



Coffee, diabetes, and weight control^{1,2}

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ABSTRACT

Several prospective epidemiologic studies over the past 4 y concluded that ingestion of caffeinated and decaffeinated coffee can reduce the risk of diabetes. This finding is at odds with the results of trials in humans showing that glucose tolerance is reduced shortly after ingestion of caffeine or caffeinated coffee and suggesting that coffee consumption could increase the risk of diabetes. This review discusses epidemiologic and laboratory studies of the effects of coffee and its constituents, with a focus on diabetes risk. Weight loss may be an explanatory factor, because one prospective epidemiologic study found that consumption of coffee was followed by lower diabetes risk but only in participants who had lost weight. A second such study found that both caffeine and coffee intakes were modestly and inversely associated with weight gain. It is possible that caffeine and other constituents of coffee, such as chlorogenic acid and quinides, are involved in causing weight loss. Caffeine and caffeinated coffee have been shown to acutely increase blood pressure and thereby to pose a health threat to persons with cardiovascular disease risk. One short-term study found that ground decaffeinated coffee did not increase blood pressure. Decaffeinated coffee, therefore, may be the type of coffee that can safely help persons decrease diabetes risk. However, the ability of decaffeinated coffee to achieve these effects is based on a limited number of studies, and the underlying biological mechanisms have yet to be elucidated. *Am J Clin Nutr* 2006;84:682–93.

KEY WORDS Coffee, caffeine, tea, diabetes, weight loss, glucose tolerance

INTRODUCTION

Coffee consumption, which probably originated in northeast Africa, spread throughout the Middle East in the 15th century and thence to Europe (1). It is estimated that more than half of the US population now consumes coffee (2). Of the 20 epidemiologic studies of coffee that were identified (3–22), 17 (3–19) found evidence that coffee consumption can reduce the risk of type 2 diabetes, improve indicators of normal glucose metabolism, or both (**Table 1**). It has been estimated that diabetes will afflict $\approx 12\%$ of Americans (23) and that 220 million cases of type 2 diabetes will exist worldwide by 2010 (24). The epidemiologic findings offer the promise that coffee, or one or more of its many constituents (25), may prove to be useful in the development of strategies for the prevention or treatment of diabetes.

This review discusses epidemiologic and laboratory studies of the effects of coffee and its constituents on diabetes risk. We focused on factors related to diabetes risk, such as weight loss and glucose metabolism. To provide an empirical basis for assessing the overall health effects of coffee consumption, we included studies of other health effects of coffee. Only studies published in peer-reviewed journals were considered. We first used MEDLINE to locate relevant studies published during the past decade. Reference lists in these studies were used to find relevant older studies. A summary of findings relevant to the possibility of using coffee or its constituents for diabetes prevention and suggestions for future research are included here.

EPIDEMIOLOGIC STUDIES

Only 3 (20–22) of the 20 identified published epidemiologic studies of the association between habitual coffee consumption and diabetes risk, healthy glucose metabolism, or both (3–22) did not find a protective effect, and none found a deleterious effect (**Table 1**). Eleven of the reported analyses were prospective cohort studies (3–11, 18, 19), one of which was a meta-analysis (9). Ten were cross-sectional studies (7, 12–17, 20–22). Seven found the protective effect to be dose-related (3–5, 7, 10, 11, 14). The 4 studies that tested decaffeinated coffee found a protective effect (5, 10, 11, 17), and 1 of those studies found the same results in 2 separate, large prospective cohorts (5). Four studies concluded that coffee constituents other than caffeine were involved in the protective effect (10, 11, 12, 17). One prospective study did not find a protective effect from instant coffee (10), but another study did find such an effect (11).

One study that assessed the effect of weight change found a prospective protective effect of beverage consumption that occurred only in participants who had previously lost weight (10). The protective effect occurred subsequent to the weight loss and was related to the weight loss in a dose-response

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TABLE 1Epidemiologic studies of habitual coffee consumption and diabetes risk¹

