Inverse association between coffee drinking and serum uric acid concentrations in middle-aged Japanese males

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Consumption of caffeine-rich beverages, which have diuretic properties, may decrease serum uric acid concentrations. We examined cross-sectionally the relationship of coffee and green tea consumption to serum uric acid concentrations in 2240 male self-defence officials who received a pre-retirement health examination at four hospitals of the Self-Defence Forces between 1993 and 1994. The mean levels of coffee and green tea consumption were 2·3 and 3·1 cups/d respectively. There was a clear inverse relationship between coffee consumption and serum uric acid concentration. When adjusted for hospital only, those consuming less than one cup of coffee daily had a mean serum uric acid concentration of 60 mg/l, while that of those drinking five or more cups of coffee daily was 56 mg/l ($P < 0.0001$). No such relationship was observed for green tea, another major dietary source of caffeine in Japan. The relationship between coffee consumption and serum uric acid concentration was independent of age, rank in the Self-Defence Forces, BMI, systolic blood pressure, serum creatinine, serum total cholesterol and serum HDL-cholesterol concentrations, smoking status, alcohol use, beer consumption and intake of dairy products. These findings suggest that coffee drinking may be associated with lower concentrations of serum uric acid, and further studies are needed to confirm the association.

Serum uric acid: Coffee: Green tea: Caffeine

Uric acid is the end-product of purine metabolism in human beings. Because of the poor solubility of uric acid, human beings function near the maximal tolerable level under normal conditions, and modest alterations in the production, solubility or excretion of uric acid can produce high serum concentrations (Baldree & Stapleton, 1990). Uric acid is excreted primarily by renal tubular secretion (Rieselbach & Steele, 1974; Kahn *et al*. 1985). Renal tubular secretion of urate is a direct function of the serum uric acid concentration, providing a homeostatic mechanism that tends to minimize the hyperuricaemic response to an increase in uric acid synthesis (Steele & Rieselbach, 1967).

Serum uric acid determination is a standard component of many automated blood chemistry panels for routine clinical tests. Hyperuricaemia may result from increased production of uric acid, decreased renal excretion, or both. Serum uric acid has been found to be related not only to risk of clinical gout (Zalokar *et al*. 1974) but also to risk of CHD (Myers *et al*. 1968; Kagan *et al*. 1974; Goldbourt *et al*. 1980), diabetes mellitus (Yano *et al*. 1977; Goldbourt *et al*. 1980; Tuomilehto *et al*. 1988) and hypertension (Myers *et al*. 1968; Yano *et al*. 1977).

Coffee and green tea are the most popular non-alcoholic beverages in Japan. Caffeine is an important component of each of these drinks and is widely used in other foods and medications. The complex pharmacogenetic and physiological effects of caffeine have prompted a great deal of investigation into the health consequences of caffeine ingestion (Curatolo & Robertson, 1983). Because caffeine is known to have a diuretic action probably associated with an increase in renal blood flow, we hypothesized that caffeine-rich beverages might increase the renal excretion of uric acid, thereby lowering serum uric acid concentrations. The present study aimed to assess the relationship of

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coffee and green tea drinking to serum uric acid concentrations, allowing for known or suspected behavioural and biochemical correlates of serum uric acid.

Subjects and methods

Study subjects

Study subjects were male self-defence officials who received, between January 1993 and December 1994, a pre-retirement health examination at the Self-Defence Forces Fukuoka, Kumamoto, Sapporo and Central Hospitals, as part of a nationwide programme offering free comprehensive medical examinations for those retiring from the Self-Defence Forces. All of the retiring self-defence officials are to receive the pre-retirement health examination, although it is not mandatory. Details of the health examination and a self-administered questionnaire on lifestyle have been documented elsewhere (Kono *et al*. 1990, 1992*a*,*b*, 1994).

We excluded the following subjects (*n* 416) in the consecutive series of 2656 men: those under medication for gout and/or hyperuricaemia (*n* 66), hypertension (*n* 248) or hyperlipidaemia (*n* 55); those with renal disease (*n* 17); those with diabetes mellitus under dietary or drug treatment (*n* 77) and those with indeterminate glucose tolerance (*n* 4); those with serum triacylglycerols greater than 11·29 mmol/l (*n* 2); and one who did not answer dietary questions (*n* 1). As a result, 2240 men remained for the present analysis. Age ranged from 49 to 59 years (mean 52·0 years). The characteristics of the study population are shown in Table 1.

