

Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine¹⁻³

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ABSTRACT

Background: Accumulating evidence suggests that certain dietary polyphenols have biological effects in the small intestine that alter the pattern of glucose uptake. Their effects, however, on glucose tolerance in humans are unknown.

Objective: The objective was to investigate whether chlorogenic acids in coffee modulate glucose uptake and gastrointestinal hormone and insulin secretion in humans.

Design: In a 3-way, randomized, crossover study, 9 healthy fasted volunteers consumed 25 g glucose in either 400 mL water (control) or 400 mL caffeinated or decaffeinated coffee (equivalent to 2.5 mmol chlorogenic acid/L). Blood samples were taken frequently over the following 3 h.

Results: Glucose and insulin concentrations tended to be higher in the first 30 min after caffeinated coffee consumption than after consumption of decaffeinated coffee or the control ($P < 0.05$ for total and incremental area under the curve for glucose and insulin). Glucose-dependent insulinotropic polypeptide secretion decreased throughout the experimental period ($P < 0.005$), and glucagon-like peptide 1 secretion increased 0–120 min postprandially ($P < 0.01$) after decaffeinated coffee consumption compared with the control. Glucose and insulin profiles were consistent with the known metabolic effects of caffeine. However, the gastrointestinal hormone profiles were consistent with delayed intestinal glucose absorption.

Conclusions: Differences in plasma glucose, insulin, and gastrointestinal hormone profiles further confirm the potent biological action of caffeine and suggest that chlorogenic acid might have an antagonistic effect on glucose transport. Therefore, a novel function of some dietary phenols in humans may be to attenuate intestinal glucose absorption rates and shift the site of glucose absorption to more distal parts of the intestine. *Am J Clin Nutr* 2003;78:728–33.

KEY WORDS Caffeine, caffeoylquinic acids, chlorogenic acids, coffee, glucose-dependent insulinotropic polypeptide, GIP, glucagon-like peptide 1, GLP-1, glucose tolerance, glycemic effects, insulin, phenolic acids, polyphenols

INTRODUCTION

Coffee contains a multitude of substances, many of which are potentially biologically active (1), although the main physiologic effects resulting from its consumption are usually ascribed to the presence of caffeine (2). However, coffee is also an extremely rich

source of chlorogenic acids (CGA) (3)—an important group of biologically active dietary phenols, the best known of which is 5-caffeoylquinic acid (5-CQA); see **Figure 1** (4). Phenolic compounds are widespread in nature and are found primarily in foods of plant origin (5). The daily intake of CGA by coffee drinkers ranges from 0.5 to 1.0 g (3, 6). CGA exhibit antioxidant properties in vitro (7), and it is suggested that the polyphenols of higher plants may contribute to the cardioprotective effects associated with diets rich in foods of plant origin.

There is, however, a growing interest in the biological properties of phenolic compounds in addition to their antioxidant effects, and accumulating evidence suggests that certain dietary phenols, through a variety of mechanisms, may result in an altered pattern of intestinal glucose uptake. Reduced glucose transport as a consequence of exposure to phenolic compounds was first shown in 1922 by Nakazawa (8) using phloridzin (phloretin 2'-O- β -D-glucoside). More recently, a phenolic acid-mediated decrease in intestinal brush border membrane (BBM) D-glucose uptake (9) and a flavonoid-mediated inhibition of sodium-dependent vitamin C transporter 1 and facilitated glucose transporter 2—intestinal transporters for vitamin C and glucose, respectively (10)—have been shown. Moreover, Andrade-Cetto et al (11) showed that extracts prepared from the leaves of *Cecropia obtusifolia*, a plant traditionally used for the treatment of diabetes, lowered plasma glucose concentrations in streptozotocin-induced diabetic rats to a concentration comparable with that of the reference compound glibenclamide (11). The main constituents in these extracts have been identified with the use of the preferred nomenclature of the International Union of Pure and Applied Chemistry (4) as 5-CQA, the major CGA of coffee.

