Effects of coffee consumption on glucose metabolism: A systematic review of clinical trials

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ABSTRACT

Epidemiological studies indicate an inverse association of coffee consumption with risk of type 2 diabetes mellitus. However, studies to determine the clinical effects of coffee consumption on the glucose metabolism biomarkers remain uncertain. The aim of this systematic review was to evaluate the effects of coffee consumption on glucose metabolism. A search of electronic databases (PubMed and Web of Science) was performed identifying studies published until September 2017. Eight clinical trials (n = 247 subjects) were identified for analyses. Participants and studies characteristics, main findings, and study quality (Jadad Score) were reported. Short-term (1–3 h) and long-term (2–16 weeks) studies were summarized separately. Short-term studies showed that consumption of caffeinated coffee may increase the area under the curve for glucose response, while for long-term studies, caffeinated coffee may improve the glycaemic metabolism by reducing the glucose curve and increasing the insulin response. The findings suggest that consumption of caffeinated coffee may lead to unfavourable acute effects; however, an improvement on glucose metabolism was found on long-term follow-up.

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1. Introduction

Coffee is one of the most frequently consumed beverages worldwide, and has gained special attention in relation to its beneficial effects on several chronic diseases, specially type 2 diabetes mellitus (T2DM).[1] Coffee is a complex beverage composed of numerous bioactive substances, such as caffeine, phenolic compounds, including chlorogenic acids (CGA), and nutrients (minerals and vitamins). Collectively, coffee exerts functional and beneficial effects on human health.[2] Epidemiological studies link moderate consumption of coffee with a reduced risk of developing T2DM. This association has been shown in several studies with different populations showing a consistent dose-response effect.[3–9]

Studies suggest that drinking 3–4 cups of coffee per day is associated with an approximately 25% lower risk of developing T2DM compared to consuming none or less than 2 cups per day.[3–6] The relative risk of T2DM for the highest level of coffee intake (>6 cups/day) was 0.71 (0.67–0.76) for caffeinated coffee and 0.79 (0.69–0.91) for intake of decaffeinated coffee.[7] In addition, people who increase their consumption of coffee (+1 cup/day) had a decrease of 11% on T2DM risk in the subsequent 4 years. On the one hand, people who decreased their coffee intake by more than 1 cup/day had a 17% higher risk for T2DM in 4 years.[5] It seems that intake of both caffeinated and decaffeinated coffee can decrease T2DM risk. Dose-response analysis suggested that incidence of T2DM decreased by 12% (0.88 (0.86–0.90)) for intake of every 2 cups/day of caffeinated coffee, and 11% (0.89 (0.82–0.98)) for intake of every 2 cups/day of decaffeinated coffee.[7]

During the past few years, the number of studies on this topic has increased. Several studies have linked the effects of coffee consumption to glucose metabolism parameters (blood glucose and insulin concentrations, homeostasis model assessment insulin resistance index (HOMA-IR), and insulin sensitivity index) that could explain its beneficial epidemiological findings.[10–12] To date,

no systematic review has explored the link between coffee consumption and glucose metabolism parameters. Therefore, the aim of this study is to analyse the clinical trials that evaluated the effects of coffee consumption on glucose metabolism.

2. Materials and methods

2.1. Data sources and searches

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The protocol for this systematic review was registered in the PROSPERO database of prospectively registered systematic reviews (www.crd.york.ac.uk/PROSPERO): CRD42016043300. A systematic literature search was conducted on PubMed and Web of Science databases seeking articles published until September 2017 using a combination of the following Medical Subject Headings terms and keywords: coffee 'AND' (glucose 'OR' insulin 'OR' type 2 diabetes 'OR' glucose metabolism). Constraints were used for advanced search: adults (aged 19 years or more), human, clinical trial, and search fields: title/abstract. Additionally, we scrutinised references within identified papers as well as articles that had come to our attention through other means.

