Caffeine ingestion increases the insulin response to an oral-glucose-tolerance test in obese men before and after weight loss \(^1\text{-}^3\)

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ABSTRACT

**Background:** Caffeine ingestion decreases the insulin sensitivity index (ISI) for an oral-glucose-tolerance test (OGTT) and decreases insulin-induced glucose disposal in lean male subjects during a hyperinsulinemic clamp.

**Objective:** We examined the effects of caffeine ingestion on insulin and glucose homeostasis in obese men before and after a nutrition and exercise intervention.

**Design:** Nine sedentary, obese [body mass index (in kg/m\(^2\)): 34.0 ± 1.0] men who had refrained from exercise and caffeine ingestion for 48 h underwent 2 oral-glucose-tolerance tests (OGTTs). The subjects randomly received caffeine (5 mg/kg) or placebo 1 h before each OGTT. After a 12-wk nutrition and exercise intervention, during which time the subjects avoided dietary caffeine, the OGTTs were repeated.

**Results:** The intervention resulted in decreases (\(P \leq 0.05\)) in body weight (8.5 ± 1.5 kg), percentage body fat (2.8 ± 0.7%), and fasting glucose, insulin, and proinsulin concentrations and increases in the ISI for the placebo OGTT (\(P \leq 0.05\)). Caffeine caused a greater (\(P \leq 0.05\)) OGTT insulin response and a lower (\(P \leq 0.05\)) ISI both before and after weight loss. The proinsulin-insulin ratio indicated that neither weight loss nor caffeine affected the nature of the \(\beta\) cell secretion of insulin.

**Conclusions:** A nutrition and exercise intervention improved, whereas caffeine ingestion impaired, insulin-glucose homeostasis in obese men. The results are consistent with previous findings that caffeine ingestion contributes to insulin resistance. *Am J Clin Nutr* 2004;80:22–8.

KEY WORDS Insulin resistance, type 2 diabetes, carbohydrate, proinsulin, \(\beta\) cell function, hyperinsulinemia, oral-glucose-tolerance test, exercise, insulin sensitivity index

INTRODUCTION

Obesity is associated with impaired glucose tolerance (IGT) and type 2 diabetes (1–4). Common to both IGT and type 2 diabetes are hyperinsulinemia and insulin resistance, which result from the impairment of insulin’s action on insulin-sensitive tissues such as skeletal muscle (5). Insulin resistance can be characterized by elevated basal serum insulin concentrations, an elevated insulin response to glucose ingestion, and a decrease in glucose uptake in the peripheral tissues, especially skeletal muscle (6, 7). Increased hepatic glucose output and hyperglycemia generally ensue (5). Many investigators have associated these metabolic characteristics with visceral adiposity (8-10).

Lifestyle interventions, such as reductions in energy and saturated fat intakes and increases in physical activity, have resulted in improvements in insulin and glucose control in obese persons (11–13). However, the influence of caffeine on glucose tolerance and insulin sensitivity has not been studied. Ingestion of caffeine by lean persons before an oral-glucose-tolerance test (OGTT) was shown to result in a greater insulin response and no decrease in the glucose response (14, 15). Studies using hyperinsulinemic euglycemic clamps have confirmed that caffeine ingestion reduces whole-body glucose disposal by 15–30% (16, 17) and glucose uptake in the leg (muscle) by \(\approx\)50% (18). Although it is known that skeletal muscle is the major tissue that becomes insulin-insensitive after caffeine ingestion, the mechanism of action is uncertain. Although many potential mechanisms exist, considerable evidence indicates that physiologic concentrations of caffeine antagonize adenosine receptors (19–21) both in skeletal muscle (21–23) and in the central nervous system, with the latter resulting in an increase in sympathetic activity (15, 20, 21).

