Caffeinated Coffee, Decaffeinated Coffee, and Caffeine in Relation to Plasma C-Peptide Levels, a Marker of Insulin Secretion, in U.S. Women

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OBJECTIVE — Coffee consumption is associated with reduced risk of type 2 diabetes, but the mechanism is not clearly understood. Elevated C-peptide, as a marker of insulin secretion, has been linked to insulin-resistant type 2 diabetes. In this study, we examined consumption of caffeinated and decaffeinated coffee and total caffeine in relation to concentrations of plasma C-peptide.

RESEARCH DESIGN AND METHODS — Plasma C-peptide concentrations were measured in a cross-sectional setting among 2,112 healthy women from the Nurses’ Health Study I who provided blood samples in 1989–1990. Consumption of caffeinated and decaffeinated coffee and total caffeine was assessed using a semiquantitative food-frequency questionnaire in 1990.

RESULTS — Intakes of caffeinated and decaffeinated coffee and caffeine in 1990 were each inversely associated with C-peptide concentration in age-adjusted, BMI-adjusted, and multivariable-adjusted analyses. In multivariable analysis, concentrations of C-peptide were 16% less in women who drank >4 cups/day of caffeinated or decaffeinated coffee compared with nondrinkers (P < 0.005 for each). Women in the highest quintile compared with the lowest quintile of caffeine intake had 10% lower C-peptide levels (P = 0.02). We did not find any association between tea and C-peptide. The inverse association between caffeinated coffee and C-peptide was considerably stronger in obese (27% reduction) and overweight women (20% reduction) than in normal weight women (11% reduction) (P = 0.005).

CONCLUSIONS — Our findings suggest a potential reduction of insulin secretion by coffee in women. This reduction may be related to other components in coffee rather than caffeine.

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Coffee intake has been associated with a reduction in the risk of type 2 diabetes (1–4). Because of its widespread consumption, understanding the relationship between coffee intake and insulin secretion may have implications in the prevention and treatment of diabetes.

In contrast, short-term studies have consistently shown that acute administration of caffeine induces insulin resistance and impairs glucose tolerance (3,5,6). Long-term effects of caffeine and other components of coffee, which may be more relevant on insulin secretion, have been less well studied. In a recent cross-sectional study of 936 elderly men without diabetes, coffee was associated with increased insulin sensitivity but not with decreased secretion (7). However, this study did not distinguish between caffeinated and decaffeinated coffee, did not study women, and measured only the early insulin response under glucose stimulation.

C-peptide is cleaved from proinsulin and released into the bloodstream in equivalent amounts with insulin (8). Increased C-peptide has been associated with insulin resistance and diabetes (9), cardiovascular disease (10), and colon cancer (11). According to the National Coffee Association, 54% of adults in the U.S. drank coffee in 2000, with average per capita daily consumption of 1.9 cups for men and 1.4 cups for women (12). We found that C-peptide was positively associated with glycemic load and fructose intake (13). We thus assessed caffeinated coffee, decaffeinated coffee, and total caffeine intake in relation to plasma C-peptide levels cross-sectionally among 2,112 women from the Nurses’ Health Study I.

RESEARCH DESIGN AND METHODS — The Nurses’ Health Study I, established in 1976, consists of 121,700 female registered nurses 30–55 years of age who completed a mailed questionnaire and provided medical history and lifestyle information at baseline and on subsequent biennial questionnaires. Diet has been assessed approximately every 4 years using a previously validated (14,15) semiquantitative food-frequency questionnaire (SFFQ). Between 1989 and 1990, blood samples were collected as described previously from 32,826 cohort members who were then 43–69 years of age (13,16). A total of 2,112 women were included in this analysis; all were control participants in four nested case-control studies of breast can-
cer, colon cancer, hypertension, and diabetes. None had previously diagnosed cancer, cardiovascular diseases, or diabetes at time of blood draw. We included only those women who had both a measurement of C-peptide and provided a dietary questionnaire in 1990. The institutional review board of the Brigham and Women’s Hospital in Boston approved the study.

