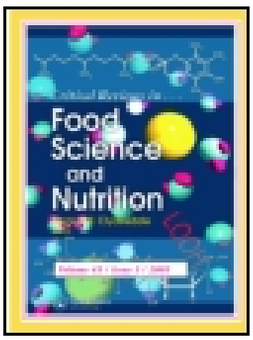

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Consumption of coffee or caffeine and serum concentration of inflammatory markers: a systematic review

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Abstract

Coffee consumption is associated with reduced risk of conditions that share low-grade inflammation as their physiopathological basis. We therefore summarized the effects of coffee or coffee components on serum levels of inflammatory markers. Clinical trials assessing the effect of coffee, caffeine or other coffee components on inflammatory markers were searched without restriction to publication date. Fifteen studies (8 involving coffee and 7 caffeine) were included. Increased adiponectin levels were found in four of seven trials comparing filtered coffee/caffeinated coffee with placebo or comparing its levels at baseline and after consumption of medium or dark roasted coffee, but no change was seen in caffeine trials. None of the five studies assessing the effects of coffee found changes in C-reactive protein (CPR), but one out of

three trials found decreased CPR levels in response to caffeine. Interleukin (IL)-6 was increased by caffeinated coffee compared with placebo in one of four coffee trials, and by caffeine in three out of five studies. Caffeine increased IL-10 levels in two of three trials. These data suggest a predominant anti-inflammatory action of coffee but not of caffeine consumption. Moreover, the proinflammatory and anti-inflammatory responses to caffeine point to its complex effects on the inflammatory response.

Key words

inflammatory markers, inflammatory response, coffee, caffeine.

Introduction

Coffee is among the most commonly consumed beverages worldwide and there has been a great interest in understanding its effects in health outcomes and diseases (Lopez-Garcia et al., 2014, Mejia and Ramirez-Mares, 2014, Zhao et al., 2015, Preedy, 2015). Coffee is rich in bioactive compounds with antioxidant and anti-inflammatory properties (Gómez-Ruiz et al. 2007), including chlorogenic acid, magnesium, lignanes, quinides, trigonelline, diterpenes and N-methylpyridine (Clifford, 2000, Lang et al., 2013). Likewise, coffee consumption is associated with reduced risk of clinical conditions that share low-grade inflammation and oxidative stress as their physiopathological basis (Schulze et al., 2005), such as cardiovascular disease (Kleemola et al., 2000, Zhang et al., 2009), certain types of cancer, obesity (Greenberg et al., 2006, Bidel et al., 2010, Vinson et al., 2012), type 2 diabetes (Sartorelli et al., 2010, Ding et al., 2014) and metabolic syndrome (Shang et al., 2016). In addition, moderate coffee consumption is inversely related to total mortality (Zhang et al., 2009, Freedman et al., 2012).

Metabolic syndrome is a cluster of cardiovascular risk factors affecting around 25% of the adult population worldwide (Eckel et al., 2005). Its most important component is hyperglycemia, either in the prediabetic or diabetic range. Type 2 diabetes, specifically, is currently a global health challenge due to its growing prevalence, complications and mortality (IDF, 2015). Hyperglycemia in type 2 diabetes is due to both insulin resistance and pancreatic beta cell dysfunction that, in turn, are associated with chronic oxidative stress and activation of inflammatory pathways in key sites of insulin action and also in beta cells (ADA, 2017).

