Key messages

- Cigarette smokers consume 50% more caffeine than non-smokers, but their caffeine metabolism is faster, resulting in lower blood concentrations
- Blood caffeine concentrations during pregnancy are not related to birth weight
- Caffeine intake assessed by questionnaire is negatively associated with birth weight, with evidence that this effect is apparent only in smokers
- As most studies have limited power to detect an interaction between smoking and effects of caffeine intake on birth weight, a meta-analysis of existing studies is recommended
- It seems reasonable to advise women who smoke to reduce their caffeine intake as well as to stop smoking during pregnancy

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Comparison of effect of cafetière and filtered coffee on serum concentrations of liver aminotransferases and lipids: six month randomised controlled trial

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Abstract

***Objective*—To study the effects of prolonged intake of cafetière coffee, which is rich in the diterpenes cafestol and kahweol, on serum aminotransferase and lipid concentrations.**

***Design*—Randomised parallel controlled trial.**

Subjects—46 healthy men and women aged 19 to 69.

***Intervention*—Consumption of five to six strong cups (0.9 litres) a day of either cafetière (22 subjects) or filtered coffee (24 subjects) for 24 weeks.**

***Main outcome measures*—Mean changes in serum aminotransferase and lipid concentrations.**

***Results*—Cafetière coffee raised alanine aminotransferase concentration by up to 80% above baseline values relative to filtered coffee. After 24 weeks the rise was still 45% (9 U/l (95% confidence interval 3 to 15 U/l), P = 0.007). Alanine aminotransferase concentration exceeded the upper limit of normal in eight of the 22 subjects drinking cafetière coffee, being twice the upper limit of normal in three of them. Cafetière coffee raised low density lipoprotein cholesterol concentrations by 9-14%. After 24 weeks the rise was 0.26 mmol/l (0.04 to 0.47 mmol/l) (P = 0.03) relative to filtered coffee. Triglyceride concentrations initially rose by 26% with cafetière coffee but returned close to baseline values within six months. All increases were reversible after the intervention was stopped.**

***Conclusions*—Daily consumption of five to six cups of strong cafetière coffee affects the integrity of liver cells as suggested by small increases in serum alanine aminotransferase concentration. The effect does not subside with prolonged intake. High intakes of coffee brews rich in cafestol and kahweol may thus be responsible for unexplained increases in this enzyme activity in apparently healthy subjects. Cafetière coffee also raises low density lipoprotein cholesterol concentration and thus the risk of coronary heart disease.**

Introduction

Scandinavian boiled coffee raises serum cholesterol concentrations in humans.[1-4] The diterpenes cafestol and kahweol are responsible for this effect.[5 6] They do not pass through paper filters, which explains why filtered coffee does not raise cholesterol concentrations,[7 8] but they do occur in other unfiltered coffee brews, such as cafetière coffee and Turkish coffee.[9]

Cafestol and kahweol seem to affect liver cells: short term intake of boiled coffee[5] or preparations rich in cafestol and kahweol [5 10-12] raise the serum concentration of

alanine aminotransferase. However, lifelong consumers of boiled coffee in Norway did not have higher alanine aminotransferase concentrations than matched lifelong consumers of filtered coffee.[5] One explanation for this could be that alanine aminotransferase concentrations return to normal with prolonged intake of cafestol and kahweol.

We examined this hypothesis and the effects on serum lipid concentrations in a randomised trial of cafetiere versus filtered coffee.

Subjects and methods

The trial lasted from October 1994 to July 1995. It consisted of a four week run in period, 24 weeks of treatment (intervention), and 12 weeks of follow up. The study was approved by the local human ethics committee.

