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Review article

Coffee and metabolic impairment: An updated review of epidemiological studies

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ABSTRACT

Background: Coffee is one of the most consumed beverages worldwide. In the last years, coffee consumption has been associated with a number of beneficial effects against metabolic impairment. The aim of this narrative review was to report the most updated and comprehensive evidence from epidemiological and experimental studies as well as mechanisms of action of coffee on metabolic impairment.
Methods: A search in electronic databases (PUBMED and EMBASE) was performed to retrieve systematic and pooled analyses on coffee and diabetes, hypertension, and dyslipidemia. Furthermore, the most accredited hypotheses and mechanisms of action of coffee have been described.
Results: Coffee consumption has been associated with reduced risk of diabetes in observational studies. However, the effect seems not to be mediated by caffeine. Contrasting results have been found in pooled analyses of observational studies on hypertension, despite short- and long-term follow-ups that have been demonstrated to influence the outcome. Poor or little effect on plasma lipids has been reported in studies on acute administration of coffee, yet depending on the type of coffee preparation. The main beneficial effects of coffee consumption seem to rely on the content of antioxidant and anti-inflammatory compounds (i.e., polyphenols). Among the most important, chlorogenic acids have demonstrated direct anti-hypertensive action through beneficial effect on endothelial function, and significant improvement in glucose and insulin metabolism. Also, diterpenes and melanoidins are major candidates as antioxidant compounds showing the capacity to inhibit the production of inflammatory mediators. However, caffeine and diterpenes may also exert negative effects, such as acute rise in blood pressure and serum lipids.
Conclusion: In light of the most recent evidence, coffee consumption seems to be favorably related with health and to protect by metabolic impairment.
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1. Introduction

Metabolic disorders, such as obesity, dysregulated glucose homeostasis, dyslipidemia, and abnormal elevation of systolic and diastolic blood pressure are important risk factors for cardiovascular disease (CVD) and are among the major contributors for overall mortality [1]. Overweight and obese population have rapidly increased worldwide leading to a concomitant rise of type 2 diabetes incidence, especially in the highest income regions [2]. Hypertension and dyslipidemia affect 20%–40% of the population, showing a significant association with elevated BMI, waist circumference, and fasting blood glucose [3]. Altogether, these conditions represent a major public health issue that could potentially be reduced by the adoption of a healthier lifestyle. Besides well-known risk factors, such as sedentary and smoking habits, dietary habits show a crucial impact toward metabolic disorders. Several investigations pointed out the important role of certain dietary patterns, such as the Mediterranean diet or the Dietary Approach to Stop Hypertension (DASH), as significant protective factors against metabolic disorders and CVD risk factors [4–7]. Cohort studies demonstrated positive effects of these dietary patterns in both Mediterranean and non-Mediterranean countries [8,9]. However, their application in non-Mediterranean areas is somehow limited and some important foods have not been taken into account when considering such dietary patterns. In the last ten years, research on coffee drinking has increased dramatically suggesting that coffee consumption is not as negative as it was hypothesized in earlier studies [10]. In a recent State-of-the-Art review, a moderate coffee consumption (2 to 3 cups per day) has shown potential benefits on cardiometabolic disease, cardiovascular health, and all-cause mortality [11]; although in other studies, high coffee consumption (>4 cups per day) could have adverse effects [12]. The findings recently published pointed out convincing hypotheses on its beneficial effects in preventing metabolic impairment and laboratory research on its components provided biological plausibility for its action [13]. In this narrative review, we report the most important epidemiological evidence on coffee consumption and metabolic impairment, showing the inconsistency between epidemiological and experimental studies as a result of the biological differences between short- versus long-time consumption. Furthermore, the most accredited hypotheses and mechanisms of action have been described.