Regular coffee consumption reduces serum levels of oxidative stress and inflammation markers (Akash et al., 2014), in addition to increasing serum levels of anti-inflammatory factors, such as adiponectin (Kempf et al., 2010, Wedick et al., 2011) and interleukins 4 and 10 (Akash et al., 2014). However, the effects of coffee consumption on glucose homeostasis seem more complex. Data from clinical studies and also meta-analysis indicate that coffee intake or caffeine administration may acutely increase insulin resistance and blood glucose levels due to blockade of adenosine A1 receptors by caffeine and increased secretion of the counterregulatory hormone epinephrine (Akash et al., 2014). On the other hand, long term coffee consumption dose-dependently increases insulin sensitivity (Akash et al., 2014). The mechanisms underlying this effect are not completely understood but may involve modulation of gut microbiota with an increase of bacteria species that favorably affect metabolic health (Jaquet et al., 2009, Cowan et al., 2013) increased secretion of the incretin hormones glucagon-like peptide 1 and gastric inhibitory peptide, and also reduced oxidative stress and low-grade inflammation (Santos and Lima, 2016). The anti-inflammatory effect of coffee consumption, specifically, has gained recent attention as the possible basis for the positive health benefits of this beverage (Bhattacharya, 2017).

We conducted a systematic review of the available evidence from clinical studies addressing the effect of coffee or coffee components consumption on the serum concentration of inflammatory markers in adults with or without increased weight, waist circumference or glucose levels.

Methods

The methods were consistent with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement (Liberati et al., 2009).

Search Strategy and study selection

Controlled clinical trials, either randomized or nonrandomized, addressing the effect of coffee or its components on inflammatory markers were searched using MEDLINE (via PubMed; National Library of Medicine, Bethesda, Maryland), Science Direct (via Scopus, Elsevier, Philadelphia, USA) and Web of Knowledge (via Web of Science, Thomson Reuters, New York, USA), from inception January 2017, independently by two investigators. Searches were also conducted by screening the reference lists of eligible articles. A combination of two categories of search terms were used: inflammatory markers ("CRP" or "c-reactive protein" or "IL-1 beta" or "interleukin-1 beta" or "IL-1 receptor antagonist" or "IL-1RA" or "IL-6" or "interleukin-6" or "interleukin-8" or "IL-8" or "interleukin-18" or "IL-18" or "8-isoprostane" or "interleukin-10" or "IL-10" or "interleukin-12" or "IL-12" or "TNF-alpha" or "Tumor Necrosis Factor-alpha" or "macrophage migration inhibitory factor" or "MIF" or adiponectin or "amyloid A" or "SAA" or nitrotyrosine or inflammation) and intervention (coffee or caffeine or "chlorogenic acid" or trigonelline or "decaffeinated coffee"). Articles published in English, Spanish or Portuguese were included. The search results were exported to the reference manager software EndNote® version X7 (Thomson Reuters, New York, USA).

Studies were eligible if participants were adults and received coffee (caffeinated or decaffeinated), caffeine or another coffee component, and if serum concentration of an inflammatory marker was included in the outcomes. In addition, participants receiving one of the

above-mentioned interventions had to be compared either to a control group (receiving placebo) or before and after the intervention (pre-post studies).

Data extraction and quality assessment

The following data were extracted: authors, country in which the study was conducted, year of publication, study design and duration, sample size, age, gender, health status of the participants, daily dose of the intervention and control/placebo, medium in which the intervention was diluted, if there was a washout period before and/or during the study, the type of inflammatory marker measured as the outcome and the methodology used to determine its serum/plasma concentration. If not reported, the authors were contacted by email to obtain data about baseline concentrations of inflammatory markers or concentrations achieved after intervention. If these data were not obtained, the study was excluded.

We used the Effective Public Health Practice Project (EPHPP) (Thomas et al., 2004) tool to assess the methodological quality of included studies. According to adherence to six criteria (selection bias, study design, confounders, blinding, data collection methods and withdrawals and dropouts) studies were classified as “strong”, “moderate” or “poor” with respect to methodological quality.

Two reviewers (CLRSP and BTSB) independently undertook each step in this review. Following each step, any disagreements were resolved after discussion with a third (AAA) and fourth reviewer (THMC).

Results

Study selection

The initial search identified 4508 articles, of which 56 were selected for further evaluation. We included information from a total of 15 articles (8 coffee and 7 caffeine studies) in the final review (Figure 1). No studies addressing the effects of chlorogenic acid or trigonelline fulfilled the inclusion criteria.