Volunteers were recruited through advertisements in newspapers and university buildings. We carefully explained the study protocol to them before they gave written informed consent. Subjects were eligible if they had a body mass index <30 kg/m^2; did not use any drugs known to affect serum concentrations of liver enzymes or lipids; were not pregnant, lactating, or on a prescribed diet; and drank more than four cups of coffee and less than three drinks containing alcohol a day. Candidates filled out a medical questionnaire, which was reviewed by an independent internist. Candidates with a history of gastrointestinal, liver, or kidney disease were excluded, as were those with glucosuria; proteinuria; anaemia; a serum concentration of total cholesterol >6.5 mmol/l or of fasting triglycerides >2.3 mmol/l; or concentrations of alanine or aspartate aminotransferase or γ-glutamyltransferase above the upper limits of normal.

Sixty four subjects entered a run in period, which served to select those who were able to comply with our requirements. All subjects consumed 0.9 l of filtered coffee a day. Eleven subjects reported that they could not comply, mainly because they thought that the coffee was too strong. We stratified the remaining 53 subjects for sex and alanine aminotransferase concentration (above or below the median) and allocated them to either filtered or cafetiere coffee by tossing a coin.

In the treatment period, subjects consumed 0.9 litres a day of either filtered or cafetière coffee. They were asked to maintain their usual diet and lifestyle. Intakes of dietary fatty acids and cholesterol were estimated once in the run in period and three times in the treatment period.[13] All subjects kept daily records of illness and deviations from the protocol. Body weights were measured monthly.

Six subjects withdrew during the treatment period; two had problems complying, two became ill, one moved, and one had personal reasons. Another subject was withdrawn after 20 weeks as his aminotransferase concentrations exceeded our predefined limits. He had started taking drugs with potential hepatotoxicity daily during the treatment period, and his data were excluded. Inclusion of his values did not materially alter the results (for instance, a rise of alanine aminotransferase after eight weeks of treatment of 19 U/l instead of 16 U/l). Forty six subjects completed the study (table 1).

PREPARATION OF COFFEE

Subjects brewed their coffee at home according to instructions that we gave them before the study. All ground coffee was Roodmerk (Douwe Egberts, Utrecht), a blend of Arabica and Robusta beans widely used in the Netherlands.[8]

For filtered coffee, subjects scooped 78 ml (33 g) of fine ground coffee into a paper filter (Melitta, Gorinchem, the Netherlands) in a conical holder, which was placed on an insulated jar (0.5 litre, Thermos). They poured boiling water on to the grounds until the jar was full. For cafetière coffee, subjects scooped 92 ml (39 g) of coarse grounds into a cafetière (Kaffee Primo, BMF, Germany, 1 litre) and poured 0.6 litre of boiling water on to the grounds. More coffee was used so as to provide the same amount of caffeine as filtered coffee.[14] Subjects stirred the brew for 10 seconds, allowed it to stand for two to five minutes, pushed down the plunger to separate the grounds from the brew, and decanted the brew into a jar.

One jar provided two to three cups of coffee, and two jars were prepared and consumed each day. Subjects were allowed to dilute the brew with water if they considered it too strong. Cafetière coffee provided 38 (SD 6) mg cafestol and 33 (5) mg kahweol a day (mean of 22 samples). Filtered coffee provided less than 1 mg of either diterpene a day (mean of six samples).

Table 1—*Characteristics of the participants at the end of the run in period. Values are numbers of subjects unless stated otherwise*

Variable	Filtered coffee (n = 24)	Cafetière coffee (n = 22)
Sex (male/female)	12/12	11/11
Mean (SD) (range) age (years)	29 (9) (19-52)	30 (11) (20-69)
Mean (SD) body mass index (kg/m^2)*	22 (3)	23 (3)
Smoking (yes/no)	10/14	6/16
Women using contraceptives (yes/no)	6/6	5/6
Mean No (SD)of alcohol drinks daily†	1.0 (0.6)	0.7 (1.0)
Mean No (SD) of coffee cups drunk daily†	5 (2)	5 (1)
Cream in coffee (yes/no)	10/14	8/14

*Body weights were measured without shoes or heavy clothing.
†Self reported consumption before study.