The results of studies that have examined the effects of chronic coffee consumption on the risk of type 2 diabetes are inconsistent. van Dam and Feskens (24) reported epidemiologic data indicating that high coffee consumption is associated with a reduced risk of type 2 diabetes, even in those with other lifestyle...
factors that may increase the risk of type 2 diabetes. In contrast, a prospective study of Pima Indians by Knowler et al (25) found no evidence for any relation between coffee consumption and type 2 diabetes. We elected to examine the acute effects of caffeine ingestion on glucose and insulin homeostasis in obese subjects before and after a nutrition and exercise intervention. We hypothesized that caffeine ingestion before an OGTT would result in an exaggerated insulin response. It is plausible that weight loss and increased fitness would improve metabolic homeostasis and decrease the sensitivity to adenosine (26, 27). Thus, we hypothesized that a nutrition and exercise program would lead to significant improvements in glucose and insulin control and in the amelioration of caffeine-induced insulin resistance.

SUBJECTS AND METHODS

Subjects

Potential subjects were screened by a physician to confirm no history of disease, including diabetes mellitus, and no drug or alcohol abuse. Eligibility criteria included young (19–34 y), obese [BMI (in kg/m\(^2\)) ≥ 30], and sedentary (physical activity <3 times/wk) men with a stable body weight (maximum fluctuation of 2 kg within the previous 2 mo). Subjects were also required to have a systolic blood pressure ≤160 mm Hg and a diastolic blood pressure ≤100 mm Hg, not be using drugs or dietary supplements, and to have not partaken in any weight-loss program within the previous 2 mo. Subjects provided written consent after receiving detailed verbal and written explanations of the study, which had received approval from the Human Subjects Committee of the University of Guelph, Ontario, Canada.

Preintervention period

During a 2-wk baseline (preintervention) period, a nutritionist analyzed the subjects’ usual diets. Measurements of waist and hip circumference, height (to the nearest 0.5 cm), and body weight (to the nearest 0.1 kg) were made, and percentage body fat was determined by dual energy X-ray absorptiometry. Subjects walked on a treadmill at progressively increasing speeds and slopes for the determination of maximal oxygen consumption (\(\text{VO}_2\text{max}\)). Subjects were verbally encouraged and \(\text{VO}_2\text{max}\) was accepted when 2 of the following 3 criteria were achieved: no increase in oxygen consumption (\(\text{VO}_2\)) despite further increases in treadmill grade, the heart rate met or exceeded the predicted maximum (220 – age), and the respiratory exchange ratio exceeded 1.1. The relation between \(\text{VO}_2\) and the heart rate was used to estimate the energy expended during each exercise session of the nutrition and exercise program.

Two OGTTs were conducted, separated by ≥72 h. The subjects entered the laboratory in the morning after a 12-h overnight fast and after having refrained from exercise and caffeine ingestion for 48 h. A catheter was placed in the antecubital vein by a qualified technician and was kept patent with a normal saline drip. In a randomized, double-blind fashion, the subjects received either placebo or caffeine capsules (5 mg/kg body wt) 1 h (time 0) before ingestion of the 75-g glucose solution (TRUTOL 75; Nerl Diagnostics, East Providence, RI) at time 60. Venous blood samples were taken at −30, 0, 60, 75, 90, 120, 150, and 180 min.

Nutrition and exercise intervention

The nutrition and exercise intervention was 12 wk in duration. During this time, subjects were provided with an individualized target of a daily energy decrement of 1260 kJ (300 kcal), with 20–30% of their energy intake derived from fat, and were instructed to refrain from caffeine in any form. To maximize compliance with the dietary instructions, subjects were educated about how to avoid dietary caffeine and how to calculate the amount of energy and the percentage fat from energy in their foods and beverages. Daily food intake diaries were reviewed every other day by researchers and every 4 wk by a registered dietitian. One 3-d food diary was randomly selected every 2 wk (6 sets in total) to undergo analysis of energy, macronutrient, and micronutrient intakes by using the Food Processor software program (version 7.11; ESHA Research, Salem, OR). Subjects completed a 24-h urine collection at 0, 4, 8, and 12 wk for the assessment adherence to caffeine abstinence. Any subject that had a positive result for caffeine was removed from the study.