2.2. Study selection

The total hits obtained from searching the databases were screened by reading the article 'title' and 'abstracts'. Studies that did not match the aims of the review were excluded. The selected trials had the methods section analysed, and those that did not satisfy the established criteria were also excluded. Clinical trials were included if they met the following criteria: (i) individuals who had not been previously diagnosed with type 1 diabetes mellitus; (ii) consumption of coffee (caffeinated and/or decaffeinated) versus a control (placebo or water); (iii) evaluation of the effects of coffee on biomarkers of glucose metabolism (i.e., blood glucose and/or insulin concentrations and/or insulin resistance and/or insulin sensitivity). These inclusion criteria were assessed by reading the respective study protocol. When necessary, additional information data were requested from the study's corresponding author. Studies were discarded after being judged as irrelevant to the review's objectives, duplicate publications, inappropriate study design, population type, and interest outcomes.

2.3. Quality assessment

Quality of the studies was judged by two independent reviewers (C.E.G.R. and T.H.M.C.) based on the Jadad Score[14] that includes randomisation, generation of random order, double-blinding, discrimination of the blinding method and reporting of withdrawals. For each trial, a score was attributed to each addressed item, with a possible score of 0–5 (5 being the highest level of quality). Studies with a score ≥3 reflected 'good' reporting quality, whereas score of <3 indicated a poor quality study, impacted by a low relative validity. Studies that scored <3 points were not considered for further evaluation. The analysis was performed separately by each reviewer, and the results were compared so as to arrive at a final conclusion. Those articles evaluated that recorded discrepant scores were analysed again for a final score. The risk of bias was included within the narrative synthesis as recommended.

2.4. Data synthesis and analysis

Data summary of the studies are presented in Tables 1 and 2. The studies are organised as short-term (follow-up of 1–3 h) and long-term effects (follow-up of 2–16 weeks). The units of glucose and insulin were standardised according to the International System of Units: mmol/L for glucose and pmol/L for insulin. Data are presented as mean ± SEM (standard error of the mean). SEM was used to standardise the study data variability. For studies reporting standard deviation (SD), the SEM was calculated dividing the SD by the square root of the sample size of the corresponding arm of the trial.

3. Results

3.1. Literature search results

The search strategy is summarized in Fig. 1. The literature search identified 740 studies distributed in PubMed and Web of Science. No additional articles were identified by other types of search. After removing the 'not suitable' (n = 700), duplicates (n = 10), and those references that did not match the aims (n = 6), we ended up with 24 trials.[15–38] After Jadad evaluation, 8 trials[15–19,35–38] were included in the analysis.

3.2. Data quality

Table 1 ranks all the clinical trials: of 24 studies reviewed, 4% (n = 1) high quality (score = 5), 29% (n = 7) good quality (score = 3–4), 25% (n = 6) low quality (score = 1–2), and 42% (n = 10) were classified as poor quality (score = 0). Overall, the Jadad Score identified a methodological weakness (score < 3) for 16 trials that were excluded from the review analyses. Eight studies showed a score ≥3: five short-term,[15–19] and three long-term follow-up.[35–38]

3.3. Characteristics of the selected studies

Table 2 summarises relevant data of the selected short-term (n = 5) and long-term (n = 3) studies. Overall, the trials were from various countries/populations: two were from The Netherlands, and one from each of the following countries: Canada, Greece, the United States of America, England, Japan and New Zealand. Half the studies (n = 4) enrolled males exclusively, while the other half enrolled both males and females. Six studies evaluated healthy individuals [mean body mass index (BMI) ranging from 21.3 to 30.0 kg/m^2]; one study evaluated individuals with T2DM, and one enrolled overweight individuals diagnosed with impaired glucose tolerance. The mean age and BMI of the short-term trials were, respectively, 26.6 (SD 2.7) years and 37.4 (SD 9.7) kg/m^2; for the long-term trials, mean age and BMI were 26.0 (SD 2.4) years and 42.4 (SD 11.3) kg/m^2, respectively. The coffee and caffeine dose in the short-term studies ranged from 200 to 633 mL and 100–526 mg, respectively; in the long-term trials the coffee dose ranged from 500 to 1000 mL, and the caffeine dose ranged from 345 to 1100 mg. The methods for the preparation of coffee were, instant or regular, paper-filtered or espresso. For glucose and insulin response curve, the trapezoidal method for calculation of the area under the curve (AUC) was used.

3.4. Metabolic response

Table 3 presents the glycaemic and insulinaemic AUC results from the short-term and long-term clinical trials.

