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The Effect of Coffee Consumption on Blood Glucose Levels

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Abstract

Coffee is one of the greatest widely and frequently drunk beverages globally. Epidemiological trends suggest that consumption is progressively rising due to the emergence of research indicating its varied health benefits and greater awareness of such information among laypersons. This literature review aimed to explore the relationship between coffee and health and disease, particularly whether consumption can improve blood glucose metabolism and the risk or control of diabetes mellitus. A systematic search for evidence was performed using the databases of MEDLINE and Web of Science in March 2021 using key search terms. Evidence deemed pertinent to the review was considered for inclusion. Overall, most studies found that coffee consumption with caffeine doses approaching 400 mg per day positively affected blood glucose metabolism via varied insulin-dependent and insulin-independent mechanisms. In turn, studies showed that habitual and more frequent intake of cups per day (4-6) significantly lowered the risk of type 2 diabetes than lower or absent intake. Notably, the evidence also revealed that the intake of decaffeinated coffee resulted in comparable effects on blood glucose handling, which suggests that the favorable metabolic effects of coffee are not entirely attributed to caffeine but also chemicals and minerals within coffee beans. Finally, coffee consumption with caffeine doses <400mg or <2.5mg/kg was found to be safe for children, adults, and pregnant women, with other evidence showing that adverse effects and toxicity tend to only occur with doses exceeding 2-5g caffeine.

Keywords: Caffeine, Coffee consumption, Glucose metabolism, Diabetes mellitus

Introduction

Extent of Consumption and Safety of Caffeine

Coffee is one of the extensively consumed beverages worldwide, with epidemiological evidence showing that consumption exceeds 166 million kg bag equivalents each year (Cornelis, 2015; ICO, 2021; Najim *et al*., 2022; Remizova *et al*., 2022). Trends in the data have also shown that consumption has progressively increased year on year by 0.3%, which equates to approximately one million kg of bags of coffee per annum (ICO, 2021). It is estimated that more than 80% of adults consume caffeine daily, with a mean intake of 180mg per day and the source predominantly being coffee. Still, a proportion of individuals ingest caffeine from other sources, such as tea, energy drinks, cocoa, and synthetic supplements (Temple *et al*., 2017). Safety data recommend that daily caffeine intake should not exceed 400mg due to the increased risk of adverse effects and toxicity that observe a dose-response relationship (Cornelis, 2015). Notably, habitual coffee consumption or the regular consumption of other sources can induce caffeine tolerance, with evidence showing that physiological change and adverse effects may not occur until ingested doses exceed 750mg to 1g (Soares *et al*., 2018) . Overt toxicity almost always occurs in amounts exceeding 2g, and doses approaching 4g tend to be fatal due to excess and unabated activation of the sympathetic nervous system and the development of life-threatening cardiac arrhythmias (Andrade *et al*., 2018; Daivasigamani *et al*., 2022). Among coffee consumers, the average number of cups drank per day is 2-4 within western countries, and thus, caffeine intake tends to fall below the threshold of adverse effects. However, subclinical changes to physiology are recognized, and these are suggested to have several essential health benefits (Cornelis, 2014; Alturki *et al*., 2022).

General Health Benefits

A recent systematic review and meta-analysis showed that habitual coffee consumption was associated with positive effects for over 30 health outcomes. Few adverse health effects were observed, contradicting prior speculation that caffeine is deleterious to health (Cornelis, 2014). For diabetes mellitus, research has shown that caffeine intake can improve glycaemic control and optimize glucose distribution and insulin sensitivity, which can help reverse or prevent diabetes of type 2 disease (Adiga *et al*., 2019; Aditama *et al*., 2021; AlHussain *et al*., 2022; Madhukar, 2022). The effects of caffeine on blood glucose are described in additional detail in the relevant subsection of this report (Mehrizi *et al*., 2020). Importantly, evidence has shown that caffeine consumption can significantly reduce the risk of disease-specific and all-cause mortality (Kim *et al*., 2019). In this cited meta-analysis based on 40 studies and over 3.8 million subjects, the authors showed an inverse association between coffee consumption and mortality. For persons who consumed 3.5 cups of coffee per day, there was a significantly 15% lower risk of mortality (RR 0.85; 95% CI 0.82, 0.89). Significant survival benefits were still observed for lower consumption levels. The relative consequences about 0.83 (95% CI 0.80, 0.87) when consumed 2.5 cups of coffee daily regarding cardiovascular disease-related mortality, and 0.96 (95% CI 0.94,

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0.99) for 2.0 cups of coffee per daily regarding cancer-related mortality. The authors also showed that moderate coffee consumption, from two to four cups per day, was linked with reducing the risk of mortality due to respiratory disease and diabetes mellitus than no coffee consumption (Kim *et al*., 2019). The health benefits of coffee are attributed to caffeine, and various metabolites and nutrients present within the beverage, including phenolic compounds and multiple vitamins and minerals (Hernández *et al*., 2019).