**Dietary assessment**

An SFFQ in 1984, 1986, and 1990 assessed average consumption of caffeinated and decaffeinated coffee and tea over the previous year (frequency responses: never, one to three per month, one per week, two to four per week, five to six per week, one per day, two to three per day, four to five per day, and ≈ six per day). Using sources on food composition including the U.S. Department of Agriculture, we estimated caffeine content as 137 mg/cup for coffee, 47 mg/cup for tea, and 46 mg/bottle or can for cola beverages. We assessed the total caffeine intake by summing the caffeine content for a specific amount of each item (one cup for coffee or tea, one 12-ounce bottle or can for carbonated beverages, and 1 oz for chocolate) multiplied by a weight proportional to the frequency of its use. Our validation study found a high correlation for intake of coffee and other caffeinated beverages from food-frequency questionnaires and four 1-week diet records (coffee, r = 0.78; tea, r = 0.93; and decaffeinated sodas, r = 0.85) (17).

**Measurement of nondietary factors**

Height, current weight, and smoking history were reported at baseline and weight and smoking status were updated biennially. The correlation coefficient between self-reported weight and weight as measured by trained personnel was 0.96 (18). The reproducibility and validity of the physical activity questionnaire has been described elsewhere (19).

**Assay of C-peptide**

C-peptide was measured with enzyme-linked immunosorbent assay and radioimmunoassay as described previously (13). Samples were standardized on quality controls. We obtained a coefficient of variation of <12%.

**Statistical analysis**

We used linear regression models with a robust variance estimate, which allows for valid inference without the assumption of normal distribution in the dependent variable (20). We conducted all statistical analyses with SAS software (Version 8; SAS Institute, Cary, NC). In multivariable models, we adjusted for age, BMI, physical activity, smoking, hours since last meal, laboratory batch, menopausal status, and dietary variables, including total energy, calcium intake, cereal fiber intake, glycemic load, and alcohol consumption. Because alcohol consumption (21) and calcium are inversely associated with C-peptide levels, and cereal fiber and glycemic load are significant predictors of C-peptide (13), we included these variables in our final model. Magnesium and trans fatty acids were not statistically significant and did not change the results substantially when controlled for these, so we did not include them in the final model.

We adjusted all micronutrients and glycemic load for total energy intake with the residual method (22,23). The residual method controls for confounding by total energy intake. We regressed the nutrient intake on total energy; the residuals from regression represent the differences between each individual and are not confounded by total energy intake. Because the residual has negative and positive values, a constant (usually a predicted mean intake) was added to convey an actual nutrient intake. Because consumption of caffeinated coffee and decaffeinated coffee was negatively correlated (r = -0.21, P < 0.05), we included both in the multivariable model.

In our primary analyses, we used the 1990 SFFQ, which assesses intake over the previous year, and the covariates in 1990 in relation to C-peptide level in 1989–1990. Secondary analyses used average intake in 1984, 1986, and 1990 to examine whether intake over a longer period increased predictive accuracy for C-peptide. We averaged the values of continuous covariates and regrouped categorical covariates over this period. Overall results did not change when we excluded the 10% of women who fasted <8 h before blood drawing. We conducted subgroup analysis stratified by BMI, smoking status, physical activity, and alcohol intake. In the model with main effects and the interaction term, we used the Wald test P value for the interaction term to determine statistical significance for interaction.

**RESULTS**

— Women who consumed more caffeinated coffee were more likely to smoke and to drink alcohol (Table 1). Caffeinated coffee consumption was positively associated with intake of total energy, fat, magnesium, alcohol, and caffeine and inversely associated with BMI, intake of trans fatty acids, carbohydrate, cereal fiber, total calcium, and glycemic load (Table 1). The overall pattern for the associations between decaffeinated coffee and covariates were somewhat different from those for caffeinated coffee. However, alcohol intake was inversely associated with consumption of decaffeinated coffee. Women who drank decaffeinated coffee were more likely to have lower intakes of energy and alcohol and caffeine but a higher intake of calcium. Intakes of total fat, trans fatty acids, and carbohydrates were not related to consumption of decaffeinated coffee.

In the cross-sectional analysis, after adjustment for age, BMI, fasting hours, and laboratory batch, consumption of both caffeinated coffee and decaffeinated coffee was statistically significantly associated with lower levels of plasma C-peptide (Table 2). The association did not change after further adjustment for other covariates. In the multivariable model, the magnitude of the decrease of C-peptide was similar for decaffeinated coffee or caffeinated coffee. In addition, we observed an inverse association between total caffeine intake and C-peptide in age-adjusted, BMI-adjusted, and multivariable-adjusted analyses (Table 3).

