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Effects of caffeine on glucose tolerance: A placebo-controlled study

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Objective: The investigation was performed to study the effects of 200 mg oral caffeine on glucose tolerance.
Design: Single-blind Latin square with active treatment (caffeine) and placebo.
Setting: The University of Padova, Department of Internal Medicine.
Subjects: 30 nonsmoking healthy subjects aged 26–32 years who abstained not only from coffee but also from tea, chocolate and cola for 4 weeks and who had given their informed consent.
Interventions: A 75 g oral glucose tolerance test (OGTT) was performed after giving caffeine or placebo (highly decaffeinated coffee).
Results: The glycaemic curve was normal in all subjects and was similar in the two groups until the second hour; in subjects taking caffeine a shift towards the right was detected at the 2nd, 3rd and 4th hours in comparison to those taking the placebo. Blood insulin levels were comparable after caffeine and after placebo along the entire OGTT.
Conclusions: The data suggest that caffeine intake induces a rise in blood glucose levels that is insulin independent.
Sponsor: Department of Clinical and Experimental Medicine, University of Padova, Italy.
Descriptors: caffeine; glucose; human; insulin

Introduction

The effects of coffee or caffeine ingestion on serum cholesterol (Little *et al*, 1966; Heyden *et al*, 1979; Thelle *et al*, 1983; Shirlow & Mathers 1983, Hofman *et al*, 1983; Kovan *et al*, 1983; Curb *et al*, 1986), triglycerides (Avogaro *et al*, 1973; Phillips *et al*, 1981), free fatty acids (Bellet *et al*, 1965, 1968; Williams *et al*, 1985), apolipoproteins (Robertson *et al*, 1978), and liver enzymes (Casiglia *et al*, 1993) have been known for many years.

However, the effects of caffeine on glucose tolerance are still controversial. In the few studies conducted several years ago, blood glucose was found to be increased (Labbé & Theodoresco, 1924; Cheraskin *et al*, 1967; Jankelson *et al*, 1967; Wachman *et al*, 1970), decreased (Deakins *et al*, 1939; DeCastro *et al*, 1969) or unchanged (Denaro *et al*, 1981; Brown & Benowitz, 1989) after coffee or caffeine administration.

The purpose of the present study was to evaluate whether glucose levels can be modified by acute caffeine intake, and whether this effect is insulin dependent.

Subjects, materials and methods

The study group included 30 nonsmoking healthy subjects aged 26–32 years (12 males and 18 females), who gave their informed consent to the study in accordance with the principles of the declaration of Helsinki, and who were defined as healthy on the basis of a physical examination, a routine blood analysis, and a preliminary oral glucose tolerance test (OGTT) (WHO 1980; Kull *et al*, 1982). Their general characteristics are summarised in Table 1.

All subjects abstained for at least 4 weeks not only from coffee but also from other foodstuffs containing caffeine or analogues, such as tea, chocolate and cola. These subjects were usually drinking no more than two 'espresso' coffees a day; symptoms of abstinence were therefore not present at the beginning of the study. Caffeine status was then evaluated by random blood sampling during the 4 weeks of the abstinence, showing blood caffeine levels near to zero in all subjects.

The experimental design was a single-blind Latin square with active treatment and placebo.

The same supplier provided both decaffeinated coffee and caffeine. Caffeine was chemically pure and did not contain any sort of filler.

All subjects received 50 ml decaffeinated cold coffee without sugar, where caffeine content was < 0.1 mg/ml (placebo), or 50 ml of the same decaffeinated coffee, to which 200 mg caffeine was added without altering the colour, flavour or taste (active treatment). The choice between the two treatments was made randomly according to a list of random numbers.

Two weeks later, the experiment was repeated according to the same protocol, but subjects who had previously received active treatment received a placebo and vice versa.

Decaffeinated coffee was brewed by the 'espresso' Italian method (Casiglia *et al*, 1991), and the decaffeinated-plus-caffeine mixture was prepared in another room

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Table 1 General characteristics of the 30 subjects included in the study

Sex (m : f)	12 : 18
Age (y)	28.6 ± 4.6
Weight (kg)	62.6 ± 14.3
Height (cm)	167.2 ± 9.7
Body mass index (kg/m^2)	22.1 ± 3.3
Body surface area (m^2)	1.70 ± 0.23
Fasting blood glucose (mmol/l)	4.85 ± 0.40
Fasting circulating insulin(μU/ml)	14.7 ± 10.2

Values are mean ± s.d.

immediately before ingestion by an operator who was not aware of the aim or the design of the study.