Study	n	Participants	Type of study	Outcome measures	Significant findings
Prospective studies					
van Dam and Feskens, 2002 (3)	17 111	Dutch adults 30–60 y old	Prospective; mean follow-up of ≈7 y	Incidence of type 2 diabetes (306 cases) from self-reports	Dose-response protective effect from coffee
Saremi et al, 2003 (20)	2680	US Pima Indian adults, mean age 27 y	Prospective; mean follow-up of 11 y	Incidence of diabetes (824 cases) from OGTT	No significant effect from coffee
Ruenanen et al, 2003 (21)	19 518	Finnish adults 20–98 y old	Prospective; mean follow-up of ≈15 y	Incidence of type 2 diabetes (855 cases) from national registries	No significant effect from coffee
Tuomilehto et al, 2004 (4)	14 629	Finnish adults 35–64 y old	Prospective; mean follow-up of 12 y	Incidence of type 2 diabetes (381 cases) from national registries	Dose-response protective effect from coffee
Salazar-Martinez et al, 2004 (5)	41 934 men, 84 276 women	US male health professionals 40–75 y old and female nurses 30–55 y old	Prospective; mean follow-up of ≈13 y for men and ≈18 y for women	Incidence of type 2 diabetes (1333 cases in men and 4085 cases in women) from confirmed self-reports	Dose-response protective effect from caffeinated coffee; non-dose-related protective effect from caffeine
Rosengren et al, 2004 (6)	1361	Swedish women 39–65 y old	Prospective; mean follow-up of 18 y	Incidence of diabetes (74 cases) from self-reports and national registries	Protective effect from coffee
van Dam et al, 2004 (7)	1312	Dutch adults 50–74 y old	Prospective; mean follow-up of 6.4 y	Incidence of type 2 diabetes (128 cases) from fasting blood tests and OGTT; impaired glucose tolerance (118 cases) from OGTT; impaired fasting hyperglycemia (275 cases)	Dose-response protective effect for glucose intolerance from coffee
Carlsson et al, 2004 (8)	10 652	Finnish twins 30–60 y old	Prospective; mean follow-up of 20 y	Incidence of type 2 diabetes (408 cases) from national registries	Protective effect from coffee
van Dam and Hu, 2005 (9)	193 473	Meta-analysis using 9 international cohort studies, adults 20–98 y old	Prospective; mean follow-up of ≈23 y	Incidence of type 2 diabetes (8394 cases) from a variety of measurements	Protective effect from coffee
Greenberg et al, 2005 (10)	7006	US adults 32–89 y old	Prospective; mean follow-up of 8.4 y	Incidence of type 2 diabetes and death from diabetes (309 cases) from self-reports	Dose-response protective effect (but only if preceded by weight loss) from ground caffeinated coffee, ground decaffeinated coffee, and caffeine
van Dam et al, 2006 (11)	88 259	US female nurses 24–46 y old	Prospective; mean follow-up of 9.8 y	Incidence of type 2 diabetes (1263 cases) from confirmed self-reports	Dose-response protective effect from caffeinated coffee, decaffeinated coffee, and caffeine
Cross-sectional studies					
Isogawa et al, 2003 (12)	4620	Japanese adults 40–50 y old	Cross-sectional	Prevalence of fasting hyperglycemia	Protective effect from coffee and caffeine
Arnlov and Vessby, 2004 (13)	936	Swedish adults 69.5–74.1 y old	Cross-sectional	Insulin sensitivity and secretion by hyperinsulinemic-euglycemic clamp	Protective effect for insulin sensitivity from coffee, no effect for insulin secretion from coffee

(Continued)

TABLE 1 (Continued)

Study	n	Participants	Type of study	Outcome measures	Significant findings
Agardh et al, 2004 (14)	7949	Swedish adults 39–56 y old	Cross-sectional	Prevalence of type 2 diabetes (107 cases) and prevalence of impaired glucose tolerance (330 cases) from OGTT; insulin sensitivity and β -cell function from glucose homeostasis	Dose-response protective effect for type 2 diabetes and impaired glucose tolerance from coffee; protective effect for insulin resistance and β -cell function from coffee
van Dam et al, 2004 (7)	456–2280 ²	Dutch adults 50–74 y old	Cross-sectional	Levels of hyperglycemia from various measures; insulin sensitivity from glucose homeostasis; postload glucose tolerance from OGTT	Protective effect for insulin sensitivity and postload glucose tolerance from coffee
Soriguer et al, 2004 (15)	1226	Spanish adults	Cross-sectional	Prevalence of diabetes; fasting glucose and insulin sensitivity from glucose homeostasis; postload glucose tolerance by OGTT	Protective effect for diabetes plus postload glucose tolerance from coffee
Yamaji et al, 2004 (16)	3225	Japanese men 46–59 y old	Cross-sectional	Prevalence of fasting hyperglycemia; postload glucose tolerance by OGTT and type 2 diabetes (358 cases)	Dose-response protective effect for postload hyperglycemia (glucose tolerance) from coffee
Wu et al, 2005 (17)	2112	US female nurses 42–69 y old	Cross-sectional	Insulin secretion, from C-peptide concentrations in blood samples	Protective effect from caffeinated coffee, decaffeinated coffee, and caffeine, especially in obese and overweight women
Faerch et al, 2005 (18)	262 cases, 4627 controls	Danish adults 30–60 y old	Case-control (cross-sectional)	Prevalence of diabetes	Protective effect from coffee
Bidel et al, 2006 (19)	2434	Finnish adults 45–64 y old	Cross-sectional	Fasting glucose and insulin; postload glucose tolerance by OGTT	Protective effect from coffee
Mackenzie et al, 2006 (22)	≈14 900	US adults 18–75 y old	Cross-sectional	Glycosylated hemoglobin concentrations in blood samples	No protective effect

¹ OGTT, oral-glucose-tolerance test. Fasting glucose and insulin sensitivity were measured in blood samples drawn after the subjects had fasted overnight. The source of outcome variables and the number of cases are not specified here if they are not specified in the original article.

² A range is presented because the article cited had different numbers of subjects in different analyses.

manner, which suggested that the weight loss was the key. In addition, this study found that intakes of ground caffeinated and ground decaffeinated coffee were independently associated with the prior weight loss, which implies that both caffeine and noncaffeine compounds in coffee may help people decrease body weight. This idea is supported by the results of a recent, larger, prospective epidemiologic study, which found that increases in the intakes of caffeine, coffee, and decaffeinated coffee were inversely associated with weight gain over a 12-y period (26). However, the effects were relatively modest, which suggests that any weight loss caused by caffeine or coffee is unlikely to explain the negative association of either substance with diabetes risk.

LABORATORY STUDIES

Weight loss

Studies have shown that long-term consumption of caffeine (27–29), caffeinated cola (30), and caffeinated tea (31) decreases body weight in rodents. Some studies have also found decreases in adipose-pad weight (27–31) and the number of adipocytes (28), sometimes without a decrease in daily caloric intake (27, 30, 31). Bukowiecki et al (32) found that adding cola to an ad libitum Purina chow diet increased total energy intake by 50% and decreased the rate of body weight gain in rats.