Study characteristics

Fifteen clinical trials addressing the effect of coffee or its components on inflammatory markers were included (Tables 2 and 3), comprising 591 participants (63% male and 37% female). All trials were published between 2007 and 2016; nine were conducted in Europe (Walker et al., 2007, Alexopoulos et al., 2008, Kempf et al., 2010, Gavrieli et al., 2011, Ramakers et al., 2011, Tauler et al., 2013, Riedel et al., 2014, Kempf et al., 2015, Tauler et al., 2016), three in the United States (Wedick et al., 2011, Correa et al., 2013, Bloomer et al., 2013) and three in Asia (Saito et al., 2011, Shechter et al., 2011, Ohnaka et al., 2012). The mean age of study participants ranged from 22 to 54 years and the samples size ranged from 12 to 114. Six trials (Walker et al., 2007, Saito et al., 2011, Ramakers et al., 2011, Tauler et al., 2013, Riedel et al., 2014, Tauler et al., 2016) included only healthy individuals, whereas nine trials were conducted in participants with overweight (Alexopoulos et al., 2008, Kempf et al., 2010, Wedick et al., 2011, Gavrieli et al., 2011, Ohnaka et al., 2012, Correa et al., 2013, Bloomer et al., 2013, Kempf et al., 2015) or obesity (Kempf et al., 2010). Some participants of the latter studies also had mild to moderate fasting hyperglycemia (Ohnaka et al., 2012), diabetes, hypertension and/or hyperlipidemia (Shechter et al., 2011).

Only one study did not describe a washout period before intervention (Bloomer et al., 2013). Seven trials (Walker et al., 2007, Alexopoulos et al., 2008, Saito et al., 2011, Gavrieli et al., 2011, Shechter et al., 2011Correa et al., 2013, Riedel et al., 2014) had a crossover design. Among them, four did not have a washout period between interventions (Walker et al., 2007, Alexopoulos et al., 2008, Shechter et al., 2011, Correa et al., 2013). The volume of coffee consumed ranged from 125 to 750 mL, and the amount of caffeine consumed was heterogeneous, varying from 125 mg to 500 mg or 4mg/kg to 6mg/kg of body weight. The duration of the studies ranged from 2 to 20 weeks for coffee intervention and 60 minutes to 12 weeks for caffeine intervention.

Inflammatory markers in controlled clinical trials

Four controlled trials addressed the effects of coffee on serum levels of CRP, cytokines (adiponectin, IL-6, IL-18), IL1-RA, 8-isoprostane, and/or fetuin A (Table 1) (Kempf et al., 2010, Wedick et al., 2011, Saito et al., 2011, Gavrieli et al., 2011, Ohnaka et al., 2012, Correa et al., 2013, Riedel et al, 2014, Kempf et al., 2015). In two trials, filtered coffee (Kempf et al., 2010) and caffeinated coffee (Wedick et al., 2011) increased adiponectin levels, whereas in two other trials no change in adiponectin levels was seen in response to coffee consumption, either compared with control (Gavrieli et al., 2011, Ohnaka et al., 2012).

CRP levels were assessed in three studies (Kempf et al., 2010, Wedick et al., 2011, Ohnaka et al., 2012) and no change was seen in response to coffee consumption. Caffeinated coffee consumption significantly increased IL-6 levels in only one (Wedick et al., 2011) out of three trials (Kempf et al., 2010, Gavrieli et al., 2011, Wedick et al., 2011).

Two trials assessed IL-18 (Kempf et al., 2010, Gavrieli et al., 2011), but only one found significantly decreased concentrations of this cytokine in response to coffee (Kempf et al., 2010). One trial that examined IL-1RA levels, and no change was seen after coffee intervention (Kempf et al., 2010). One trial showed that filtered coffee decreased 8-isoprostane levels (Kempf et al., 2010), whereas in another study decaffeinated coffee decreased fetuin-A levels (Wedick et al., 2011).