Few data exist on the absorption and bioavailability of CGA in humans. However, Olthof et al (6) showed that 33% of a 2.8-mmol load of CGA was absorbed by ileostomy patients. This suggests

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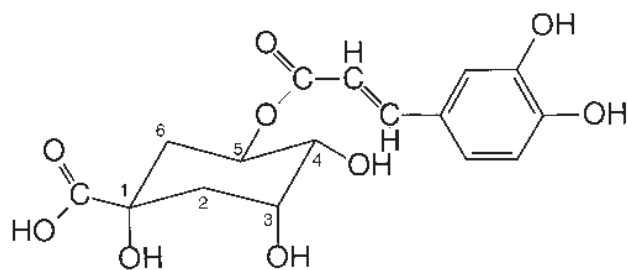


FIGURE 1. Structure of 5-caffeoylquinic acid, which shows the preferred IUPAC (International Union of Pure Applied Chemistry) numbering for the quinic acid residue.

that a certain amount of dietary CGA will enter into the blood circulation via absorption from the small intestine, possibly via interaction with one or more of the BBM transporters. The direct measurement of plasma glucose concentrations in addition to the quantification of certain gastrointestinal hormones could provide insight into the mechanism by which CGA exert their possible hypoglycemic effects because many gastrointestinal hormones are secreted only in response to the active absorption of glucose via sodium-dependent glucose transporter 1 (12). Thus, the aim of this study was to investigate whether coffee consumption modulates glucose uptake in healthy volunteers and, if so, whether there are consequential effects on circulating gastrointestinal hormones and insulin concentrations.

SUBJECTS AND METHODS

Subjects

The study was approved by the University of Surrey Ethics Committee (ACE/2000/66/SBLS), and subjects were recruited from within the School of Biomedical and Life Sciences. Subjects were excluded if they had a body mass index (in kg/m²) > 25, had a significant current or previous medical history, were regularly taking medication (other than oral contraceptives) that may have affected the gastrointestinal or central nervous system, consumed > 20 units alcohol/wk, smoked, or had donated blood within the 4–6 mo before the study began. Nine volunteers (4 men and 5 women) with a mean (\pm SD) age of 26 ± 3.2 y were admitted to participate after they were interviewed and gave their written consent.

General procedure

The study design was a 3-way, single-blind, randomized, crossover with each subject serving as his or her own control. On 3 separate occasions, subjects were required to come to the clinical investigation unit at 0800 after having fasted overnight beginning at 2000. The subjects were asked to refrain from strenuous exercise and to not consume alcohol or caffeine the night before each study day. They were also asked to consume a diet high in carbohydrate (> 200 g) on the day before the study; a sample menu was provided to them. On arrival at the clinical investigation unit, an intravenous cannula was inserted into a forearm (antecubital) vein, and a baseline blood sample was taken. The subjects then consumed one of three 400-mL beverages:

caffeinated coffee, decaffeinated coffee, or glucose dissolved in water (control). Blood samples were taken at frequent intervals for the following 3 h.

Standardization of test beverages

Nine brands of caffeinated coffee and 6 brands of decaffeinated commercially available instant coffee granules were purchased from local retail outlets and were screened by HPLC for their contents of CQAs (*see below*). The mean (\pm SEM) amounts of 3-, 4-, and 5-CQA in the caffeinated coffees were 6.68 ± 0.85 , 6.97 ± 0.86 , and 10.79 ± 1.76 mg/g and in the decaffeinated coffees were 6.73 ± 0.44 , 7.666 ± 0.51 , and 10.03 ± 0.62 mg/g. The amounts of 3-, 4-, 5-, and total CQA in the caffeinated (Nescafé Kenjara; Nestlé Consumer Services, York, United Kingdom) and decaffeinated (Nescafé decaffeinated; Nestlé Consumer Services) brands chosen for use in the study were 10.60 and 8.26, 10.65 and 9.27, 19.96 and 11.91, and 41.22 and 29.44 mg/g, respectively. The coffee granules were weighed (within ± 0.01 mg) and dissolved together with 25 g glucose into 200 mL boiling water. This was then made up to a final volume of 400 mL with the use of water and left to equilibrate to room temperature. The final concentration of total CQA in the test beverages was 2.50 mmol/L. The control beverage consisted of 25 g glucose dissolved in 400 mL water.

