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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.

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.

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](#)).

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](#)).

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

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.

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

(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 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 dipyridamole, 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.

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

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, dipyridole, 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

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

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 decaf-caffeinated 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.

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.

The scientists want to expand on these studies and determine the exact mechanism of NOX inhibition. At this point, the scientists are beginning to understand the initial inhibitive effects of EGCg but further research is warranted to pin down the exact mechanisms.

[Green Tea for Weight Loss?](#) - Information about the University of Geneva study, from the *American Journal of Clinical Nutrition*.

REVIEW ARTICLE

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

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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](#)).

[A Cup of Tea](#) - This article explains how the polyphenols in green tea act on cancer cells.

The Health Benefits of Green Tea

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For many years, green tea has been associated with positive health benefits. In a recent study by researchers at Purdue University, the nature of these benefits was codified. The researchers found that epigallocatechin gallate (EGCg), a compound found in the tea, inhibited the growth of cancer cells. The compound also killed cancer cells without causing harm to healthy tissue. This is one of the first studies to provide a direct link between epigallocatechin gallate and cancer inhibition.

Green tea leaves are potent in EGCg. The study suggests that consumption of four to five cups of green tea may slow cancer. Previous studies have found a lower incidence of cancer in those who consume this amount of green tea but the exact compound that produced this cancer inhibition was unknown.

All tea comes from the same botanical source.

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Unlike other types of tea, green tea is processed differently. In green tea, the leaves are not allowed to oxidize but instead are steamed. This process allows the natural ingredients in the leaves to be preserved. Other types of tea were not nearly as successful as green tea in inhibiting the cancerous cells. Green tea was approximately ten times more potent than the other types.

Quinol oxidase or NOX is the enzyme that is inhibited by EGCg. NOX is present in cancer cells and is required for growth in cancer cells as well as normal cells. Under normal conditions, cells only express NOX due to hormonal stimulation. Cancerous cells, however, express NOX all of the time. The researchers found that, at certain levels, EGCg inhibited NOX on cancerous cells and not on normal cells. By limiting the growth and development of the cancerous cells, the cells did not grow to the required minimum size to divide and cell apoptosis occurred.

There are as many answers to this question as there are researchers investigating the natural properties of green tea. For example, *Herbs for Health* magazine cites a Japanese report stating that men who drank ten cups of green tea per day stayed cancer-free for three years longer than men who drank less than three cups a day (there are approximately 240 - 320 mg of polyphenols in three cups of green tea). Meanwhile, a study by Cleveland's Western Reserve University concluded that drinking four or more cups of green tea per day could help prevent rheumatoid arthritis, or reduce symptoms in individuals already suffering from the disease. And Japanese scientists at the Saitama Cancer Research Institute discovered that there were fewer recurrences of breast cancer, and the disease spread less quickly, in women with a history of drinking five cups or more of green tea daily.

It gets more confusing. A University of California study on the cancer-preventative qualities of green tea concluded that you could probably attain the desired level of polyphenols by drinking merely two cups per day. On the other hand, a company selling a green tea capsule formula insists that ten cups per day are necessary to reap the maximum benefits.

How can you make sense of these conflicting claims? Given all the evidence, it is probably safe to plan on drinking four to five cups of green tea per daily. If you're a real devotee, by all means drink more; but whether or not you'll derive added health benefits remains to be determined by further research.

How to Brew a Cup of Green Tea

Producing the perfect cup of green tea is a tricky process. If not handled properly, those same polyphenols that provide health benefits can ruin the flavor, making the tea taste "gassy." It's particularly important not to overbrew. While it's best to follow the manufacturer's instructions for each variety of green tea, here are some general instructions:

0. Use one tea bag, or 2 - 4 grams of tea,* per cup.
0. Fill a kettle with cold water and bring to a boil.
0. After unplugging the kettle, allow it to stand for up to 3 minutes.
0. Pour the heated water over the tea bag or tea, and allow it to steep for up to 3 minutes. If using a tea bag, remove the bag.
0. Allow the tea to cool for three more minutes.

*One to two teaspoons, depending on the variety of green tea you are brewing.