3.5. Short-term trials

Results from the short-term trials show a temporary impairment on the 2–3-h postprandial glucose response following

Table 1
Jadad score value of clinical trials that evaluated the effects of coffee consumption on biomarkers of glucose metabolism.

Author, year	Jadad Score	Randomisation[a]	Randomisation method reported[b]	Double-blind[a]	Blinding method reported[b]	Dropouts described[a]
Short-term						
Moisey et al., 2008[15]	4	1	1	1	1	0
van Dijk et al., 2009[16]	4	1	1	1	1	0
Krebs et al., 2012[17]	4	1	1	1	1	0
Robertson et al., 2015[18]	4	1	1	1	1	0
Gavrieli et al., 2013[19]	3	1	1	0	N.A.	1
Thom et al., 2007[20]	2	1	−1	1	1	0
Moisey et al., 2010[21]	2	1	−1	1	1	0
Gavrieli et al., 2011[22]	2	1	1	0	N.A.	0
Rakvaag et al., 2015[23]	1	1	−1	0	N.A.	1
Hatonen et al., 2012[24]	1	1	−1	0	N.A.	1
Johnston et al., 2003[25]	0	1	−1	0	N.A.	0
Battram et al., 2006[26]	0	1	−1	1	−1	0
Louie et al., 2008[27]	0	1	−1	0	N.A.	0
Aldughpassi et al., 2009[28]	0	1	−1	0	N.A.	0
Greenberg et al., 2010[29]	0	1	−1	0	N.A.	0
Buscemi et al., 2010[30]	0	1	−1	1	−1	0
Beaudoin et al., 2011[31]	0	1	−1	0	N.A.	0
Al-Mssallem et al., 2013[32]	0	1	- 1	0	N.A.	0
Alkaabi et al., 2013[33]	0	0	N.A.	0	N.A.	0
Long-term						
Sarriá et al., 2016[34]	1	1	- 1	1	- 1	1
Wedick et al., 2011[35]	5	1	1	1	1	1
vanDam et al., 2004[36]	3	1	1	0	N.A.	1
Ohnaka et al., 2012[37]	3	1	1	0	N.A.	1
Kempf et al., 2010[38]	0	0	N.A.	0	N.A.	0

Symbols: [a], Yes = + 1 point; Not = 0 point; [b], Yes = + 1 point; Not = - 1 point; N.A., Not applied.

Table 2
Description of the studies of short- and long-term effects of coffee consumption on glucose metabolism.

Authors, year	Country[a]	Sample size[b]	Health condition[c]	Design[d]	Follow-up time[e]	Coffee Dose (mL)	Coffee dose	Coffee preparation	Caffeine dose (mg)
Short-term									
Moisey et al., 2008[15]	Canada	10 M	Healthy, lean	Crossover RCT	1 h + 2 h meal test[f]	633[g]	633 mL[g]	Filtered	393
van Dijk et al., 2009[16]	Netherlands	15 M	Healthy, overweight	Crossover RCT	30 min + 2 h OGTT	270	270 mL	Instant	N.A.
Krebs et al., 2012[17]	New Zealand	9 M/9 F	T2DM	Single-blind crossover RCT	1 h + 2 h OGTT = 3 h	200	200 mL	Espresso	180
Robertson et al., 2015[18]	England	10 M	Healthy, overweight	Double-blind Crossover RCT	2 h	400[i]	400 mL[i]	Instant	100
Gavriel et al., 2013[19]	Greece	8 M/8 F 9 M/8 F	Healthy, lean overweight	Crossover RCT	3 h meal test[h]	200	200 mL	Instant	383 526
Long-term									
Wedick et al., 2011[35]	U.S.A.	45 (16 M/ 29 F)	Healthy, overweight	Double-blind RCT	8 wk	885	885 mL	Instant	345
van Dam et al., 2004 (Study 1)[36]	Netherlands	26 (10 M/ 16 F)	Healthy, lean	Crossover RCT	4 wk	1000	1000 mL	Filtered	1100
van Dam et al., 2004 (Study 2)[36]	Netherlands	45 (20 M/ 25 F)	Healthy, lean	Crossover RCT	2 wk	900	900 mL	Filtered	820
Ohnaka et al., 2012[37]	Japan	45 males	Overweight IGT	RCT	16 wk	5 cups[j]	5 cups[j]	Instant	250

