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REVIEW ARTICLE

Caffeine Intake: Insights into Its Effects on Diabetes, Hypertension, and Heart Failure

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KEYWORDS

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ABSTRACT: Caffeine is one of the major pharmacologically active substance intakes from food products all over the world. Large-scale intake of any type of coffee, tea, and beverages may be inducing the intake of large quantities of caffeine in the population. Harmful effects of caffeine ingestion on human health are dependent on the way of intake of caffeinated products because the time and the composition. The role of caffeine intake on chronic illness such as diabetes, hypertension, and heart failure has emerged as a significant public health matter. The review aims to clarify the impact of caffeine on this kind of illness and suggest ways of maximizing utilization. As diabetes and related illnesses rise in prevalence, it is imperative to stay in control of caffeine intake. Additionally, information about the effect of caffeine on hypertension, being a significant risk factor must be considered for the prevention of adverse cardiovascular outcomes. Based on evidenced data, moderate daily consumption of caffeine-contained product mainly coffee up to the defined quantity of caffeine is not associated with diseases to diabetes, hypertension, and heart failure. Certainly, excessive use can increase severe health threats. This study examines the acute and chronic effects of caffeine on glucose metabolism, blood pressure regulation, and cardiovascular disease. These findings highlight the importance of well-balanced public health messages regarding the use and consumption of caffeine.

INTRODUCTION

Caffeine is an active constituent used in various foodstuffs, mostly in coffee, tea, and energy drinks. Over-the-top daily use of caffeine is due to its some psychoactive effects such as increased alertness and reduced drowsiness by people of all ages[1, 2]. The positive or adverse effect of caffeine on health was being researched for decades. It has been considered as a central nervous system stimulant and its physiological effect coupled with little nutritional value provoked more interests. Caffeine is linked to some medical issues depending on the extent of intake and route

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of administration [1, 2]. Excessive intake of caffeine can result in some health issues such as psychomotor agitation, insomnia, gastrointestinal disturbances, and effects on diabetes, hypertension, and heart failure [Fig1]. Research shows that moderate use of caffeine reduces the risk of certain chronic conditions such as type 2 diabetes and heart disease, while excessive intake is associated with adverse effects such as anxiety, hypertension, and disturbance of sleep, especially in sensitive individuals such as children, adolescents, and pregnant women [3-5].

In diabetes, studies indicate that coffee caffeine is responsible for improving glucose metabolism and insulin sensitivity and hence reducing type 2 diabetes risk [6]. Daily consumption of coffee has been linked to lower diabetes risk most likely due to impacting fat oxidation, preservation of beta-cell function, and other metabolic advantages [7, 8]. Caffeine consumption has also been extensively studied in relation to hypertension. Research has a complex association, moderate coffee use, for example, not significantly raising the risk of hypertension but excessive doses of caffeine, especially from drinks like energy drinks, causing blood pressure increases, particularly among individuals with pre-existing hypertension or cardiovascular disease [9, 10]. The effects of caffeine are altered by genetics, metabolism, and lifestyle [11, 12].

While others suggest a possible protective role of moderate caffeine consumption on hypertension risk, albeit most prominently through coffee constituents, others suggest that high levels of caffeine consumption are linked with increased blood pressure [13]. In addition, mortality from all causes studies suggest that moderate amounts of caffeine consumption lower the risk for death in patients with hypertension, albeit the relationship is not linear and is influenced by the amount of caffeine ingested and medical status of the individual[9]. Similarly, the role of caffeine in heart failure is complex. Some studies have proven an inverse association between moderate coffee intake and heart failure risk, while others show no significant impact [14]. Variation in outcomes can be due to variations in population, sources of caffeine, and comorbidities. Such conflicting results necessitate individualized advice for caffeine consumption, particularly in cardiovascular disease patients. This review attempts to synthesize the current evidence concerning the relationship between caffeine intake and significant health conditions, including diabetes, hypertension, and heart failure.