These animal studies and the prospective epidemiologic studies on weight loss (11, 26) suggest that long-term caffeine and



coffee consumption could decrease body weight in humans. There is little evidence from trials in humans, and the findings are equivocal. In one 24-wk placebo-controlled trial in humans, caffeine did not induce significant weight loss in obese subjects (33). It is possible that caffeine may induce significant weight loss in nonobese subjects because caffeine has been shown to cause greater thermogenesis, lipolysis, and fat oxidation (*see* Thermogenesis) and insulin secretion (*see* Insulin secretion) in nonobese than in obese persons. Kovacs et al (34) found no significant difference in weight regain during the 13 wk after a very-low-energy diet between participants who ingested caffeine in green tea and those who ingested placebo.

Noncaffeine compounds may also exist in coffee that induce weight loss, which could help explain the epidemiologic finding that increasing consumption of ground decaffeinated coffee was significantly associated with weight loss (10).

Research is needed on the possibility that long-term caffeine and coffee consumption can help reduce body weight in humans. Such weight reduction would probably decrease the risk of diabetes, because weight loss lowers diabetes risk (35).

Thermogenesis and lipid metabolism

Thermogenesis

Considerable evidence from studies in humans supports the hypothesis that coffee consumption induces weight loss by increasing thermogenesis. It has been estimated that a habitual consumption of 6 cups coffee (ie, 600 mg caffeine/d) causes an increase in energy expenditure (EE) of ≈ 100 kcal/d (36), which could indeed lead to significant weight loss. This estimate does not apply equally to all types of coffee. EE has been found to be elevated for several hours after either injection of caffeine (30) or ingestion of caffeine (36–39), ground caffeinated coffee (40), or instant caffeinated coffee (41, 42). There is evidence that the increase in energy consumption is related to the dose of caffeine consumed (38, 39). In addition, 24-h EE has been found to be raised by the ingestion of caffeine (43) and instant-caffeinated coffee (44). Similarly, it has been shown that the thermic effect of food is increased by the ingestion of caffeine (36) and instant-caffeinated coffee (42, 44). The one study in human subjects of the consumption of decaffeinated coffee, in the form of ground decaffeinated coffee, did not find an increase thermogenesis (40).

This accumulated evidence from human studies suggests that caffeine is the primary, and possibly the sole, ingredient in coffee that is responsible for coffee's thermogenic effect, given that the one study of decaffeinated coffee and EE found no significant effect (40). On the other hand, the lack of a link between decaffeinated coffee consumption and EE is based on only one study. No studies of the influence of decaffeinated coffee intake on the thermic effect of food have been conducted.

Tolerance does not appear to develop to caffeine's thermogenic response in persons who are regular coffee or tea drinkers, because Jung et al (37) found increases in thermogenesis in regular drinkers. Astrup et al (38) found the same result in subjects who had fasted overnight, which suggests that, if tolerance erodes with time, it takes >12 h to do so.

Lipid metabolism

Coffee may increase thermogenesis in part by increasing fat oxidation. In long-term rodent studies, caffeine ingestion reduces adipose-pad size (27–31) and the number of adipocytes (28). These findings suggest that caffeine and coffee consumption could help individuals lose weight by reducing body fat, possibly by increasing lipid metabolism. Using a lowered respiratory exchange ratio as an indicator of greater fat oxidation in human subjects, some investigators concluded that fat oxidation is increased in humans by consumption of caffeine (42, 45, 46) and caffeinated coffee (42, 44). Decaffeinated coffee was the placebo when caffeinated coffee was tested (42, 44), which suggests that it is the caffeine that induces the fat oxidation, although no one has yet compared the effects of decaffeinated coffee with the effects of a noncoffee, noncaffeine placebo.

Not all investigators have found that caffeine increases fat oxidation in human subjects. Dulloo et al (47) observed no significant change in the respiratory exchange ratio after ingestion of caffeine by healthy young male subjects, and Arciero et al (48) also found no such change in old and young adult male subjects.

Lipolysis

Lipolysis is another indicator of lipid metabolism, and greater lipolysis has frequently been observed after caffeine or coffee intake by human subjects. Investigators have used either plasma free fatty acids (FFA) and glycerol assays as indicators of lipolysis, and glycerol is considered the more reliable indicator (49). Several human studies found that an acute increase in lipolysis resulted from ingestion of caffeine (45, 46, 37, 50–52), ground caffeinated coffee (45) and instant caffeinated coffee (44, 50, 53, 54). No increase in lipolysis was found after ingestion of decaffeinated coffee (45), instant decaffeinated coffee (50) or ground decaffeinated coffee (55); these results derive from only one human study for each type of decaffeinated coffee.

Obesity

Some evidence exists that caffeine's ability to increase thermogenesis, fat oxidation, and lipolysis and thereby to help persons lose weight is greater in nonobese than in obese persons. Some (37, 42, 44), but not all (37), human studies found that caffeine increases thermogenesis more in nonobese than in obese subjects. Similarly, Acheson et al (42) and Daubresse et al (50) found that caffeine induced greater increases in lipolysis in nonobese than in obese subjects, and Acheson et al (42) found the same pattern for fat oxidation. In contrast, Bracco et al (44) did not find that caffeine ingestion increased fat oxidation more in nonobese than in obese female subjects. Acheson et al (42) suggested that the generally lower sensitivity to lipolytic stimuli observed in obese subjects than in nonobese subjects may be responsible for causing greater effects in nonobese subjects.

