Caffeine Ingestion Is Associated With Reductions in Glucose Uptake Independent of Obesity and Type 2 Diabetes Before and After Exercise Training

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OBJECTIVE — We investigated the effect of caffeine ingestion on insulin sensitivity in sedentary lean men ($n = 8$) and obese men with ($n = 7$) and without ($n = 8$) type 2 diabetes. We also examined whether chronic exercise influences the relationship between caffeine and insulin sensitivity in these individuals.

RESEARCH DESIGN AND METHODS — Subjects underwent two hyperinsulinemic-euglycemic clamp procedures, caffeine (5 mg/kg body wt) and placebo, in a double-blind, randomized manner before and after a 3-month aerobic exercise program. Body composition was measured by magnetic resonance imaging.

RESULTS — At baseline, caffeine ingestion was associated with a significant reduction ($P < 0.05$) in insulin sensitivity by a similar magnitude in the lean (33%), obese (33%), and type 2 diabetic (37%) groups in comparison with placebo. After exercise training, caffeine ingestion was still associated with a reduction ($P < 0.05$) in insulin sensitivity by a similar magnitude in the lean (23%), obese (26%), and type 2 diabetic (36%) groups in comparison with placebo. Exercise was not associated with a significant increase in insulin sensitivity in either the caffeine or placebo trials, independent of group ($P > 0.10$).

CONCLUSIONS — Caffeine consumption is associated with a substantial reduction in insulin-mediated glucose uptake independent of obesity, type 2 diabetes, and chronic exercise.

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P revious studies have shown that caffeine ingestion is associated with a marked impairment in glucose tolerance (1–4) and insulin sensitivity (5–7) in humans. Indeed, Greer et al. (6) report that moderate caffeine consumption is associated with a 24% reduction in glucose uptake in lean young men. Whether this remains true for obese individuals with or without type 2 diabetes is unknown. Conversely, it is established that both acute and chronic exercise is associated with improvements in glucose tolerance (8–10) and insulin sensitivity (11–13) in obese and type 2 diabetic individuals. Further, Petrie et al. (2) report that caffeine ingestion is associated with an impairment in glucose tolerance, which remained after diet- and exercise-induced weight loss in a small number of obese men. Whether chronic exercise counteracts the negative effect of caffeine on insulin-mediated glucose uptake in obese individuals with and without type 2 diabetes is unknown.

Given the established effects of caffeine on insulin sensitivity and that insulin resistance is an antecedent to the development of type 2 diabetes, we examined the effect of a single caffeine ingestion on insulin-mediated glucose uptake in sedentary lean men and obese men with and without type 2 diabetes. We further investigated whether 3 months of aerobic exercise without weight loss influenced caffeine-mediated insulin resistance in these individuals.

RESEARCH DESIGN AND METHODS
— Eight lean men (BMI <25 kg/m^2), eight obese men with type 2 diabetes (BMI >27 kg/m^2), and eight obese men without type 2 diabetes (BMI >27 kg/m^2) were recruited from Kingston, Ontario, via the general media. All subjects were Caucasian and weight stable (± 2 kg) for 6 months before the beginning of the study. Participants were nonsmokers who consumed on average less than two alcoholic beverages per day and led a sedentary lifestyle (no participation in any regular physical activity for the previous 6 months). Self-reported caffeine consumption based on coffee and tea drinking ranged from low (two subjects were non–caffeine drinkers) to moderate (1–5 cups/day). The obese men

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without type 2 diabetes underwent an oral glucose tolerance test (OGTT) before participation to screen for normal glucose tolerance. All but one subject with type 2 diabetes had been diagnosed within the last 5 years (one subject was diagnosed 10 years earlier). Subjects with type 2 diabetes were not taking insulin or insulin sensitizers and were free of other complications (cardiovascular disease, nephropathy, neuropathy, or retinopathy) as confirmed by their physicians. Four subjects with type 2 diabetes were treated with glyburide and their dosage remained constant throughout the exercise intervention. One subject with type 2 diabetes was not administered caffeine, as confirmed by methylxanthine measurement, and could not comply with the exercise regimen due to leg injury. Thus, seven subjects made up the type 2 diabetic group for all pre- versus postexercise analyses. All subjects gave their fully informed and written consent before participation in the study, which was conducted in accordance with the ethical guidelines of Queen's University.