BLOOD SAMPLING AND ASSAYS

Venous blood samples were taken after an overnight fast after 3 and 4 weeks during the run in period, after 2, 4, 6, 8, 12, 16, 20, 23, and 24 weeks of treatment, and after 4, 8, and 12 weeks of follow up. Serum samples were obtained by centrifugation and stored at −80°C. Alanine and aspartate aminotransferase,[15] alkaline phosphatase,[16] and γ-glutamyltransferase[17] were measured at 37°C using Abbott Spectrum reagents (Irving, Texas). The mean bias for Monitrol control samples (Baxter Dade, Düdingen, Switzerland) ranged from 0% to 2%. The coefficient of variation within runs ranged from 2% to 8%. Upper limits of normal were 54 U/l for alanine aminotransferase, 40 U/l for aspartate aminotransferase, 92 U/l for alkaline phosphatase, and 63 U/l and 35 U/l for γ-glutamyltransferase in men and women respectively. Serum samples were analysed enzymatically for total[18] and high density lipoprotein cholesterol[19] and triglycerides.[20] Mean bias for control samples provided by the Centers for Disease Control in Atlanta was −1% for total and high density lipoprotein cholesterol and 10% for triglycerides. The coefficient of variation within runs ranged from 0.9% to 1.7%. Low density lipoprotein cholesterol concentration was calculated.[21]

Alanine aminotransferase and cholesterol concentrations were measured in three separate sessions, each comprising 12 weeks of the trial. All other variables were measured in a single session. Samples from one subject were analysed in the same run.

STATISTICS

Baseline values were calculated as the means of the two values obtained after the run in period. Responses

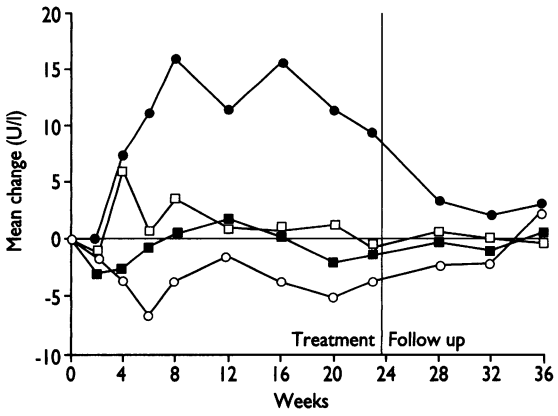

Fig 1—*Mean changes from baseline values in alanine (•) and aspartate aminotransferase (□), alkaline phosphatase (○), and γ-glutamyltransferase (■) in 22 subjects drinking 0.9 litre daily of cafetière coffee for 24 weeks. For each time point, mean changes from baseline in 24 subjects drinking filtered coffee were subtracted from those in the subjects drinking cafetière coffee to correct for random drifts in time*

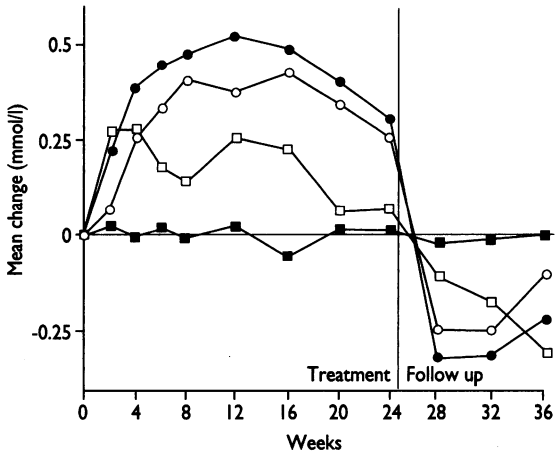

Fig 2—*Mean changes from baseline values in serum concentrations of total cholesterol (•), triglycerides (□), low density lipoprotein cholesterol[21] (○), and high density lipoprotein cholesterol (■) in 22 subjects drinking 0.9 litre cafetière coffee daily for 24 weeks. For each time point, mean changes from baseline in 24 subjects drinking filtered coffee were subtracted from those in the subjects drinking cafetière coffee to correct for random drifts in time*

were calculated by subtracting baseline values from values obtained during treatment. The means of the values obtained after 23 and 24 weeks of treatment were used as end values. Differences in responses between the groups were compared using the Mann-Whitney U and unpaired *t* tests. As the results were similar, only the latter are presented.