Blood glucose was measured before (fasting), and 1, 2, 3 and 4 h after a 75 g oral glucose load. Glucose was given 5 min after active treatment or placebo. A preliminary test performed in our laboratory had showed no interference on absorption or kinetics between glucose, decaffeinated coffee and caffeine (data not shown).

Blood caffeine concentrations were also detected 1, 2, 3 and 4 h after the glucose load, by a method described elsewhere (Casiglia *et al*, 1991).

All values were averaged and expressed as mean ± s.d. As glycaemic and insulinaemic curves were peaked *vs* time, their trend in serial measurements both after caffeine and after placebo was compared using the area under curve (AUC) and the summary measures method (Mattews *et al*, 1990). Correlations were evaluated with Pearson's correlation coefficient and Bonferroni's conservative correction.

Results

Fasting conditions

Fasting blood glucose levels were 4.85 ± 0.40 mmol/l after decaffeinated coffee and 4.75 ± 0.42 mmol/l after 200 mg caffeine (NS), and fasting insulin levels were 14.68 ± 10.21 μU/ml and 15.01 ± 10.76 μU/ml, respectively (NS).

Caffeine levels

Circulating caffeine level was 0.09 ± 0.05 μmol/l before decaffeinated coffee, and remained practically unchanged 1, 2, 3 and 4 h after placebo. In contrast, an increase to 12.73 ± 5.51, 21.78 ± 7.04, 22.88 ± 7.03 and 20.85 ± 5.78 μmol/l was observed on respectively the 1st, 2nd, 3rd and 4th hours after active treatment with the decaffeinated-plus-caffeine mixture.

Glucose load

Blood glucose and insulin levels detected 1, 2, 3 and 4 h after blood glucose load in both groups of subjects (those receiving decaffeinated + 200 mg caffeine and those receiving decaffeinated alone) are summarised in Figures 1 and 2, respectively. No influence of gender was observed in this respect.

AUC of glycaemia was 22.3 ± 2.2 (95% CI 20.3–24.2) after placebo and 24.5 ± 2.6 (95% CI 22.5–22.6) after active treatment. This difference was statistically significant ($P < 0.001$) and entirely due to the terminal phase of the curve (3 and 4 hours). AUC of insulinaemia was 225.2 ± 60.8 (95% CI 169.1–281.4) and 229.3 ± 56.6 (95% CI 185–272.8), respectively (NS) (Table 2).

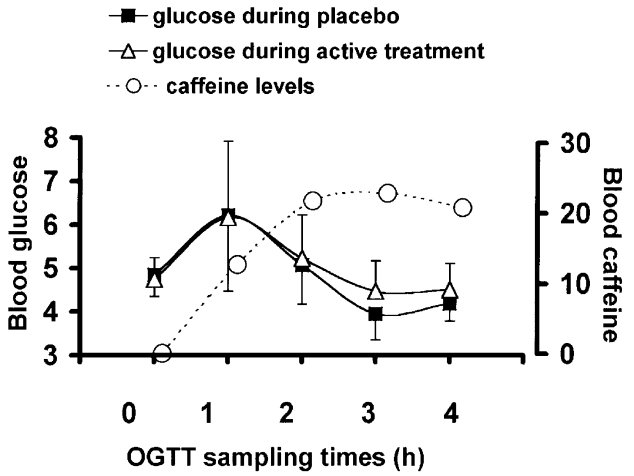

Figure 1 Blood glucose levels (mmol/l ± s.d.) at fasting and 1, 2, 3 and 4 h after ingesting 75 g glucose. Plasma caffeine concentrations (μmol/ls.d.) detected in subjects taking active treatment are also shown. The curves of blood glucose diverge significantly ($P = 0.008$) after the 2nd hour, when the highest levels of caffeine were detected.

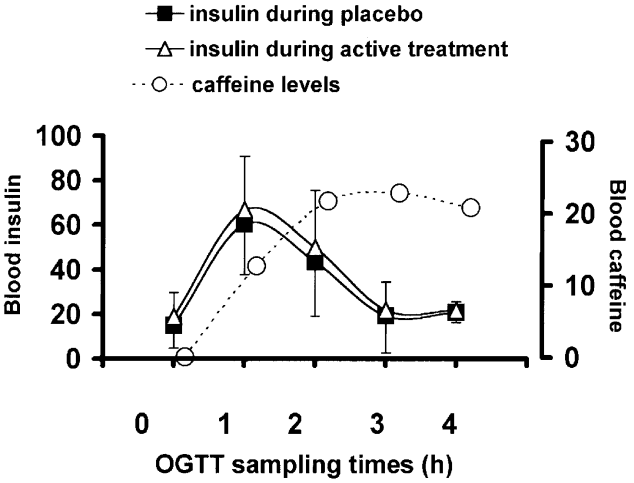

Figure 2 Blood insulin levels (μU/ml ± s.d.) at fasting and 1, 2, 3 and 4 h after ingesting 75 g glucose. Plasma caffeine concentrations (μmol/l ± s.d.) are also shown for subjects taking active treatment. The curves of blood insulin had a similar trend in subjects taking active treatment or placebo and were independent of circulating caffeine, beginning to decrease when caffeine was at the highest levels.