Diet and exercise regimen

During the 4-week baseline period, daily energy requirements for all subjects were determined by estimating resting energy expenditure and multiplying the obtained value by a factor of 1.5 (14). During this period, all subjects followed a weight maintenance diet (55–60% carbohydrate, 15–20% protein, and 20–25% fat). Body weight was monitored during this period to determine the accuracy of the prescribed energy requirement and was adjusted accordingly so that body weight was maintained. During the 13-week exercise intervention period, all subjects were asked to maintain body weight and thus consumed the calories required to compensate for the energy expended during the regular exercise session. Body weight was measured before each exercise session to help ensure weight maintenance. All subjects were free-living and consumed foods that were self-selected. No vitamins or other nutritional supplements were prescribed. Subjects were instructed that the composition of weight maintenance diet as follows: 55–60% carbohydrate, 15–20% protein, and 20–25% fat. Subjects kept daily, detailed food records for the duration of the entire study period ($\sim$17 weeks) that were re-

viewed by the study dietitian on a weekly basis to ensure compliance.

All subjects participated in a 13-week aerobic exercise program, either walking or light jogging on a treadmill for 60 min, five times per week at a moderate intensity ($\sim$60% $V_{O_{2max}}$). Energy expenditure during each exercise session was determined using the heart rate and oxygen consumption data obtained from the pretreatment graded exercise test, and adjusted using the subsequent test results performed at weeks 4 and 8. Heart rate was monitored every 5 min during every exercise session using an automated heart rate monitor (Polar Oy, Kempele, Finland). All exercise sessions were by appointment and were supervised.

Measurement of insulin sensitivity

To help ensure normal muscle glycogen levels, subjects were asked to consume at least 200 g of carbohydrate and avoid strenuous exercise for a minimum of 4 days before measurements of insulin sensitivity. Glucose uptake was measured using a 3-h hyperinsulinemic (40 mU $\cdot$ m^{-2} $\cdot$ min^{-1}) euglycemic clamp procedure. All subjects performed two clamp trials (caffeine and placebo) before and after exercise training. The trials were randomized in a double blind manner and separated by $\sim$1 week. Postexercise clamp measurements were obtained 12 and 13 weeks postexercise. Each clamp measurement was obtained 4 days after the last exercise session. The measures of insulin sensitivity were obtained 4 days postexercise to control for the well-established effects of acute exercise on glucose uptake (11). To avoid the potential detraining effect on insulin sensitivity, all the participants exercised 1 week (five times) between the two clamp measurements (between 12 and 13 weeks). $V_{O_{2max}}$ was determined at the end of the 12th and 13th weeks and confirmed that cardiorespiratory fitness was not different between the time points, regardless of group (data not shown).

Subjects were asked to abstain from all methylxanthine-containing products for 3 days before each trial. Individuals with type 2 diabetes were asked to not take their oral hypoglycemic agent for 48 h preceding the euglycemic clamp measurement. Subjects recorded and submitted a dietary food record for this time. On the day of the clamp procedure, subjects arrived at the hospital at 5:30 A.M.