Caffeine was the only coffee component investigated in clinical trials addressing serum levels of inflammatory response-related markers (Walker et al., 2007, Alexopoulos et al., 2008, Ramakers et al., 2011, Shechter et al., 2011, Bloomer et al., 2013, Tauler et al., 2013, Tauler et al., 2016) (Table 2). Five trials (Walker et al., 2007, Alexopoulos et al., 2008, Ramakers et al., 2011, Tauler et al., 2013, Tauler et al., 2016) assessed IL-6; in three of them caffeine administration increased serum IL-6 levels (Walker et al., 2007, Tauler et al., 2013, Tauler et al., 2016) and in two studies (Alexopoulos et al, 2008, Ramakers et al., 2011) no change was seen after caffeine administration when compared with control group or baseline levels of this cytokine.

In three trials assessing CRP (Alexopoulos et al, 2008, Shechter et al, 2011, Bloomer et al., 2013), only one found significantly decreased CRP levels in response to caffeine (Shechter et al., 2011). IL-10 was significantly higher after caffeine administration in two (Tauler et al., 2013, Tauler et al., 2016) out of three trials evaluating this cytokine (Ramakers et al., 2011, Tauler et al., 2013, Tauler et al., 2016). No change was observed in TNFα (Ramakers et al., 2011), IL-1RA (Ramakers et al., 2011), IL-1β (Alexopoulos et al, 2008), adiponectin (Shechter et al., 2011) and IL-12p40 (Tauler et al., 2016) in participants who received caffeine compared with control group or with baseline levels of these cytokines.

Inflammatory markers in pre-post clinical trials

Eight pre-post trials addressed the effects of coffee on serum levels of CRP and/or cytokines (adiponectin, IL-6, IL-1beta, TNF-α) (Table 3) (Kempf et al., 2010, Wedick et al., 2011, Saito et al., 2011, Gavrieli et al., 2011, Ohnaka et al., 2012, Correa et al., 2013, Riedel et al., 2014, Kempf et al., 2015). No studies examining caffeine or other coffee components with this design were found. In two out of three trials, medium roasted coffee (Kempf et al., 2015) and coffee (Saito et al., 2011) increased adiponectin levels, whereas on trial found no change (Riedel et al., 2014). CRP levels were assessed in two studies (Correa et al., 2013, Kempf et al., 2015) and no change was seen in response to coffee consumption. Only one study examined IL-6 levels and found no change after medium light roast or medium roast coffee intervention (Correa et al., 2013). In only one trial that evaluated IL-1b and TNF-α levels (Correa et al., 2013), no change was seen after coffee intervention.

Table 4 presents a summary of the results from all coffee and caffeine trials included in the review.

Quality assessment

Quality assessment using the EPHPP (Supplementary Table 1) tool indicated that six trials were of strong quality (Alexopoulos et al., 2008, Wedick et al., 2011, Saito et al., 2011, Gavrieli et al., 2011, Riedel et al., 2014, Kempf et al., 2015), whereas nine trials were of moderate quality (Walker et al., 2007, Kempf et al., 2010, Shechter et al., 2011, Ramakers et al, 2011, Ohnaka et al., 2012, Correa et al., 2013, Bloomer et al., 2013, Tauler et al., 2013, Tauler et al., 2016).

Discussion

The current systematic review of clinical trials supports an overall anti-inflammatory action of coffee consumption, but not of caffeine, in adults. However, the data were viewed as insufficient to support a definite role of caffeine consumption on serum levels of inflammatory response-related markers.

The most frequently markers assessed on clinical trials involving coffee administration were adiponectin (7 studies), CRP (5 studies), and IL-6 (4 studies), but their results varied considerably. The possibility that these differences were due to study quality issues was considered low, since all trials were rated as strong or moderate quality. However, variable aspects of study participants characteristics or study design may have contributed, such as coffee type (caffeinated, decaffeinated, low-, medium- or dark-roasted coffee), its preparation method (filtered, instant, espresso) and the amount administered, the duration of the intervention, in addition to age and health status of study participants (weight, adiposity and fasting blood glucose levels).