In multivariable models, C-peptide decreased with every additional cup of decaffeinated coffee (0.057 ng/ml; P < 0.0001) and with every additional cup of decaffeinated coffee (0.063 ng/ml; P = 0.0003). For every 100-mg increase of caffeine intake, C-peptide decreased 0.03 ng/ml (P = 0.02). We found a statistically significant inverse association between decaffeinated coffee and C-peptide levels among women who drank no caffeinated coffee; the estimates were somewhat stronger than when we included those women. Tea consumption was not significantly associated with C-peptide, with or without adjustment for caffeinated or decaffeinated coffee (Table 2). The coefficient estimates for C-peptide levels of...
Coffee, caffeine, and C-peptide levels

Table 1—Baseline characteristics according to caffeinated coffee and decaffeinated coffee consumption among women in the Nurses’ Health Study I

<table>
<thead>
<tr>
<th>Caffeinated coffee consumption in 1990 (cups/day)</th>
<th>Decaffeinated coffee consumption in 1990 (cups/day)</th>
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</thead>
<tbody>
<tr>
<td>Participants (n)</td>
<td></td>
</tr>
<tr>
<td>Age (not standardized)</td>
<td></td>
</tr>
<tr>
<td>C-peptide (ng/ml)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td></td>
</tr>
<tr>
<td>Premenopausal women (%)</td>
<td></td>
</tr>
<tr>
<td>Physical activity (METS/week)</td>
<td></td>
</tr>
<tr>
<td>Alcohol (g/day)</td>
<td></td>
</tr>
<tr>
<td>Total energy (kcal)</td>
<td></td>
</tr>
<tr>
<td>From fat (%)</td>
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<tr>
<td>From trans fatty acid (%)</td>
<td></td>
</tr>
<tr>
<td>From carbohydrate</td>
<td></td>
</tr>
<tr>
<td>Cereal fiber (g/day)</td>
<td></td>
</tr>
<tr>
<td>Magnesium (mg/day)</td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/day)</td>
<td></td>
</tr>
<tr>
<td>Caffeine (mg/day)</td>
<td></td>
</tr>
<tr>
<td>Glycemic load</td>
<td></td>
</tr>
</tbody>
</table>

Cereal fiber, magnesium, calcium, caffeine, and glycemic load intake were energy-adjusted using the residual method. MET, metabolic equivalent.

total coffee (sum of caffeinated and decaffeinated coffee) were similar to those of caffeinated or decaffeinated coffee. When we included total coffee and caffeine in the multivariable model, the coefficient estimates for total coffee but not for caffeine remained statistically significant.

We analyzed average consumption in 1984, 1986, and 1990 and found that the overall associations of caffeinated and decaffeinated coffee and caffeine with C-peptide were similar to those in 1990 and were statistically significant. When we added coffee in 1990 and in 1984–86 simultaneously, the caffeinated and decaffeinated coffee and caffeine intake in 1990 but not intake in 1984–86 remained significantly related with C-peptide. This finding indicated that plasma levels of C-peptide were more closely related to current or relatively recent coffee intake.

Stratified analyses of the 1990 showed that the inverse association between caffeinated or decaffeinated coffee and C-peptide did not differ significantly according to smoking status, physical activity, or alcohol consumption. The inverse association between caffeinated coffee and C-peptide levels was strongest in obese women, weaker in overweight women, and weakest in the normal weight group (P = 0.005) (Fig. 1). A similar but weaker trend was found for decaffeinated coffee (P = 0.2). For total coffee intake, the trend was similar to that for caffeinated coffee but slightly stronger (P = 0.0007).

CONCLUSIONS — Both caffeinated and decaffeinated coffee were inversely associated with C-peptide levels, particularly in obese and overweight women. Because our questionnaire assessed average intake over the past year, we could not precisely determine how quickly a change in coffee consumption altered insulin resistance and secretion to achieve equilibrium. Because the cross-sectional 1990 analysis captured the association and use of the 1984–86 questionnaires did not provide additional predictive ability, it is likely that this effect would be achieved within one or several years, or possibly much less, rather than over many years. Although acute administration of caffeine induces insulin resistance (3,6), complete tolerance can develop after several days, as assessed by blood pressure, plasma renin activity, and plasma catecholamines (24,25). Our findings provide support for the potential benefit of chronic coffee and caffeine consumption on insulin secretion and possibly diabetes (2).

The decreased insulin secretion (90% of women were fasting) in our study is consistent with the increased insulin sensitivity observed by Arnlov et al. (7). In contrast, Arnlov et al. (7) did not observe a decrease in insulin secretion as assessed by early insulin response under glucose stimulation (7). However, C-peptide has a longer half-life than insulin and thus may better represent insulin secretion than insulin levels do (26). Also, our participants were women 42–69 years old; the subjects of Arnlov et al. were men 69.5–84 years old.

