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The Effect of Chlorogenic Acid Enriched Coffee on Glucose Absorption in Healthy Volunteers and Its Effect on Body Mass When Used Long-term in Overweight and Obese People

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The results from a clinical study performed in 12 healthy volunteers with different coffee products containing glucose show that instant coffee enriched with chlorogenic acid induced a reduction in the absorption of glucose of 6.9% compared with the control. No such effects were seen with normal or decaffeinated instant coffee. In a second, comparative, randomized, double-blind, 12-week study we investigated the effect on the body mass of 30 overweight people, compared with normal instant coffee. The average losses in mass in the chlorogenic acid enriched and normal instant coffee groups were 5.4 and 1.7 kg, respectively. We conclude that chlorogenic acid enriched instant coffee appears to have a significant effect on the absorption and utilization of glucose from the diet. This effect, if the coffee is used for an extended time, may result in reduced body mass and body fat when compared with the use of normal instant coffee.

KEY WORDS: Chlorogenic Acid; Coffee; Glucose; Diet

Introduction

Coffee is the world's favourite beverage, with an estimated 1.5 billion cups being drunk every day. Despite decades of research on coffee and centuries of consumption, there are many misconceptions concerning the potential health risks associated with it.[1]

Coffee is a complex mixture of chemicals that provides significant amounts of chlorogenic acid and caffeine. Unfiltered coffee is a significant source of cafestol and kahweol, which are diterpenes that have been implicated in the cholesterol-raising effects of coffee. The results of several epidemiological studies suggest that coffee may help prevent several chronic diseases, including type-2 diabetes. Coffee consumption is, however, associated with an increase in several cardiovascular disease risk factors, including raised blood pressure and plasma homocysteine.[2]

Some groups, including people with hypertension, children, adolescents and the elderly, may be more vulnerable to the

adverse effects of caffeine (1,3,7-trimethylxanthine). In addition, currently available evidence suggests that it may be prudent for pregnant women to limit coffee consumption to 3 cups/day in order to provide no more than 300 mg/day of caffeine, thereby avoiding any increased probability of spontaneous abortion or impaired fetal growth.[2] A number of recent publications have focused on the disease-preventive and weight-reducing effects of coffee.[3,4]

From a pharmacological point of view, coffee is an extremely complex substance. It is a major source of caffeine, which is the most widely consumed stimulant in the world, and has been implicated in the development of cardiovascular diseases such as acute myocardial infarction. Coffee contains a multitude of other substances, however, many of which are potentially biological active. It is also an extremely rich source of chlorogenic acids.

The amounts of chlorogenic acids and caffeine in coffee are comparable.[5,6] Chlorogenic acids are an important group of biologically active dietary phenols; the best known being 5-caffeoylquinic acid. The daily intake of chlorogenic acids by coffee drinkers is considered to be in the range 0.5 – 1.0 g[5-7] and chlorogenic acids have been found to exhibit antioxidant activity *in vitro*.[7] In addition to their antioxidant effects, there has been growing interest in the other biological properties of phenolic compounds[7-9] and accumulating evidence suggests that certain dietary phenols, through a variety of mechanisms, may result in an altered pattern of intestinal glucose uptake.

Chlorogenic acids have been shown to influence postprandial blood sugar concentration, glucose tolerance, serum lipid concentration and glucose absorption from the intestine. They have been found to reduce the intestinal absorption of glucose in rats by encouraging dispersal of the Na^+ electrochemical gradient, which draws glucose into the enterocytes,[10] and to inhibit the activity of hepatic glucose-6-phosphatase, which is implicated in glucose homeostasis.[11,12] This has been confirmed in an *in vivo* study investigating chlorogenic acid extracts from coffee, and their derivatives, on blood sugar concentrations and the secretion of an incretin, glucose-dependent insulinotropic polypeptide (GIP). The study showed that coffee (decaffeinated or caffeinated) when compared with a control drink, significantly attenuated the postprandial release of GIP in the proximal part of the small intestine. As the quantity of glucose absorbed at the intestinal barrier determines the magnitude of the GIP response, these results suggest that coffee decreases the absorption of glucose from the small intestine.[13,14]

Based on this information, we carried out clinical studies to: (i) investigate the effect of chlorogenic acid supplemented coffee on the glucose profile of healthy volunteers, compared with that of normal coffee; and (ii) evaluate the effect of chlorogenic acid supplemented coffee when taken as part of a regular diet in overweight and obese subjects.