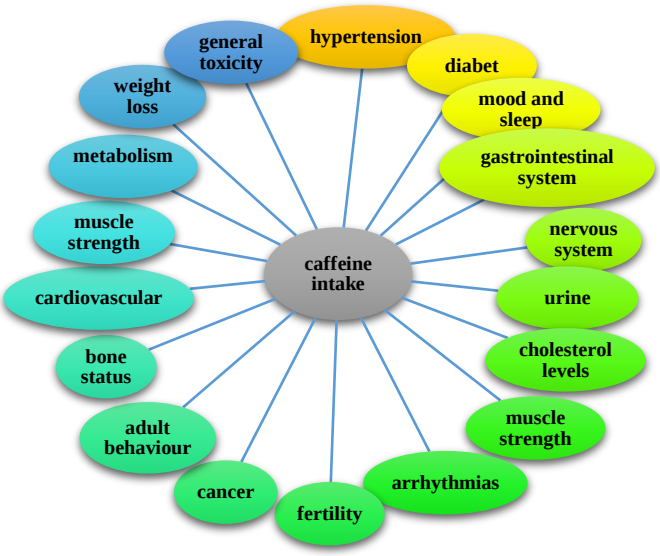

Figure 1. The most health issues related to caffeine intake.

The association of caffeine intake and diabetes

Diabetes is a metabolic disease and a global public health problem, with an estimated figure of millions of affected people globally. Components of diet, such as caffeine intake, have been extensively researched to ascertain their possible role in modulating and managing the risk of diabetes [1-3]. Caffeine can impact glucose and insulin homeostasis through various physiological mechanisms. It is an adenosine receptor antagonist that acts on insulin sensitivity and glucose metabolism. Caffeine also triggers the release of catecholamines and impacts the activity of the hypothalamic-pituitary-adrenal axis, with the potential outcome of disturbed glucose[4]. A series of studies reveal an inverse relationship between higher caffeine consumption and type 2 diabetes incidence [5, 6], with some providing strong evidence for the conclusion that increased levels of caffeine consumption

are associated with lower risk of type 2 diabetes in the long term [7, 8].

These relationships are open to confounding by age, body Mass index, and previous medical conditions. Literature regarding the effect of caffeine on glucose and insulin homeostasis is controversial, with some studies reporting acute caffeine intake impairing glucose tolerance and insulin sensitivity, but others reporting no effect or even a beneficial effect on glycemia [9, 10].

The effect of caffeine intake interacting with diabetes can be influenced by various factors. Genetic variation in caffeine metabolism and insulin-sensitive tissue sensitivity may influence an individual's glucose and insulin response to caffeine[5, 11]. Further, whether the caffeine is from coffee or tea or energy drinks, etc., may have differing effects because it has other bioactive compounds [12]. The nature and timing of caffeine consumption, the status of underlying medical conditions, and lifestyle traits also play a role in the interaction between caffeine and glucose homeostasis [13]. While some studies discuss possible beneficial effects of caffeine on glucose regulation and risk for diabetes, others report no significant effect or even adverse effects, contingent on individual and situational factors. Doctors must consider the balance between the possible harms and benefits when providing dietary recommendations regarding caffeine consumption to diabetic patients or individuals at risk of developing the disease. Additional research is needed to further elucidate the precise mechanisms and the moderating factors involved in the association between caffeine and diabetes in order to design evidence-based public health policy guidelines and individualized clinical treatments. The reported associations between caffeine intake and diabetes in some recent studies are shown in Table 1.

Table1. The association between caffeine intake and diabetes in recent studies.