Chemical analysis of commercial instant coffee granules

Briefly, 100 mg instant coffee powder was dissolved into 10 mL Milli-Q water (Millipore Systems, Bedford, MA) and was vigorously mixed by vortex until the granules had dissolved. This was then treated with Carrez reagent (0.5 mL A plus 0.5 mL B) and centrifuged at $1200 \times g$ for 20 min at 4°C to remove all colloidal matter (13). The clarified samples were then diluted 1 in 4 with Milli-Q water and analyzed with the use of a gradient HPLC system consisting of a Spectra Physics P4000 gradient pump (San Jose, CA) coupled to an AS3000 autosampler (ThermoFinnigan, San Jose, CA) with detection by Spectra Physics UV2000 ultraviolet-visible detector monitoring at 280 and 315 nm. Chromatographic and spectral data collection and integration were performed with the use of Spectra Focus software, and external standard calibration curves were prepared with the use of 5-CQA (Sigma-Aldrich, Poole, United Kingdom). Separation was achieved on a 250-mm \times 4.6-mm column packed with Spherisorb 5 μ ODS-2 (HiChrom Ltd, Theale, United Kingdom) with the use of the following gradient: solvent A (0.5% trifluoroacetic acid in water) linearly to solvent B (a mixture of acetonitrile and solvent A; 45:55 by vol) in 45 min, with 10 min to reset.

Blood samples

Blood samples were collected into heparin-containing tubes containing 200 KIU/mL aprotinin (Sigma Chemical Laboratories Ltd, Poole, United Kingdom) for the analysis of insulin, glucose-dependent insulintropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1) and into tubes containing fluoride oxalate for glucose analysis. The samples collected for glucose and hormone analyses were centrifuged immediately at $1200 \times g$ for 10 min at 4°C, and the plasma was separated, portioned, and frozen at -20°C until analyzed.

Laboratory assays

Venous plasma glucose concentrations were analyzed with an automated enzymatic colorimetric method with the Cobas Mira

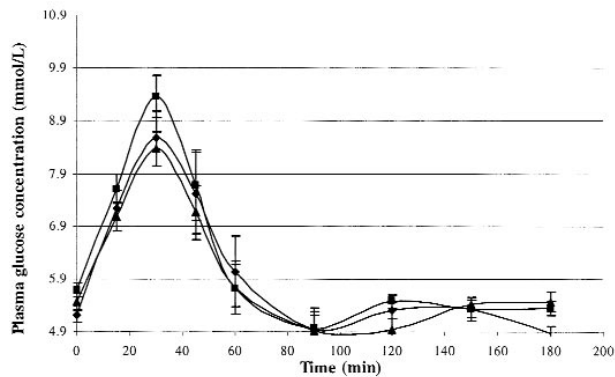


FIGURE 2. Mean (\pm SEM) plasma glucose concentrations after consumption of the control beverage (\blacklozenge), caffeinated coffee (\blacksquare), or decaffeinated coffee (\blacktriangle). There were no significant differences between the control and treatment groups by two-factor repeated-measures ANOVA, $P > 0.05$.

Biochemical Analyser (Roche Products Ltd, Welwyn Garden City, United Kingdom) with a glucose GOD/PAP test kit (Randox Laboratories, Co, Antrim, United Kingdom). Plasma immunoreactive insulin, GIP, and GLP-1 concentrations were measured in unextracted plasma by double-antibody radioimmunoassays with the use of polyclonal antisera; the radioimmunoassays are described in detail elsewhere (14). Limits of assay detection were as follows: 16 pmol/L for insulin, 16 pmol/L for GIP, and 6 pmol/L for GLP-1. The interassay CVs for glucose and hormone measurements were as follows: 2% and 3% for glucose, 6% and 10% for insulin, 20% and 7% for GIP, and 18% and 19% for GLP-1 in plasma obtained from fasting and postprandial samples, respectively.

Statistical analyses

Statistical analysis of the results was performed by using STATISTICA for WINDOWS (1997; StatSoft, Inc, Tulsa, OK). Total area under the curve (TAUC) and incremental AUC (IAUC) responses were calculated by using the linear trapezoidal rule, and significant differences were measured by using two-factor repeated-measures analysis of variance (ANOVA). Two-factor repeated-measures ANOVA was used to compare differences between plasma concentrations of glucose, insulin, GIP, and GLP-1; differences were determined by using Tukey's post hoc analysis. P values < 0.05 were considered significant. Results are expressed as means \pm SEMs unless otherwise stated.