2. Epidemiological versus experimental evidence

2.1. Diabetes mellitus, glucose tolerance, and insulin sensitivity

Two recent systematic reviews and meta-analyses analyzing the specific association between coffee (data from 28 studies with information on 1,109,272 participants) [14], and decaffeinated coffee (10 studies, 491,485 participants) [15] on incidence of type 2 diabetes found a nonlinear dose–response relationship between coffee intake and subsequent risk of type 2 diabetes, with a decrease of about 8% of risk for every 1 cup/day increment in coffee intake after adjustment for potential confounding factors (Table 1). Since similar results were shown for decaffeinated coffee, it is likely that the protective effect may exist aside from the influence of caffeine intake. Another systematic review including 13 cohort studies with 9473 type 2 diabetes cases and 47,387 participants, found a reduction in type 2 diabetes incidence in those subjects who consumed 4 or more cups per day compared with less than 2 cups drinkers [16] (Table 1). Advantage emerged comparing intake of filtered coffee over pot boiled and decaffeinated coffee over caffeinated coffee. However, by analyzing single studies reporting inconclusive results, a relation with factors that could explain such results (i.e., type of coffee or country) could not be found. In addition to the previous systematic reviews, more recent observational studies are in line with the hypothesis that coffee intake may be linked to a lower risk of diabetes [17–21], reduced risk of deterioration of glucose metabolism [22,23], and insulin resistance [24–27].

Generally, results from randomized controlled trials (RCT) exploring the effect of coffee consumption on glucose metabolism and biological risk factors for type 2 diabetes widely contrasted those from observational studies. A recent meta-analysis of RCT in people with type 2 diabetes reported substantial negative effect of caffeine intake on blood glucose control [28] (Table 1). As expected, a major limitation of the trials included in the pooled analysis was the short period of study. Indeed, the beneficial effects of caffeinated and decaffeinated instant coffee on glucose metabolism were found in a recent study that lasted 16 weeks [29], but studies exploring the acute effects following the meal reported opposite or inconclusive results. An experimental study conducted on healthy volunteers resulted in an increasing insulin response and decreased insulin sensitivity index after a 75 g oral glucose tolerance test, compared to water [30]. While in another RTC on healthy subjects, coffee consumption increased glucose concentration and lowered insulin concentrations in the first 30 min after a standardized meal [31]. Caffeinated coffee, after either a high or low glycemic index meal, significantly impaired acute blood glucose management and insulin insensitivity compared with ingestion of decaffeinated coffee [32,33], despite these effects being stronger after a lipid-rich meal [34]. Moreover, coffee consumption during a carbohydrate meal seems to decrease the insulin sensitivity of a second carbohydrate meal, even without an additional coffee intake [35]. Some other experimental studies reported poorly significant results of caffeinated coffee on postprandial glycemic tolerance and insulin sensitivity [36,37] or increase of coffee-derived compounds but no changes of markers of glucose metabolism at an oral glucose tolerance test were found [38].

2.2. Hypertension

Epidemiological studies exploring the role of coffee consumption on the development of hypertension showed inconclusive results. Among the several pooled analysis that have been conducted during last 10 years, the most recent meta-analysis of epidemiological studies, including 6 prospective cohorts with a total of 172,567 participants and 37,135 incident cases of hypertension, concluded that the summary relative risks (RRs) for hypertension was 1.09 (95% confidence interval (CI): 1.01, 1.18) for consumption of 1–3 cups per day, whereas no significant risk was found for higher categories (>3 cups/day) [39] (Table 1). A meta-analysis of experimental and observational epidemiological studies on coffee consumption and hypertension reported low-quality evidence, unable to show any statistically significant effect of coffee consumption on blood pressure or the risk of hypertension [40] (Table 1). Another meta-analysis investigating the role of coffee/caffeine intake in hypertensive subjects results in an acute increment of BP for ≥3, without any long-term association between coffee intake and BP [41] (Table 1). These findings seem to confirm the results of a previous meta-analysis of RCT conducted with regard to the intake of both coffee and caffeine [42] (Table 1). They reported a significant rise of 2.04 mmHg (95% CI: 1.10, 2.99) in systolic blood pressure and 0.73 mmHg (95% CI: 0.14, 1.31) in diastolic blood pressure for pooled analysis of coffee and caffeine trials. When coffee trials and caffeine trials were analyzed separately, blood pressure elevations appeared to be significant only for caffeine but not for coffee, suggesting that despite the biochemical mechanism of action of caffeine supporting the biological plausibility that acute ingestion of such compounds may increase blood pressure, when ingested through coffee, the blood pressure effect of caffeine was somehow attenuated. It is noteworthy that most recent investigations found a significantly reduced risk of hypertension evaluated in both cross-sectional and prospective design only when analysis was stratified by smoking status [43,44].

