# Acute Effects of Decaffeinated Coffee and the Major Coffee Components Chlorogenic Acid and Trigonelline on Glucose Tolerance

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**OBJECTIVE** — Coffee consumption has been associated with lower risk of type 2 diabetes. We evaluated the acute effects of decaffeinated coffee and the major coffee components chlorogenic acid and trigonelline on glucose tolerance.

**RESEARCH DESIGN AND METHODS** — We conducted a randomized crossover trial of the effects of 12 g decaffeinated coffee, 1 g chlorogenic acid, 500 mg trigonelline, and placebo (1 g mannitol) on glucose and insulin concentrations during a 2-h oral glucose tolerance test (OGTT) in 15 overweight men.

**RESULTS** — Chlorogenic acid and trigonelline ingestion significantly reduced glucose (−0.7 mmol/l, $P = 0.007$, and −0.5 mmol/l, $P = 0.024$, respectively) and insulin (−73 pmol/l, $P = 0.038$, and −117 pmol/l, $P = 0.007$) concentrations 15 min following an OGTT compared with placebo. None of the treatments affected insulin or glucose area under the curve values during the OGTT compared with placebo.

**CONCLUSIONS** — Chlorogenic acid and trigonelline reduced early glucose and insulin responses during an OGTT.

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In prospective cohort studies, higher coffee consumption has been associated with a lower risk of type 2 diabetes (1,2). Associations have been similar for caffeinated and decaffeinated coffee (1,3–5), suggesting that coffee components other than caffeine have beneficial effects on glucose homeostasis. Coffee is a major source of the phenolic compound chlorogenic acid (6) and the vitamin B3 precursor trigonelline (7), which have been shown to reduce blood glucose concentrations in animal studies (5–8). This is the first study to investigate the acute effects of chlorogenic acid and trigonelline on glucose tolerance in humans.

## RESEARCH DESIGN AND METHODS

Fifteen male, healthy, nonsmoking, overweight (BMI 25.0–35.0 kg/m$^2$) coffee consumers were enrolled. All subjects provided written informed consent.

Subjects were randomly assigned to a unique treatment order through computer-generated randomization by the pharmacy. Four supplements were tested in this crossover trial: 12 g decaffeinated coffee (Nescafé Gold, Nestlé, the Netherlands), 1 g chlorogenic acid (Sigma Aldrich, Switzerland), 500 mg trigonelline (Sigma Aldrich), and 1 g mannitol as placebo (Spruyt Hillen Bufa, the Netherlands). Based on laboratory measurements (9,10), the decaffeinated coffee used in our study provided 264 mg chlorogenic acid and 72 mg trigonelline. All supplements were dissolved in 270 ml water, and treatments except for decaffeinated coffee were double blind. Starting 1 week before the trial, participants were requested to restrict their coffee consumption to maximally one cup per day, and on the days before each study visit no coffee was allowed.

The study consisted of four visits separated by at least 6 days. During each visit, participants ingested one of the supplements 30 min before a 75-g oral glucose tolerance test (OGTT). Seven venous blood samples were taken via a cannula in the antecubital vein on each visit following an overnight fast. The first blood sample was taken 30 min before the start of the OGTT, immediately followed by ingestion of the supplement. The second blood sample was taken just before the OGTT, and the other samples were taken 15, 30, 60, 90, and 120 min after the start of the OGTT.

Laboratory analyses were conducted at the VU University Medical Center. Plasma glucose concentrations were measured using the glucose hexokinase method with an interassay coefficient of variation (CV) of 1.3% (Roche Diagnostics, Mannheim, Germany). Serum insulin concentrations were measured using an immunoradiometric assay (Bayer Diagnostics, Mijdrecht, the Netherlands); the intra-assay CV was 4%, and the interassay CV was 8%.

The area under the curve values for glucose and insulin were calculated using the trapezoidal method. Main treatment effects were analyzed using linear mixed regression models. Comparisons of mean glucose and insulin concentrations for individual time points were conducted using paired *t* tests. All tests were two-sided, and $P$ values <0.05 were considered statistically significant. Analyses were conducted using SPSS (version 15.0).

## RESULTS

The participants had a mean ± SD age of 39.9 ± 16.5 years and a mean BMI of 27.6 ± 2.2 kg/m$^2$. There

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**Table 1—*Glucose and insulin concentrations during an OGTT following ingestion of chlorogenic acid, decaffeinated coffee, trigonelline, or placebo in 15 healthy overweight men***