Literature Review

Search Strategy

A search for literature related to the impact of caffeine intake on blood glucose and the risk of diabetes was undertaken using the databases of MEDLINE and Web of Science in March 2021, where this article does not contain any studies with human or animal subjects performed by any of the authors. The search terms and Boolean combinations applied to searching are summarised in **(Table 1)**. The process of evidence selection is shown in **(Figure 1)**.

Table 1. Search strategy

	Population	Exposure	Outcomes
Final Search Terms (columns combined with "AND") (*truncation)	1-Adult* 2-Diabetes mellitus 3-Type2 diabetes mellitus 4-T2DM	5-Coffee 6-Caffeine 7-Caffeinated 8-Decaffeinated	9-Blood glucose 10-Glycaemia 11-Glycaemic 12-Glycemia 13-Glycemic 14-Insulin
Boolean Combinations	1 AND 2 OR 3 OR 4	5 OR 6 OR 7 OR 8	9 OR 10 OR 11 OR 12 OR 13 OR 14

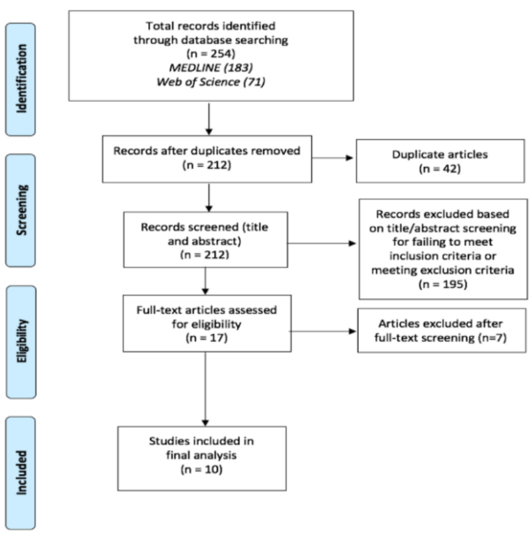

Figure 1. Evidence selection using the PRISMA method.

Role of Caffeine in Lowering Blood Glucose Levels and Risk of Diabetes

In specific regard to the endocrine system, caffeine has been shown to exert several effects on blood glucose levels, and as a result of its potential in helping to tackle the global burden of type 2 diabetes, an extensive body of research has explored its preventative and treatment effects (Reis *et al*., 2018). Several credible and pertinent studies have been selected for critical evaluation regarding the impact of coffee consumption on blood glucose, which is described in the following text **(Figure 2)**. Firstly, Bhupathiraju *et al.* (2014) prospectively analyzed data from three extensive cohort studies, including the Nurses Health Studies I and II and the Health Professionals Follow-up Study and comprised of more than 100,000 adults, to explore the changes in coffee consumption and the risk of type 2 diabetes mellitus. The data was collected using self-reported surveys with dietary intake recorded every four years and the onset of type 2 diabetes mellitus noted at the time of diagnosis. Based on over 1.6 million person-years of follow-up data, the authors found that there were 7,269 incident of type 2 diabetes mellitus cases, and subjects who had increased coffee intake by one cup per day observed a 10% lower risk of the disease over the proceeding four years, than compared to those who did not increase their coffee consumption (95% CI 3%, 18%). On the contrary, subjects who reduced their coffee intake by more than one cup per day observed a 17% greater risk of type 2 diabetes than those with an intake that did not decrease (95% CI 8%, 26%). However, the study was limited by its reliance upon self-reported data, which presents a risk of recall bias, and residual confounding as dietary factors other than coffee and caffeine may have accounted for some of the variances in blood glucose level change.