Insight	Outcomes	ref
Caffeine intake and all-cause cardiovascular mortality in diabetes and pre-diabetes	Significant dose-response association with the risk of all-cause mortality and CVD mortality in individuals with diabetes and pre-diabetes	[4]
Coffee intake and insulin sensitivity, post-load glucose responses, and truncal adiposity	Higher coffee intake was associated with enhanced post-load glucose metabolism and insulin sensitivity, and lower truncal adiposity	[14]
Coffee consumption and diabetic complications	Positive linkage between coffee intake and the risk of diabetes complications: significantly improve the risk of diabetic nephropathy, diabetic neuropathy, and diabetic peripheral angiopathy, and possibly progression of diabetic ocular complications	
Habitual coffee consumption and type 2 diabetes in individuals with a history of gestational diabetes (GDM)	- High caffeine- coffee consumption was associated with lower fasting insulin and C-peptide concentrations -In females with a history of GDM, high consumption of coffee was associated with a lower risk of T2D and a better metabolic profile	[15]
Maternal caffeine, coffee and cola drink intake and gestational diabetes **(Cohort study)**	- Moderate coffee intake in the first trimester were less diagnosed with gestational diabetes - A minor non-significant decrease was observed with moderate coffee intake - Higher consumption of cola drinks was associated with an increased risk of gestational diabetes	[8]

Observational studies all show an inverse association between caffeine and risk of diabetes, but this is not a causal relationship. All the studies employ self-reporting of caffeine consumption, which is prone to biases. Moreover, the effect of caffeine may be modified by various genetic factors that control metabolism of caffeine. For instance, rapid caffeine metabolizers may have different health effects than slow metabolizers. There is also heterogeneity in the effects according to whether coffee, tea, or energy drinks are the source [16-18]. Follow-up studies must include randomized controlled trials that account for these genetic and metabolic differences in order to more clearly understand caffeine's long-term effect on diabetes.

The association of caffeine intake and hypertension

Hypertension, a significant global health issue, is one of the leading risk factors for cardiovascular disease. The relationship between caffeine consumption and hypertension has been extensively researched due to its potential effects on blood pressure regulation [19]. This review synthesizes current evidence on caffeine's influence on the development and management of hypertension. As an adenosine receptor antagonist, caffeine impacts various physiological mechanisms that play a role in blood pressure regulation, such as vascular tone, sympathetic nervous activity, and the renin-angiotensin-aldosterone system. These mechanisms all play significant roles in blood pressure homeostasis. Caffeine further impacts cardiac contractility, heart rate, and peripheral resistance, providing yet another level of modulation to blood pressure [20].

Observational data illustrate a complex relationship between caffeine consumption and hypertension risk. Various cross-sectional and cohort studies associate greater caffeine consumption with elevated blood pressure or greater hypertension prevalence [21]. These associations are, however, strongly confounded by age, gender, genetic susceptibility, and baseline cardiovascular status [22]. Randomized controlled trials and clinical trials repeatedly demonstrate that acute caffeine intake elevates systolic and diastolic blood pressure transiently, especially in patients with pre-existing hypertension or cardiovascular disease. Also related to chronic high-dose consumption of caffeine is a chronic rise in blood pressure [23].

However, there are studies that have shown no significant relationship between hypertension and moderate use of caffeine, some reporting an inverse association. Genetic polymorphism in the metabolism of caffeine and cardiovascular tissue sensitivity dictate individuals' responses to caffeine[24]. Additionally, the route of caffeine administration, i.e., coffee, tea, or energy drinks, may affect blood pressure via other bioactive compounds found in the beverages. Lifestyle factors such as physical activity, dietary habits, and concomitant comorbidities also combine with caffeine intake to modulate blood pressure control[25]. In general, the relationship between caffeine and hypertension is complex and multifaceted. While excessive caffeine consumption is most commonly linked to increased blood pressure, moderate consumption has no tangible correlation or, in some cases, a negative one. Susceptibility based on genetics, source of caffeine, and individual health are the main factors to take into account in the relationship[26]. More research needs to be one to explain the mechanisms involved and make personalized nutritional recommendations for preventing and treating hypertension. Besides, a prospective cohort study found that tea and some beverages but not coffee may benefit individuals with hypertension. Intake of tea was associated with reduced risks of all-cause mortality and cardiovascular disease[27]. A cross-sectional study also recorded the complex effect of caffeine and its metabolites on blood pressure, reporting associations with reduced systolic and increased diastolic blood pressure. These findings indicate the importance of considering caffeine intake in the control of hypertension. The relations of caffeine intake with hypertension in some recent studies, as observed, are presented in Table 2.