RESULTS

Plasma concentrations of glucose, insulin, GIP, and GLP-1 after consumption of the 3 beverages are shown in Figures 2–5 and in Tables 1 and 2. Two-factor repeated measures ANOVA over the entire time course of the experiment showed no significant differences in plasma glucose concentrations between treatments (Figure 2). However, significant differences in the absolute glucose response were seen over the first 30 min after beverage consumption when a comparison of TAUCs was made ($P < 0.05$). Post hoc analysis showed plasma glucose concentrations to be higher after consumption of the caffeinated coffee than after consumption of both the control beverage and the decaffeinated coffee (Table 1).

TABLE 1

Total area under the curve (TAUC) and incremental AUC (IAUC) integrated responses for glucose, insulin, and glucose-dependent insulintropic polypeptide (GIP) from 0 to 30 min after consumption of the control beverage, caffeinated coffee, or decaffeinated coffee¹

		Coffee	
	Control beverage	Caffeinated	Decaffeinated
TAUC			
Plasma glucose (mmol/L)	212.0 ± 7.3 ^a	227.1 ± 6.9 ^b	210.2 ± 6.6 ^a
Plasma insulin (pmol/L)	5322 ± 342	5702 ± 611	4520 ± 270
Plasma GIP (pmol/L)	3760 ± 350 ^c	3073 ± 426 ^b	2327 ± 391 ^a
IAUC			
Plasma glucose (mmol/L)	55.6 ± 6.8	56.4 ± 5.1	46.2 ± 5.2
Plasma insulin (pmol/L)	4462 ± 341 ^{a,b}	4782 ± 578 ^b	3730 ± 256 ^a
Plasma GIP (pmol/L)	2130 ± 308 ^b	1596 ± 224 ^{a,b}	1101 ± 281 ^a

¹ $\bar{x} \pm$ SEM; $n = 9$. Means with different superscript letters are significantly different, $P < 0.05$ (one-way ANOVA with a Tukey's post hoc test).

Two-factor repeated-measures ANOVA showed no significant treatment effect between the means of plasma insulin concentrations after consumption of either coffee beverage compared with the control beverage and no treatment-by-time interaction (Figure 3). However, a significant difference in the relative insulin response was seen in the IAUC from 0 to 30 min ($P < 0.05$). Post hoc analysis showed plasma insulin concentrations to be higher after consumption of the caffeinated coffee than after the decaffeinated coffee (Table 1).

Plasma GIP concentrations are illustrated in Figure 4. Two-factor repeated-measures ANOVA showed a significant difference between treatments over the entire 180-min time period ($P < 0.0005$) and a significant treatment-by-time interaction ($P < 0.0001$). Post hoc analysis showed GIP concentrations to be significantly higher after consumption of the control beverage than after both the caffeinated and decaffeinated coffee ($P < 0.0005$) and a trend toward lower plasma GIP concentrations ($P < 0.10$) after consumption of the decaffeinated coffee than after the caffeinated coffee. A significant difference in both the TAUC ($P < 0.0005$) and IAUC ($P < 0.01$) were observed from 0 to 30 min (Table 1). Post hoc

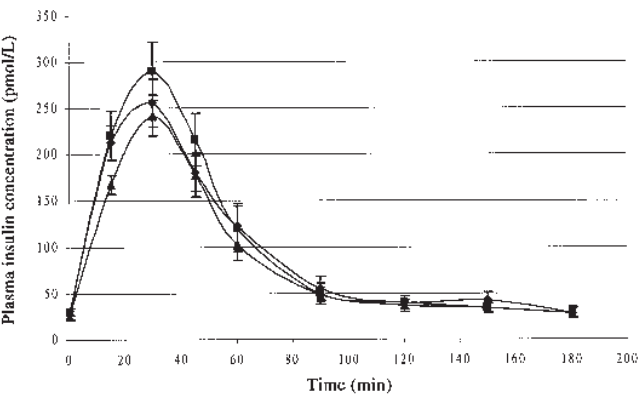


FIGURE 3. Mean (\pm SEM) plasma insulin concentrations after consumption of the control beverage (\blacklozenge), caffeinated coffee (\blacksquare), or decaffeinated coffee (\blacktriangle). There were no significant differences between the control and treatment groups by two-factor repeated-measures ANOVA, $P > 0.05$. $n = 9$.