Biological mechanisms

The laboratory evidence presented above makes it seem likely that caffeine is the main ingredient that gives coffee its ability to induce weight loss, fat oxidation, lipolysis, and thermogenesis. However, the specific mechanisms by which caffeine induces these effects are not presently known. As pointed out by Graham (43), most of the evidence about such mechanisms is derived from animal or in vitro models. It is still not clear which specific



mechanisms in which tissues in the intact animal are involved in caffeine's responses.

Astrup et al (38) conducted a study in humans that illustrates the possible links between caffeine intake, fat oxidation, lipolysis, thermogenesis, and weight loss. They measured EE, blood pressure, heart rate, and plasma hormone and substrate concentrations in response to caffeine intake in 6 healthy human subjects. Using regression techniques, they found that caffeine-induced changes in heart rate, plasma lactate, and plasma triacylglycerol responses accounted for 67% of the variation in the thermic effect of caffeine. It seems likely, therefore, that a sizeable portion of the thermogenic effect of caffeine may be due to increased cardiovascular work and to thermogenic processes associated with the production of lactate and triacylglycerol. The increase in cardiovascular work is probably due to caffeine's increasing the peripheral resistance (56), which raises blood pressure. The increase in lactate could involve the Cori cycle, in which glucose and glycogen are converted to lactate. As suggested by Astrup et al (38) and Graham (43), the association between thermogenesis and triacylglycerol concentrations may be due to the extra energy required for the increased reesterification involved in producing triacylglycerol. The increased reesterification is thought to take place in the liver and to be induced by increased hepatic uptake of FFA triggered by increases in plasma FFA due to caffeine intake. These ideas are consistent with studies showing that caffeine ingestion does not increase the energy cost of exercise in women (44).

Despite the multitude of studies that have investigated coffee and caffeine, there is still no clear, well-accepted understanding of their mechanisms of action. In a review of caffeine, Daly (54) concluded, "[I]t will undoubtedly be years before a satisfactory understanding of the complex mechanism of the action of caffeine is attained." It seems likely that the same is true of the many noncaffeine constituents of caffeine, which have not been researched as well as has caffeine.

Caffeinated coffee has been studied much more frequently than decaffeinated coffee, and caffeine appears to be responsible for some of the actions of caffeinated coffee. The 4 most popular mechanisms thought to underlie caffeine's effects are adenosine receptor antagonism; increased concentrations of catecholamines, particularly epinephrine; inhibition of cyclic nucleotide phosphodiesterases; and increased intracellular calcium. It seems unlikely that the last 2 mechanisms play an important role. For caffeine to act as a phosphodiesterase inhibitor or stimulator of calcium-release channels, pharmacologic or lethal concentrations (500–5000 μmol caffeine/L) are needed. These concentrations are an order of magnitude higher than concentrations achieved by normal coffee drinking—from 5 to 20 μmol caffeine/d (57). Moreover, according to Daly and Fredholm (58), caffeine is only a weak phosphodiesterase inhibitor, even at pharmacologic or lethal concentrations.

Caffeine has been shown to have many *in vivo* pharmacologic effects that are opposite to those of adenosine (59). It has also been found that the function of adenosine receptors is partially blocked by caffeine at plasma concentrations of 5–10 $\mu\text{mol/L}$. Caffeine is 1,3,7-trimethylxanthine, which is demethylated to 3 pharmacologically active dimethylxanthines after ingestion: theophylline, theobromine, and paraxanthine. Paraxanthine is the primary metabolite found in blood after caffeine ingestion (59). The structure of xanthines is similar to that of adenosine, which allows the xanthines to bind to and antagonize adenosine receptors. Methylxanthines, including caffeine, are widely used as

antagonists for adenosine receptors (59), which are ubiquitous in the body. In rats, they occur in the nervous system, brain, vascular endothelium, heart, liver, kidney, adipose tissues, and muscle (60, 61).

Caffeine has been shown to cross the blood-brain barrier and to increase circulating concentrations of epinephrine in humans (62, 63), which suggests that some of caffeine's effects are modulated by sympathetic stimulation. For example, epinephrine is known to increase thermogenesis in humans, so it seems logical to attribute part of the caffeine-induced increase in thermogenesis (*see* Thermogenesis) to β -adrenergic stimulation.

It is likely that adenosine-receptor antagonism (37) plays a part in caffeine's ability to increase lipolysis. Adenosine suppresses lipolysis in rats (64), and thus adenosine-receptor blockade by caffeine should increase lipolysis. In addition, good reasons exist to believe that elevated catecholamine concentrations mediate caffeine's effects on lipolysis in humans (52). Catecholamines have been found to be important regulators of lipolysis, and elevated concentrations of epinephrine have been found to elevate lipolysis in humans (65). Catecholamines and adenosine-receptor antagonism are thought to increase lipolysis by raising adipose tissue concentrations of cyclic AMP, which has been shown to increase cellular lipase and lipolysis in humans (53).

Some researchers assessed the relative importance of catecholamine elevation and adenosine-receptor antagonism in the relation between caffeine and lipolysis, and several investigators concluded that the major factor is increased epinephrine concentrations. Thong and Graham (52), for instance, found that caffeine-induced elevations in plasma FFA and glycerol in 7 healthy young men were eliminated by administration of a β -adrenergic receptor blocker, propranolol. Keijzers and De Galan (51) found that an adenosine reuptake inhibitor, dypiramide, which does not cross the blood-brain barrier, did not elevate epinephrine or plasma FFA in 12 healthy volunteers. In contrast, they found that caffeine, which is an adenosine-receptor antagonist and which does cross the blood-brain barrier where it can act to elevate epinephrine, elevated both epinephrine and plasma FFA.