Materials and methods

PRODUCTS USED

The test coffee product used in the studies was Coffee Slender® (Med-Eq Ltd, Tønsberg, Norway), packed in sachets each containing 2200 mg instant coffee (equal parts of Arabica and Robusta coffees). A total of 200 mg per 2200 mg of the Coffee Slender® product comprises an extract of green coffee, obtained by a traditional process, from the beans of *Coffea canephora robusta* Pierre (Svetol®; Berkem SA, Gardonne, France). This is particularly rich in chlorogenic acids (45 – 50% by weight [90 – 100 mg]), with equal

amounts of the three isomers, 5-, 4- and 3-caffeoylquinic acid. The extraction process is performed with alcohol as the solvent and the extract contains < 2% caffeine, and is also virtually free from cafestol and kahweol; as mentioned earlier these latter two substances might be linked to the cholesterol raising effect of coffee.

Nescafé® Gold Norwegian blend (caffeinated) and Nescafé® Gold Norwegian blend decaffeinated instant coffee (Nestlé, Vevey, Switzerland) were used as the comparative products. The content of chlorogenic acids is the same in both these coffees, the literature indicating that instant coffees contain 30 – 40 mg/g of chlorogenic acid.[13]

STUDY 1

Study 1 investigated the effects of a single drink of the different coffee products on the absorption of glucose.

Volunteer recruitment, study design and treatment

The volunteers recruited into the study were healthy non-smokers, of normal weight (body mass index [BMI] < 25.0 kg/m^2) and not taking any drugs on a regular basis for the treatment of chronic diseases.

The study was designed as a three-way double-blind randomized crossover study with each subject serving as his or her own control. The coffee products used were packed in similar boxes in order to keep the study blind. The different treatment regimes were: (i) 25 g of sucrose in 400 ml of water (control); (ii) 25 g of sucrose and 10 g of Coffee Slender® in 400 ml water; (iii) 25 g of sucrose and 10 g of normal instant coffee (Nescafé® Gold Norwegian blend) in 400 ml water; and (iv) 25 g of sucrose and 10 g of decaffeinated instant coffee (Nescafé® Gold Norwegian blend) in 400 ml water.

After overnight fasting an oral glucose tolerance test (control) was performed on all the volunteers. Glucose levels were followed for 2 h after intake with measurement at 15, 30, 45, 60, 90 and 120 min and they were then immediately randomized to one of the treatments, with glucose levels again followed for 2 h after intake with measurement at 15, 30, 45, 60, 90 and 120 min. There was a 1-week washout period between the different treatments, intake was always performed after an overnight (12 h) fast, the fasting glucose level was measured each time prior to treatment, and glucose levels were always followed for 2 h after each treatment and measured at 15, 30, 45, 60, 90 and 120 min.

All participants gave written informed consent before entering the study. A regional ethics committee (REK East) approved the study, which was conducted according to the principles of the Declaration of Helsinki, good clinical practice and local regulations.

Statistical analysis

Data were analysed by calculating the total area under the curve (AUC) using the linear trapezoidal rule. Significant differences between plasma concentrations of glucose were measured by using two-factor repeated measures analysis of variance (ANOVA). A P-value < 0.05 was considered to be statistically significant.

STUDY 2

Study 2 was carried out to evaluate the effect of several drinks of Coffee Slender® compared with the effect of several drinks of normal instant coffee on weight when taken as part of a regular diet in slight to moderately overweight volunteers.

