1. Cumulative rates of and multivariate hazard ratios for the incidence of liver dysfunction over 4 years according to coffee drinking assessed by Kaplan-Meier method and Cox Proportional Hazards model in 1221 liver dysfunction-free Japanese male office workers aged 35 to 56 years*

Coffee drinking (cups/day)	n	Serum AST and/or ALT											
		≥40 IU/l				≥50 IU/l				≥60 IU/l			
		%	95% CI	HR	95% CI	%	95% CI	HR	95% CI	%	95% CI	HR	95% CI
None	160	20.0	(13.8–26.2)	1.00	(reference)	12.5	(7.4–17.6)	1.00	(reference)	7.5	(3.4–11.6)	1.00	(reference)
1–2	677	15.2	(12.5–17.9)	0.73	(0.49–1.08)	8.0	(5.9–10.0)	0.60	(0.36–1.00)	3.7	(2.3–5.1)	0.45	(0.23–0.91)
≥3	384	13.5	(10.1–17.0)	0.58	(0.37–0.91)	5.5	(3.2–7.7)	0.36	(0.19–0.69)	2.3	(0.8–3.8)	0.29	(0.12–0.70)

*Subjects with normal level of serum AST and ALT ≤39 IU/l and without medical care for or past history of liver disease. Hazard ratios (HRs) and 95% confidence intervals (CIs) for drinking 1–2 cups/day and ≥3 cups/day of coffee, compared with non-drinking of coffee, were calculated, controlling for age, body mass index, alcohol intake, and cigarette smoking.

relationship with the development of serum AST and/or ALT ≥40 IU/l (p=0.019 by test for tendency), ≥50 IU/l (p=0.002), and ≥60 IU/l (p=0.007), controlling for age, body mass index, alcohol intake, and cigarette smoking. Adjusted hazard ratios for both 1–2 and ≥3 cups/day of coffee drinking relative to non-drinking decreased as the cutoff point of serum AST and/or ALT increased from 40 to 60 IU/l.

In this study, coffee drinking was independently inversely associated with the incidence of increased levels of serum AST and/or ALT. The inverse relation between coffee drinking and the incidence of increased levels of serum AST and/or ALT was progressively stronger as the cutoff point of serum AST and/or ALT increased from 40 to 60 IU/l. These results suggest that coffee may inhibit the elevation of serum AST and/or ALT levels and that its effect is more pronounced in the protection of the development of higher serum AST and/or ALT levels.

The mechanism of the possible decreasing effect of coffee on serum AST and/or ALT are still uncertain. The diterpenes cafestol and kahweol (non-triglyceride lipids present in coffee) are shown to be responsible for the hyper-cholesterolemic effects of boiled coffee[9, 12], and cafestol has been shown to decrease serum liver enzymes[9]. We did not obtain information regarding brewing methods of coffee, but instant coffee is most popular in Japan, followed by brewed (mostly filtered) coffee, whereas use of unfiltered coffee is virtually absent[13]. The negative association between filtered or instant coffee and serum AST and/or ALT levels has been found in several different cross-sectional studies[7, 8]. Cafestol is as minimally contained in instant coffee as in filtered coffee[14], but we consider that cafestol does not fully explain the inverse association between coffee and the development of increased serum AST and/or ALT levels.

The negative association between coffee and the development of increased serum AST and/or ALT levels might also be to some extent to caffeine, which is one of the major ingredients contained in coffee with various biological actions and possibly plays a crucial role in the observed associations of coffee intake. However, green tea, another popular source of caffeine in Japan, has not been found to be inversely related to serum AST and/or ALT levels[4, 7]. Sugar and cream in coffee might have the potential effect on serum AST and/or ALT, but they did not attain statistical significance for the development of increased serum AST and/or ALT levels. As for the relationship between coffee drinking and other lifestyle factors, coffee drinking was significantly positively related to cigarette smoking and snack intake between meals[15]. Influences of coffee drinking on serum AST and/or ALT might be indirectly mediated through coping mechanisms of these lifestyle factors. Further studies are warranted to elucidate whether coffee is responsible for decreased serum AST and/or ALT levels or the protection of raised serum AST and/or ALT in the liver.

In connection with our findings, it is interesting to note that a large-scale prospective study in the USA has observed a decreased risk of alcoholic cirrhosis among coffee drinkers[1]. The potential beneficial effect of coffee on the liver dysfunction or disease among the healthy populations deserves further investigation.

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