2.3. Dyslipidemia and lipid metabolism

The early epidemiological studies published in the 1980s demonstrated a significant association between coffee consumption and

Table 1
Characteristics of meta-analysis and systematic review included in this review.

Author	Year	Number and design of the studies	Participants	Cases	Outcome	Exposure	Main results and RR (95% CI)
Diabetes mellitus, glucose tolerance, and insulin sensitivity							
Ding et al. [14]	2014	28 PCS	1,109,272	43,335	T2DM incidence	0 coffee cup/d 1 coffee cups/d 2 coffee cups/d 3 coffee cups/d 4 coffee cups/d 5 coffee cups/d 6 coffee cups/d	1 0.92 (0.90, 0.94) 0.85 (0.82, 0.88) 0.79 (0.75, 0.83) 0.75 (0.71, 0.80) 0.71 (0.65, 0.79) 0.67 (0.61, 0.74)
Jiang et al. [15]	2014	26 PCS	1,096,647	50,595	T2DM incidence	Coffee lowest vs highest	0.71 (0.67, 0.76)
		10 PCS	491,485	29,165	T2DM incidence	Decaffeinated coffee lowest vs highest	0.79 (0.69, 0.91)
		6 PCS	321,960	9302	T2DM incidence	Caffeine, lowest Vs highest	0.70 (0.65, 0.75)
Whitehead et al. [28]	2013	2 RCTs	53 T1DM individuals	N/A	Hypoglycemic episodes	Caffeine 400–500 mg	Increased awareness and decreased duration of hypoglycemic episodes
		6 RCTs	73 T2DM individuals	N/A	Blood glucose and insulin sensitivity	Caffeine 200–500 mg	Increased blood glucose (16%–28%) and insulin levels (19%–48%). Decreased insulin sensitivity by 14%–37%.
		1 RCT	8 GDM individuals	N/A	Blood glucose and insulin sensitivity	Caffeine 200 mg	Increased blood glucose (19%) and insulin level (29%) and reduced insulin sensitivity by 18%.
Muley et al. [16]	2012	13 PCS	12,47,387	9473	T2DM incidence	Coffee	T2DM incidence was reduced in subjects who drank 4–6 cups/d and 6–7 cups/d compared with <2 cups/d drinkers
Hypertension							
Mesas et al. [41]	2011	5 RCTs	85 hypertensive individuals	N/A	Acute effect on BP	Caffeine 200–300 mg)	SBP 8.14 mmHg (5.68, 10.61) DBP 5.7 mmHg (4.1, 7.4)
		6 RCTs	364 hypertensive individuals	N/A	Long-term effect on BP	Coffee or caffeine	No change in BP
Zhang et al. [39]	2011	6 PCS	172,567	37,135	Hypertension incidence	<1 coffee cup/d 1–3 coffee cups/d 3–5 coffee cups/d >5 coffee cups/d	1 1.09 (1.01, 1.18) 1.07 (0.96, 1.20) 1.08 (0.96 ,1.21)
Noordzija et al. [42]	2005	16 RTCs	110	N/A	BP	Coffee	SBP 1.22 mmHg (0.52, 1.92) DBP 0.49 mmHg (−0.06, 1.04)
						Caffeine	SBP 4.16 mmHg (2.13, 6.20) DBP 2.41 mmHg (0.98, 3.84)
						Caffeine and coffee	SBP 2.04 mmHg (1.10, 2.99) DBP 0.73 mmHg (0.14, 1.31)
Dyslipidemia and lipid metabolism							
Cai et al. [54]	2012	12 RCT	1017	N/A	Serum lipids	Coffee 2.4 to 8.0 cups/day	TC 8.05 mg/dl (4.48,11.62) LDL-C 5.44 mg/dl (1.38,9.51) HDL-C -0.12 mg/dl (−0.62, 0.38) TG 12.55 mg/dl (3.47, 21.64)