Study methods

Described here are procedures relevant to the present study. Venous blood was taken for serum biochemical measurements after an overnight fast. The methods for determination of serum uric acid concentrations and other biochemical measurements have been described in detail in previous papers (Kono *et al*. 1990, 1992*a*,*b*, 1994). A 75 g oral glucose tolerance test was carried out after an overnight fast, and subjects were classified as normal, impaired or having diabetic glucose tolerance according to WHO criteria (World Health Organization, 1980). A single reading of blood pressure on the first day of admission was recorded for the study. Blood pressure was determined by ward nurses using the standard Hg sphygmomanometer on the right arm after at least 5 min rest on the bed. BMI (kg/m^2) was used as a measure of obesity. Current medication use was also recorded.

Usual intakes of thirty-three items of food and non-alcoholic beverages were ascertained, mostly in terms of consumption frequency. Six categories of consumption frequency were prepared for twenty-seven food items (none, once weekly, 2–3 times per week, 4–5 times per week, almost once daily or once daily, and more than once daily); weekly or daily intakes were reported for the other six items (coffee, green tea, milk, rice, soya paste soup and noodles). A summary consumption frequency score for dairy products was calculated by adding together consumption frequencies of milk, yoghurt and ice-cream. Likewise, consumption values for the five meat dishes were also combined into total meat consumption by adding frequencies per week; a coefficient of 0·5 was used for the two meat dishes that included vegetables. Information on the brewing method of coffee was not collected. In Japan, instant coffee is most popular, followed by brewed, mostly filtered, coffee, whereas use of unfiltered coffee is negligible (All Japan Coffee Association, 1995). The amount of caffeine per cup of instant or brewed coffee is approximately 60 mg (Resources Council, Science and Technology Agency, 1982; International Agency for Research on Cancer, 1991*a*), while the amount in a cup of green tea is 14–28 mg (Resources Council, Science and Technology Agency, 1982). Past smokers and past drinkers were separated from lifelong non-smokers and non-drinkers

Table 1. Characteristics of the study population
(Mean values, standard deviations and ranges for 2240 subjects)

Variable	Mean	SD	Range
Age (years)	52·0	0·9	49–59
BMI (kg/m^2)	23·9	2·5	15·8–35·9
Dietary variables			
Alcohol (ml ethanol/d)	37·1	34·3	0–206
Prevalence of drinkers (%)	79·4		
Cigarettes (no./d)	16·4	12·8	0–70
Prevalence of smokers (%)	49·0		
Coffee (cups/d)	2·3	2·1	0–15
Green tea (cups/d)	3·1	2·5	0–20
Dairy products* (times/week)	7·3	6·3	0–54·5
Biochemical and biological variables			
Serum uric acid (mg/l)	58·2	12·4	5·0–119·0
Serum total cholesterol (mmol/l)	5·23	0·85	2·20–8·71
Serum HDL-cholesterol (mmol/l)	1·43	0·37	0·52–3·15
Serum creatinine (mg/l)	10·1	1·3	4·3–15·9
Systolic blood pressure (mmHg)	124·0	17·1	82–210

* Summary consumption frequency score of dairy products was calculated from consumption frequencies of milk, yoghurt and ice-cream.

respectively. Current drinkers reported consumption frequency and amount of each of five alcoholic beverages (sake, shochu, beer, whisky/brandy and wine) on average in the past year. Total ethanol intake (ml) was estimated using the approximate volume concentration of ethanol in each beverage.

Statistical analysis

Statistical analysis was performed with the PC/SAS statistical package (release 6.03, 1988; SAS Institute Inc., Cary, NC, USA). Hospital was always controlled for. Selected a priori as potential confounding variables were age, rank in the Self-Defence Forces, BMI, serum total cholesterol, serum HDL-cholesterol, serum creatinine, systolic blood pressure, alcohol intake, smoking status and glucose tolerance. Since drinking beer is considered to elevate the concentrations of serum uric acid because of its high purine content (Kono *et al*. 1994) and consumption of dairy products is suspected to decrease serum uric acid concentrations (Loenen *et al*. 1990; Ghadirian *et al*. 1995), these dietary factors were also taken into account. Meat consumption was also considered as a potential confounder because meat is a purine-rich food. Age was divided into three classes (< 52, 52 and > 53 years old); rank into three (low, middle and high); smoking habit into four (never, past and current smokers consuming ≤ 20 or > 21 cigarettes/d); alcohol use into five (never, past and current drinkers consuming < 30, 30–59 or > 60 ml ethanol/d); BMI into four quartiles (< 22·0, 22·0–23·6, 23·7–25·3 and > 25·4 kg/m^2); glucose tolerance into three (normal, impaired and diabetic); summary consumption frequency of dairy products into four quartiles (0–2·0, 2·5–5·5 , 6·0–8·5 and > 9·0 times/week); summary consumption of meat into four quartiles (0–2·5, 2·75–4·25, 4·5–6·25 and > 6·5 times/week); coffee and green tea into four (< 1, 1–2, 3–4, and > 5 cups/d). The remaining covariates were treated as continuous variables.