Volunteer recruitment, study design and treatment

The volunteers recruited into the study were

slightly to moderately overweight (BMI 27.5 – 32.0 kg/m^2) non-smokers not taking any drugs on a regular basis for the treatment of chronic diseases. They had been drinking coffee daily before the study. All the volunteers were asked to follow the same life-style that they had prior to entering the study and not to commence other weight loss programmes whilst participating in the study. They did not receive any information on diet and were also told to maintain their current physical exercise programme.

The study was designed as a randomized, placebo-controlled study. Half of the volunteers drank Coffee Slender® [five cups (sachets)/day (11 g/day of coffee)] while the other half drank normal Nescafé® Gold Norwegian blend instant coffee [five cups/day (11 g/day of coffee)]. The coffee in both groups was taken black. The duration of the study was 12 weeks and the volunteers were also followed-up after 1 and 3 months.

Anthropometric measurements, including height, mass and body fat composition were made initially, and mass and body fat composition measurements were repeated at the two follow-up visits. The body mass of the subjects wearing ordinary light indoor clothing without shoes was measured to an accuracy of 0.1 kg and height was measured to the nearest 0.5 cm. Body fat was measured using bioimpedance equipment.

All volunteers gave written informed consent before entering the study. A regional ethics committee (REK East) approved the study, which was conducted according to the principles of the Declaration of Helsinki, good clinical practice and local regulations.

Statistical analysis

Data were presented as means ± SD. Student's *t*-test (parametric test) or the Mann–Whitney test (non-parametric test) were used to compare differences between values. Differences with a *P*-value < 0.05 were considered to be statistically significant.

Results

STUDY 1

Twelve healthy volunteers participated in this study (six females, six males) with a mean ± SD age of 24.2 ± 3.2 years and normal weight (BMI < 25.0 kg/m^2).

The mean plasma concentrations of glucose after consumption of the four beverages are shown in Table 1, and mean ± SE data for AUC are shown in Table 2. The AUC was 778 ± 10.2 mmol/l per min after intake of the control, 724 ± 8.2 mmol/l per min after intake of Coffee Slender®, 788 ± 10.1 mmol/l per min after intake of normal Nescafé® Gold Norwegian blend instant (caffeinated) coffee and 818 ± 10.9 mmol/l per min after intake of Nescafé® Gold Norwegian blend instant decaffeinated coffee. The reduction in AUC after intake of

TABLE 1
Mean plasma glucose concentrations (mmol/l) following intake of four different beverages by 12 healthy volunteers

	Time after intake (min)						
Beverage	0	15	30	45	60	90	120
Glucose solution (control)	5.48	7.00	8.36	7.48	6.50	5.76	5.25
Coffee Slender®	5.23	5.82	6.50	7.50	6.23	5.76	5.00
Nescafé® instant coffee (caffeinated)	5.48	5.23	6.10	7.80	8.25	6.40	5.40
Nescafé® decaffeinated coffee	5.50	6.60	7.70	8.40	7.30	6.60	5.80

TABLE 2
Mean ± SE area under the curve (AUC) data for plasma glucose concentration over the 120 min study period following intake of four different beverages by 32 healthy volunteers

	Glucose solution (control)	Coffee Slender®	Nescafé® instant coffee (caffeinated)	Nescafé® decaffeinated coffee
Plasma glucose AUC	778 ± 10.2	724 ± 8.2[a]	788 ± 10.1	818 ± 10.9

[a]$P < 0.05$ compared with control.

Coffee Slender® was, therefore, significantly reduced compared with after intake of the control beverage ($P < 0.05$). No significant effects were seen compared with the control after intake of normal instant coffee or decaffeinated instant coffee.

STUDY 2

Thirty volunteers (BMI 27.5 – 32.0 kg/m^2) were enrolled in this study; 15 received the Coffee Slender® and the others received the normal instant coffee (Nescafé® Gold Norwegian blend).

Table 3 presents the anthropometric parameters for the two groups of participants, which reveals that both groups were comparable at the start of the study with respect to the parameters of interest.