Improvement of inflammatory markers was described in two (Saito et al., 2011, Kempf et al., 2015) out of three (Saito et al., 2011, Riedel et al., 2014, Kempf et al., 2015) trials which used espresso coffee, one (Wedick et al., 2011) out of three (Wedick et al., 2011, Gavrieli et al., 2011, Ohnaka et al., 2012) studies which used instant coffee, and one (Kempf et al., 2010) out of two (Kempf et al., 2010, Correa et al., 2013) studies which used filtered coffee, suggesting a more marked effect of espresso coffee.

Only one study addressed a dose-response effect of coffee administration on serum levels of inflammation markers (Kempf et al., 2010), and found that 8 but not 4 cups of coffee per day, for

12 weeks, improved the inflammatory response when compared with no coffee. In fact, a dose-response effect of coffee was observed in studies addressing other metabolic outcomes that share the inflammatory response as their physiopathological basis, such as type 2 diabetes risk (Van Dam and Hu, 2005, Nordestgaard et al., 2015), obesity, and metabolic syndrome (Nordestgaard et al., 2015). Although the amount of coffee administered in the different trials varied, pooling their data to investigate a dose-response effect was not considered due to the several differences in their design.

Differences among the included studies regarding their design and included subjects are important to be considered, since they may affect the response to regular coffee consumption. Most included studies comprised healthy overweight or overweight/obese participants with metabolic disturbances, such as fasting hyperglycemia and hyperlipidaemia. Among the four trials that showed improvement of serum inflammatory markers in response to coffee administration (Kempf et al., 2010, Wedick et al., 2011, Saito et al., 2011, Kempf et al, 2015), only one comprised normal weight-healthy subjects (Saito et al, 2011). One can speculate that overweight and obese participants had increased abdominal adiposity, and that since the latter is associated with insulin resistance and subclinical inflammation (McArdle et al., 2013), it is possible that their inflammation-related markers were altered at baseline, enabling a more marked response to coffee compared with that from normal weight-healthy subjects. Likewise, Kempf et al (2010) analyzed their data by categorizing participants into subgroups with low or high insulin resistance, according to the median HOMA-IR value, and found that the effect of coffee in suppressing the proinflammatory markers IL-18 and 8-isoprostane was significant only in the subgroup with high insulin resistance.

Moreover, the age of participants with overweight and obesity ranged from 40 to 54 years (Kempf et al., 2010, Wedick et al., 2011, Ohnaka et al., 2012, Correa et al., 2013, Kempf et al., 2015), whereas that from normal weight-healthy participants ranged from 22 to 28 years (Saito et al., 2011, Gavrieli et al., 2011, Riedel et al., 2014). This might also have contributed to the more pronounced effects of coffee administration in overweight and obese subjects, since more advanced age is also associated with subclinical inflammation (Gouin et al., 2008).

Other factors that could potentially explain the varied results include different dietary patterns of participants from different studies, physical activity levels, the duration of the washout period before and between the interventions, the total duration of the study, different coffee preparation methods used in each study, fasting previously to blood sample collections, and time period between the intervention (coffee or caffeine) and sample collection for the determination of serum levels of inflammatory markers. However, there were not enough data to indicate these aspects affected the results from the current review.

A Mediterranean-style diet has anti-inflammatory properties (Estruch et al., 2006, Cao et al., 2016), whereas a Western diet is associated with a proinflammatory state (Giugliano et al., 2006). All but two trials (Kempf et al., 2010, Saito et al, 2011) described the dietary patterns, assessed by food questionnaires, and there were no marked differences among participants from each of these two studies. Therefore, this could argue against the influence of divergent dietary patterns on the results. Only three (Wedick et al., 2011, Gavrieli et al., 2011, Kempf et al., 2015) out of eight coffee trials described the level of physical activity of study participants. In these three studies, almost all participants were considered physically active, but their results with