N.A.: not applied.
Abbreviations and symbols:
  [a] U.S.A.: United States of America; U.K.: United Kingdom.
  [b] M: males; F: females.
  [c] T2DM: type 2 diabetes mellitus; IGT: Impaired glucose tolerance.
  [d] RCT: randomised controlled trial.
  [e] h: hours; OGTT: 75 g oral glucose tolerance test; min: minutes; wk: week. 1 h + 2 h: carbohydrate consumption 1 h before (time - 1 h) the beverage test (time 0), follow by 2 h of evaluation; 30 min + 2 h: carbohydrate consumption 30 min before (time −30 min) the beverage test (time 0), follow by 2 h of evaluation; 1 h + 2 h OGTT = 3 h: carbohydrate consumption 1 h before (time − 1 h) the beverage test (time 0), follow by 2 h of evaluation, data analysis of 3 h of intervention. 3 h: carbohydrate consumption with beverage test (time 0), follow by 3 h of evaluation.
  [f] 75 g of available carbohydrate.
  [g] Mean coffee volume was calculated using the data shown in the paper (dose of caffeine/kg body weight, average weight of the subjects and coffee caffeine content).
  [h] 22 g of available carbohydrate.
  [i] 2 g of instant decaffeinated coffee, plus 100 mg of caffeine with 50 g of glucose.
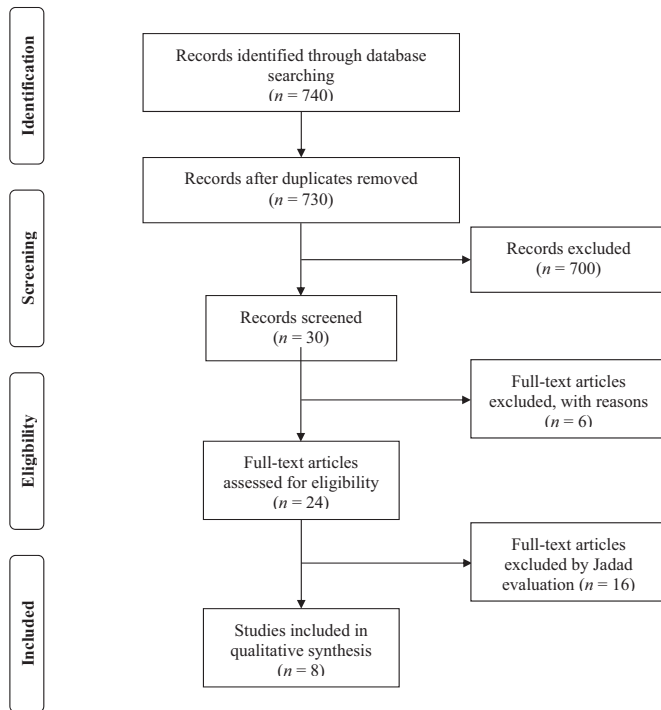 [j] Coffee dose is not clear in the text, but seems to be of 500 ml.

Fig. 1. Flow diagram of the study selection.

3.6. Lean and healthy subjects

Moisey et al. (Table 3) showed that compared with caffeinated coffee the decaffeinated beverage improved the glucose metabolism. They studied 10 healthy men in a crossover randomised clinical trial (RCT); caffeinated and decaffeinated coffees were taken 1 h after a high glycaemic index meal (75 g of available carbohydrate). Compared with decaffeinated coffee, the caffeinated coffee resulted in 145.6% and 28.5% greater 2 h AUC for glucose (p < 0.001) and insulin (p = 0.16), respectively. In addition, the insulin sensitivity (Matsuda Index) was significantly reduced by 40% (p = 0.02) after ingestion of caffeinated coffee compared with decaffeinated coffee.[15] Gavrieli et al. (Table 3) reported no significant effects of caffeinated coffee on glucose and insulin concentrations, and AUCs compared with control (water). In this crossover RCT, 16 healthy males and females were evaluated for coffee intake after 3 h postprandial response.[19]