TABLE 3
Mean ± SD anthropometric parameters for overweight volunteers taking Coffee Slender® (total 11 g/day) or Nescafé® instant coffee (total 11 g/day) for 12 weeks

Group	No. of volunteers	Start weight (kg)	BMI (kg/m^2)	Height (cm)	Gender
Coffee Slender®	15	85.2 ± 4.5	29.2 ± 2.5	171 ± 5.2	8F/7M
Nescafé® instant coffee (caffeinated)	15	84.3 ± 4.3	29.9 ± 2.4	168 ± 4.3	10F/5M

BMI, body mass index.

TABLE 4
Mean ± SD weight for overweight volunteers taking Coffee Slender® (total 11 g/day) or Nescafé® instant coffee (total 11 g/day) for 12 weeks

	Weight (kg)				
Group	Start	Week 4	Week 12	Difference (start – week 12)	P-value
Coffee Slender®	85.2 ± 4.5	83.6 ± 4.1	79.8 ± 3.9	5.4 ± 0.6	$P < 0.05$[a]
Nescafé® instant coffee (caffeinated)	84.3 ± 4.3	83.7 ± 4.1	82.6 ± 4.2	1.7 ± 0.9	NS

[a]The difference in weight loss between the two groups was statistically significant ($P < 0.05$) and the weight loss in the Coffee Slender® group (start – week 12) was also statistically significant ($P < 0.05$).
NS, not significant ($P \geq 0.05$).

TABLE 5
Mean ± SD percentage of body fat for overweight volunteers taking Coffee Slender® (total 1.1 g/day) or Nescafé® instant coffee (total 1.1 g/day) for 12 weeks

	Body fat (%)				
Group	Start	Week 4	Week 12	Difference (start – week 12)	*P*-value
Coffee Slender®	27.2 ± 2.0	25.6 ± 1.8	23.6 ± 1.7	3.6 ± 0.3	$P < 0.05$
Nescafé® instant coffee (caffeinated)	26.9 ± 2.1	26.7 ± 2.0	26.2 ± 2.0	0.7 ± 0.4	NS

[a]The difference in loss of body fat between the two groups was statistically significant ($P < 0.05$) and the loss in the Coffee Slender® group (start – week 12) was also statistically significant ($P < 0.05$).
NS, not significant ($P \geq 0.05$).

Results from the weight study (Table 4) show that the mean ± SD weight reductions for Coffee Slender® and normal instant coffee drinkers were 5.4 ± 0.6 and 1.7 ± 0.9 kg, respectively. The difference in weight loss between the two groups was statistically significant ($P < 0.05$) and the weight loss in the Coffee Slender® group by the end of study was also statistically significant ($P < 0.05$) compared with the start.

During the study, the percentage of body fat in the Coffee Slender® group showed a statistically significant reduction from 27.2% at the start to 23.6% at the end of the study. This means that approximately 80% of the weight reduction in the Coffee Slender® group was due to loss of fat. Body fat reduction in the group using instant coffee did not reach statistical significance (Table 5).

All the participants completed the study according to the protocol. The tolerability was equally good in both groups and none of the participants reported any side-effects that could be related to the treatment they received.

Discussion

Obesity and overweight are serious health problems in most industrialized countries and different programmes have been launched over the past decade to try and cope with it. Despite these, however, the average body weight of both males and females is still increasing. Weight problems can have a negative impact on quality of life and, in the case of obesity, can even lead to a significant reduction in life expectancy. With the exception of serious neuroendocrine pathologies, weight problems are mainly due to lifestyle.

There is a link between the amount of dietary carbohydrates and the amount of fat found in the adipose reserves. This is because carbohydrates are responsible for most calorific intake in the diet and their intake in the form of sugars reduces the need for calorific consumption from reserves as a result of normal insulin production and activity, ensuring that they are metabolized first and not stored in the body. On the other hand, if the amount of glucose in the blood is in excess of what is required and hepatic glycogenesis occurs, the excess glucose enters into the adipocytes where it is stored as fat reserves (activated by insulin in response to hyperglycaemia). The consequences are that the fat reserves are not used for energy and an increase in adipocytes takes place.