Table2. The association between caffeine intake and hypertension in recent studies.

Insight	Outcomes	ref
Coffee and the risk of hypertension (cohort study)	-The risk of hypertension was lower in consuming rate of 1–3 cups/day -The association between coffee consumption and hypertension depended on the smoking status -A decreased risk of hypertension was observed in never smokers who consumed 1–3 cups/per day	[28]
Caffeine Intake and all-cause and cardiovascular mortality in elderly patients with hypertension	Moderate caffeine intake (200 to <300 mg/day) was related to reduced risk of all-cause and cardiovascular mortality	[29]
Coffee and risk of hypertension in Adults (Meta-Analysis)	-Higher coffee consumption was related to 7% reduced risk of hypertension - Studies characteristics (region, participants' sex, study quality, and sample size) affected results. - An inverse association was obtained between coffee and hypertension risk in both cross-sectional and cohort studies.	[30]
Coffee and the risk of hypertension (Meta-Analysis of Cohort Studies)	- Coffee intake was not significantly associated with the risk of hypertension - A decreased risk of hypertension was observed in studies in America - Coffee intake dosage, gender, coffee type (decaffeinated or caffeinated), smoking, and years of follow-up, were not significantly associated with the risk of hypertension.	[31]
caffeine and all-cause and cause-specific mortality in American adults with hypertension	- A nonlinear association between average caffeine consumption and all-cause mortality - Moderate caffeine intake is suggested beneficial for hypertensive patients -Regarding cancer, diabetes, and kidney disease, caffeine intake >300 to ≤400 mg/day was significantly associated with decreased mortality	[32]
Daily coffee and vascular function in patients with hypertension	- Drinking half a cup to 2.5 cups/day had lower odds ratios for endothelial dysfunction - Appropriate daily coffee intake seems to have a beneficial influence on endothelial function and vascular smooth muscle function in patients with hypertension.	[33]

Inconsistent results in studies of caffeine and hypertension are generally due to differences in study design and population structure. Short-term randomized trials typically show that caffeine increases blood pressure acutely but the long-term status is unclear. The heterogeneity in such findings could be due to individual factors such as pre-existing cardiovascular disease or genetic variability in caffeine metabolism[24]. Further, studies comparing different sources of caffeine [coffee, tea, energy drinks] reveal that the presence of other bioactive constituents in these beverages also influences the effect of caffeine on blood pressure[34]. Future research must focus on long-term well-controlled trials to ascertain whether moderate caffeine consumption is detrimental to blood pressure in the long term.

The association of caffeine intake and heart failure

Heart failure is a progressive cardiovascular disease that overwhelms public health globally. Dietary and lifestyle habits, including caffeine consumption, have been examined for their potential role in the development and management of heart failure [35]. Caffeine, a common stimulant, affects the cardiovascular system through its action on adenosine receptors, regulating myocardial contractility, vascular tone, and neuroendocrine regulation. These mechanisms can be implicated in the modulation of the development of heart failure through the modification of blood pressure, fluid balance, and inflammation[36]. Observational studies reveal a complex relationship between caffeine intake and heart failure. Other studies show a U-shaped or J-shaped relationship, with low and high levels of caffeine consumption suggesting increased risk for heart failure [37, 38]. Other studies have reported no appreciable

association or have proposed protective effects from moderate caffeine intake [39, 40].Varying results may be attributed to age, gender, and history of cardiovascular disease[39, 41]. Randomized controlled trials have provided contradictory evidence of caffeine's impact on heart failure. While some trials indicate that caffeine will transiently increase heart rate, blood pressure, and myocardial oxygen demand, possibly aggravating heart failure, other trials have found no clinically significant unfavorable effects on cardiac performance or exercise capacity in patients with heart failure. Long-term effects of chronic caffeine consumption on the development and prognosis of heart failure remain unclear and need further research[42].