The independent association between decaffeinated coffee and C-peptide indicates active ingredients other than caffeine. Previous studies have suggested that plasma glucose concentrations are reduced by chlorogenic acid (also a strong antioxidant) (27), which may combine with other antioxidants in coffee to decrease oxidative stress. Antioxidants may improve insulin sensitivity (28,29) in type 2 diabetes and decrease insulin levels in rats (30). Tea also has many different types of antioxidants; however, total concentrations are much higher in coffee (11.1 mmol) than in tea (1.4 mmol) (31). Furthermore, the effect of caffeine may also depend on other components of coffee. We did not observe an association between C-peptide and tea, which pro-
Table 2—Plasma C-peptide levels by the amount of coffee and tea consumption

<table>
<thead>
<tr>
<th>Consumption in 1990</th>
<th>Age and BMI adjusted</th>
<th>Multivariable adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE (ng/ml)</td>
<td>Change (%)</td>
</tr>
<tr>
<td>Caffeinated coffee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2.09 ± 0.05</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt;1 cup/day</td>
<td>2.06 ± 0.07</td>
<td>−2</td>
</tr>
<tr>
<td>1 cup/day</td>
<td>2.10 ± 0.06</td>
<td>0.3</td>
</tr>
<tr>
<td>2–3 cups/day</td>
<td>2.03 ± 0.05</td>
<td>−3</td>
</tr>
<tr>
<td>≥4 cups/day</td>
<td>1.85 ± 0.06</td>
<td>−12</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Decaffeinated coffee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2.13 ± 0.04</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt;1 cup/day</td>
<td>2.04 ± 0.05</td>
<td>−4</td>
</tr>
<tr>
<td>1 cup/day</td>
<td>1.94 ± 0.06</td>
<td>−8</td>
</tr>
<tr>
<td>2–3 cups/day</td>
<td>1.98 ± 0.05</td>
<td>−7</td>
</tr>
<tr>
<td>≥4 cups/day</td>
<td>1.80 ± 0.08</td>
<td>−15</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>Tea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2.00 ± 0.04</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt;1 cup/day</td>
<td>2.05 ± 0.05</td>
<td>3</td>
</tr>
<tr>
<td>1 cup/day</td>
<td>2.10 ± 0.07</td>
<td>5</td>
</tr>
<tr>
<td>2–3 cups/day</td>
<td>2.04 ± 0.07</td>
<td>2</td>
</tr>
<tr>
<td>≥4 cups/day</td>
<td>2.24 ± 0.17</td>
<td>12</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

The multivariable model was adjusted for dietary factors, including total energy intake (quintiles), alcohol intake (0, 0.1–4.9, 5–14.9, 15–29.9, ≥30 g/day), calcium intake (continuous), cereal fiber intake (continuous), glycemic load (continuous), and other factors, including age (five categories), smoking (never, past, current), BMI (continuous), physical activity (quintiles), fasting hours, laboratory batch, and menopausal status.

Some limitations of our study need to be addressed. First, we did not test insulin sensitivity with the gold standard of the hyperinsulinemic clamp, which requires complicated procedures and could not be used in this epidemiologic study. If we also measured fasting glucose, we would be able to calculate insulin resistance using the homeostatic model assessment, an insulin sensitivity index validated against the gold standard (35). However, both fasting insulin and insulin resistance calculated from the homeostatic model as-

...
assessment model were strong predictors of type 2 diabetes, although insulin resistance is a stronger predictor (36). Another limitation was that we assumed lower fasting insulin reflected greater insulin sensitivity but it could also reflect a failure of the pancreatic β-cell to produce insulin. However, this second possibility is unlikely for several reasons. First, β-cell dysfunction usually follows hyperinsulinemia and is a long, cumulative process. If the inverse association between coffee and C-peptide were due to β-cell dysfunction, we would have expected a stronger effect of long-term average coffee consumption on insulin secretion than cross-sectional data. However, we observed the opposite. Second, we excluded subjects who had diabetes, and the proportion of undiagnosed diabetes in healthy subjects should be small. Finally, coffee consumption has been associated with decreased development of diabetes in our and several other cohorts (1–4), providing internal and external validity to the conclusion that coffee consumption is unlikely to lead to a failure of the pancreatic β-cell dysfunction.