following a 10- to 12-h overnight fast. The clamp procedure started at 7:30 A.M. The subjects rested in a supine position for 2 h before the clamp. Thirty minutes before the start of the clamp measurement, the baseline blood sample was taken and subjects ingested a gelatin capsule containing either placebo (dextrose) or caffeine (5 mg/kg body wt) with 250 ml of water. Five mg/kg is equivalent to about 2–3 cups of coffee (1 cup = 8 oz) (15). A catheter was inserted into the anticubital vein for the infusion of a normal saline (0.9% NaCl) drip, insulin, glucose, and potassium. Insulin was infused at a rate of 40 mU $\cdot$ m^{-2} $\cdot$ min^{-1} for 3 h. A 20% glucose solution was infused at a rate required to maintain plasma glucose concentration at $\sim$5 mmol/l. A second catheter was placed in a heated hand vein, which was used to draw arterialized blood samples. Plasma glucose was monitored using an automated glucose analyzer (YSI 2300 Glucose Analyzer; YSI, Yellow Springs, OH) every 5 min and glucose infusion was adjusted accordingly. Blood samples were taken at baseline and every 30 min for the duration of the clamp to measure insulin concentration. At each hour of the clamp, blood was drawn for the determination of free fatty acids (FFAs). Indirect calorimetry was performed during the last 30 min of glucose infusion using an open-circuit spirometry metabolic monitoring system (DeltaTrac, Anaheim, CA) to estimate glucose oxidation. Glucose uptake rate was calculated using the average infusion rate during the final 30 min of the clamp. Nonoxidative glucose component was determined by subtracting glucose oxidation as determined by calorimetry from glucose uptake. The glucose uptake data were expressed as the ratio of the amount of glucose metabolized to the prevailing plasma insulin levels [M (mg $\cdot$ kgSM^{-1} $\cdot$ min^{-1})/I (μU/ml) $\times$ 100] during the last 30 min of the euglycemic clamp.

Analytical methods

All blood samples were analyzed using an established protocol described in detail previously (6). Briefly, blood samples for the determination of methylxanthines and FFAs were immediately separated into two aliquots: 3 ml was transferred to a nontreated tube for the analysis of serum FFAs, and 7 ml was transferred to a sodium heparinized tube for the analysis of other metabolites. Plasma caffeine, paraxanthine, theophylline, and theo-

Table 1—Subject characteristics

	Lean		Obese, nondiabetic		Obese, type 2 diabetes	
	Baseline	Post-training	Baseline	Posttraining	Baseline*	Posttraining†
Age (years)	47.5 ± 6.7		47.1 ± 8.1		51.0 ± 8.0	
Body weight (kg)	73.9 ± 6.6	73.5 ± 6.6	97.6 ± 8.9‡	97.2 ± 8.9‡	93.5 ± 7.6‡	92.7 ± 8.5‡
BMI (kg/m²)	24.5 ± 1.3	24.3 ± 1.2	32.4 ± 1.6‡	32.2 ± 1.7‡	29.9 ± 3.2‡	29.1 ± 2.2‡
Total skeletal muscle (kg)	27.7 ± 3.5	28.0 ± 3.3	32.9 ± 3.9‡	33.3 ± 4.1‡	32.7 ± 3.9‡	33.5 ± 4.4 ‡¶
Total fat (kg)	20.7 ± 3.9	19.5 ± 3.9¶	35.8 ± 4.2‡§	33.8 ± 4.4‡¶	30.1 ± 4.5‡	27.2 ± 3.4‡¶
Visceral fat (kg)	2.0 ± 0.9	1.8 ± 0.8¶	4.0 ± 0.9‡	3.4 ± 0.8‡¶‖	3.8 ± 0.9‡	2.9 ± 0.9‡¶‖
Peak VO₂ (ml/kg/min)	42.6 ± 5.8	53.1 ± 3.7¶	32.7 ± 3.5‡	39.3 ± 4.0‡¶	33.0 ± 4.4‡	44.3 ± 5.0‡¶
Fasting glucose (mmol)	4.6 ± 0.4	4.7 ± 0.4	4.8 ± 0.6	4.6 ± 0.4	7.9 ± 2.2**	7.4 ± 2.3**

Data are means ± SD. *$n = 8$; †$n = 7$; ‡$P < 0.05$ vs. the lean group; §$P < 0.05$ vs. the type 2 diabetic group; ¶significant within-group differences (baseline vs. posttraining), $P < 0.05$; ‖$P < 0.05$ vs. the lean group; ** $P < 0.05$ vs. the lean and obese groups.