Spearman's rank correlation coefficients were used to examine the univariate relationship of coffee and green tea consumption to potential confounders. Adjusted mean concentrations of serum uric acid were derived from the analysis of covariance. *P* values for trend as regards coffee and green tea consumption were obtained by treating these factors as ordinal variables with ordinal values from 0 to 3 assigned to the four consumption levels. Analysis of covariance was used to examine an independent association of each factor under study with serum uric acid levels. All the *P* values are two-sided and the *P* values less than 0·05 were considered statistically significant.

Results

As shown in Table 1, serum uric acid concentrations ranged from 5 mg/l to 119 mg/l with a mean value of 58 mg/l. Prevalence rate of hyperuricaemia defined as ≥ 70 mg/l was 17·5 %. Table 2 presents the rank correlation of coffee and green tea drinking with potential confounders. Coffee consumption was positively related to smoking and showed a modest, negative correlation with green tea drinking. Median numbers of cups of coffee per day among men with normal, impaired and diabetic glucose tolerance were all 2·0, and all of the corresponding values for green tea were 3·0.

Table 2. Spearman's rank correlation coefficients for coffee and green tea with selected variables

Variable	Coffee (cups/d)	Green tea (cups/d)
BMI (kg/m^2)	–0·015	0·003
Serum total cholesterol (mmol/l)	0·013	–0·061**
Serum HDL-cholesterol (mmol/l)	–0·082****	–0·056*
Serum creatinine (mg/l)	–0·032	0·076***
Systolic blood pressure (mmHg)	–0·116****	–0·062**
Alcohol (ml ethanol/d)†	–0·059*	–0·058*
Cigarettes (no./d)†	0·213****	–0·026
Dairy products (times/week)‡	–0·011	0·031
Meat (times/week)§	0·037	0·037
Green tea (cups/d)	–0·152****	–

* $P < 0·01$, ** $P < 0·005$, *** $P < 0·001$, **** $P < 0·0001$.
† Past smokers and past drinkers were combined with lifelong non-smokers and non-drinkers respectively.
‡ Summary consumption frequency score was calculated from consumption frequencies of milk, yoghurt and ice-cream.
§ Summary consumption frequency score was calculated from consumption frequencies of the corresponding five dishes; a coefficient of 0·5 was used for two meat dishes that included vegetables.

Serum uric acid concentrations in relation to demographic and health-related factors

Table 3 shows the hospital-adjusted means of serum uric acid concentrations in relation to demographic and health-related factors. Despite a narrow age range, the differences in serum uric acid concentrations among age groups were found to be statistically significant (*P* = 0·0003). Serum uric acid concentrations were higher in subjects aged more than 52 years (60·1 mg/l) than in those aged 52 years (57·5 mg/l). Serum uric acid concentrations varied significantly with smoking status (*P* < 0·0001), rank (*P* = 0·003), BMI (*P* < 0·0001) and glucose tolerance (*P* = 0·005). While serum uric acid concentrations were progressively higher with increasing levels of BMI and in men at higher ranks, the relationships with smoking and glucose tolerance were not straightforward. Among the four categories of smoking, the highest serum uric acid concentration was observed in ex-smokers, followed by non-smokers. The concentrations of serum uric acid were similar between current smokers with low and high cigarette consumption. The concentrations of serum uric acid were highest in subjects with impaired glucose tolerance, and lowest in diabetics.

Serum uric acid concentrations in relation to dietary factors

The relationships between selected dietary factors and serum uric acid concentrations are summarized in Table 4. Coffee drinking (*P* < 0·0001) and the frequency of intake of dairy products (*P* = 0·003) were significantly related to lower concentrations of serum uric acid. There was a small difference between those consuming less than one cup of coffee daily (60 mg/l) and those drinking five or more cups of coffee daily (56 mg/l). No clear association was noted between serum uric acid concentrations and green tea drinking. Alcohol use was significantly positively

Table 3. Serum uric acid concentrations (mg/l) of Japanese men in relation to categorized demographic and health-related variables

(Mean values and 95 % confidence intervals)