Other investigators concluded that adenosine-receptor antagonism by caffeine accounts for caffeine's ability to induce lipolysis in humans. Jung et al (37), for instance, found in regular caffeine-beverage drinkers that caffeine ingestion or injection did not increase plasma concentrations of epinephrine but did increase plasma FFA and glycerol. Their conclusion was that it was not via the sympathoadrenal mechanisms that caffeine elevated plasma FFA and glycerol, because their subjects had developed tolerance to the ability of caffeine to elevate epinephrine. Their conclusion is supported by research showing that sympathetomized animals have a normal response to caffeine (66). The mechanisms and pathways involved in caffeine's thermogenic and lipolytic effects have yet to be clarified.

Physical activity

Caffeine or coffee could also cause weight loss by inducing increases in physical activity. First, caffeine or other coffee compounds may stimulate a spontaneously higher rate of physical activity. Caffeine has been found to increase motor activity in rodents at doses between 3 and 30 mg/kg and to reduce motor activity at higher doses (55). Nonexercise activity thermogenesis was found to consume up to 350 kcal/d in humans (67), and Bracco et al (44) found that spontaneous physical activity did not

increase in humans who drank 5 cups instant caffeinated coffee/d, as assessed by a radar motion-detection system. It is possible that the physical activity response is biphasic in humans, as it has been found to be in rodents, and that the caffeine dose used by Bracco et al was high enough to induce decreases in physical activity.

Second, there is abundant evidence that ingestion of caffeine by human subjects improves exercise performance (67), which could lead them to increase their level of physical activity. Caffeine, but not coffee, has been shown to have an ergogenic effect—ie, to increase endurance, speed, power output, or all 3—in human exercise activities lasting from 1 min to 2 h (43). This finding suggests that there are noncaffeine compounds in coffee that counteract the ergogenic effects of caffeine.

Glucose metabolism

Evidence in humans and rodents

The results of most studies of the acute effects of caffeine ingestion on glucose metabolism and insulin sensitivity, as measured by using an oral-glucose-tolerance test or hyperinsulinemic euglycemic or hypoglycemic clamp shortly after caffeine intake, are at odds with the epidemiologic study findings that long-term coffee consumption can increase insulin sensitivity and decrease diabetes risk. Lane et al (68) cautioned that the consumption of caffeinated beverages by persons with diabetes could increase the risk of diabetes complications. This finding is consistent with findings in most studies in humans that glucose metabolism is impaired shortly after the ingestion of caffeine (51, 68–72), ground caffeinated coffee (73), or instant caffeinated coffee (74–76). A minority of these studies have found no impairment in glucose metabolism after ingestion of caffeine (50) or instant caffeinated coffee (34, 38). It is interesting that many studies showed that ingestion of coffee or caffeine without inclusion of a carbohydrate meal does not lead to significant changes in plasma glucose or insulin concentrations (50, 52, 54, 68, 70, 71, 73).

Two human studies that distinguished between caffeinated and decaffeinated coffee suggest a possible resolution of the difference between caffeine's negative short-term effects on glucose metabolism and coffee's long-term ability to decrease diabetes risk. Naismith et al (77) found that consumption of decaffeinated coffee for 14 d decreased blood glucose in healthy volunteers accustomed to consuming 560 mg caffeine/d. They used a crossover design without randomization, and the 20 volunteers served as their own controls. Battram et al (73), using a similar design with randomization and 10 volunteers, found that the ingestion of caffeine increased plasma glucose and insulin more than did that of ground caffeinated coffee and also that the ingestion of ground caffeinated coffee increased plasma glucose more than did that of ground decaffeinated coffee, which actually decreased plasma glucose. The findings of Naismith et al and Battram et al suggest that there are noncaffeine compounds in coffee that counteract caffeine's acute impairment of glucose metabolism and hence contribute to the ability of long-term consumption of ground coffee to enhance glucose tolerance and insulin sensitivity. The findings of Battram et al also suggest that ground decaffeinated coffee has stronger potential than does ground caffeinated coffee to enhance insulin sensitivity and reduce diabetes risk over the long term.

It is possible that tolerance develops to caffeine's impairment of glucose metabolism, although no evidence of this exists as yet in humans (51). In a randomized controlled trial, van Dam et al (78) found that such tolerance did not develop in a period of 4 wk. Choi et al (30) found that rats fed caffeinated cola for 28 wk had insulin sensitivity significantly higher than that of controls, which suggested that such tolerance does develop in rats. Petrie et al (70) and Robinson et al (71) found evidence that, when tolerance does develop in humans, it is reversed by ≤ 48 h of abstinence.

Biological mechanisms

Current evidence suggests that caffeine induces a decrease in insulin sensitivity primarily by diminishing the glucose uptake in skeletal muscle. Caffeine ingestion has been shown to increase glucose uptake in the liver in dogs (79) and to decrease it in human skeletal muscle (80). It seems likely that, in humans, the decrease in skeletal muscle is larger than the increase in the liver because skeletal muscle comprises ≈ 35 –40% of the human body; skeletal muscle is responsible for 50–85% of glucose clearance after carbohydrate ingestion and infusion (81). Thong et al (80), using direct Fick techniques during an insulin clamp test, observed that human leg muscle glucose uptake was suppressed by $\approx 50\%$ after caffeine ingestion. Because caffeine is known to antagonize adenosine receptors, and adenosine is known to facilitate the action of insulin on the glucose uptake by adipocytes, it is possible that adenosine-receptor blockade is a key mechanism by which caffeine intake decreases insulin sensitivity (82).