3.7. Overweight subjects

Gavrieli et al. (Table 3) showed that compared with control (water) the overweight/obese subjects (n = 17) had significantly elevated glucose 3 h AUC after 3 mg (8.7%) and 6 mg (13.3%) of caffeinated coffee intake (p = 0.03 and p = 0.02, respectively). In addition, 6 mg caffeinated coffee results in lower insulin concentrations at 15 and 30 min, and elevated glucose concentrations at 60 and 90 min compared to water (p < 0.05). However, no significant difference was found for insulin AUC between the treatments.[19] In addition, Robertson et al. (Table 3) investigated in a randomised double-blind crossover study the effects of 2, 4 or 8 g of instant decaffeinated coffee with caffeine added (100, 200 or 400 mg), plus 50 g of glucose on glucose and insulin levels for 2 h with 10 healthy overweight men. The ingestion of 2 g instant decaffeinated coffee with 100 mg of caffeine led to a significant increase in glucose AUC compared with water (p = 0.008). There were no differences between treatments for postprandial insulin or insulin sensitivity as measured by the Matsuda Index. No dose-dependent effect was found.[18]

ingestion of coffee. Compared to decaffeinated coffee and water, the caffeinated beverage may impair the glycaemic AUC response in short-term duration. Overall, there were no significant differences for insulin concentration and AUC, and insulin sensitivity index. In addition, no consistent results were found for consumption of decaffeinated coffee on glucose metabolism biomarkers[15–19] (Table 3).

Table 3
Short- and long-term effect of coffee intake clinical trials on glucose and insulin AUC in lean healthy, overweight and T2DM subjects[*].

Authors, year	GLUCOSE[§]						INSULIN[§]						ISI[‡]
	Coffee		Control[¥]		Decaf		Coffee		Control[¥]		Decaf		
	AUC	SEM	AUC	SEM	AUC	SEM	AUC	SEM	AUC	SEM	AUC	SEM	
Short term													
Lean healthy													
Moisey et al., 2008[15]	253[a]	40	–	–	103[b]	39	42727	11155	–	–	33241	14541	DC↑[1]
Gavrieli et al., 2013[19]	8.98	0.43	8.20	0.30	–	–	283.35	23.61	278.49	30.55	–	–	–
Overweight													
van Dijk et al., 2009[16]	–	–	962	134	958	134	–	–	54727	21658	52324	21658	–
Gavrieli et al., 2013[19]	9.41[a]	0.30	8.35[b]	0.24	–	–	332.66	28.47	324.33	25.00	–	–	–
Robertson et al., 2015[18]	237[a]	102	172[b]	89	–	–	10294	7376	8238	6114	–	–	NS[1]
T2DM													
Krebs et al., 2012[17]	2547[a]	120	2443[b]	101	2455[ab]	118	66769	10528	65866	9299	68943	9695	NS[1]
Long term[‡]													
Wedick et al., 2011[35]	13.0	#	13.8	#	14.3	#	618	#	697.5	#	771	#	NS[1,2]
Ohnaka et al., 2012[37]	16.9[a]	#	21.1[b]	#	20.3[ab]	#	1114	#	917	#	633	#	NS[1,2]

[*]: Data extracted from the original papers.
[¥]: Water.
[§]: Means in the same row without a common superscript letter differ significantly p < 0.05.
NS: no statistically significant difference was found between study groups.
[‡]: van Dam et al. (2004)[35] was removed from the table because they did not performed the AUC calculation[#].
–: non-applicable.
[#]: Raw data not provided.
[‡]: ISI: Insulin Sensitivity Index.
[1]: Matsuda Index for decaffeinated coffee.
[2]: HOMA-IR: homeostasis model assessment of insulin resistance.