Variable	*n*	Serum uric acid (mg/l) Mean* (95 % CI)	Statistical significance of difference between categories: *P*=
Age (years)			
49–51	613	58·6 (57·9, 59·9)	
52	1072	57·5 (56·7, 58·3)	
53–59	555	60·1 (59·0, 61·2)	0·0003
Rank			
Low	1120	57·4 (56·7, 58·2)	
Middle	451	58·9 (57·8, 60·1)	
High	669	60·0 (59·0, 61·1)	0·0003
BMI (kg/m^2)			
$<$ 22·0	500	55·0 (53·9, 56·0)	
22·0–23·6	566	57·1 (56·1, 58·1)	
23·7–25·3	606	59·2 (58·2, 60·2)	
25·4–35·9	568	62·1 (61·1, 63·2)	$<$0·0001
Smoking (cigarettes/d)			
Never	630	58·6 (57·6, 59·6)	
Past	513	60·5 (59·4, 61·6)	
1–20	719	57·2 (56·3, 58·1)	
$>$ 21	378	57·7 (56·5, 59·0)	$<$0·0001
Glucose tolerance			
Normal	1729	58·3 (57·7, 58·9)	
Impaired	396	59·9 (58·6, 61·1)	
Diabetic	115	55·8 (53·5, 58·1)	0·005

* Adjusted for hospital.

Table 4. Serum uric acid concentrations (mg/l) of Japanese men in relation to categorized dietary variables

(Mean values and 95 % confidence intervals)

Variable	*n*	Serum uric acid (mg/l) Mean* (95 % CI)	Statistical significance of difference between categories: *P*=
Coffee (cups/d)			
$<$1	727	59·9 (58·9, 60·8)	
1–2	572	58·6 (57·5, 59·6)	
3–4	586	57·9 (56·9, 59·0)	
$>$ 5	355	56·0 (54·7, 57·3)	$<$0·0001
Green tea (cups/d)			
$<$1	449	57·4 (56·1, 58·6)	
1–2	527	59·0 (57·9, 60·1)	
3–4	674	58·5 (57·6, 59·5)	
$>$ 5	590	58·7 (57·6, 59·7)	0·22
Alcohol (ml ethanol/d)			
Never	402	55·8 (54·6, 57·0)	
Past	59	56·4 (53·3, 59·5)	
1–29	633	57·8 (56·8, 58·8)	
30–59	646	59·6 (56·9, 58·8)	
$>$ 60	500	59·9 (58·5, 60·6)	$<$0·0001
Dairy products (times/week)†			
0–2·0	464	58·8 (57·7, 59·9)	
2·5–5·5	666	58·9 (58·0, 59·8)	
6·0–8·5	518	58·6 (57·5, 59·6)	
$>$ 9·0	592	56·6 (55·6, 57·6)	0·003

* Adjusted for hospital.

† Summary consumption score was calculated from consumption frequencies of milk, yoghurt and ice-cream.

Table 5. Results from analysis of covariance of coffee and green tea and serum uric acid concentrations (mg/l)
(Mean values and 95 % confidence intervals)

	Serum uric acid (mg/l)	
	Mean* (95 % CI)	Trend P=†
Coffee (cups/d)		
<1	58·8 (57·5, 60·0)	
1–2	57·5 (56·2, 58·8)	
3–4	56·9 (55·5, 58·2)	
>5	55·6 (54·1, 57·2)	<0·0001
Green tea (cups/d)		
<1	56·4 (55·0, 57·9)	
1–2	57·9 (56·6, 59·3)	
3–4	57·3 (56·1, 58·6)	
>5	57·1 (55·8, 58·4)	0·66

* Adjusted for hospital, age, serum total cholesterol, serum HDL-cholesterol, serum creatinine, systolic blood pressure, BMI, rank, beer, alcohol , smoking status, meat, dairy products, and either coffee or green tea.
† P values for trend as regards coffee and green tea consumption were obtained by treating these factors as ordinal variables with ordinal values from 0 to 3 assigned to the four consumption levels.

related to serum uric acid concentrations ($P < 0{\cdot}0001$). Meat consumption was totally unrelated to serum uric acid concentration (results not shown).

Analysis of covariance in relation to coffee and green tea and serum uric acid concentrations

Results of the analysis of covariance are summarized in Table 5. The inverse association between coffee drinking and serum uric acid concentration remained highly significant (trend $P < 0{\cdot}0001$) after controlling for hospital, age, serum total cholesterol, serum HDL-cholesterol and serum creatinine concentrations, systolic blood pressure, BMI, rank, beer, alcohol, smoking status, meat, dairy products and green tea; green tea consumption was unrelated to serum uric acid concentration in the multivariate analysis as well.