There are several factors that may change the relationship between caffeine consumption and heart failure, including genetic variations in caffeine metabolism andcardiovascular tissue sensitivity. In addition, individual health status and lifestyle factors such as exerciseand diet could affect the risk and implications associated with caffeine use in heart failure patients [29]. All in all, while certain studies suggest possible harmful effects associated with too much caffeine intake, other studies point to neutral or even beneficial effects with moderate intake. Physicians need to weigh these findings with caution when counseling patients at risk of or with heart failure. Further research must elucidate mechanisms and determinants underlying the association between caffeine and heart failure with the ultimate goal of guiding personalized clinical recommendations and public health guidance. Described associations of caffeine intake with heart failure in chosen recent studies are summarized in Table 3.

Table 3. The association between caffeine intake and heart failure in recent studies.

Insight	Outcomes	ref
Coffee and incident heart failure (cohort study)	- Moderate coffee consumption (<1 cups/d, 1–2 cups/d, 3–4 cups/d) associated with a reduce risk of heart failure incidence - Caffeine intake >6 cups/d may be associated with a higher risk of heart failure	[43]
Prognostic cardiovascular and dietary caffeine (cohort study)	- Caffeine intake >230 mg/day for men shows a reduced risk of heart failure - Caffeine intake >280 mg/day for men a reduced risk of cerebrovascular events and arrhythmic events	[44]
Caffeine and heart arrhythmias	- No strong associations between caffeine consumption and arrhythmias - An increased risk of arrhythmias reported in infants, psychiatric patients, and athletes by caffeine consumption - It may contribute to cardiovascular issues, including high blood pressure, and is recommended to be consumed in doses ranging from 40 to 180 mg/day.	[45]
Caffeine and cardiovascular system and performance	- It is recommended that caffeine intake should be higher than 75mg for better effects. - Caffeine intake > 600mg caffeine in a day related to side effects, especially on the heart. - It is recommended to consume caffeine at least 45 minutes before planned activity to allow for complete absorption	[46]

The conflicting evidence of studies on caffeine and heart failure could be due to variation in how studies identify risk of heart failure and the amount of caffeine consumed. Some studies show that there is U-shaped association, with both low and high caffeine consumption potentially being associated with increased heart failure risk[37-39]. However, these results are typically confounded by lifestyle factors such as diet, exercise, and smoking, which are not always adequately controlled for in observational studies. Randomized controlled trials must examine the long-term impact of caffeine on heart failure risk, especially among individuals with pre-existing cardiovascular disease.

Caffeine and side effects

Caffeine, have various side effects depending on how much and for how long one has been taking it. Facts have established that moderate intake of caffeine is antioxidant, anti-inflammatory, and protective against such diseases as cardiovascular diseases, obesity, diabetes, cancers, and liver diseases[47]. However, excessive caffeine intake can cause adverse effects, including gastrointestinal upset, palpitations, elevated blood pressure, restlessness, and insomnia. These side effects are especially noted when caffeine is administered in the form of caffeine citrate injections, often used to treat apnea of prematurity and persistent pulmonary hypertension in newborns. It is essential to balance caffeine intake to maximize its benefits while minimizing potential risks, particularly in vulnerable populations[48-50]. Research also suggests that caffeine affects DNA repair enzymes, induces premature chromatin condensation, and alters cell cycles, potentially influencing cancer cell proliferation and viral spread. Furthermore, Mendelian randomization studies have highlighted that coffee consumption may have lasting effects on brain structure, with compounds like theobromine and theophylline playing significant roles in certain regions of the brain[51, 52]. Understanding the varied effects of caffeine and coffee on metabolism, DNA repair, cardiovascular health, and brain function is vital for assessing their overall impact on human physiology[53].