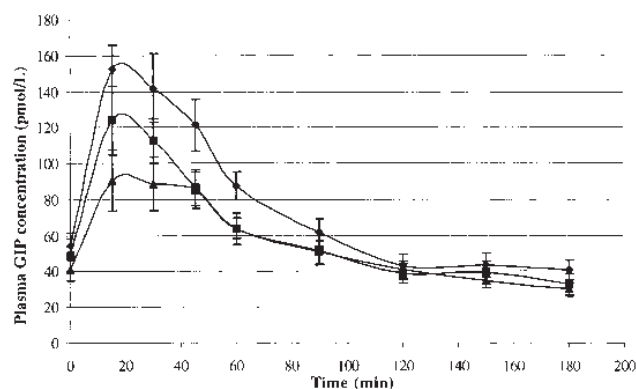


FIGURE 4. Mean (\pm SEM) plasma glucose-dependent insulinotropic polypeptide (GIP) concentrations after consumption of the control beverage (\blacklozenge), caffeinated coffee (\blacksquare), or decaffeinated coffee (\blacktriangle). There was a significant treatment effect ($P < 0.0005$) and a significant treatment-by-time interaction ($P < 0.0001$) on the basis of a two-factor repeated-measures ANOVA with a Tukey's post hoc test. $n = 9$.

analysis showed plasma GIP concentrations to be lower after both caffeinated and decaffeinated coffee consumption than after consumption of the control beverage (Table 1)

Plasma GLP-1 concentrations are illustrated in **Figure 5**. Two-factor repeated-measures ANOVA showed neither a significant treatment effect nor a treatment-by-time interaction on GLP-1 concentrations over the entire 180-min time period (Figure 5). AUC data for GLP-1 are shown in **Table 2**. Two-way ANOVA showed no significant differences in the TAUC for GLP-1, examined in 30-min increments between 0 and 120 min. However, two-way ANOVA showed a significant treatment effect in the IAUC for GLP-1 between 0 and 120 min ($P < 0.05$). Post hoc analysis showed the differences to be the result of higher concentrations of GLP-1 after consumption of decaffeinated coffee than after consumption of the control beverage ($P < 0.01$).

DISCUSSION

The objective of this study was to assess whether the consumption of dietary amounts of CGA in coffee had any effects on plasma concentrations of glucose, insulin, GIP, and GLP-1 in humans. Welsch et al (9) postulated that 5-CQA-mediated dissipation of the Na^+ electrochemical gradient was responsible for the observed decrease in glucose uptake in rat BBM vesicles; therefore, we suggest that coffee consumption in humans would have similar effects on intestinal glucose transport. This study showed that both caffeinated and decaffeinated coffee drinks significantly attenuated postprandial GIP secretion compared with the control beverage. Postprandial secretion of GIP occurs in the proximal region of the small intestine and is stimulated by the absorption of nutrients from the gut rather than by their presence in the intestinal lumen (12). The rate of absorption of glucose determines the magnitude of the GIP response (15); therefore, these data strongly suggest that coffee decreases the rate of intestinal absorption of glucose.

Glucose homeostasis is known to be achieved by a coordinated physiologic response to the ingestion of food, the 2 main effectors of which are 1) limitations on the delivery of glucose into the

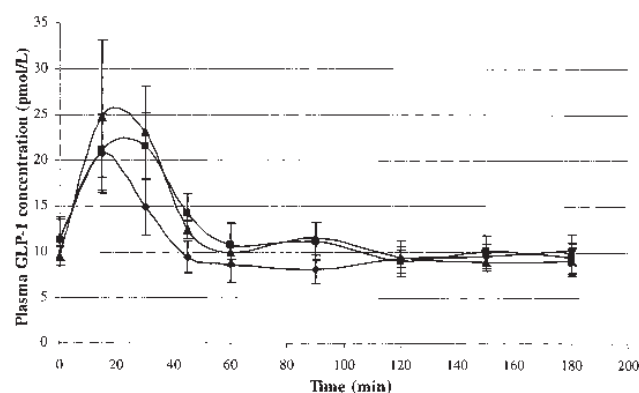


FIGURE 5. Mean (\pm SEM) plasma glucagon-like peptide 1 (GLP-1) concentrations after consumption of the control beverage (\blacklozenge), caffeinated coffee (\blacksquare), or decaffeinated coffee (\blacktriangle). There were no significant differences between the control and treatment groups by two-factor repeated-measures ANOVA. $n = 9$.