CI, confidence interval; BP, blood pressure; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable; PCS, prospective cohort study; RTC, randomized controlled trial; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride.

increased serum cholesterol levels [45–48]. The hypercholesterolemic effect of coffee has been demonstrated to depend on the diterpenes cafestol and kahweol, and by the method of brewing [49]. Contrarily, filtered coffee consumption seems to have poor or no association with serum lipid levels compared to boiled coffee, maybe due to the retention of diterpenes by the paper filter [50]. Thus, results from epidemiological studies reported contrasting results with strong country-specific characteristics due to the different bioactive compounds contained in coffee in different countries and type of preparation method used [51–53].

Contrasting with observational studies, a recent meta-analysis of RCT evaluated the effects of coffee intake on serum lipids in 12 studies conducted on 1017 subjects [54] (Table 1). On average, drinking coffee for 45 days was associated with an increase of 8.1 mg/dl (95% CI: 4.5, 11.6) for total cholesterol, 5.4 mg/dl (95% CI: 1.4, 9.5) for LDL-C, and 12.6 mg/dl (95% CI: 3.5, 12.6) for triglycerides. Meta-regression analysis also revealed a positive dose–response relation between coffee intake and total cholesterol, LDL-C, and triglycerides. However, other more recent studies (thus not included in the previous meta-analysis) reported poor or little influence on plasma lipids following acute ingestion of coffee [55] or even a suppression of postprandial hyperlipidemia [56], significant decrease of triglycerides, and increase of HDL-cholesterol [55].

3. Potential beneficial mechanisms of action

3.1. Glucose and insulin metabolism regulation

Despite the acute ingestion of caffeine resulting in a reduction of insulin sensitivity due to decreased glucose storage [57,58], this short-term effect cannot be observed after long-time consumption of coffee because of an overall impairment of effects of caffeine after continued intake [59]. Coffee has been reported to be the main contributor of a number of antioxidant compounds, including some polyphenols such as chlorogenic acids [60]. This family of polyphenols (mostly caffeic and ferulic acid) demonstrated the ability to affect some metabolic pathways [61,62]. In animal models, consumption of chlorogenic acids reduced fasting plasma glucose [63–65], increased sensitivity to insulin

[66], and slowed the appearance of glucose in circulation after glucose load [67,68]. This particular family of molecules showed a specific competitive inhibition of the glucose-6-phosphate translocase in rat liver microsomes [69] an enzyme highly involved in the regulation of homeostasis and blood glucose levels. At the cellular level, chlorogenic acids activate adenosine monophosphate-activated protein kinase (AMPK), a sensor and regulator of cellular energy balance, leading to beneficial metabolic effects, such as the inhibition of fatty acid synthesis and hepatic glucose production. Thus, chlorogenic acid by the activation of AMPK may contribute to lipid and glucose metabolism regulation [70]. Further hypotheses on the mechanism through which chlorogenic acids may prevent diabetes consist in their capacity to reduce sodium-dependent glucose transport in brush border membrane vesicles isolated from rat small intestine [71], and to inhibit α-amylase [72,73] and α-glucosidase activity [74,75], two key enzymes responsible for digestion of dietary carbohydrates, resulting in a reduction of intestinal absorption of glucose.