An observational study does not allow us to draw firm conclusions about cause and effect. However, it is unlikely that lower C-peptide levels caused women to increase coffee consumption. In addition, we controlled for many factors that influence insulin resistance and secretion. Although uncontrolled or re-

Figure 1—Consumption of total and caffeinated coffee in 1990. Total coffee included caffeinated and decaffeinated coffee. Model was adjusted for dietary factors, including total energy intake (quintiles), alcohol intake (0, 0.1–4.9, 5–14.9, 15–29.9, ≥30 g/day), calcium intake (continuous), and other demographic factors including age (five categories), smoking (never, past, current), BMI (continuous), physical activity (quintiles), fasting hours, laboratory batch, and menopausal status. For consumption of caffeinated coffee, model was adjusted for decaffeinated coffee (continuous).
sidual confounding cannot be dis-
counted, caffeinated and decaffeinated
drinks had dissimilar patterns with covari-
ates (Table 1), so it would be unusual for a
colluding factor to influence these similarly.

In conclusion, we provide evidence that chronic consumption of caffeinated and/or decaffeinated coffee reduces insulin secretion. Adequately powered clinical trials are needed to investigate the long-term effects on insulin secretion and sensitivity, glucose homeostasis, and hemodynamic variables. If our results are confirmed in other populations, caffeinated and decaffeinated coffee consumption might prove to be an effective strategy for reducing insulin resistance, especially in overweight women.