Discussion

In the present study we demonstrated an inverse relationship between coffee consumption and serum uric acid concentration independent of known behavioural and biochemical correlates. To the best of our knowledge, this is the first report on the association between coffee consumption and serum uric acid concentration. We had hypothesized that a diuretic action of caffeine might affect serum uric acid concentration. However, intake of green tea, another major dietary source of caffeine, was unrelated to the concentrations of serum uric acid. Even in non-coffee drinkers, green tea consumption was not correlated with serum uric acid concentration at all (results not shown). These findings suggest that a constituent or constituents of coffee other than caffeine may be responsible for the inverse relationship between coffee and serum uric acid concentration.

Statistical adjustment was made for a wide range of factors, which are known or suspected to be associated with serum uric acid concentrations (Myers *et al*. 1968; Kagan *et al*. 1974; Zalokar *et al*. 1974; Yano *et al*. 1977; Goldbourt *et al*. 1980; Tuomilehto *et al*. 1988; Kono *et al*. 1994). As reported elsewhere, serum creatinine and BMI were major determinants of serum uric acid concentration in the present study as well. Serum uric acid concentrations varied substantially according to alcohol use and glucose tolerance status. In agreement with several previous studies (Zalokar *et al*. 1974; Kono *et al*. 1994), the present study also showed raised serum uric acid concentrations among past smokers. Serum total cholesterol concentration, systolic blood pressure and serum HDL-cholesterol concentration were also, to lesser extents, correlated with serum uric acid concentration (results not shown). Coffee drinking was in fact associated with some of these variables such as smoking (positively), but unrelated to the two major determinants of serum uric acid concentration, i.e. serum creatinine level and BMI. Statistical adjustment may not necessarily have eliminated the confounding effects of these factors, and undetermined factors characteristic of coffee drinkers may explain part of the observed relationship between coffee drinking and serum uric acid concentration. However, it seems unlikely that the lower concentrations of serum uric acid associated with coffee drinking could be ascribed entirely to uncontrolled confounding effects.

We cannot currently provide any explanation with regard to the biological mechanism underlying the observed inverse association between coffee drinking and serum uric acid concentration. Reduction in serum uric acid concentration occurs through either decreased synthesis or increased renal excretion of uric acid; the latter results from enhancement of tubular secretion and inhibition of tubular reabsorption. Coffee contains several species of xanthines other than caffeine (International Agency for Research on Cancer, 1991*b*). For example, theobromine and theophylline are present in coffee but not in green tea (International Agency for Research on Cancer, 1991*b*). Allopurinol is one of the hypoxanthine isomers used as a drug inhibiting production of uric acid. Thus, it is possible that non-caffeine xanthines in coffee may have a similar effect on uric acid synthesis.

In the present study, a high consumption frequency of dairy products was significantly associated with decreased serum uric acid concentrations; the trend of the association was also statistically significant without (trend $P = 0{\cdot}002$) and with adjustment for the covariates (trend $P = 0{\cdot}009$). However, our estimate of dairy product consumption was based only on consumption frequencies, and was necessarily crude. A limited number of studies have previously addressed the relationship between dairy products and serum uric acid concentrations. Loenen *et al*. (1990) demonstrated that serum uric acid concentrations were inversely associated with consumption of milk products among Dutch women, and Ghadirian *et al*. (1995) observed, in a randomized controlled trial of postmenopausal women in Canada, that plasma uric acid concentrations increased in those allocated to a dairy-product-free diet while those taking 30 g dairy protein daily showed no change. An earlier study also showed that intake of casein (milk protein) resulted in a decrease in serum uric acid concentration in normal subjects (Verdy *et al*. 1987). It is not clear whether these reported effects are due to dairy protein and/or Ca, or to other components of milk and its products. Although underlying mechanisms are unclear, our findings add to evidence that dairy products decrease the serum uric acid concentration.

Finally, the observed difference in serum uric acid concentrations associated with coffee consumption was relatively small, and such a small difference may not be of clinical importance. However, a small shift of the population mean generally results in a large change in the proportion of aberrant individuals in the population (Rose & Day, 1990). A change in the mean from 58·8 mg/l (for men not drinking coffee daily) to 55·6 mg/l (for men drinking five or more cups daily) is only a 5 % reduction. Yet, assuming that the standard deviation is 12·4 mg/l, the proportion of hyperuricaemics (defined as those with serum uric acid concentrations 70 mg/l or greater) is estimated to change from 18 % to 12 %, which is a 33 % reduction. Our study subjects were men serving in the Self-Defence Forces until retirement. They may differ from men in the general population in various lifestyle characteristics, and our findings may not be directly generalized. Because the data used in the present study were not collected specifically to address the relationship between coffee drinking and serum uric acid concentration, the reported association between coffee drinking and serum uric acid concentration may be simply due to chance. Further studies are needed to confirm the association in different populations.

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