Coffee consumption and caffeine intake

Coffee is one of the most widely consumed beverages globally, primarily valued for its psychoactive effects. However, its extensive consumption has sparked significant interest in its potential health benefits and risks. The main concerns surrounding coffee consumption are its adverse effects on cardiac arrhythmias and elevated blood pressure. The style of coffee consumption, including the amount, type [caffeine concentration], and timing, plays a crucial role in determining its safety and health effects[21]. Coffee consumption varies significantly from country to country and even among individuals within the same family. The caffeine content in a single homemade cup of coffee can range from 30 to 175 mg, which makes it essential to monitor daily intake[4, 32]. It is recommended that consumers control their coffee consumption, keeping it at low to moderate levels for optimal safety [Figure 2]. Studies suggest that low [1 cup/day] to moderate [2-5 cups/day] coffee consumption is appropriate for most individuals, depending on their health status [32]. Research indicates that a moderate caffeine intake of up to 300 mg/day is generally considered safe. However, higher daily consumption has been associated with potential health risks. Some studies suggest that an intake of up to 400 mg/day may still be safe for most healthy adults[44, 46]. Ultimately, caffeine intake reflects the amount of coffee consumed, and careful regulation is necessary to avoid adverse effects.

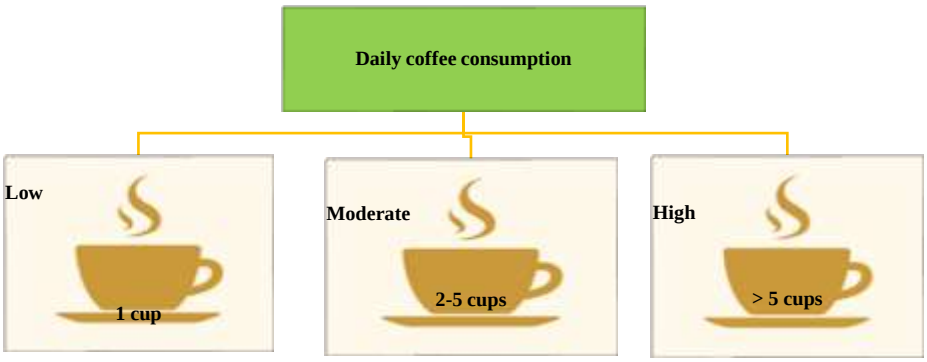

Figure 2. Daily coffee consumption.

Characterization of caffeine-based products

Caffeine content is different in caffeine-based products. caffeine levels in products mainly are influenced by the type of product and processing method. Some type of coffee may be containing high caffeine percentage (8.90%) compared to other coffee and tea products. Energy drinks have indicative amount of caffeine (266 to 340 mg/l), while tea and tea products contain a lower caffeine concentration (13 to 183 mg/l). Besides, some industrial byproducts may contain more caffeine levels than the initial product. There are various food items contain caffeine such as coffee, coffee-based beverages, energy drinks, tea, colas, coffee-flavored yoghurts and chocolate[54]. The determination of caffeine in caffeine-based product have been performed in monitoring program using high performance liquid chromatography (HPLC) with UV detection[55]. The analysis study showed a significant level of caffeine founded in short coffee and instant coffee. However, the concentration of caffeine in coffee-based products should be considered in the study of caffeine intake routs in individuals.

Practical applications for clinicians

Given the variability in caffeine's effects, clinicians should tailor their recommendations based on individual patient factors. For patients at risk of hypertension or heart failure, reducing caffeine intake, particularly from high-concentration sources like energy drinks, may be advisable. In contrast, moderate coffee consumption may be beneficial for individuals at risk for type 2 diabetes, as it has been linked to improved insulin sensitivity. Clinicians should also consider genetic factors, as certain individuals metabolize caffeine differently, potentially altering its impact on their health.

CONCLUSIONS

Moderate use of caffeine is safe and may be protective for some diseases, such as the prevention of type 2 diabetes. Overuse, however, leads to serious health effects such as diabetes, hypertension, and heart failure. Numerous evidence-based research has focused on the impact of caffeine with variables such as use, underlying health conditions, age, sex, and caffeine metabolism genotype. Regulation of caffeine consumption on a daily basis is crucial as the possible harms of extreme consumption might overrule the possible benefits. Caffeine's effects greatly rely on personal considerations, and therefore personal consumption advice is necessary to make available the balance between possible benefits and harms. Further research is required to establish the long-term effects of caffeine on the outcome of chronic disease so that in the end it can affect public health policy and clinical practice.

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Conflict of interest

The authors hereby assert that there exists no conflict of interests.

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