Evidence suggests that caffeine acutely inhibits insulin sensitivity and glucose tolerance primarily by increasing epinephrine in humans. First, there are reports that caffeine increases circulating concentrations of epinephrine (51, 52, 63) and simultaneously decreases insulin sensitivity (51, 52) in human subjects. Second, some studies in humans showed that adrenalin activates the β -adrenergic receptor and decreases insulin stimulation of whole-body glucose metabolism (83, 84). Third, reports exist that caffeine ingestion in humans with impaired epinephrine response has no effect on glucose or insulin concentrations (85). Fourth, Keijzers and De Galan (51) found that ingestion of caffeine by human subjects increased epinephrine and decreased insulin sensitivity, whereas ingestion of dipyrindamole, an adenosine reuptake inhibitor, did not induce either of these changes. Fifth, Thong and Graham (52) found that insulin sensitivity in human subjects was reduced and plasma concentrations of insulin were increased when caffeine was administered alone but not when caffeine was administered together with propranolol, a nonselective β -adrenergic receptor blocker.

Insulin secretion

Evidence suggests that caffeine induces acute increases in β -cell insulin secretion that could be involved in the impairment of glucose tolerance and the decrease in insulin sensitivity brought on by caffeine. Thong and Graham (52) found that C-peptide, an indicator of insulin secretion, was elevated by 39% by ingestion of caffeine in a controlled trial involving an oral-glucose-tolerance test in healthy young men. Using a similar experimental design, Robinson et al (71) found evidence of a nonsignificant caffeine-induced increase in insulin secretion in men with type 2 diabetes, and Petrie et al (70) found no increase



in such insulin secretion in obese men. Arnlov and Vessby (13), in a cross-sectional epidemiologic study of 946 elderly adults, found that concentrations of early insulin response in a hyperinsulinemic-euglycemic clamp, an indicator of insulin secretion, were not elevated in habitual coffee drinkers. Wu et al (17), also in a cross-sectional epidemiologic study, found that greater intakes of caffeinated coffee, decaffeinated coffee and caffeine were associated with lower fasting C-peptide concentrations in 2112 healthy female nurses. They concluded that coffee consumption was associated with decreased insulin secretion and stated that this finding was consistent with an association of coffee consumption with increased insulin sensitivity. Wu et al also found that the effect was significantly stronger in obese and overweight than in normal-weight nurses; this finding may be related to the finding of Petrie et al that caffeine acutely increased insulin secretion in normal-weight but not in obese subjects.

In vitro evidence exists that caffeine increases β -cell insulin secretion. Shi (86) found this to be true by using mice islets, and Bruton et al (87) found the same effect in mice β -cells. They also found evidence that this effect was due in part to sensitization of the ryanodine receptor by caffeine, rather than being solely due to the inhibition of cyclic AMP-phosphodiesterases. It is also of interest that Bruton et al found that caffeine stimulated insulin secretion only in the presence of high concentrations of glucose. This finding is consistent with the fact that most of the epidemiologic studies that assessed fasting and postload glucose concentrations found that habitual coffee consumption was associated with postload but not fasting glucose concentrations (7, 9, 12, 14–16).

Satiety

Conceivably, caffeine or other compounds in coffee may enhance satiety, and hence long-term consumption of caffeine or coffee may help persons lose weight. In fact, the finding by Westerterp-Plantenga et al (88) that satiety assessed in a cross-sectional survey of 76 human subjects was positively correlated with the subjects' reported habitual caffeine consumption. Kovacs et al (34) found higher satiety and lower leptin concentrations in habitual caffeine-beverage drinkers who reported higher daily caffeine intake. Zheng et al (27) found in mice that long-term caffeine intake decreased body-weight growth and intraperitoneal adipose-pad weight without changes in food intake. Apparently the caffeine increased satiety, because the animals were fed ad libitum. The possibility that coffee intake influences satiety has not been well researched in humans.

OTHER HEALTH EFFECTS

The pressor effect

Ingestion of caffeine and some types of coffee by humans has been shown to acutely increase blood pressure (51, 89, 90) and peripheral circulatory resistance (90), an effect referred to as the pressor effect. The pressor effect is important to the relation between coffee and diabetes for 2 reasons. First, the extra energy required for the pressor effect may contribute to the increased thermogenesis observed after ingestion of caffeine. And this increased thermogenesis may help persons lose weight and hence reduce diabetes risk. Thus, the pressor effect may contribute

toward coffee's ability to decrease diabetes risk. Second, the pressor effect could increase the risk of cardiovascular disease (CVD) events, particularly in persons with hypertension or other CVD risk factors. Therefore, given the high prevalence of CVD risk factors in the US population, the pressor effect could substantially reduce the usefulness of coffee or its constituents in diabetes prevention or treatment.

The pressor effect is probably caused by caffeine because most investigators have found the pressor effect to occur after the ingestion of caffeine (51, 54, 89–97), ground caffeinated coffee (40), instant caffeinated coffee (56, 97), and caffeinated Italian coffee, ie, espresso (90). However, a few investigators found that caffeinated coffee did not induce the pressor effect. Noordzij et al (98) found that blood pressure increased more when the caffeine was ingested alone than when it was ingested in coffee. Bracco et al (44) found that ingestion of instant caffeinated coffee did not induce a significant pressor effect, and Horst et al (40) concluded that ground decaffeinated coffee did not induce a pressor effect.