pool, ie, the maximum rate of glucose absorption, and 2) the rate of disposal of glucose into the tissues, which is itself mainly a consequence of increased insulin action (16). Up until 30 min, the increase in plasma glucose concentrations can be attributed solely to increased delivery into the circulation as a result of increased intestinal absorption in response to the load. Once this has peaked, peripheral metabolism of glucose (ie, delivery into muscle and fat tissue in addition to hepatic glucose metabolism) will have a significant effect on overall plasma concentrations and, thus, any differences seen cannot be solely attributed to effects on absorption (17). Glucose, insulin, and GIP profiles were therefore analyzed over the initial postprandial time period. Differences in GLP-1 were additionally assessed during the latter parts of the study,

TABLE 2

Total area under the curve (TAUC) and incremental AUC (IAUC) integrated responses for glucagon-like peptide 1 (GLP-1) from 0 to 30 min, 30 to 60 min, 60 to 90 min, and 90 to 120 min after consumption of the control beverage, caffeinated coffee, or decaffeinated coffee¹

	Control beverage	Coffee	
		Caffeinated	Decaffeinated
TAUC (pmol/L)			
0 to 30 min	509.4 ± 85.2	565.7 ± 72.6	619.5 ± 120
30 to 60 min	318.8 ± 61.9	455.6 ± 69.2	435.5 ± 43.9
60 to 90 min	253.9 ± 53.0	330.9 ± 64.5	323.8 ± 35.3
90 to 120 min	263.0 ± 52.2	304.4 ± 48.2	316.4 ± 42.0
IAUC (pmol/L)			
0 to 30 min	165.2 ± 80.1	262.6 ± 48.1	330.5 ± 124
30 to 60 min	−25.44 ± 32.6	116.5 ± 39.0	146.5 ± 51.3
60 to 90 min	−90.31 ± 29.8	−8.20 ± 22.16	34.79 ± 16.4
90 to 120 min	−81.24 ± 31.3	−34.66 ± 23.3	27.38 ± 16.0

¹ $\bar{x} \pm \text{SEM}$; $n = 9$. Statistical analyses were performed with the use of a two-way ANOVA with Tukey's post hoc test if $P < 0.05$. There was a significant treatment effect. There was a significant time effect ($P < 0.001$) for TAUC data. For IAUC data, there were significant treatment ($P < 0.05$) and time ($P < 0.001$) effects but no significant time \times treatment interaction. Post hoc analysis of IAUC showed significant differences between the decaffeinated coffee and the control beverage ($P < 0.01$).

because this hormone is secreted from the distal region of the small intestine (18).

Plasma glucose concentrations were significantly higher after consumption of caffeinated coffee than after consumption of the control beverage or decaffeinated coffee when a comparison of the means and of the TAUCs was made. The nature of the interaction between coffee consumption and glucose tolerance remains controversial. However, most of the physiologic effects of coffee can be attributed to the presence of caffeine (19). The physiologic effects of coffee began to receive attention when caffeine was first shown to inhibit the action of phosphodiesterase, an enzyme involved in the catabolism of cyclic adenosine monophosphate (cAMP) (20). Increased concentrations of cAMP have been shown to increase glycogenolysis, which may be partially responsible for the significantly impaired glucose tolerance seen after consumption of the caffeinated coffee compared with both the control and the decaffeinated coffee beverages. Caffeine is also an adenosine receptor antagonist (21) and therefore can inhibit muscle glucose uptake, even in the presence of insulin (22). Moreover, Sharp and Debnam (23) have shown that acute luminal exposure of enterocytes to cAMP *in vivo* has stimulatory effects on sugar transport across the BBM and the basolateral membrane, and Debnam et al (24) provided evidence for a similar effect of cAMP in the regulation of sodium-dependent glucose transporter-mediated glucose transport across isolated rat renal BBM. Taking into consideration the known actions of caffeine, we propose that the differences in plasma glucose profiles further confirm the potent pharmacologic actions of caffeine but also imply that CGA has an antagonistic effect on glucose transport, because integrated glucose concentrations were lowest after consumption of the decaffeinated coffee beverage.