bromine were measured using fully automated high-performance liquid chromatography (HPLC) (Waters). An aliquot of plasma (150 μl) was added to 40 mg ammonium sulfate and 50 μl of 0.05% acetic acid. After adding 25 μl of an internal standard solution (7-*B*-hydroxypropyl theophylline) and 3 ml of chloroform/isopropyl alcohol (85:15 vol/vol) extracting solvent, the mixture was vortexed for 30 s and centrifuged for 10 min at 2,500 rpm. The organic phase was transferred and dried under oxygen-free N_2, resuspended in HPLC mobile-phase solvent (3% isopropanol, 0.05% Hac, and 0.5% methanol), and 100 μl was injected into a Beckman Ultrasphere IP C18 5-μl column. Methylxanthines were measured at 282 nm wavelength. Reagents for standards were obtained from Sigma Chemical. Serum was analyzed enzymatically in duplicate for FFAs (16). Plasma insulin was measured using a radioimmunoassay (RIA) kit supplied by Diagnostic Products (Los Angeles, CA), and C-peptide was measured using an RIA kit supplied by Linco Research (St. Louis, MO).

Measurement of total fat and skeletal muscle by magnetic resonance imaging
Whole-body (~46 equidistant images) magnetic resonance imaging (MRI) data were obtained with a General Electric 1.5-Tesla magnet using an established protocol (17). Once acquired, the MRI data were transferred to a stand-alone workstation for analysis using specially designed computer software (Tomovision, Montreal, Canada), the procedures for which have been described previously (17). Total fat and skeletal muscle mass

were determined using all 46 images. Visceral fat was calculated using the five images extending from 5 cm below to 15 cm above L4–L5. Fat and skeletal muscle volume units (liters) were converted to mass units (kg) by multiplying the volumes by the assumed constant density for fat (0.92 kg/l) and fat-free skeletal muscle (1.04 kg/l) (18).

Statistical analyses
A one-way ANOVA was used to examine differences in subject characteristics at baseline. A repeated-measures ANOVA (group × time) or (group × treatment) was used to evaluate main effects and group interactions for body composition measurements, insulin sensitivity, and metabolic data. When the ANOVA P value was <0.05, a Tukey's post hoc com-

parison test was used to locate treatment and/or group differences. Statistical procedures were performed using SPSS version 11.0 (SPSS, Chicago, IL). All data are presented as means ± SD.

RESULTS

Subject characteristics
Subject characteristics in Table 1 reveal that the obese and type 2 diabetic groups were different ($P < 0.05$) from the lean group for all measures of body composition and peak V_{O_2}. Fasting glucose was significantly higher ($P < 0.05$) in the type 2 diabetic group than in the lean and obese nondiabetic groups. Further, with respect to glucose uptake, the nonoxidative component was markedly lower in the type 2 diabetic group than in the lean
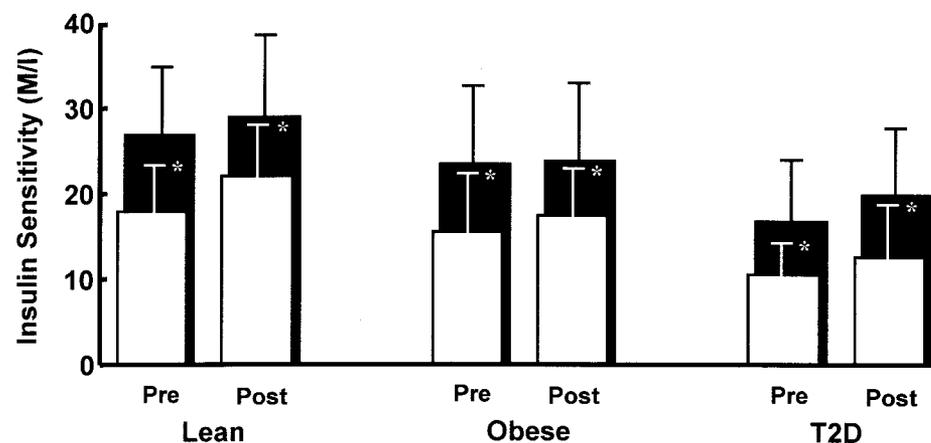
Figure 1—*Insulin sensitivity in the lean, obese, and type 2 diabetic (T2D) groups before and after 3 months of exercise. Insulin sensitivity is expressed as the ratio of the amount of glucose metabolized to the prevailing plasma insulin levels [M (mg·kgSM⁻¹·min⁻¹)/I (μU/ml) × 100] during the last 30 min of the euglycemic clamp. *Glucose uptake is significantly lower (P < 0.05) in the caffeine trial (□) compared with the placebo trial (■), independent of group and exercise training.*