Tolerance to the caffeine-induced pressor effect develops within 4 d (62). This tolerance is partial in that it reduces, but does not negate, the effect observed in subjects with no tolerance (92, 99). Attenuation of the pressor effect starts 20 h after the ingestion of caffeine (56, 100).

Other health effects

Coffee is generally considered safe when consumed in moderation (101). For example, the Canadian government's Guidelines to Healthy Eating recommend limiting caffeine intake to 400–450 mg/d, which would be the amount ingested in consuming approximately three 8-oz (237-mL) cups of brewed caffeinated coffee (102). However, the toxic compounds in coffee (103) could have negative effects in pregnant or breastfeeding women and in children. Caffeine at high concentrations has been found to be teratogenic in animal studies (104). Browne (105) concluded, on the basis of a review of epidemiologic studies, that the evidence was not adequate to ascertain the possibility of risk of congenital abnormalities resulting from maternal caffeine consumption. Caffeine has been found to potentiate the teratogenic effect of other substances, such as tobacco and alcohol (106). Whereas the effects of coffee on infertility and prematurity have not been established, it does appear that ingestion of > 3 cups/d decreases fetal birth weight (107, 108). The Canadian guidelines recommend limiting caffeine consumption to 300 mg/d in pregnant and breastfeeding women, and to 85, 62.5, and 45 mg/d in children aged 10–12, 7–9, and 4–6 y, respectively (102).

Dependency on caffeine is characterized by the development of tolerance, as reflected by increases in dose size with time, persistent desire, and withdrawal symptoms (43). High doses can cause anxiety, nervousness, sleep disturbance, irritability, agitation, and gastrointestinal disturbances (109). Withdrawal symptoms include headaches, irritability, anxiety, depression, drowsiness, and fatigue.

Evidence shows that caffeine may have some deleterious effects in the elderly, such as increasing the risk of kidney stones (110). However, a large prospective epidemiologic study involving middle-aged women concluded that daily consumption of 8 oz caffeinated coffee, decaffeinated coffee, or tea was independently associated with a small (8–10%) reduction in the risk of kidney stone formation (111). Caffeine may also contribute to



osteoporosis, because it increases urinary concentrations of calcium, and the resulting negative effects on calcium metabolism and bone grow with increasing age (110). Rapuri et al (112), for instance, found that the intake of > 18 oz coffee/d was associated with accelerated spinal bone loss in elderly postmenopausal women, and Hasling et al (113) found that > 29.5 oz coffee/d could induce a loss of an additional 1.6 mmol Ca/d in postmenopausal osteoporotic women. Harris and Dawson-Hughes (114) found that higher coffee intake accelerated bone loss in healthy postmenopausal women but only in those women whose calcium intake was below the recommended daily allowance of 800 mg.

As summarized above (*see* Evidence in humans and rodents), strong evidence exists that caffeine and caffeinated coffee decrease insulin sensitivity shortly after ingestion in humans. This hazard may be more likely in obese than in nonobese persons because caffeine reduces insulin sensitivity more in obese than in lean subjects (115). It may also be hazardous for patients with diabetes, because a caffeine-induced decrease in insulin sensitivity has been found in persons with type 2 (40) and type 1 (116) diabetes.

Several investigators found an epidemiologic association between coffee consumption and the elevation of serum lipids in Nordic countries in the 1980s, as discussed by James (117). Subsequent research showed that it is only boiled coffee, which was commonly consumed in the Nordic countries in the 1980s, that elevates serum lipids. Filtered coffee, which is the most common type of brewed coffee consumed in the United States, does not affect serum lipid concentrations (1).

Although caffeine has exhibited mutagenic potential in *in vitro* studies, researchers have found that caffeine has little, if any, carcinogenic potential in humans (118). To date, most human studies have been epidemiologic, and they suggest a weak potential for inducing bladder and pancreatic cancer and a weak protective effect for colon cancer (118). A large body of epidemiologic and laboratory evidence suggests that caffeine protects dopaminergic neurons and thereby may help prevent the onset of Parkinsonism (119). Caffeine has been used for a number of therapeutic purposes, eg, in bronchial asthma, as a cardiac stimulant, and as a diuretic (59).

NONCAFFEINE COMPOUNDS IN COFFEE

A relatively small, but increasing, amount of research has been done on the effects of noncaffeine constituents in coffee. Various studies suggest that such constituents could induce some of the effects in this review. Graham et al (120) found that caffeine, but not caffeinated coffee, was effective as an ergogenic aid in humans. They concluded that a noncaffeine constituent of coffee was involved and cited the discovery by Tse (121) of a substance in coffee that appeared to lower blood pressure and heart rate. The finding of Graham et al is relevant here because ergogenic potential—ie, the potential for physical work—could be associated with thermogenesis, lipolysis, fat oxidation, glucose metabolism, and the pressor effect.