respect to inflammatory markers were divergent. Gavrieli et al (2011) did not find any change in adiponectin, IL-6 or IL-18 following coffee administration, whereas data from Wedick et al (2011) and Kempf et al (2014) indicated a favorable effect of coffee on inflammation-related markers. However, the first study was conducted in normal weight or overweight-healthy participants and had a shorter duration (2 weeks), whereas the latter two involved only overweight-healthy subjects and lasted 8 and 12 weeks, respectively. These other differences between them preclude conclusions about the contribution of physical activity levels to the effects of coffee on inflammatory marker levels.

Study duration and the presence and duration of washout were variable, but were not found to be associated with the effects of coffee on inflammatory response. Inflammatory marker serum levels vary according to fasting or postprandial state (Schauren et al., 2014), but most studies described that serum inflammatory markers levels were assessed in the fasting state (Kempf et al., 2010, Correa et al., 2013, Riedel et al, 2014, Kempf et al., 2015). Moreover, given that coffee flavonoids are rapidly metabolized into bioactive compounds (Del Rio et al., 2010), it is also possible that the time period of inflammatory marker levels determination following coffee consumption may have affected the results. Most coffee studies assessed inflammatory markers after an overnight fast following the last day of coffee consumption, and in only one study (Gavrieli et al., 2011) inflammatory markers were measured 30 to 120 min following coffee consumption. Therefore, we could not address this aspect in the current review.

The studies included in this review varied with respect to the type of coffee consumed by study subjects. Some studies used espresso (Kempf et al 2015, Riedel et al. 2014) coffee, whereas

others used filtered (Kempf et al 2010, Correa et al 2013) or instant (Gavrieli et al 2011, Wedick et al 2011, Ohnaka et al 2012) coffee. Filtered coffee preparation involves extraction of water-soluble compounds from ground-roasted coffee beans, and its composition is dependent upon the temperature of the water and the duration of coffee contact with water, among other factors. Moreover, most of the lipophilic fraction (containing diterpenes and sterols) and solid materials remain in the filter (Naidoo et al., 2011; Farah, 2012). On the other hand, espresso preparation uses hot water under pressure for a short period of time, which is more efficient to extract the water-soluble components, such as chlorogenic acids, caffeine, nicotinic acid, soluble melanoidins and hydrophilic volatile compounds. Additionally, the absence of a paper-filter increases the diterpene content of the brew (Farah, 2012). Instant coffee is produced from previously prepared ground-roasted coffee extracted with high-pressure hot water and then dried (high temperature and pressure), sublimated (freeze-drying) or agglomerated (steam/water and/or oil) to a final powder (Farah, 2012). The differences in composition between the instant and filtered/espresso coffee arise from the use of Robusta and Arabica species, respectively. Robusta species contain higher amounts of soluble solids, caffeine and chlorogenic acids (Farah, 2012). Despite the possibility that the distinct types of coffee preparation may affect inflammatory markers differently, we could not find an association between coffee type and its effect on these markers in the current review.

Subclinical inflammation has a key role in the development of type 2 diabetes. On this basis, several observational studies addressed the effects of coffee on inflammatory response-related markers to investigate whether the protective effect of coffee consumption on type 2 diabetes risk (Jacobs et al., 2014, Koloverou et al., 2015) could be explained by an anti-inflammatory

action of this dietary component. An inverse association between usual coffee consumption and circulating concentrations of proinflammatory markers was described in women with low levels of coffee consumption from the Nurses' Health Study I (Schulze et al., 2005), in diabetic women from the Nurses' Health Study II (Lopez-Garcia et al., 2006) and in Japanese women (Kotani et al., 2008). On the other hand, among healthy Greek subjects consumption of more than 200 mL of coffee per day was associated with increased serum levels of inflammatory markers when compared with no coffee consumption (Zampelas et al., 2004). In the current systematic review, most coffee trials involved healthy or overweight/obese subjects and indicated either a neutral (Wedick et al., 2011, Kempf et al., 2010, Gavrieli et al., 2011, Ohnaka et al., 2012, Correa et al., 2013, Kempf et al., 2015) or a suppressive (Kempf et al., 2010, Wedick et al., 2011) effect on serum concentrations of inflammatory markers. Only the study of Wedick et al (2011) found that caffeinated coffee increased serum IL-6 levels, despite not changing other proinflammatory markers (CRP and fetuin-A). Taken together, these data suggest a favorable overall effect of coffee consumption on low-grade systemic inflammation.