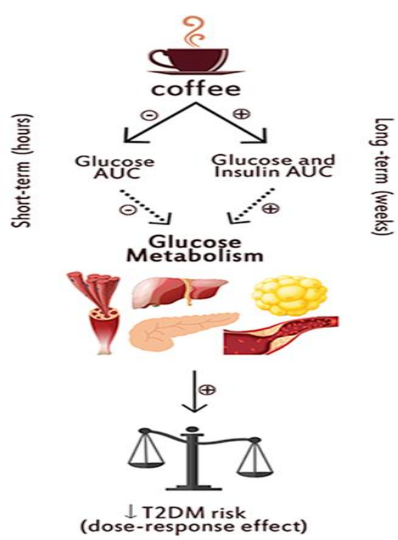

Figure 2. Overview of the role of coffee in lowering the risk of type 2 diabetes (Reis *et al*., 2018)

In another observational study, Yarmolinsky *et al*. (2015) sought to investigate whether coffee consumption could benefit glucose control in persons with newly diagnosed diabetes. Thus, it contrasted the cohort evaluated by Bhupathiraju *et al*. (2014). The authors extracted data from more than 12,500 subjects who were a part of the Longitudinal Study of Adult Health – Brazil and analyzed the effect of consumption on various measures of glycemia. The results showed that there was after adjusting for many covariates with a mean intake, a negative relationship between coffee consumption and recently diagnosed diabetes was identified of 2-3 and >3 cups per day being associated with a significant 23% and 26% reduced risk of diabetes, respectively, than compared to those with rare or never coffee intake (p=0.02). There was also an association between increasing coffee intake and oral glucose tolerance testing with glycemia decreasing progressively (>3 cups per day: 7.12 mmol/L v. <=1 cup per day: 7.57 mmol/L, p<0.0001). Moreover, a relationship between increasing coffee intake and lower fasting blood glucose was observed, but the effect was marginally insignificant (p=0.07). Furthermore, coffee intake was associated with lower insulin levels post 2-hour glucose challenge (>3 cups per day: 262.2 pmol/L v. never/rare intake: 287.2 pmol/L, p=0.0005), but this was not observed for fasting insulin levels (p>0.05), which suggests that coffee exerted a protective effect against diabetes and a potential mechanism involving optimized post-prandial glucose homeostasis and handling (Yarmolinsky *et al*., 2015). However, the study was methodologically affected by its observational design that precluded inferences of causation between coffee intake and improved glycemia.

Several systematic reviews and meta-analyses have also explored the effect of coffee intake on the blood glucose levels and the risk of type 2 diabetes. In one example, Huxley *et al*. (2009) reviewed data from 18 studies deriving a total of 457,000 subjects. They identified an inverse relationship between coffee intake and the risk of diabetes mellitus, with each additional cup of coffee consumed per day lowering the risk by 24% (RR 0.76; 95% CI 0.69, 0.82, p=0.01). Notably, the authors also found a similar relationship between the intake of decaffeinated coffee and tea and diabetes mellitus risk (RR 0.84; 95% CI 0.73, 0.94), albeit with a smaller and non-significant overall effect size (p=0.46). Such findings suggested that the glucose-lowering effects of coffee were not solely due to caffeine, but other chemicals and nutrients present within coffee beans. However, the meta-analysis outcomes may have been at risk of confounding bias, which was exacerbated by the limited analyses conducted among the authors of the informing studies. In addition, the results were based on a population comprising over 80% of white Caucasians. Thus, the findings cannot be reliably generalized to other ethnic groups at risk of type 2 diabetes mellitus. In a later systematic review of the literature, that was based on 13 cohort studies and more than 47,000 subjects, Muley *et al*. (2012) concluded that regular coffee consumption was linked to a decreased risk of type 2 diabetes. among those consuming 4-7 cups per day, as compared to persons consuming <2 cups per day. Moreover, the authors also found that filtered and decaffeinated coffee conferred a strong protective effect against type 2 diabetes among persons aged <60 years than compared to boiled and caffeinated coffee, which again suggested that the positive blood glucose and insulin effects were related to other constituents of coffee rather than caffeine alone. However, a similar risk of residual confounding bias existed, as did the issues with generalisability given the poor diversity of cohorts included in the original studies.