Discussion

The topic of interaction between coffee consumption and glucose tolerance has been controversial for many decades. In 1924 Labbé (Labbé & Theodoresco, 1924) described a caffeine-induced reduction of glucose tolerance, followed by observations of other authors. Cheraskin (Cheraskin *et al*, 1967) found higher blood glucose levels $\frac{1}{2}$, 1 and 2 h after ingestion of 250 mg caffeine compared with placebo. Jankelson (Jankelson *et al*, 1967) found a shift to the right of the OGTT curve after 2 cups of instant coffee but not after water, and Wachman (Wachman *et al*, 1970) observed an impaired glucose tolerance after 'espresso' but not after decaffeinated coffee.

On the other hand, Deakins (Deakins *et al*, 1939) demonstrated a depression, rather than an increase, of the

Table 2 Summary measures of glycaemia (mean ± s.d.) and insulinaemia (mean ± s.d.) during the time-course of the oral glucose tolerance test, both after placebo and after active treatment

	AUC[a] *initial phase (≤ 2nd hour)*	*95% CI*[b]	*AUC*[a] *terminal phase (3rd and 4th hours)*	*95% CI*
Glycaemia				
Placebo	13.7 ± 2.5	12.8–14.7	6.0 ± 0.5	5.7–6.4
Active	13.8 ± 2.6	12.8–14.8	6.7 ± 0.8	6.1–7.4
Insulinaemia				
Placebo	114.4 ± 55.5	90.3–132.5	34.8 ± 8.1	28.0–41.5
Active	126.3 ± 67.9	199.5–152.1	36.1 ± 6.6	31.4 ± 40.9

[a]AUC, area under curve.
[b]CI, confidence interval.

peak of the curve as well as a delay in the return of blood glucose to baseline values when an OGTT was performed after large doses of caffeine intake in comparison to non-caffeine controls. De Castro *et al* (1969) showed a 90 min duration leftward shift of the OGTT cure after coffee ingestion in dogs. Finally, in an open study, Avogaro (Avogaro *et al*, 1973) did not demonstrate any modification in blood glucose levels in a 4 h duration OGTT after 200 mg oral caffeine.

In the present study, performed in non-coffee-drinking subjects abstaining from coffee, a single administration of 200 mg caffeine (corresponding to 4 cups of 'espresso' Italian coffee) (Casiglia *et al*, 1991), increased blood glucose levels at the 3rd and 4th hour of the OGTT (Figure 1). This effect, which was particularly evident for the highest levels of circulating caffeine, demonstrates the existence of a late caffeine-induced decrease of glucose tolerance.

Although the mechanism of action of caffeine on glucose metabolism remains uncertain, our data demonstrate that it is independent of insulin action. In fact, post-OGTT insulin levels were not different in subjects taking active treatment and in those taking placebo, and the curves of such categories of subjects were comparable even for the highest levels of circulating caffeine (Figure 2). This is partially in disagreement with the data of Lambert (Lambert *et al*, 1967) and of Islam (Islam *et al*, 1995), who found a caffeine-induced stimulation of insulin release from cultured pancreatic β-cells, and with those of Turtle, who demonstrated an increased insulin secretion with another xanthine (theophylline) (Turtle *et al*, 1967) and suggested that the *in vivo* insulin response to caffeine may be completely different from that detected *in vitro*.

There is a possibility that the glycaemic trend observed in our study is due to caffeine-induced catecholamine release (Robertson *et al*, 1978; Denaro *et al*, 1981; Jung *et al*, 1981; Onrot *et al*, 1985; Kerr *et al*, 1993; Nehlig & Debry, 1994; Takiyyuddin *et al*, 1994; Leblanc *et al*, 1995). Caffeine is also an adenosine receptor antagonist (Leblanc & Soucy, 1994) and therefore able to inhibit muscle glucose uptake even in the presence of insulin (Vergauwen *et al*, 1994), and this is another hypothesis to be verified.

In conclusion, caffeine does not modify fasting glucose levels but it decreases glucose tolerance when administered acutely to non-coffee-drinkers. This acute hyperglycaemic effect of caffeine is insulin independent.

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