Subjects visited the laboratory every other day throughout the entire 12-wk intervention, during which time body weight was measured, food diaries were reviewed, and supervised treadmill exercise sessions were completed. Heart rates were monitored during the exercise sessions and were used to estimate when a 2090-kJ (500-kcal) expenditure was achieved. Subjects were instructed to avoid any exercise other than that performed during their supervised laboratory visits. Overall, the combined dietary changes and the exercise program were designed to create a total energy deficit of 15 060–17 150 kJ/wk (3600–4100 kcal/wk) to elicit a weight loss of ≈0.5 kg/wk.

Postintervention period

At the conclusion of the 12-wk program, the subjects underwent dual energy X-ray absorptiometry, \(\text{VO}_2\text{max}\) testing and 2 OGTTs (caffeine compared with placebo). The OGTTs were scheduled to occur no sooner than 72 h after the subjects’ last supervised exercise session or their posttesting \(\text{VO}_2\text{max}\) test in an effort to eliminate any effect of the previous exercise session on glucose tolerance.

Blood and urine sampling and analyses

Each venous sample consisted of ≈14 mL blood; ≈7 mL was transferred to a sodium heparin–treated tube, and the remainder was placed in an untreated tube. The blood from the untreated tube was allowed to clot and was then centrifuged at 1200 × g at room temperature for 12 min. The serum was frozen at −20 °C for subsequent analysis of insulin (Coat-a-Count Radioimmunoassay kit; Diagnostic Products Corporation, Los Angeles), proinsulin (Human Proinsulin kit; Linco Research Inc, St Charles, MO), C-peptide (Human C-Peptide Radioimmunoassay kit; Linco Research Inc), free fatty acids (FFAs) (NEFA kit; Wako Bioproducts, Richmond, VA), and glycerol (28). Two hundred microliters of heparin-treated blood was transferred to 1 mL of 0.6 nmol perchloric acid/L and then centrifuged at 2400 × g at room temperature for 3 min. The supernatant fluid was stored at −20 °C until analyzed for glucose (29) and lactate (30). The proinsulin assay has a specificity of <0.1% for human insulin, 100% for intact proinsulin, and 95% for des-31,32 proinsulin. Thus, the actual measurement is proinsulin-like compounds, but for simplicity we refer to this as proinsulin.
TABLE 1
Dietary analysis of self-reported dietary intakes recorded before and during the 12-wk intervention

<table>
<thead>
<tr>
<th>Diet component</th>
<th>Before intervention</th>
<th>After intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kJ)</td>
<td>11046 ± 435</td>
<td>9372 ± 385(^{2})</td>
</tr>
<tr>
<td>Fat (% of energy)</td>
<td>31 ± 2</td>
<td>26 ± 1(^{2})</td>
</tr>
<tr>
<td>SFA (% of energy)</td>
<td>11 ± 1</td>
<td>8 ± 0.5(^{2})</td>
</tr>
<tr>
<td>MUFA (% of energy)</td>
<td>10 ± 1</td>
<td>8 ± 0.5</td>
</tr>
<tr>
<td>PUFA (% of energy)</td>
<td>4 ± 0.5</td>
<td>4 ± 0.5</td>
</tr>
<tr>
<td>Cholesterol (mg)</td>
<td>290 ± 45</td>
<td>276 ± 24</td>
</tr>
<tr>
<td>Carbohydrate (%)</td>
<td>50 ± 3</td>
<td>53 ± 1</td>
</tr>
<tr>
<td>Fiber (g)</td>
<td>19 ± 1</td>
<td>22 ± 1(^{2})</td>
</tr>
<tr>
<td>Protein (% of energy)</td>
<td>16 ± 1</td>
<td>19 ± 1</td>
</tr>
</tbody>
</table>

\(^{1}\) All values are \(\bar{x} \pm SEM; n = 9\). SFAs, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

\(^{2}\) Significantly different from before intervention, \(P \leq 0.05\) (paired \(t\) tests).