Results

Diaries kept by the subjects and anonymous questionnaires administered after the trial showed that over 98% of the prescribed amount of coffee was consumed. In both groups mean changes in body mass index during treatment were less than 0.5 kg/m^2 and changes in intake of saturated, monounsaturated, or polyunsaturated fatty acids were less than 1% of energy.

Liver enzymes—The mean alanine aminotransferase concentration with cafetière coffee increased by up to 80% (table 2). After 24 weeks the rise was 9 (SE 3) U/l or 45% over baseline, relative to filtered coffee (P = 0.007). In eight of the 22 subjects drinking cafetiere coffee compared with one of the 24 drinking filtered coffee the concentration of alanine aminotransferase exceeded the upper limit of normal on at least one occasion. Alanine aminotransferase concentration exceeded twice the upper limit of normal in three of the eight subjects drinking cafetière coffee. Concentrations of aspartate aminotransferase, alkaline phosphatase, and γ-glutamyltransferase were less affected (fig 1). After discontinuation of cafetière coffee, enzyme concentrations returned to normal in all subjects.

Lipids—Cafetière coffee raised cholesterol concentrations mostly because of an increase in low density lipoprotein cholesterol (fig 2, table 2). After 24 weeks low density lipoprotein cholesterol concentrations were raised by 0.26 (SE 0.11) mmol/l, or 9% over baseline values, relative to filtered coffee (P = 0.03). High density lipoprotein cholesterol concentration was not affected. Triglyceride concentrations were raised by 26% within two weeks and by 7% after 24 weeks of treatment. After discontinuation of cafetière coffee concentrations of total and low density lipoprotein cholesterol and of triglycerides fell below baseline values (fig 2).

Discussion

We found that a daily intake of five to six cups of strong cafetière coffee raises alanine aminotransferase concentration and low density lipoprotein cholesterol concentration (to values seen after drinking Scandinavian boiled coffee) for at least six months. These

Table 2—*Mean serum concentrations of alanine aminotransferase and lipids before, during, and after consumption of filtered or cafetière coffee for six months*

Variable	Baseline	Treatment period						Treatment effect (95% confidence interval)*	Follow up			
		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24		Week 28	Week 32	Week 36	Week 64†
Alanine aminotransferase (U/l):												
Filtered coffee (n = 24)	20	21	22	21	21‡	20	19		18‡	18‡	18‡	19
Cafetière coffee (n = 22)	19	27	36‡	31	35	30	27	9 (3 to 15)	20	19	19	15
Total cholesterol (mmol/l)¶:												
Filtered coffee (n = 24)	4.99	5.04	5.13	5.08	4.79‡	4.94	4.94		4.97‡	5.06‡	4.94‡	5.25
Cafetière coffee (n = 22)	4.91	5.35	5.56‡	5.52	5.24	5.26	5.16	0.31 (0.01 to 0.61)	4.62	4.68	4.63	4.88
Low density lipoprotein cholesterol (mmol/l)¶:												
Filtered coffee (n = 24)	2.99	3.03	3.09	3.06	2.76‡	2.93	2.92		2.98‡	2.97‡	2.89‡	3.20
Cafetière coffee (n = 22)	2.99	3.29	3.51‡	3.42	3.24	3.28	3.18	0.26 (0.04 to 0.47)	2.78	2.76	2.78	2.92
Triglycerides (mmol/l):												
Filtered coffee (n = 24)	1.05	1.11	1.14	1.05	1.05‡	1.07	1.18		1.05‡	1.16‡	1.26‡	1.19
Cafetière coffee (n = 22)	1.07	1.41	1.32‡	1.34	1.31	1.16	1.26	0.07 (−0.23 to 0.37)	0.96	1.03	1.01	1.03