On the other hand, van Dijk et al. (Table 3) conducted a crossover RCT to analyse the effects of decaffeinated coffee on concentrations of glucose and insulin during a 2 h oral glucose tolerance test (OGTT) in 15 healthy overweight men. Decaffeinated coffee did not significantly change glucose or insulin concentrations at any time points, or AUC values compared with control.[16]

3.8. T2DM subjects

Krebs et al. (Table 3) studied the effects of espresso caffeinated and decaffeinated coffee consumed 1 h before the 2 h OGTT on glucose tolerance and insulin sensitivity in 18 subjects with T2DM in a crossover RCT. Glucose 3 h AUC was higher after caffeinated coffee than water (p = 0.03), and marginally higher when compared with decaffeinated coffee (p = 0.055). There were no differences in insulin AUC (p = 0.87) and insulin sensitivity (Matsuda Index) (p = 0.47) following consumption of the beverage. Compared with water and decaffeinated coffee, espresso results in a marginally greater excursion of glucose during an OGTT in T2DM subjects. This effect does not appear to be mediated by changes in insulin sensitivity.[17]

3.9. Long-term trials

Ohnaka et al. (Table 3) studied the effects of consumption of 5 cups of caffeinated and decaffeinated coffee per day on glucose metabolism in a 16-week RCT (n = 45). Compared with control (water), the caffeinated coffee decreases the 2 h glucose AUC (p < 0.05). In addition, 2 h insulin AUC was 21.5% higher for caffeinated coffee compared with control, but not significant. Also, no significant differences were found for decaffeinated coffee and control groups on glucose and insulin responses, and insulin sensitivity index (composite ISI and HOMA-IR).[37]

Van Dam et al. (Table 3) conducted two clinical trials to evaluate the effects of caffeinated coffee and caffeine on glucose metabolism. The first study was a 4-week crossover trial that compared the effects of consumption of 1 L caffeinated coffee with abstinence from coffee in 26 volunteers. After 4 weeks, fasting insulin concentrations were higher after the caffeinated coffee group than the no-coffee group (p = 0.002), and no appreciable effect was observed to glucose response (p = 0.94). However, the second study (n = 45) had no significant effects on concentrations of fasting glucose and insulin (p = 0.42 and p = 0.15, respectively). The authors have not performed the AUC calculation.[36] Similar to these results, Wedick et al. (Table 3) (n = 45) showed no significant differences for glucose tolerance, insulin sensitivity, and insulin secretion after the consumption of 5 cups per day of caffeinated and decaffeinated coffee, or no coffee for 8 weeks.[35]

Despite the limited data of long-term trials, the results show that consumption of caffeinated coffee may improve the glycaemic metabolism by the reduction on glucose and increase on insulin response.[35–37] In addition, no impairment on glucose metabolism was found opposing the results suggested by short-term trials.

Summing up, the results for short-term trials showed that consumption of caffeinated coffee may increase the glucose AUC response, whereas, for long-term studies, the caffeinated coffee may improve the glycaemic metabolism by reducing the glucose response curve and increasing the insulin response, thus corroborating the epidemiologic studies that showed a reduction of T2DM risk.

4. Discussion

This is a systematic review of clinical trials that evaluated the effects of coffee consumption on glucose metabolism, summarising

data from eight studies involving a total of 247 subjects. Although there is heterogeneity among the studies, the results suggested impairment on glucose response for consumption of caffeinated coffee in the short-term (hours), and an improvement on glucose metabolism (glucose and insulin response) in long-term duration (weeks). Moreover, no significant change was observed for insulin sensitivity. The benefits of coffee consumption may manifest in the long-term, as indicated in the reduction of T2DM risk in epidemiological studies (years) (Table 4).

Contrary to the results from the trials with consumption of caffeinated coffee on glucose metabolism, meta-analysis of epidemiological studies have consistently shown that regular consumption of coffee (caffeinated or decaffeinated) is associated with lower risk of T2DM.[5–7] The protective effect of habitual coffee consumption is seen with both caffeinated and decaffeinated coffee, with one study suggesting that the effect may be greater for decaffeinated coffee.[39] Nonetheless, these results need to be interpreted with caution because of the inseparable association between coffee and caffeine consumption.[6]

There is some debate about the role of caffeine and its effects in the development of insulin resistance and T2DM. A recent meta-analysis (2016) demonstrated that acute caffeine ingestion reduces insulin sensitivity in healthy subjects.[40] Acute administration of caffeine impairs the insulin resistance and glucose tolerance through the antagonism of the A1 and A2 subtypes of the adenosine receptor relating to glucose uptake in skeletal muscles. In addition, caffeine has a synergistic interaction with adrenalin and noradrenalin, the main neurotransmitters of the sympathetic nervous system.[41] The acute effects of the coffee consumption may occur due the negative effects of caffeine on glucose metabolism. As the caffeine is fast metabolized in the majority of the population[42] is probably the only factor acting on the acute effects. The effects of caffeine on glucose metabolism are consistent with the results of the short-term trials, and contradictory to the epidemiological findings, suggesting a reduction of T2DM risk with habitual consumption of coffee.