Calculations and statistics

Areas under the curve (AUCs) for glucose, insulin, C-peptide, FFAs, glycerol, and lactate were calculated with the trapezoid method (32) by using the time 0 value as the baseline. The ratio of proinsulin to insulin was calculated at 60 (0 min of the OGTT) and time 90 (30 min of the OGTT). The insulin sensitivity index (ISI), developed by Matsuda and DeFronzo (33), was used to estimate whole-body insulin sensitivity. The ISI, which provides a number between 0 and 12, is significantly correlated with whole-body insulin sensitivity as assessed by the hyperinsulinemic euglycemic clamp (*r* = 0.73, *P* < 0.0001) (33).

To examine the effect of the 12-wk intervention on energy and nutrient intakes, paired \(t\) tests (SAS, version 8.1999; SAS Institute, Cary, NC) were used to examine the effects of the nutrition and exercise program did not significantly alter the body glucose AUC (Table 3), it significantly lowered the fasting glucose concentrations from 4.6 ± 0.1 to 4.0 ± 0.1 mmol/L. Ingestion of

RESULTS

Seventeen subjects began the nutrition and exercise intervention, but 8 subjects either withdrew from the study because of illness (\(n = 1\)), injury (\(n = 2\)), or time constraints (\(n = 4\)) or were removed from the data analysis because of noncompliance (ie, methylxanthines were detected in the urine; \(n = 1\)). The 9 remaining subjects ranged in age from 23 to 34 y (30.6 ± 1.2 y). All subjects were caffeine consumers and had intakes ranging from one chocolate bar a week to an occasional maximum of 5 cups coffee/d.

Compared with values before the 12-wk intervention began, intakes of total energy, fat, and saturated fatty acids decreased significantly; the intake of dietary fiber increased (Table 1); and \(V_\text{O}_2\max\) increased (Table 2). Mean body weight, BMI, percentage body fat, fat mass, fat-free mass, and waist and hip circumferences all significantly decreased after the intervention (Table 2).

Blood glucose concentrations

Blood glucose concentrations before and after the intervention are summarized in Figure 1. Although the 12-wk nutrition and exercise program did not significantly alter the body glucose AUC (Table 3), it significantly lowered the fasting glucose concentrations from 4.6 ± 0.1 to 4.0 ± 0.1 mmol/L. Ingestion of
caffeine did not elicit any significant changes in blood glucose concentrations before administration of the glucose beverage during either OGTT nor was the AUC for blood glucose significantly affected.

**Serum insulin concentrations**

Insulin concentrations before and after the intervention are summarized in Figure 2. The intervention resulted in a decrease ($P \leq 0.05$) in fasting serum insulin concentration from 89.5 ± 6.5 to 53.4 ± 3.6 pmol/L. Although the 36% decrease in the AUC for insulin (Table 3) in the placebo conditions was not significant ($P = 0.08$), the ISI increased significantly as a result of the 12-wk intervention (Table 3). There was a significantly greater insulin response to the OGTT in the caffeine group than in the placebo group both before and after the intervention (Table 3).

**Serum C-peptide concentrations**

Fasting serum C-peptide concentrations decreased ($P \leq 0.05$) after the intervention. The C-peptide response to the OGTTs, before and after the intervention, are illustrated in Figure 3. There was a significant decrease in fasting serum C-peptide ($P \leq 0.05$) at the 60-min time point (Table 4), but the proinsulin-insulin ratio did not change significantly before or after the intervention. There were no significant differences in proinsulin concentrations between the placebo and caffeine groups before the OGTT. During the OGTT, the proinsulin concentration increased ($P \leq 0.05$) 30 min after all 4 treatments, and the proinsulin-insulin ratio increased ($P \leq 0.05$). The intervention did not significantly affect this ratio, but it was lower ($P \leq 0.05$) with caffeine.