*After 23-24 weeks; calculated by subtracting the mean change from baseline while drinking filtered coffee from that while drinking cafetière coffee.
†Based on 20 subjects who had received cafetière coffee and 15 who had received filtered coffee.
‡Value of one subject missing.
¶Calculated according to Friedewald *et al.*[21]

findings should also apply to Turkish coffee, which contains similar amounts of cafestol and kahweol per cup to cafetière and boiled coffee. These effects would be seen after drinking about 25 cups a day of Italian espresso coffee because of the small cup sizes. Instant and percolator coffee will have negligible effects on serum aminotransferase and lipid concentrations because of their low concentrations of cafestol and kahweol.[9]

LIVER ENZYME CONCENTRATIONS

The rise in alanine aminotransferase would be expected to be transient with prolonged intake of cafetière coffee as long term consumers of boiled coffee did not have raised alanine aminotransferase concentrations.[5] However, our results show that liver cells only partly adapt to cafestol and kahweol within the first six months of daily consumption.

Alanine aminotransferase concentrations exceeded the upper limit of normal in 36% of subjects drinking cafetière coffee and were twice the upper limit in 14%. Thus, a high intake of strong, unfiltered coffee might explain some cases of raised alanine aminotransferase concentrations in apparently healthy people. It might be prudent for patients with raised alanine aminotransferase values to drink no more than a few cups of cafetière, Turkish, or boiled coffee a day on a regular basis.

However, should we really expect unfiltered coffee to affect the risk of liver disease in healthy people? Cafetière coffee only marginally raised aspartate aminotransferase concentrations, which excludes extensive damage to liver cells. γ-Glutamyltransferase and alkaline phosphatase concentrations were reduced rather than raised (fig 1), and reduced levels of γ-glutamyltransferase were also observed in long term consumers of boiled coffee.[22,23] In Scandinavian countries, which used to have high intakes of boiled coffee, death rates from liver cirrhosis are low and seem to be unaffected by the change from drinking boiled to drinking filtered coffee over the past decades.[24] Therefore, clinically relevant damage to liver cells with regular use of unfiltered coffee appears unlikely, although we cannot yet fully exclude subclinical injury to hepatocytes.

LIPID CONCENTRATIONS

Cafetière coffee raised total cholesterol concentration by 6-10% and low density lipoprotein cholesterol concentration by 9-14%, which is similar to the effects observed with Scandinavian boiled coffee.[2-4,7,8] These increases persisted with prolonged consumption of cafetière coffee. Our study thus shows that cholesterol metabolism remains disturbed with prolonged intake of cafestol and kahweol, as was previously suggested by observational studies in subjects drinking boiled coffee.[5,25-28] Therefore, high intakes of cafetière coffee will be associated with an increased risk of coronary heart disease, similar to that associated with boiled coffee.[29] An increase in cholesterol concentration of 6-10% is estimated to increase coronary risk by 12-20%[30]; larger increases may be expected in young people because reducing cholesterol concentration should reduce the risk of coronary disease more in younger than older people.[31]

High triglyceride concentrations are also associated with increased coronary risk.[32] Triglyceride concentrations initially increased by 26% with cafetière coffee, but most of the rise disappeared with prolonged intake (fig 2). This was unlikely to be due to seasonal influences, as we expressed all changes relative to those in the concurrent control group. Experiments with boiled coffee show larger changes in triglyceride concentrations[2,3,7,8] than observational studies comparing subjects drinking boiled coffee with others drinking filtered coffee.[5,28] Our results may explain this: triglyceride concentrations partly normalised with prolonged intake of cafestol and kahweol.