| | Glucose (mmol/l) | | | | | | | | Insulin (pmol/l) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | −30 min | Time 0 | 15 min | 30 min | 60 min | 90 min | 120 min | AUC (mmol/l × 120 min) | −30 min | Time 0 | 15 min | 30 min | 60 min | 90 min | 120 min | AUC (pmol/l × 120 min) |
| Placebo | 5.7 ± 0.2 | 5.6 ± 0.2 | 7.7 ± 0.3 | 8.8 ± 0.5 | 8.7 ± 0.7 | 8.1 ± 0.7 | 6.8 ± 0.6 | 962 ± 134 | 70.3 ± 9.9 | 63.3 ± 9.1 | 384.0 ± 48.9 | 572.7 ± 79.7 | 513.6 ± 71.0 | 489.5 ± 94.6 | 367.5 ± 98.1 | 54,727 ± 21,658 |
| Chlorogenic acid | 5.5 ± 0.1 | 5.5 ± 0.1 | 7.0 ± 0.2* | 8.6 ± 0.3 | 8.2 ± 0.6 | 7.4 ± 0.7 | 6.9 ± 0.6 | 912 ± 134 | 67.0 ± 9.6 | 56.7 ± 10.1* | 310.7 ± 55.7* | 491.2 ± 74.6 | 521.1 ± 101.2 | 480.2 ± 142.2 | 407.2 ± 118.0 | 52,285 ± 21,658 |
| Decaffeinated coffee | 5.6 ± 0.2 | 5.6 ± 0.1 | 7.6 ± 0.2 | 9.2 ± 0.3 | 8.9 ± 0.7 | 7.7 ± 0.7 | 6.6 ± 0.7 | 958 ± 134 | 63.3 ± 9.6 | 65.0 ± 9.9 | 331.6 ± 34.4 | 511.9 ± 51.7 | 535.5 ± 73.5 | 463.5 ± 106.8 | 358.4 ± 111.9 | 52,324 ± 21,658 |
| Trigonelline | 5.6 ± 0.1 | 5.5 ± 0.1 | 7.2 ± 0.2* | 9.0 ± 0.3 | 8.7 ± 0.5 | 7.9 ± 0.6 | 6.9 ± 0.6 | 952 ± 134 | 61.6 ± 7.6 | 53.9 ± 9.5 | 267.0 ± 27.5* | 501.0 ± 82.0 | 580.3 ± 113.6 | 495.6 ± 83.3 | 361.3 ± 91.2 | 53,380 ± 21,658 |

Data are means ± SE unless otherwise indicated. Baseline values are fasting concentrations and were determined right before supplement ingestion; Time 0 was half an hour after supplement ingestion and right before the start of the OGTT. *$P < 0.05$ using paired $t$ tests compared with the placebo value. AUC, area under the curve.

were no drop-outs during the trial, and no adverse events were reported.

Glucose concentrations tended to be lower after chlorogenic acid ingestion compared with those after placebo (Table 1), but this difference was only statistically significant 15 min after the start of the OGTT (difference 0.69 mmol/l [95% CI 0.22–1.17]; $P = 0.007$). In addition, the mean insulin concentration was 6.6 pmol/l (95% CI 0.11–13.0; $P = 0.047$) lower at the start of the OGTT and 73.3 pmol/l (4.7–142.0; $P = 0.038$) lower at 15 min for chlorogenic acid compared with placebo.

Trigonelline also resulted in significantly lower glucose (−0.51 mmol/l [95% CI −0.95 to −0.08]; $P = 0.024$) and insulin (−117.0 pmol/l [−196.5 to −37.4]; $P = 0.007$) concentrations at 15 min after the start of the OGTT compared with placebo. Decaffeinated coffee did not significantly change mean glucose or insulin concentrations at any of the time points following the OGTT, although the insulin concentration tended to be lower at 15 min. None of the treatments significantly changed the insulin or glucose area under the curve values (Table 1).

**CONCLUSIONS**— In this randomized crossover trial in healthy men, chlorogenic acid and trigonelline ingestion led to significantly lower glucose and insulin concentrations 15 min after an oral glucose load but did not significantly reduce the OGTT insulin and glucose areas under the curve compared with placebo.

Battram et al. (11) found a significantly lower OGTT glucose area under the curve after decaffeinated coffee compared with that after placebo, but no significant effect was found in the current study or two smaller previous studies (12, 13). Further research is needed to elucidate whether these differences in study results are due to chance or to differences in study methods. Trigonelline (5) and chlorogenic acid (6–8) have been shown to reduce blood glucose concentrations in rats, but data in humans are sparse. In a study of 10 diabetic patients, intake of 500 mg trigonelline had mixed and nonsignificant effects on glucose concentrations (9).

Several mechanisms have been suggested for effects of chlorogenic acid on glucose metabolism. In vitro, chlorogenic acid has been shown to inhibit α-glucosidase and glucose-6-phosphatase, suggesting that it may delay intestinal glucose uptake (8,14). This effect could also reduce postprandial hyperglycemia through improved glucose-induced insulin secretion as a result of increased glucagon-like peptide-1 secretion (12). Inhibition of glucose-6-phosphatase could also reduce hepatic glucose output (15), which may have contributed to the reduction of fasting insulin concentrations that we found for chlorogenic acid.

In our study, the multiple tests conducted for different time points increased the likelihood of chance findings, and confirmation of our results is therefore needed. In addition, the decaffeinated coffee supplement contained substantially less chlorogenic acid and trigonelline than the doses administered in isolation, complicating the comparison of the treatment effects.

In conclusion, chlorogenic acid and trigonelline reduced early glucose and insulin responses during the OGTT. This finding is consistent with the hypothesis that these compounds contribute to the putative beneficial effect of coffee on development of type 2 diabetes.

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