**Blood lactate concentrations**

There was no significant effect of the 12-wk intervention on the blood lactate AUC (Table 3), yet there was a small ($P \leq 0.05$)

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**TABLE 3**

Area under the curve data for glucose, insulin, C-peptide, lactate, free fatty acids, and glycerol and the insulin sensitivity index in response to an oral-glucose-tolerance test in subjects who received caffeine or placebo before and after a nutrition and exercise intervention.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Before intervention</th>
<th>After intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol · L⁻¹·2h)</td>
<td>234 ± 62ᵃ</td>
<td>258 ± 41ᵃ</td>
</tr>
<tr>
<td>Insulin (nmol · L⁻¹·2h)</td>
<td>51.14 ± 9.93ᵇ</td>
<td>58.41 ± 7.6ᵇ</td>
</tr>
<tr>
<td>C-peptide (nmol · L⁻¹·2h)</td>
<td>1573 ± 187ᵃ</td>
<td>1522 ± 157ᵃ</td>
</tr>
<tr>
<td>Lactate (mmol · L⁻¹·2h)</td>
<td>18 ± 7ᵃ</td>
<td>24 ± 13ᵃ</td>
</tr>
<tr>
<td>Free fatty acids (mmol · L⁻¹·2h)</td>
<td>-33.01 ± 5.02ᵇ</td>
<td>-54.62 ± 7.63ᵇ</td>
</tr>
<tr>
<td>Glycerol (µmol · L⁻¹·2h)</td>
<td>-2684 ± 1142ᵇ</td>
<td>-3226 ± 862ᵇ</td>
</tr>
<tr>
<td>ISI</td>
<td>5 ± 1ᵃ</td>
<td>4 ± 1ᵇ</td>
</tr>
</tbody>
</table>

*All values are x ± SEM; n = 9. Means in a row with different superscript letters are significantly different. $P \leq 0.05$ (PROC MIXED procedure followed by Tukey’s test for multiple comparisons).*
TABLE 4
Serum proinsulin concentrations and the proinsulin-insulin ratio in response to an oral-glucose-tolerance test in subjects who received caffeine or placebo before and after a nutrition and exercise intervention.*

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Concentration (pmol/L)</th>
<th>Proinsulin/insulin ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before intervention</td>
<td>Placebo</td>
<td>7.7 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td>9.9 ± 0.8</td>
</tr>
<tr>
<td>After intervention</td>
<td>Placebo</td>
<td>6.1 ± 0.4²</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td>7.3 ± 0.8²</td>
</tr>
<tr>
<td>90 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before intervention</td>
<td>Placebo</td>
<td>30.0 ± 5.5</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td>28.2 ± 4.0</td>
</tr>
<tr>
<td>After intervention</td>
<td>Placebo</td>
<td>17.6 ± 3.0²</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td>19.8 ± 2.6²</td>
</tr>
</tbody>
</table>

* All values are x ± SEM; n = 9.
² Significantly different from the corresponding value before intervention, P ≤ 0.05.
³ Significantly different from the corresponding placebo value, P ≤ 0.05 (paired t tests).
⁴ Significantly different from the corresponding placebo value, P ≤ 0.05 (paired t tests).

decrease in fasting blood lactate concentrations (data not shown) by the end of the 12-wk program. Ingestion of caffeine did not elicit a significant change in fasting blood lactate concentrations or in the blood lactate response to the OGTT.

Serum free fatty acid and glycerol concentrations

Fasting serum FFAs (Figure 4) and glycerol (data not shown) concentrations increased (P ≤ 0.05) in the hour after caffeine ingestion. This elevation did not significantly differ before or after the intervention (P > 0.05). At time 60, when the OGTT began, serum insulin concentration began to rise, which coincided with decreases in serum FFAs and glycerol concentrations to below fasting concentrations. Because of the suppression of lipolysis by insulin, the AUC for FFAs and glycerol were negative (Table 3). The AUC for FFA was significantly more pronounced during the caffeine trials, both before and after the intervention, but this finding appeared to result from the initial elevation in FFA concentrations at 60 min, because subsequently the FFA concentrations decreased similarly during both the caffeine and placebo trials (Figure 4). Although the fasting serum FFA concentration did not change as a result of the 12-wk program (P > 0.05), the serum FFA response to the placebo OGTT was more pronounced as a result of the 12-wk program (Table 3 and Figure 4). No significant effect of caffeine on the AUC for serum glycerol, before or after the 12-wk intervention, was observed (Table 3).