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References
1. Tuomilehto J, Hu G, Bidel S, Lindstrom J,
Jousilahti P: Coffee consumption and risk of
type 2 diabetes mellitus among middle-
aged Finnish men and women. JAMA 291:
1213–1219, 2004
2. Salazar-Martinez E, Willett WC, Ascherio
A, Manson JE, Leitzmann MF, Stampfer
MJ, Hu FB: Coffee consumption and risk for
type 2 diabetes mellitus. Ann Intern
Med 140:1–8, 2004
P: Caffeine can decrease insulin sensitivity
in humans. Diabetes Care 25:364–369,
2002
4. van Dam RM, Feskens EJ: Coffee con-
sumption and risk of type 2 diabetes mel-
5. Greer F, Hudson R, Ross R, Graham T:
Caffeine ingestion decreases glucose dis-
posal during a hyperinsulinemic-euglyce-
ic clamp in sedentary humans. Diabetes
50:2349–2354, 2001
6. Chensin K, Ringsdorf WM Jr: Blood-
glucose levels after caffeine. Lancet 2:689,
1968
7. Amlow J, Vessby B, Risser U: Coffee con-
sumption and insulin sensitivity. JAMA
291:1199–1201, 2004
8. Wahren J, Ekberg K, Johannson J, Hen-
rillosson M, Pramanik A, Johannsson BL,
Rigler R, Jornvall H: Role of C-peptide in
human physiology. Am J Physiol Endocri-
nal Metab 278:E759–E768, 2000
9. Jenkins DJ, Wolever TM, Buckley G, Lam
KY, Giudici S, Kalmusky J, Jenkins AL,
Patten RL, Bird J, Wong GS, et al.: Low-
glycemic-index starchy foods in the dia-
betic diet. Am J Clin Nutr 48:248–254,
1988
L: Role of fasting serum C-peptide as a
predictor of cardiovascular risk associated
with the metabolic X-syndrome. Med Sci
Monit 8:CR175–CR179, 2002
11. Kaaks R, Toniolo P, Akhmedkhanov A,
Lukanova A, Biessy C, Dechau H, Rinaldi
S, Zeleniuch-Jacquotte A, Shore RE, Riboli
E: Serum C-peptide, insulin-like growth factor (IGF-I), IGF-binding
proteins, and colorectal cancer risk in
women. J Natl Cancer Inst 92:1592–1600,
2000
12. NCA: Consumption in the USA. Avail-
able from http://www.coffeeresearch.org/
13. Wu T, Giovannucci E, Pischon T,
 Hankinson SE, Ma J, Rifai N, Rimm EB:
Fruuctose, glycemic load, and quantity and
quality of carbohydrate in relation to
plasma C-peptide concentrations in U.S.
women. Am J Clin Nutr 80:1043–1049,
2004
14. Willett WC, Sampson L, Stampler MJ,
Rosner B, Bain C, Witschi J, Hennekens
CH, Speizer FE: Reproducibility and va-
didity of a semiquantitative food fre-
quency questionnaire. Am J Epidemiol
122:51–65, 1985
15. Willett W: Nutritional Epidemiology.
New York, Oxford University Press, 1998
16. Hankinson SE, London SJ, Chute CG,
Barbieri RL, Jones L, Kaplan LA, Sacks
FM, Stampler MJ: Effect of transport con-
ditions on the stability of biochemical
3216, 1989
17. Colditz GA, Manson JE, Hankinson SE:
The Nurses’ Health Study 20: year 20 con-
tribution to the understanding of health
among women. J Womens Health 6:49–
62, 1997
18. Rimm EB, Stampler MJ, Colditz GA,
Chute CG, Litin LB, Willett WC: Validity
of self-reported waist and hip circumfer-
ences in men and women. Epidemiology
1:466–473, 1990
19. Wolf AM, Hunter DJ, Colditz GA, Man-
son JE, Stampler MJ, Corsano KA, Rosner
B, Krisa A, Willett WC: Reproducibility
and validity of a self-administered phys-
ical activity questionnaire. Int J Epidemiol
23:991–999, 1994
20. Zeger SL, Liang KY: Longitudinal data
analysis for discrete and continuous out-
21. Meyer KA, Conigrave KM, Chu NF,
Rifai N, Spiegelman D, Stampler MJ,
Rimm EB: Alcohol consumption pat-
terns and Hba1c, C-peptide and insulin
concentrations in men. J Am Coll Nutr
22. Willett W, Stampler MJ: Total energy in-
take: implications for epidemiologic anal-
23. Willett WC, Howe GR, Kushis LH: Adjust-
ment for total energy intake in epidemi-
ologic studies. Am J Clin Nutr 65:12205–
12288; discussion 12295–12315, 1997
24. Robertson D, Wade D, Workman R,
Woosley RL, Oates JA: Tolerance to the
humoral and hemodynamic effects of caf-
1981
25. Brown CR, Benowitz NL: Caffeine and
cigarette smoking: behavioral, cardiovas-
cular, and metabolic interactions. Phar-
macol Biochem Behav 34:565–570, 1989
26. Chen CH, Tsai ST, Chou P: Correlation of
fasting serum C-peptide and insulin with
markers of metabolic syndrome-X in a
homogenous Chinese population with
normal glucose tolerance. Int J Cardiol
68:179–186, 1999
27. Arion WJ, Canfield WK, Ramos FC,
Schindler PW, Burger HJ, Hemmerle H,
Schubert G, Below P, Herling AW: Chloro-
rogenic acid and hydroxynitrobenzalde-
hyde: new inhibitors of hepatic glucose
6-phosphatase. Arch Biochem Biophys 339:
315–322, 1997
28. Jacob S, Henrikson EJ, Schieman AL, Si-
mon I, Clancy DE, Tritschler HJ, Jung WI,
Augustin HJ, Dietze GJ: Enhancement of
glucose disposal in patients with type 2
diabetes by alpha-lipoic acid. Arzneimit-
telforschung 45:872–874, 1995
29. Bruce CR, Carey AL, Hawley JA, Febbraio
MA: Intramuscular heat shock protein 72
and heme oxygenase-1 mRNA are re-
duced in patients with type 2 diabetes:
evidence that insulin resistance is asso-
ciated with a disturbed antioxidant de-
defense mechanism. Diabetes 52:2338–2345,
2003
30. Thirunavukkarasu V, Anuradha CV:
Influence of alpha-lipoic acid on lipid per-
odiation and antioxidant defense system
in blood of insulin-resistant rats. Diabetes
Obes Metab 6:200–207, 2004
31. Svilaa AS, Sakhi AK, Andersen LF, Svilaa
T, Strom EC, Jacobs DR Jr, Ose L, Blom-
hoff R: Intakes of antioxidants in coffee,
wine, and vegetables are correlated with
plasma carotenoids in humans. J Nutr
134:562–567, 2004
32. Boozher CN, Daly PA, Homel P, Solomon
JL, Blanchard D, Nasser JA, Strauss R,
Meredith T: Herbal ephedra/caffeine for
weight loss: a 6-month randomized safety
and efficacy trial. Int J Obes Relat Metab
Disord 26:593–604, 2002
33. Astrup A, Toutbro S, Cannon S, Hein P,
Breum L, Madsen J: Caffeine: a double-
blind, placebo-controlled study of its
thermogenic, metabolic, and cardiovas-
cular effects in healthy volunteers. Am J

Wu and Associates