Pizziol et al (25) previously suggested that caffeine causes impaired glucose tolerance by inducing a rise in blood glucose concentrations that is independent of insulin. However, these authors use the terms caffeine and coffee interchangeably and do not consider the action of other biologically active components present in coffee, namely CGA. In our study, plasma insulin concentrations showed small differences in the early part of the postprandial period, which were consistent with the mildly impaired glucose tolerance seen after consumption of the caffeinated beverage compared with the decaffeinated beverage. However, the small differences in plasma insulin observed in this study lack the statistical power to refute the claims by Pizziol et al with any confidence.

Although glucose is the major regulator of insulin secretion, incretin gut factors have been estimated to be responsible for as much as 50% of the insulin secretion observed after an oral glucose load and the term “enteroinsular axis” was introduced to encompass the gut factors responsible for this (26–28). The secretion of the incretin hormones GIP and GLP-1 were significantly altered in response to the test beverages compared with the control. GIP secretion was attenuated after consumption of both the caffeinated and decaffeinated coffees compared with that after consumption of the control beverage. GLP-1, in contrast with GIP, is secreted from the distal portion of the small intestine and responds to the presence of nutrients in the gut lumen rather than to their absorption (29). Its secretion can be increased when the absorption of carbohydrate is delayed (30). Circulating GLP-1 concentrations were significantly enhanced after consumption of decaffeinated coffee, later in the postprandial time period. These opposing effects of incretin hormones

would have minimized any effects of coffee on insulin secretion. However, the gastrointestinal hormone data are consistent with delayed glucose uptake in the small intestine, ie, uptake occurring further down the small intestine.

We suggest that at the level of the BBM, coffee exerts its physiologic effects via CGA-mediated Na⁺ electrochemical gradient dissipation—the driving force for active glucose assimilation. This is reflected in and supported by the gastrointestinal hormone profiles but not in those for plasma insulin and glucose. However, the potent biological effects of caffeine on both hepatic glucose output and muscular uptake suggest that plasma glucose and insulin concentrations are a poor biomarker when interpreting the gastrointestinal effects of coffee on glucose transport in the small intestine.

Our previous work showed that consumption of the same volume of commercial apple juice containing significant amounts of CGA (≈ 500 $\mu\text{mol/L}$) as well as other bioactive dietary phenols, such as phloridzin (≈ 60 $\mu\text{mol/L}$), significantly delays glucose uptake and shifts absorption to a more distal region of the gastrointestinal tract, as indicated by a similar change over time in plasma GIP and GLP-1 concentrations (31). Compared with the present study, in which the test beverages contained 2.5 mmol total CQA/L (the dietary equivalent of 2 small strong cups of coffee), the effects after apple juice consumption were less pronounced but not as much as would be expected if CGA were the only agent responsible given the large difference in CQA concentrations between the 2. It is therefore likely that most of the effects seen after apple juice consumption were mediated by phloridzin, a potent competitive inhibitor of sodium-dependent glucose transporter 1 and one that is commonly used in physiologic studies to abolish glucose transport (32).

Recent evidence to support the clinical effects of dietary polyphenols is provided by van Dam and Feskens (33), who showed in a prospective cohort study that the risk of developing clinical type 2 diabetes was 0.5 times as likely in individual persons who drank ≥ 7 cups (1659 mL) coffee/d than in those who drank ≤ 2 cups (474 mL) coffee/d. The results of their study strongly suggest that coffee consumption can have clinical benefits; the results of our study suggest a possible mechanism whereby these benefits might be mediated. 

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KLJ was involved in the design of the experiment, subject recruitment, collection and analysis of data, and writing of the manuscript. MNC and LMM were involved in the design of the experiment and writing of the manuscript and provided advice. None of the authors had a conflict of interest.

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