DISCUSSION

The purpose of the present study was to examine the effects of caffeine on glucose and insulin homeostasis in an obese, sedentary population before and after a 12-week, nutrition and exercise weight-loss intervention. We hypothesized that caffeine ingestion before an OGTT would result in an exaggerated insulin response compared with placebo. We also hypothesized that the weight-loss program would lead to significant improvements in glucose tolerance and an amelioration of the caffeine-induced deterioration in glucose tolerance.

Our first hypothesis was supported. Before the 12-wk intervention the estimated ISI was low and yet caffeine ingestion decreased it significantly by ≈15%, and the insulin AUC was significantly greater during the OGTT. Previously, studies (14, 15) of lean subjects have shown that caffeine ingestion followed by an OGTT led to significantly greater insulin responses without an accompanying decrease in blood glucose concentrations and a similar relative decrease in the ISI. This hyperinsulinemia is highly suggestive of insulin resistance, and studies using hyperinsulinemic clamps and caffeine or theophylline have confirmed that these methylxanthines depress glucose disposal (16–18). The present study showed that obese men, a population that is already prone to insulin resistance, respond to caffeine similarly before and after the intervention, even after weight loss and increased aerobic fitness.

In contrast with previous work (14, 15), the serum C-peptide response to the OGTT did not significantly increase as a result of caffeine ingestion. These prior studies examined lean, moderately active men, whereas the present study examined sedentary, obese men. C-peptide and insulin are secreted in equimolar amounts and, hence, their presence in the serum usually changes in parallel (34). Obese persons can experience elevated serum insulin concentrations because of both increased insulin secretion and decreased insulin clearance. Decreased hepatic binding and extraction of insulin often characterize insulin resistance (35, 36). This could explain the lack of concordance between the serum C-peptide and insulin responses to caffeine ingestion in this group.

Caffeine could increase the insulin response by stimulating a more rapid absorption of glucose (37). This is highly unlikely; caffeine was ingested 60 min before glucose ingestion, and caffeine absorption has been shown to be complete within 45 min of ingestion (38). Furthermore, if enhanced absorption was the major cause of the greater insulin concentration, the blood glucose response would be reduced.
It has been reported that pharmacologic concentrations of caffeine could directly stimulate the β cell secretion of insulin (39). To examine whether caffeine could alter the manner of β cell secretion, we measured proinsulin concentrations. Normal β cell secretion is composed of ≈98% insulin and 2% proinsulin-like compounds (40–42). However, because of differences in clearance rates, the proinsulin-insulin ratio is commonly = 0.10 – 0.15 in both lean and obese subjects (40–43), and it is dramatically elevated in type 2 diabetes because of secretion of immature vesicles (44, 45). Fritsche et al (40) recently concluded that the ratio at rest, and particularly that at 30 min of an OGTT, is an accurate reflection of β cell secretion. To the best of our knowledge, caffeine’s possible actions on these processes have never been examined. Caffeine had no significant effect on the proinsulin-insulin ratio before the OGTT, and during the OGTT it resulted in a significantly lower ratio than the corresponding placebo value. If caffeine was interfering in the processing of proinsulin or enhancing the secretion of immature vesicles, then the secretion of proinsulin and the ratio should increase. The decreased ratio strongly suggests that caffeine did not alter β cell secretion negatively. Rather, the data support the previous finding (14–18) that caffeine ingestion resulted in insulin resistance.

The 12-wk intervention significantly improved aerobic capacity and decreased body weight, body fat, and fasting blood glucose (13%), serum insulin (40%), C-peptide (33%), and proinsulin (21%) concentrations. During the placebo OGTTs, the AUC for insulin decreased 37% (nonsignificant), and the ISI increased 69% (significant) after the intervention. A further indication of improved carbohydrate homeostasis was the observation that, before the intervention, 2 of the 9 subjects were classified as having IGT (4) and neither subject fell into this classification after the intervention. The proinsulin-insulin ratio of these 2 subjects was lower than the group mean both before and after intervention, which suggests that β cell secretion was not the problem. Rather, they may have been insulin resistant. Several reports have shown that insulin resistance is not associated with an increase in this ratio (41, 43, 46).