During dieting, the lower intake of carbohydrates forces the metabolism of fat reserves deposited in the adipocytes,

resulting in weight loss. It is possible to improve the effects of reduced consumption of carbohydrate by exploiting hepatic activity to regulate the glycaemia level. When blood glucose is < 1 g/l, the liver uses hexokinase to synthesize glucose-6-phosphate, which is then hydrolysed by means of glucose-6-phosphatase, resulting in the release of glucose into the bloodstream (glycogenolysis). Fatty deposits do not increase in this situation but are, instead, used for energy production.

The aim of our second study was to evaluate whether chlorogenic acid enriched Coffee Slender® (which is particularly rich in chlorogenic acids, including 5-caffeoylquinic acid) could reduce the weight of overweight volunteers by causing the burning-off of fat, as has been suggested by *in vitro* studies in which inhibition of hepatic glucose-6-phosphatase activity by 5-caffeoylquinic acid has been shown.[11,12]

The significant decrease in body weight and fat percentage with Coffee Slender® compared with conventional instant coffee could be due to an increase in the consumption of fatty deposits, as shown by a change in the fat mass percentage, and the prevention of fatty deposits being accumulated, as discussed above.

Chlorogenic acid might act by inhibiting glucose absorption in the small intestine.[10] In addition, inhibition of the activity of glucose-6-phosphatase[11,12] would limit the release of glucose into the general circulation[15,16] and, therefore, limit insulinaemia. This would lead to fewer fatty deposits in the adipose tissue through harder access into the adipose cells owing to reduced insulin activity and the consumption of fat reserves, due to the reduced availability of glucose as an energy source.

This proposed mechanism, however, depends on the bioavailability of chlorogenic acid (5-caffeoylquinic acid). Recently, its fate and metabolism were explored to determine the form under which this ester of caffeic acid is absorbed through different parts of the gastrointestinal tract of rats.[17] Analysis of gastrointestinal contents indicated that chlorogenic acid was stable in the stomach and the small intestine, but was cleaved into caffeic acid by microflora in the caecum.[17] Consequently, the stability of chlorogenic acid in the small intestine is coherent with glucose absorption inhibition in this part of the gut. Moreover, whereas it was shown that chlorogenic acid was hydrolysed into enterocytes before secretion on the serosal side,[18] it was absorbed intact from the stomach[17] and was found in the gastric vein and aorta without conjugation. These results suggest that chlorogenic acid is able to enter the liver without modification, which is in accordance with its inhibitory activity on hepatic glucose-6-phosphatase. These bioavailability studies on chlorogenic acid thus support the proposed mechanism of action outlined above. These findings are also consistent with recent studies of a link between chlorogenic acid and body mass in mice, which concluded that chlorogenic acid can prevent an increase in body mass and accumulation of fat.[19]

Published studies show that caffeine intake may lead to a small reduction in long-term weight gain.[20] This effect is probably due to the known thermogenetic effect of caffeine intake as well the effect of chlorogenic acid and other pharmacologically active substances known to be present in coffee. Coffee has been shown to have positive effects on several glycaemia markers: consumption is significantly and inversely associated with impaired fasting glucose, impaired glucose regulation and hyperinsulinaemia in elderly men and women.[21]

Any place that coffee products may have in future treatments for overweight and obesity will also depend on the clinical conclusions to be drawn from studies examining the association between coffee and myocardial infarction in individuals with 'slow' caffeine metabolism.[22] The risk factor might be as high as 60% in the total Caucasian population. Chlorogenic acid might also be partly responsible for raised homocysteine concentrations that have been observed in coffee drinkers.[23] Whether these effects on homocysteine influence cardiovascular disease risk remains to be established. It seems, however, that the chlorogenic acid in green coffee bean extract does not have the same effect on homocysteine.[24]

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Conflicts of interest

No conflicts of interest were declared in relation to this paper.

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