group in both placebo (4.6 ± 5.3 vs. 16.3 ± 10.3, $P < 0.05$) and caffeine trials (0.8 ± 5.7 vs. 9.6 ± 5.0, $P = 0.05$) (Fig. 1).

Effect of exercise on body composition

Body weight did not change ($P > 0.1$) in response to exercise in any of the groups. Despite being weight stable, there were significant reductions ($P < 0.01$) in both total and visceral fat, independent of group (Table 1). The reduction in total fat was not different ($P > 0.05$) between groups. However, the reduction in visceral fat was greater ($P < 0.05$) in the obese and type 2 diabetic groups than in the lean group.

Effect of caffeine on glucose uptake at baseline

Caffeine ingestion resulted in a significant reduction ($P < 0.05$) in glucose uptake in the lean (33%), obese nondiabetic (33%), and obese type 2 diabetic (37%) groups as compared with placebo (Fig. 1). Glucose oxidation was not different ($P > 0.1$) between the caffeine and placebo trials, regardless of group (data not shown). However, the nonoxidative glucose component was 41% (16.3 ± 10.3 vs. 9.6 ± 5.0), 62% (12.1 ± 8.6 vs. 4.6 ± 9.3), and 83% (4.6 ± 5.3 vs. 0.8 ± 5.7) lower ($P < 0.05$) in the caffeine trial, as compared with placebo, in the three groups, and these reductions were not different between groups ($P > 0.1$).

Effect of caffeine on glucose uptake postexercise

Caffeine ingestion was still associated with a significant reduction ($P < 0.05$) in glucose uptake postexercise by 23, 26, and 36% in the lean, obese nondiabetic, and obese type 2 diabetic groups, respectively (Fig. 1). Consistent with baseline observations, glucose oxidation was not different ($P > 0.1$) between the caffeine and placebo trials, independent of group (data not shown). However, the nonoxidative glucose component was 34% (20.9 ± 7.1 vs. 13.8 ± 7.8), 45% (14.9 ± 8.9 vs. 8.2 ± 5.7), and 67% lower (9.1 ± 5.9 vs. 3.0 ± 3.3) ($P < 0.05$) in the caffeine trial compared with placebo in the lean, obese nondiabetic, and obese type 2 diabetic groups, respectively, and these reductions were not different ($P > 0.1$) between groups.