The improvements in insulin sensitivity after the intervention could be attributable to the various lifestyle improvements made by the subjects. The subjects significantly decreased their intakes of dietary energy, total fat, and saturated fat and significantly increased their intakes of fiber, all of which were previously found to correlate with improved glucose tolerance and insulin sensitivity (47–51). The significant reductions in body fat are also considered to be contributing factors (12, 13, 52). The subjects also improved their aerobic fitness and refrained from ingestion of caffeine for 12 wk. Subjectively, there was no relation between the degree of previous regular caffeine-consumption habits and the degree of acute caffeine-induced insulin resistance. All of the aforementioned factors could have affected the results, and further studies are now required to address which of the factors is most important.

We reject our hypothesis that a 12-week lifestyle intervention would ameliorate the caffeine-induced insulin resistance observed in the obese group studied. The effects of caffeine on glucose, insulin, and C-peptide responses to the OGTT were not significantly altered over time. The caffeine dose (5 mg/kg) in this obese population was equivalent to 3–4 cups of brewed coffee. However, it is important to note that the present study used pure caffeine rather than a caffeine-containing beverage such as coffee and that the caffeine challenge was given after a 2-d withdrawal from caffeine. Coffee and other caffeinated products are composed of a myriad of compounds. In fact, caffeine constitutes only ≈2% of coffee’s chemical profile (53). The role of chronic coffee consumption is controversial; a recent epidemiologic study reported that a high coffee consumption is associated with a reduced risk of type 2 diabetes despite a high BMI, smoking, alcohol use, a low physical activity, and an unfavorable diet (24). In contrast, Knowler et al (25) found no evidence of a role for coffee consumption in type 2 diabetes in a longitudinal population-based study. One should also realize that there currently are novel caffeine-containing products such as “energy drinks” and alcoholic beverages being marketed. Well-controlled, prospective intervention studies are required to address the long-term effects of these various caffeinated products. It is not known whether one habituates to the effects of caffeine on insulin action, but it is noteworthy that, if habituation occurs, our present data show that it must be reversed within 48 h in subjects that have consumed caffeine for many years.

The present study showed that acute caffeine ingestion significantly dampened whole-body insulin sensitivity in obese, non-diabetic persons. A 12-wk weight-loss program, which consisted of the adoption of a healthy diet, regular aerobic exercise, and caffeine withdrawal led to improvements in insulin sensitivity but was unable to ameliorate the caffeine-induced deterioration in insulin sensitivity. There was no evidence that caffeine directly affects β cell secretion; rather, it appears that it directly or indirectly causes peripheral insulin resistance, which in turn stimulates greater insulin secretion. The implications for caffeine use by those who have preexisting hyperinsulinemic and hyperglycemic conditions, such as those with type 2 diabetes, remains uncertain.

We thank the subjects for their valuable participation, our research assistants, the staff of the Health and Performance Center and Human Nutraceutical Research Unit at the University of Guelph, and Premila Sathasivam and Patrick Sheridan for their technical expertise, time, and assistance.

HIP assisted with the development of the research study protocol, recruited the subjects, coodordinated the study, comanged the research assistants, performed the laboratory analyses, collected and interpreted data, and wrote the manuscript. SEC assisted with the development of the research study protocol, recruited the subjects, coodordinated the research study, comanged research assistants, recruited the subjects, performed laboratory analyses and collected data. LMB coodordinated the research study, comanged the research assistants, recruited the subjects, performed the laboratory analyses, and collected data. AMD assisted with the supervision of data collection, assisted with the data analysis and interpretation, and assisted with the manuscript preparation. DHM established the assay for proinsulin, conducted the analyses, and assisted with the data interpretation. JAC assisted with the study design and supervised the data collection and analysis. TEG designed the study, supervised the research, directed the data analysis and interpretation, and assisted with the manuscript preparation. TEG was the primary investigator of a research contract from Muscletech Inc; he received no personal financial support from the company.

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