We cannot explain the fall in lipid concentrations below baseline values after stopping drinking cafetière coffee. It is not likely to be due to dietary changes—for example, the observed reduction in low density lipoprotein cholesterol of 0.25 mmol/l would have required a shift in dietary intake from butter to margarine high in linoleic acid of 32 g daily.[33,34] These findings again emphasise the prolonged and extensive effects of cafestol and kahweol on lipid metabolism in humans.

Key messages

- Scandinavian boiled coffee increases serum concentrations of alanine aminotransferase and low density lipoprotein cholesterol because of the presence of the coffee diterpenes cafestol and kahweol, which are released from ground beans by hot water but retained by paper filters
- This randomised study found that cafetière coffee also increased alanine aminotransferase and low density lipoprotein cholesterol concentrations, and they were still raised after six months of daily intake.
- Filtered coffee had no effect
- The increase in liver enzyme activity could be innocuous, but the increase in cholesterol concentration may increase coronary risk and could be a reason to advise patients to drink filtered coffee

CONCLUSION

Daily consumption of large amounts of cafetière coffee raises alanine aminotransferase concentrations for at least six months. Long term intake of cafetière coffee also raises low density lipoprotein cholesterol concentration. The effects on aminotransferases may be innocuous, but the effects on cholesterol concentration increase coronary risk and could be a reason to advise patients to drink filtered rather than cafetière coffee.

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Ownership and uses of human tissue: Does the Nuffield bioethics report accord with opinion of surgical inpatients?

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Abstract

***Objective*—To compare opinion of surgical inpatients with the conclusions of the report of the Nuffield Council on Bioethics regarding the ownership and uses of human tissue.**

***Design*—Survey of results of questionnaires completed by patients.**

***Setting*—Large teaching hospital.**

***Subjects*—384 postoperative adult surgical patients.**

***Results*—There was strong support among patients for the use of tissues in medical education, research, and science with the exception of those tisssues which may transmit disease to others. Few patients (39; 10%) believed that they retained ownership of tissue removed at surgery. Most believed that the tissue belonged to the hospital (103; 27%), to nobody (103; 27%), or to the laboratory (77; 20%). Most patients had not been given any information about the possible uses of their tissues after removal.**

***Conclusions*—Surgical inpatients seem to endorse the conclusions of the Nuffield report regarding the ownership and uses of human tissue. The recommendations regarding patient information and consent procedures should be implemented at the earliest opportunity.**

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Introduction

The working party of the Nuffield Council on Bioethics, which examined the ethical and legal issues surrounding human tissue, proposed that tissue removed from patients in the course of treatment should be considered abandoned and that the possibility that tissue may be stored, used in the treatment of others, or used in medical education and research should be indicated in general terms in standard consent procedures for medical and surgical interventions entailing the removal of tissue for diagnosis or treatment.[1] If patients and the public were to have extremely divergent views from the working party then some of the complex issues surrounding the uses of human tissue would require reconsideration.

We provide the first detailed assessment of opinion of patients in the United Kingdom about the ownership of human tissue removed during treatment and the uses to which that tissue may, can, or should be put.

Patients and methods

Questionnaire design—The questionnaire contained no questions relating to specific research applications or the use of cadaveric, fetal, or reproductive tissue. Respondents were required to tick a box within a limited range of options (see tables 1 and 2). Case records were reviewed to determine the nature of surgical procedures and final histological diagnoses if tissue had been removed. The current hospital consent form contains no reference to the ownership or to the subsequent disposal, storage, or other uses of tissue removed during investigation or treatment, but completed consent forms were examined to determine whether references to such issues had been added during consent procedures.

Questionnaire terminology—Preliminary work clearly indicated that the term "tissue" was poorly understood. The term "diseased part of the body" was found to be an acceptable alternative for tissue within the questionnaire.

Subjects—The survey population consisted of 450 adult patients after they had undergone general surgery or an orthopaedic or urological operation during a seven week period in a large teaching centre. Twenty nine patients were too unwell to participate. Two medical students hand delivered questionnaires with an explanatory letter. The study was approved by the South Sheffield Research Ethics Committee.