More Green Tea Articles

[Traditional Chinese Brewing Method](#) - Demonstrates the traditional Chinese method of brewing green tea; with photos.

particularly epigallocatechin gallate (EGCG). EGCG is a powerful anti-oxidant: besides inhibiting the growth of cancer cells, it kills cancer cells without harming healthy tissue. It has also been effective in lowering LDL cholesterol levels, and inhibiting the abnormal formation of blood clots. The latter takes on added importance when you consider that thrombosis (the formation of abnormal blood clots) is the leading cause of heart attacks and stroke.

Links are being made between the effects of drinking green tea and the "French Paradox." For years, researchers were puzzled by the fact that, despite consuming a diet rich in fat, the French have a lower incidence of heart disease than Americans. The answer was found to lie in red wine, which contains resveratrol, a polyphenol that limits the negative effects of smoking and a fatty diet. In a 1997 study, researchers from the University of Kansas determined that EGCG is twice as powerful as resveratrol, which may explain why the rate of heart disease among Japanese men is quite low, even though approximately seventy-five percent are smokers.

Why don't other Chinese teas have similar health-giving properties? Green, oolong, and black teas all come from the leaves of the *Camellia sinensis* plant. What sets green tea apart is the way it is processed. Green tea leaves are steamed, which prevents the EGCG compound from being oxidized. By contrast, black and oolong tea leaves are made from fermented leaves, which results in the EGCG being converted into other compounds that are not nearly as effective in preventing and fighting various diseases.

Other Benefits

New evidence is emerging that green tea can even help dieters. In November, 1999, the *American Journal of Clinical Nutrition* published the results of a study at the University of Geneva in Switzerland. Researchers found that men who were given a combination of caffeine and green tea extract burned more calories than those given only caffeine or a placebo.

Green tea can even help prevent tooth decay! Just as its bacteria-destroying abilities can help prevent food poisoning, it can also kill the bacteria that causes dental plaque. Meanwhile, skin preparations containing green tea - from deodorants to creams - are starting to appear on the market.

Harmful Effects?

To date, the only negative side effect reported from drinking green tea is insomnia due to the fact that it contains caffeine. However, green tea contains less caffeine than coffee: there are approximately thirty to sixty mg. of caffeine in six - eight ounces of tea, compared to over one-hundred mg. in eight ounces of coffee.

How much Green Tea should you drink?

The following article and laboratory analysis report concerns the Chinese and Japanese, indeed, Oriental Green Tea. Please note that both tea and the precious stone opal in Oriental societies are “Green”, that is the color of plant life. Occidental societies, on the contrary, have its precious stone as the diamond whose carats determine its value by the light it reflects. The opal, on the contrary, and the green tea take their value by being the color of natural life and the opal its “green” value by its deep green which draws the eye of the beholder into the stone!

The Miracle of Green Tea

**"Better to be deprived of food for three days, than tea for one."
(Ancient Chinese Proverb)**

Is any other food or drink reported to have as many health benefits as green tea? The Chinese have known about the medicinal benefits of green tea since ancient times, using it to treat everything from headaches to depression. In her book *Green Tea: The Natural Secret for a Healthier Life*, Nadine Taylor states that green tea has been used as a medicine in China for at least 4,000 years.

Today, scientific research in both Asia and the west is providing hard evidence for the health benefits long associated with drinking green tea. For example, in 1994 the Journal of the National Cancer Institute published the results of an epidemiological study indicating that drinking green tea reduced the risk of esophageal cancer in Chinese men and women by nearly sixty percent. University of Purdue researchers recently concluded that a compound in green tea inhibits the growth of cancer cells. There is also research indicating that drinking green tea lowers total cholesterol levels, as well as improving the ratio of good (HDL) cholesterol to bad (LDL) cholesterol.

To sum up, here are just a few medical conditions in which drinking green tea is reputed to be helpful:

- 0. cancer
- 0. rheumatoid arthritis
- 0. high cholesterol levels
- 0. cardiovascular disease
- 0. infection
- 0. impaired immune function

What makes green tea so special?

The secret of green tea lies in the fact it is rich in catechin polyphenols,