Together with phenolic compounds, trigonelline and sex hormone-binding globulin (SHBG) also demonstrated a protective effect against diabetes [67,76]. The vitamin B_3 precursor trigonelline has been shown to potentially improve insulin sensitivity in animal studies by inhibiting dipeptidylpeptidase-4 and α-glucosidase activities in both plasma and small intestine [77] and ameliorating the oxidative stress in type 2 diabetic rats downregulating the gene expressions involved with NADPH oxidase and mitochondrial electron transfer system [78]. SHBG have been related with type 2 diabetes since membranes of a variety of cells are able to specifically bind them with high affinity, and SHBG mediates the steroid-signaling system at the cell membrane through the SHBG receptors and exerting direct metabolic effects [79].

3.2. Lipid metabolism regulation

It has been reported that some components present in unfiltered coffee (i.e., cafestol and kahweol) raise serum lipids, but a clear involvement in the deposition of LDL-C and/or an oxidation of this lipid fraction has not been demonstrated. Accordingly, it is still debatable if coffee consumption can affect lipid metabolism in order to significantly increase cardiovascular risk [80]. On the contrary, it has been reported that coffee intake increase LDL-C resistance to oxidative modifications probably as a result of the incorporation of the phenolic acids in coffee into the cells [81]. An experimental study evaluating the effects of chlorogenic acids on lipid metabolism in diabetic rats found a significant increase in the concentrations of plasma and tissue (liver and kidney) lipids, cholesterol, triglycerides, free fatty acids and phospholipids, and LDL and very low-density lipoproteins, respectively, and a decrease in the concentration of HDL [82]. It was demonstrated that their action depended on the capacity to increase the activity of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase in the liver and kidney and a decrease in the activities of lipoprotein lipase (LPL) and lecithin cholesterol acyl transferase (LCAT) in the plasma [82].

A number of epidemiological studies reported a positive association between coffee consumption and adiponectin levels, an insulin-sensitive hormone playing a central role in glucose and lipid metabolism, both in healthy individuals [83–86] and in those with metabolic syndrome-related disorders [87,88]. These studies remarked the inverse association between coffee consumption and obesity or visceral fat area. Experimental studies reported that coffee may play a role in the expression of adipo-R2 gene, which activate its downstream signaling pathways mainly by activating AMPK and peroxisome proliferator-activated receptors alpha (PPAR-a) [89]. Coffee polyphenols and melanoidins protected the liver from damage caused by a hypercaloric diet in an animal model, and this protection was partially mediated by a reduction in liver inflammation, through increases of adipo-R2 gene and anti-inflammatory cytokines IL-4 and IL-10 [90].

3.3. Effects on blood pressure

Despite caffeine inhibiting phosphodiesterase non-selectively, thereby causing an accumulation of cAMP, which can mediate a vasoconstrictive response [91], experimental studies reported that an acute increase in blood pressure due to coffee intake develops with rapid tolerance [92,93] and that intravenous caffeine is responsible for the increase in muscle sympathetic activity and blood pressure in both habitual and non-habitual coffee drinkers, but coffee intake led to increased blood pressure only in non-habitual coffee drinkers [94]. Several components of coffee demonstrate anti-hypertensive action [95]. Chlorogenic acids are hypothesized to exert anti-hypertensive effects by increasing nitric oxide bioavailability and improving endothelial function, which lead to a reduction of blood pressure [96]. Experimental studies also demonstrated that the depletion in roasted coffee of hydroxyhydroquinone, a particular fraction of chlorogenic acid, enhanced the anti-hypertensive effects of chlorogenic acids in a marginally dose-dependent manner [97]. Moreover, coffee is also rich in blood pressure-lowering minerals (i.e., potassium and magnesium) that may contribute to its effect on blood pressure [98].