The results obtained from the long-term trials may indicate that the reduction of the T2DM risk should occur due to chronic coffee consumption, as shown by the epidemiology studies. However, the epidemiologic observations are not fully confirmed by the human clinical trials. The possible explanation for this finding is that in the short-term trials, the hyperglycaemic effects of caffeine are dominant over the possible beneficial effects of the others constituents of the coffee. Regarding the long-term studies, there is more time (weeks) for the bioactive compounds of coffee, especially the CGA, to exert their antioxidant and anti-inflammatory effects that can lead to an improvement on glucose metabolism.[43] There is a lack of information about the metabolic effects of the others constituents of coffee and how this components can vary according with type of beans, roasting process and brewing, which may explain some part of the benefits of the coffee on T2DM.

The epidemiological results suggest that components of coffee, other than caffeine, are responsible for the beneficial effects.[6] Also, there is indication that habitual consumers develop a tolerance to the effects caused by caffeine in insulin sensitivity and glucose tolerance.[44] The later response of the long-term trials can be reflected by the tolerance to the acute caffeine effects. Additionally,

Table 4
Effect of interactions of the time of coffee consumption on glucose metabolism.

Short-term	Long-term	Epidemiologic
↑ Glucose AUC	↓ Glucose AUC ↑ Insulin AUC	↓ T2DM risk (dose-response effect)

the protective properties of coffee consumption on T2DM involve multiple mechanisms that include not only antioxidant but also anti-inflammatory effects, factors that play a crucial role in blood glucose control. The benefits of coffee can be related to the content of bioactive compounds, such as CGA, trigonelline, lignans, quinides, cafestol and kahweol, that possess anti-inflammatory properties.[41,45]

Approximately 100 mg of polyphenols are identified in a cup of coffee.[46] CGAs are the main phenolic components in coffee.[47] The hypoglycaemic effects of dietary polyphenolic compounds may be related to inhibition of carbohydrate digestion by inhibiting salivary and pancreatic alpha-amylase and alpha-glucosidase in the small intestinal brush border, inhibition of glucose absorption, and stimulation of insulin secretion. Polyphenols may suppress glucose release from the liver, and improve glucose uptake in peripheral tissues by modulating intracellular signalling.[45,48]

The coffee beverage is the richest dietary source of CGA, and this phenolic compound has been shown to reduce blood glucose concentrations in animal experiments.[41,49] In animal models, consumption of CGA reduced fasting plasma glucose, increased sensitivity to insulin, and slowed the appearance of glucose in circulation after glucose load. This particular family of molecules showed a specific competitive inhibition of the glucose-6-phosphate translocase in rat liver microsomes, an enzyme highly involved in the regulation of homeostasis and blood glucose levels. At the cellular level, CGAs 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, CGA, by the activation of AMPK, may contribute to regulation of lipid and glucose metabolism. Further, hypotheses on the mechanism through which CGA may prevent diabetes, consist in their capacity to reduce sodium-dependent glucose transport in brush border membrane vesicles isolated from rat small intestine, and to inhibit alpha-amylase and alpha-glucosidase activity, two key enzymes responsible for digestion of dietary carbohydrates, resulting in a reduction of intestinal absorption of glucose.[48,50]

Unfortunately, the fate and mode of action of CGAs after ingestion in the human body is more complex than originally anticipated because very little of the absorbed molecules retain the structure of the parent CGA present in the drink.[41] So, the health effects of polyphenols have been shown to go beyond simple antioxidant activity, because polyphenols exert modulatory effects in cells through selective action on cell-signalling pathways involved in the pathogenesis of chronic diseases.[51] Furthermore, cafestol exposure (72 h) increases insulin secretion by 34–68% in skeletal muscle cells.[52] In addition, previous studies have been shown that reduces blood glucose concentrations in humans.[16,53] This result can be explained by the regulation of key enzymes of glucose metabolism as glucokinase, glucose-6-phosphatase, alpha-glucosidase and dipeptidyl peptidase-4 activity.[54–57]