In a more recent systematic review and meta-analysis, Ding *et al*. (2014) sought to confirm whether caffeinated or decaffeinated coffee intake conferred clinically meaningful reductions in the risk of type 2 diabetes. The authors included 28 prospective studies with more than 1.1 million subjects, over 45,000 incident type 2 diabetes cases, and a follow-up duration ranging from 1-20 years. In contrast to the former reviews, the results showed that caffeinated coffee exerted a greater effect (lower risk) of type 2 diabetes mellitus than caffeine intake. For coffee intake of five cups per day, the pooled relative risk of incident type 2 diabetes was 0.70 (95% CI 0.65, 0.75), and this progressively decreased for lower daily intake: 0.80 (95% CI 0.75, 0.88) for 3.5 cups per day and 0.91 (95% CI 0.88, 0.94) for one cup per day, of which, the latter was insignificant (p=0.17). Dose-response analysis revealed that s strong inverse relationship existed with the relative risk being 0.92 (95% CI 0.90, 0.94) for one cup per day and 0.85 (95% CI 0.82, 0.88), 0.79 (95% CI 0.75, 0.83), 0.75 (95% CI 0.71, 0.80), 0.71 (95% CI 0.65, 0.76) and 0.67 (95% CI 0.61, 0.74) for 2-6 cups per day, respectively. For caffeinated coffee intake of five cups per day, the relative risk of type 2 diabetes was significantly reduced (RR 0.74; 95% CI 0.67, 0.81, p=0.005) than compared to intake of one cup per day, which was also observed for decaffeinated coffee but with a smaller effect size (RR 0.80; 95% CI 0.70, 0.91, p=0.001). However, comparable reductions in type 2 diabetes risk were observed for caffeinated and decaffeinated coffee consumption of a lower category (2-4 cups per day). The relative risk increased progressively with lower intake (RR 0.82-0.98). Further dose-response analysis revealed that an increase in caffeinated and decaffeinated coffee consumption of one cup per day yielded a relative risk of type 2 diabetes of 0.91 (95% CI 0.89, 0.94) and 0.94 (95% CI 0.91, 0.98), respectively. There was no statistically significant difference in said risk between the caffeinated and decaffeinated groups (p=0.17). Notably, this meta-analysis was subject to similar methodological flaws due to the nature of collecting coffee intake data that relied upon self-reported questionnaires, thus conferring a risk of recall and non-response biases. In addition, the authors acknowledged that it was possible to eliminate the influence of residual confounders upon the effects reported.

Consistency in this problem was also observed in a similar meta-analysis reported by Jiang *et al*. (2014), who identified the following pooled effects: RR 0.71 (95% CI 0.67, 0.76) for the highest level of available coffee intake, RR 0.79 (95% CI 0.69, 0.91) for the highest level of decaffeinated coffee intake and RR 0.70 (95% CI 0.65, 0.75) for the highest level of caffeinated coffee intake. Moreover, the dose-response analysis showed that the risk of incident type 2 diabetes increased by 11% for every two additional cups of decaffeinated coffee consumed per day and 14% for caffeinated coffee, equivalent to a 200mg per day increment. Thus, the findings of Jiang *et al*., (2014) that increasing caffeine intake by 200mg per day yielded an additional 3% reduction in the risk of type 2 diabetes compared to increases in decaffeinated coffee consumption of two cups per day.

In contrast to the former evidence, a recent review of the literature based on seven studies showed that caffeine intake was associated with increases in blood glucose concentrations and, in addition, prolonged the duration of elevated blood glucose. However, the study was not designed to elicit whether these effects were short- or long-lasting and whether they increased the risk of type 2 diabetes (Dewar & Heuberger, 2017). Whilst increases in blood glucose are undesirable for diabetes control and prognosis (the risk of micro- and macro-vascular complications), the authors revealed mixed effects with one study supporting increases in glucose as a positive effect due to protection from nocturnal hypoglycemia in those with type 1 diabetes, but other studies showed that hypoglycaemic events became significantly more frequent and intense without benefitting chronic glycaemic control (Dewar & Heuberger, 2017). Such effects were based on an approximate daily intake of caffeine of 250mg and patients with protracted durations of diabetes (>14 years) and high glycated hemoglobin levels, which could represent a limitation as an advanced disease is more likely to observe limited reversibility (treatment resistance) than those with early-stage disease (Ang, 2018). Most studies in the former review were based on populations with type 1 diabetes and thus, cannot be inferred to represent persons with type 2 diabetes, which is considered the more reversible or modifiable form of diabetes due to lacking an autoimmune-mediated cause and instead, one that is influenced by weight in the majority of cases (Franz, 2017).

Results and Discussion

Plausible Mechanisms of Caffeine in Improving Blood Glucose Metabolism

Research exploring the impact of coffee consumption upon blood glucose parameters has revealed that the process of roasting coffee beans at high temperatures and inducing Maillard reactions promotes the release of antioxidants, the transformation of antioxidants into quinides, which are known to modulate blood glucose levels and regulate the release of gut peptides that are involved in satiety signaling and insulin secretion (Tunnicliffe & Shearer, 2008; Pimentel *et al*., 2009; Natella & Scaccini, 2012). It is also thought that coffee intake may alter the gut microbiota and flora to optimize digestion, influencing the transport of carbohydrates and glucose molecules and neurohormonal signaling concerned with glucose handling post-absorption (Tunnicliffe & Shearer, 2008; Natella & Scaccini, 2012). Thus, the evidence suggests that coffee intake not only lowers the risk of type 2 diabetes through mechanisms of improved glucose handling and insulin secretion but also by inducing satiety and modulating gut hormones to limit weight gain, of which, excess adiposity is the most recognized cause of insulin resistance and accounts for over 70% of all cases of type 2 diabetes, worldwide (Pimentel *et al*., 2009; Wondmkun, 2020). Caffeine consumption was linked to a little amount of weight loss, according to a recent meta-analysis of randomized controlled trials (Beta 0.29; 95% CI 0.19, 0.40), but doubling caffeine intake increased the Beta value by two-fold (Mofrad *et al*., 2021). Given the limitations of the informing studies, the authors could not conclude whether caffeine influenced weight or other indices of adiposity, such as body mass index and percentage of body fat.