Table 2—FFA, insulin, and C-peptide concentrations during the euglycemic clamp

	Lean				Obese				Type 2 diabetes			
	Pretraining		Posttraining		Pretraining		Posttraining		Pretraining		Posttraining	
	Baseline	3 h	Baseline	3 h	Baseline	3 h	Baseline	3 h	Baseline	3 h	Baseline	3 h
FFAs (μmol/l)												
Placebo	631 ± 240	201 ± 60*	574 ± 165	199 ± 50*	589 ± 175	186 ± 59*	533 ± 369	231 ± 152*	517 ± 166	226 ± 92*	550 ± 132	197 ± 52*
Caffeine	557 ± 257	210 ± 85*	568 ± 166	230 ± 18*	580 ± 138	287 ± 171*	575 ± 157	249 ± 72*	627 ± 139	306 ± 102*	660 ± 319	251 ± 93*
Insulin (μU/ml)												
Placebo	7 ± 4	71 ± 13*	6 ± 1	69 ± 18*	8 ± 8	55 ± 21*	7 ± 3	65 ± 11*	10 ± 4	51 ± 17*	10 ± 5	58 ± 13*
Caffeine	6 ± 3	73 ± 10*	7 ± 2	72 ± 16*	12 ± 11	47 ± 14*	8 ± 4	62 ± 14*†	7 ± 4	50 ± 11*	10 ± 4	56 ± 12*
C-peptide (ng/ml)												
Placebo	1.5 ± 0.6	1.4 ± 0.5	1.6 ± 0.4	1.9 ± 0.7	2.3 ± 0.7	1.7 ± 1.0	1.2 ± 1.0	1.3 ± 1.1	2.5 ± 1.1	1.4 ± 0.6	2.6 ± 0.6	1.6 ± 0.8
Caffeine	1.6 ± 0.6	1.5 ± 0.9	1.9 ± 1.1	1.8 ± 0.7	2.1 ± 0.6	1.5 ± 0.9	1.4 ± 1.2	1.4 ± 1.2	2.4 ± 0.5	1.1 ± 0.5	2.4 ± 1.5	1.7 ± 0.6

Data are means ± SD. *$P < 0.05$ vs. baseline; †$P = 0.013$ vs. pretraining, 3 h.

Effect of exercise on insulin sensitivity

Independent of group, exercise was not associated ($P > 0.1$) with an increase in glucose uptake in either the caffeine or placebo trials (Fig. 1).

Serum FFAs and insulin during the hyperinsulinemic-euglycemic clamp

At the 3-h mark, serum FFAs were significantly ($P < 0.05$) lower compared with baseline in both the caffeine and placebo trials, regardless of group and exercise (Table 2). Plasma insulin was significantly ($P < 0.05$) higher at the 3-h mark, as compared with baseline, in both caffeine and placebo trials, independent of group and exercise. Insulin levels obtained at the 3-h mark were not different ($P > 0.05$) between the lean and type 2 diabetic groups, regardless of trials and exercise. In the obese nondiabetic group, insulin levels obtained at the 3-h mark were higher ($P < 0.05$) in the posttraining caffeine trial than in the pretraining caffeine trial. Baseline FFA and insulin levels did not change ($P > 0.1$) in response to exercise training, independent of treatment and group. Likewise, C-peptide levels at baseline and at the 3-h mark did not change ($P > 0.1$) in response to exercise training.

CONCLUSIONS — We examined the independent effects of caffeine and chronic exercise on glucose uptake in previously sedentary lean men and obese men with and without type 2 diabetes. Caffeine ingestion at a dose equivalent to drinking 2–3 cups of coffee resulted in a substantial decrease in glucose uptake independent of group. Furthermore, exercise training did not attenuate the caffeine-induced decrement in insulin sensitivity in these individuals. Our findings suggest that caffeine ingestion has a negative effect on insulin-mediated glucose uptake that is independent of obesity, type 2 diabetes, and exercise.

That regular exercise failed to alleviate the negative effect of caffeine on glucose uptake in the lean men and obese men with and without type 2 diabetes, despite significant reductions in adiposity, is a novel finding and extends the previous observation by Petrie et al. (2), who examined the effect of caffeine ingestion on insulin and glucose response to a 75-g OGTT. In that study, significant calorie restriction and regular exercise (three times per week) did not abolish the caffeine-induced impairment in insulin-glucose homeostasis in previously sedentary young obese men despite significant weight loss (-8.5 kg). Together, these observations suggest that caffeine ingestion is significantly associated with insulin resistance independent of exercise with or without weight loss.