Several studies conducted on humans and animals have demonstrated that regular consumption of coffee may significantly reduce the concentrations of pro-inflammatory biomarkers, such as interleukin (IL)-1 b, IL-6, tumour necrosis factor a, C-reactive protein, monocyte chemotactic protein 1, vascular cell adhesion molecule 1, C-peptides, endothelial-leukocyte adhesion molecule 1, IL-18, 8-isoprostane, and fetuin-A; and significantly increased the concentrations of anti-inflammatory biomarkers, such as adiponectin, IL-4, and IL-10[35,38,45] that can contribute to a reduced T2DM risk.[58] In this regard, coffee has been shown to be associated with a protection against various types of chemical stresses through the stimulation of enzymes involved in cellular antioxidant defences, resulting in increased endogenous defence mechanisms not only against electrophilic but also against oxidative insults.[59] The

bioactive compounds of coffee can exert antioxidant activity capable of scavenging free radicals, donating hydrogen and electrons, providing reducing activity and also acting as metal ion pro-oxidant chelators.[60] Therefore, the reduction of T2DM risk found in epidemiological studies may be explained by the long-term effects (years) of the bioactive compounds that down modulate the oxidative stress and chronic inflammation, thus favouring an improvement on glucose metabolism.

Findings from the current review must be interpreted with caution because the evidence is based on a limited number of studies with some caveats. The quality assessment, according to the Jadad criteria, showed limitations of the studies' methodology. Although almost all the studies specified randomisation, most of them fail to report the method of randomisation. Double blinding was also not present in half the published trials. One explanation is the difficulty in effectively blinding the subjects and researchers, due to the characteristics and aroma of coffee itself, but double blinding is observed in trials using caffeinated and decaffeinated coffee aromas.[17,21,35] Description of drop-out was not reported in the short-term follow-up trials except for Hatonen et al. (2012)[24] and Gavrieli et al. (2013).[19] Consequently, there is limited information of possible side or harmful effects on the subjects. In fact, no side or harmful effect of coffee was reported by the subjects participating in all trials, in which the majority were healthy male subjects. The results are then limited to this group of people and cannot be extrapolated to the general population, including vulnerable groups, including T2DM subjects.

The advantage of this review relies on the demonstration that short-term follow-up studies are limited to effects on fasting glucose and insulin concentrations which are insufficient markers to effectively explain the effect of coffee on reducing the risk of T2DM. Additionally, it is evident that long follow-up randomised trials are still insufficient, and should be the way forward for new research on the subject. Verifying the direct effect of consumption of coffee on biomarkers of glucose and insulin metabolism is not a satisfactory model to investigate the mechanism. In addition, the majority of clinical trials available were designed to analyse the effects of coffee consumption on glucose metabolism linking to T2DM risk without focusing on various others factors that can affect the final glycaemic metabolism. Data on the effects of coffee intake on glucose metabolism from randomised trials lasting more than 24 h are sparse and limited to effects on fasting glucose and insulin concentrations. Nevertheless, until the relationship between long-term consumption of coffee and T2DM is better understood and any mechanism involved identified, it is premature to explain how coffee prevent T2DM. Moreover, there is a need of more studies in humans using equivalent bioavailable amounts of coffee to better understand the effects on the carbohydrate metabolism.

5. Conclusions

In conclusion, caffeinated coffee may show a non-favourable acute effect, and an improvement on glucose metabolism on the long-term follow-up. Therefore, further long-term RCTs are needed to investigate how the substances contained in coffee can overcome caffeine effects, and explain the protective effects of consumption of coffee on T2DM.

Conflicts of interest

The authors declare that they have no conflict of interest.

Authorship

CEGR and THMC were responsible for the study concept and

design; they systematically reviewed the literature and analysed the data. CEGR, THMC and JGD interpreted the results and wrote the manuscript. All authors edited and approved the final version of the manuscript to be published. CEGR is the guarantor of the work.

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