Several studies have identified specific noncaffeine compounds that could affect diabetes risk. Johnston et al (74) reported that 5-caffeoylquinic acid, the major chlorogenic acid in coffee, may help explain coffee's ability to decrease diabetes risk in human subjects. They found that the ingestion of either caffeinated or decaffeinated coffee containing equal amounts of

chlorogenic acid and glucose caused acute changes in gastrointestinal hormone concentrations. They concluded that chlorogenic acid attenuated the rate of glucose uptake in the proximal small intestine and moved it to more distal regions of the small intestine. Their findings suggest that chlorogenic acid or some other noncaffeine coffee constituents antagonizes caffeine's stimulation of glucose uptake in the small intestine. Using a sugar absorption test of intestinal permeability, Nieuwenhoven et al (122) found that the addition of caffeine to a sports drink expedited glucose uptake in the small bowel in 10 athletes. The implication is that chlorogenic acid slows the absorption of glucose from the gut, whereas caffeine accelerates it. Rodriguez de Sotillo and Hadley (123) found that 3 wk of intravenous infusion of chlorogenic acid significantly lowered the postprandial peak response to a glucose challenge in insulin-resistant Zucker rats. Chlorogenic acid may have other positive effects on glucose metabolism, including enhancing the antioxidant effects of coffee (124), decreasing glucose output in the liver (125), and helping preserve β -cell function by promoting the synthesis of the homeodomain transcription factor IDX-1, which helps beta cells respond to increases in plasma glucose (126).

Shearer et al (127) found that a synthetic quinidine, 3,4-diferuloyl-1,5-quinide, which was representative of quinides found in coffee, enhanced glucose clearance and insulin action in rats. They found evidence that the effect was due not to increased skeletal muscle uptake but rather to decreased liver glucose production. Two groups of investigators have suggested that antioxidants in coffee may protect against insulin resistance (128, 129), and evidence also exists that coffee has a high antioxidant capacity, even higher than that of tea (130). Prasad et al (131) found that when secoisolariciresinol diglucoside, an antioxidant dietary lignan that occurs in coffee, was fed orally to rats for 24 d, the development of streptozotocin-induced diabetes was reduced by 75%.

Some investigators suggested that the magnesium in coffee may explain the ability of habitual coffee consumption to increase in insulin sensitivity (132). Long-term magnesium intake has been followed by a lower risk of type 2 diabetes (133).

A nonphenolic phytochemical constituent in coffee, trigonelline (*N*-methylnicotinic acid), has been found to have a hypoglycemic effect in rabbits and alloxan-diabetic rats. In a noncontrolled pilot study involving 10 diabetes patients, single doses of 500, 1000, and 2000 mg trigonelline had mixed effects on blood glucose (134).

It is not known whether tolerance develops to the effects of chlorogenic acid, quinides, antioxidants, magnesium, or other coffee compounds that have the ability to enhance insulin sensitivity. It may be that such tolerance does not develop, even though tolerance to caffeine's ability to depress insulin sensitivity does develop. If tolerance to the noncaffeine compounds does not develop, that could help explain the apparent contradiction between the long-term epidemiologic finding that coffee enhances glucose tolerance and the short-term finding that coffee impairs glucose tolerance.

CONCLUSIONS

Most of the prospective epidemiologic studies suggested that long-term consumption of coffee (3–17) and decaffeinated coffee (5, 10, 11, 17) can reduce the risk of diabetes. One of these



studies found that the intakes of caffeinated coffee, decaffeinated coffee, and caffeine were independently associated with weight loss (10). Another found that increasing intakes of these beverages were associated inversely with weight gain, but the effects were modest (26). It seems possible that long-term coffee consumption may have a weak ability to help persons achieve weight loss, and that this weight loss may contribute toward reducing the risk of diabetes.

Two of caffeinated coffee's short-term effects could cause negative health effects. First, the pressor effect could trigger CVD events (*see* The pressor effect). Second, decreases in glucose tolerance and insulin sensitivity (*see* Glucose metabolism) could lead to poor glycemic control and elevated risk of sequelae from repeated bouts of poor short-term glycemic control. These sequelae could include neuropathy and diabetic retinopathy. This idea is speculative at this time, because no studies have yet assessed the development of such complications. A few studies show that the ingestion of decaffeinated coffee does not cause either of these effects, at least in the short term (40, 73, 77).

The epidemiologic finding of a potential reduction in diabetes risk due to habitual consumption of caffeinated coffee suggests that tolerance does develop to the short-term decrease in glucose tolerance and insulin sensitivity or that coffee contains noncaffeine constituents that enhance glucose tolerance and insulin sensitivity. The epidemiologic finding that the habitual consumption of decaffeinated coffee protects against diabetes risk (10, 11, 17) also suggests a role for coffee's noncaffeine constituents. Some preliminary evidence exists that coffee constituents such as chlorogenic acid (74) and quinides (128) enhance glucose tolerance and insulin sensitivity. The findings by Johnston et al (74) suggest that chlorogenic acid can help persons lose weight by attenuating the absorption of glucose from the small intestine. However, research on the short-term effects of decaffeinated coffee and the noncaffeine constituents of coffee is in the very early stages. The same is true of the long-term effects. Only one prospective study has assessed the role of weight loss (10). It found a dose-response positive association between weight loss and ground decaffeinated coffee and found that the protective effect was limited to participants with prior weight loss.

Some preliminary evidence suggests that coffee consumption may affect levels of satiety (34, 88) or physical activity (*see* Physical activity) or both in humans. As yet, no studies have been conducted on the effect of different types of coffee on satiety and physical activity—both of which could affect weight loss and diabetes risk.

In conclusion, some early evidence exists that decaffeinated coffee, one or more of the noncaffeine constituents in coffee, or both may be better suited for enhancing glucose tolerance and insulin sensitivity than is caffeinated coffee. More research is needed to elucidate both the short- and long-term effects of decaffeinated coffee and its constituents on diabetes risk. 

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