Although it is now established that caffeine is associated with a marked reduction in insulin sensitivity, the mechanisms of action are not clear. Some (19,20) suggest that caffeine antagonizes skeletal muscle adenosine receptors, whereas others (6,7,21) suggest that caffeine results in a significant increase in epinephrine, with the latter inhibiting the ability of insulin to stimulate peripheral glucose uptake and suppress hepatic glucose production (22,23).

Our finding that caffeine ingestion is associated with a substantial reduction in insulin sensitivity is tempered by recent epidemiological findings suggesting that the consumption of coffee has an inverse relationship with the incidence of type 2 diabetes in European (24) and North American men and women (25). That is, increased coffee consumption (>5 cups) appears to protect against the development of type 2 diabetes. While this seems a paradoxical finding given our observation that caffeine attenuates insulin sensitivity, it is important to note that coffee and caffeine consumption do not equate. Two lines of evidence support this position. First, although coffee consumption is often the most common source of caffeine intake, Brown et al. (26) observed that coffee consumption alone severely underestimated the total intake of dietary caffeine and resulted in serious misclassification. Second, coffee contains many other substances besides caffeine, such as potassium, antioxidants, and magnesium that may elicit additional pharmacological effects on glucose metabolism (27). Indeed, several studies have shown that magnesium intake is associated with increased insulin sensitivity (28) and has been associated with a lower risk of type 2 diabetes (29). Further, Shearer et al. (30) demonstrated that infusion of a synthetic quinide found in roasted coffee is associated with an increase in glucose uptake in rodents. Whether the consumption of caffeine from other dietary sources (cola drinks or chocolate) has similar protective effects is unknown. Together, these observations support the view that coffee and caffeine consumption may have very different biological effects. Stated differently, the inverse relationship between coffee consumption and type 2 diabetes may occur through mechanisms unrelated to caffeine. Clearly there is a need to investigate the long-term effect of caffeine intake in any form on glucose metabolism.

Previous studies have demonstrated that regular exercise is associated with an increase in insulin sensitivity in previously sedentary individuals (2,31–33). However, these findings are confounded by the residual effect of last exercise bout (31,33) and/or weight loss (2,32). Indeed, it is well established that a single bout of exercise is associated with a marked improvement in insulin sensitivity (11). Based on this knowledge, we measured glucose uptake 4 days postexercise. In so doing, it is likely that our protocol underestimated the true influence of exercise on insulin sensitivity. Further, that exercise without weight loss was not associated with improvement in insulin sensitivity in our study is consistent with others (34), as well as with the observation that reduction in total and abdominal adiposity is a mechanism by which exercise improves insulin sensitivity. Consistent with this observation, we have previously reported that the observed increase in glucose uptake following exercise-induced weight loss did not remain significant after controlling for concomitant reductions in total and visceral fat in obese men (12) and women (13). Although we did observe a reduction in total and visceral adiposity in the present study, these changes were relatively small and likely below the threshold required to influence insulin sensitivity.

Limitations of this study warrant mention. Due to sex-specific differences in carbohydrate and caffeine metabolism, we chose to study men. Several studies have indicated that menstrual cycle, oral contraceptive use, and pregnancy can influence caffeine metabolism (27) and insulin sensitivity (35). Second, the small number of participants may have underpowered the study, and we may have been unable to detect true differences between groups. Finally, our study participants were all moderate caffeine consumers. Whether similar findings

would be observed in non– or heavy-caffeine users is unknown.

In conclusion, our observations indicate that caffeine ingestion has substantial, negative effects on insulin-stimulated glucose uptake in obese men with and without type 2 diabetes, independent of chronic exercise. Further, exercise training did not attenuate the decrease in insulin sensitivity associated with caffeine ingestion. The clinical implications of these findings remain to be determined. Nevertheless, caffeine ingestion taken orally in pill form has a detrimental effect on insulin sensitivity in obese men with or without type 2 diabetes, individuals who are already at increased metabolic risk.

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