Precisely, magnesium and theophylline; a metabolite of caffeine, are thought to interact with pancreatic beta cells to increase insulin secretion, as well as promote increases in the sensitivity of peripheral tissues to insulin to mediate glucose uptake and increases in glucagon-like peptide-1 and gastric inhibitory peptide, which are known to limit glucose absorption in the small intestine (Pimentel *et al*., 2009). Another chemical present in coffee known as chlorogenic acid, a polyphenol, is thought to further optimize glucose levels through interacting with factors at the intestinal, pancreatic, and hepatic organ systems, which ultimately reduces glucose absorption, improves peripheral glucose uptake, and limits hepatic glucose output (Lee *et al*., 2016). Furthermore, the authors suggest that other peptides present in coffee exert actions at the central level in the hypothalamus to induce anorexigenic compounds release via proopiomelanocortin and inhibit orexigenic peptide release through antagonizing the release of Agouti-related protein and neuropeptide Y (Miller, 2017).

Whilst the former mechanisms linking coffee intake to a reduced risk of diabetes appear physiologically plausible, few studies have explored the effect of coffee consumption on glycaemic parameters of diabetes. A recent systematic review sought to address this problem through the collective analysis of eight trials based on 247 subjects and found that caffeine consumption impaired the glycaemic 2-3 hour post-prandial response compared to decaffeinated coffee intake and water. Still, no meaningful difference in insulin concentration or insulin sensitivity index was identified. In healthy lean subjects, caffeinated coffee was found to improve glucose metabolism with individuals observing a significantly improved 2-hour glucose area under the curve (AUC) ($p<0.001$) and insulin sensitivity index ($p=0.02$). Similar effects were observed for studies of a longer follow-up period with improvements in glucose metabolism being observed and protective of type 2 diabetes or associated with minor improvements in glycaemic control among those with established diabetes.

Safety of Caffeine in Other Beverages

Notably, any positive effects of caffeine intake must be considered because of its potential adverse effects, which vary depending upon the type of caffeine source or beverage fortified with caffeine (Doepker *et al.*, 2018). The cited review of the adverse effects of caffeine showed that doses <400mg or <2.5mg/kg for adults, children, and pregnant women were safe with no acute toxicity or clinically significant effects resulting, however, the relationship between caffeine intake and health effects has been subject to marked confounding in the underlying evidence. More considerable concern has been observed for caffeinated energy drinks as these contain high doses of caffeine and are readily accessible to consumers, increasing the propensity to overdose and, thus, the risk of adverse effects and acute toxicity (Al-Shaar *et al*., 2017). A meta-analysis of energy drinks based on 32 studies and over 96,000 persons showed that the most common effects included insomnia, stress, depressive symptoms, gastrointestinal upset, and psychomotor over-activation (Nadeem *et al*., 2021). Other evidence has shown that caffeine can also induce diuresis and natriuresis significantly based on measures of urinary output and osmolality. However, no studies have evaluated whether diuresis and dehydration lead to acute renal impairment (Riesenhuber *et al*., 2006; Zhang *et al*., 2015).

Conclusion

In summary, this literature review explored the evidence concerning human type 2 diabetes risk and blood glucose consequences of coffee consumption. The evidence consistently shows that coffee intake in both caffeinated and decaffeinated forms can improve glucose metabolism and significantly lower the risk of incident type 2 diabetes. However, most evidence revealed more favorable effects for caffeinated, than decaffeinated coffee. Despite this, it was identified that the consumption of coffee is likely to influence glucose metabolism through varied mechanisms that are not entirely attributable to caffeine but also involve other chemicals and nutrients present in coffee, such as magnesium and various polyphenols. Whilst the underlying evidence has several methodological flaws due to unavoidable risks of confounding and recall biases, it is not possible to infer causation between coffee intake, lower blood glucose levels, and a reduced risk of type 2 diabetes. Thus, only minor to moderate confidence and certainty in the findings were reported.

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