3.4. Antioxidant activity

Oxidative stress is heavily involved in metabolism impairment pathways, as well as in the development of chronic subclinical inflammation that contribute to chronic disease incidence and progression. The inflammatory response could be mediated by many factors, such as the main phenolic compounds of coffee [99]. In particular, chlorogenic acids demonstrated strong antioxidant effect in a dose–response relationship as a results of the inhibition of the production of inflammatory mediators [100–102], by inhibiting protein tyrosine phosphatase 1B [103] and depressing the expression of pro-inflammatory cytokine genes [104,105]. These compounds also demonstrated decreased endothelial dysfunction [106] by modulating inflammatory NF-κB activation via the redox-related c-Src/ERK and NIK/IKK pathways via the reduction of oxidative stress [107]. Diterpenes are multitasking molecules that play a role in the regulation of angiogenesis and inflammation processes [108,109]. The most studied effects of cafestol regard its capacity to regulate pathological angiogenesis [108]. Kahweol has demonstrated antioxidant properties by inhibiting both cyclo-oxigenase-2 (COX-2) expression and monocyte chemoattractant protein-1 (MCP-1) secretion in endothelial cells, key proteins mediating inflammatory processes [109]. It has been reported that cafestol and kahweol regulate Sp1 target proteins, which are involved in various biological processes such as differentiation, metabolism, cell growth, angiogenesis, and apoptosis [110]. Melanoidins, compounds formed during the roasting of coffee beans, have demonstrated strong antioxidant activity and to significantly inhibit lipid oxidation [111,112]. In an animal model of steatohepatitis, melanoidins protected liver from damage caused by a high-fat diet by a reduction in hepatic fat accumulation (through increased fatty acid β-oxidation), systemic and liver oxidative stress (through the glutathione system), liver inflammation (through modulation of genes), and expression and concentrations of proteins and cytokines related to inflammation [90]. Finally, caffeine itself and its metabolites theobromine and xanthine, have been reported to possess antioxidant properties, such as DNA-protection through quenching of hydroxyl radical generating systems [113].

4. Controversial effects and future prospective

Besides the potential beneficial effects of coffee consumption, great attention should be paid in order to explain its negative effects on human health. It has been often reported a U-shaped effect of coffee on several health outcomes [42,114,115], suggesting that a detrimental effect may occur at higher quantities of consumption. Moreover, results from epidemiological and experimental studies are rarely univocal, but

rather they are opposite and biased by methodological limits. Epidemiological studies provide insight into the long-term effects of coffee consumption but observational evidence cannot demonstrate causal relationship. Moreover, cross-sectional studies may have a lack of reliability due to the phenomenon of "reverse causation", namely, an adaptation of coffee consumption after developing the disease. Prospective cohort studies should minimize such phenomenon, but control over time of coffee consumption may results difficult and the time distance between the exposure assessment (i.e., coffee intake at baseline) and the outcome evaluation may bias results. Thus, evidence from epidemiological studies is only in part demonstrated in the experimental setting, and potential confounders (i.e., cigarette smoking) may affect findings. The randomization process of RCT should, at least in part, attenuate the effects of confounders theoretically equally distributed over both intervention and control groups. However, compared to epidemiological studies, RCT are usually conducted over a limited period of time. Moreover, the effects follow generally a fixed dose of coffee (or caffeine) and controlled in a predetermined moment, thus estimating mostly acute effects of coffee and often not corresponding to "real-world" coffee drinking. Finally, regarding experimental studies, most of the data existing is based on *in vitro* and animal studies, therefore the relevance of findings for the application in humans is still unclear.

5. Conclusion

In conclusion, in light of the most recent epidemiological and experimental evidence, coffee consumption seems to be favorably related with health and to protect by metabolic impairment. Despite the mechanisms of action being not completely understood, its content in polyphenols and antioxidant compounds may be countering many of the negative effects reported in the early researches. Moreover, components with demonstrated harmful effects (i.e., caffeine and diterpenes) are nowadays also being reconsidered due to novel discoveries of new potential positive effects or new hypotheses on their interaction with metabolism regulation.

Conflict of interest

The authors declare that they have no conflict of interest.

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