Adiponectin is an adipokine with anti-inflammatory and insulin-sensitizing properties (Stofkova, 2009) that has been described to be positively associated with coffee consumption in observational studies (Williams et al., 2008, Yamashita et al., 2012). In the current review, clinical trials indicated that coffee affected plasma adiponectin concentrations either in a neutral (Kempf et al., 2010, Wedick et al., 2011, Gavrieli et al., 2011, Ohnaka et al., 2012, Ridel et al., 2014, Kempf et al., 2015) or favorable (Kempf et al., 2010, Wedick et al., 2011, Saito et al., 2011, Kempf et al., 2015) manner. Most studies in which a neutral effect was described involved the administration of instant coffee to healthy and younger normal-weight male and had a

crossover design. Moreover, studies involving two different coffee interventions, either with respect to the amount of coffee administered (Kempf et al., 2010) or type of coffee preparation (Wedick et al., 2011, Kempf et al., 2015), found that each intervention affected adiponectin levels differently, suggesting a dose-response effect of coffee intake on adiponectin levels and that specific coffee components may underlie it.

Because coffee comprises a mixture of components, one important research question is whether specific components underlie the anti-inflammatory effect. Caffeine is the most widely studied coffee components, but only few observational clinical studies investigated the effect of caffeine-only on serum levels of inflammatory response-related markers. Recently, Furman et al (2017) reported that higher caffeine consumption was associated with reduced inflammasome activation in humans and that treatment of human macrophages with caffeine at concentrations similar to those found in the plasma of coffee consumers inhibited IL-1beta secretion (Furman et al., 2017). Data from other preclinical studies, however, suggested that caffeine may have both anti-inflammatory (Koroglu et al., 2014, Owoyele et al., 2015, Muqaku et al., 2016) and proinflammatory properties (Tunc et al., 2013) and a cohort study in neonates indicated proinflammatory actions of caffeine (Chavez et al., 2011). However, a definite effect of caffeine on the inflammatory response was not supported by the data from the clinical trials included in this review.

Two coffee components, trigonelin (Tharaheswari et al., 2014, Antonisamy et al., 2016) and chlorogenic acid (Ye et al., 2017, Palocz et al., 2016), were reported to suppress the inflammatory response in cell-based and animal studies, and are also plausible candidates to

mediate the anti-inflammatory effects of coffee. However, no clinical studies addressing the effects of trigonelin, chrologenic acid or other coffee components on serum levels of inflammatory markers were found.

Clinical trials that assessed the effects of caffeine on inflammatory response-related markers had a different design when compared to those investigating the effect of coffee. Most involved healthy subjects, other simultaneous interventions, such as an exercise session or the administration of carbohydrate or a meal, and in all but one study inflammatory markers were assessed less than 24 hours after the administration of caffeine (Ramakers et al., 2011). Moreover, their results were not consistent.

Three trials described a neutral effect of caffeine on inflammatory markers (Alexopoulos et al., 2008, Ramakers et al., 2011, Bloomer et al., 2013), one trial described a proinflammatory action of caffeine (Walker et al., 2007), one trial found an anti-inflammatory effect of caffeine (Shechter et al., 2011) and two trials (Tauler et al., 2013, Tauler et al., 2016) found that caffeine administration increased serum levels of a proinflammatory (IL-6) and an anti-inflammatory (IL-10) cytokine. These diverse findings may reflect either the complex effects of caffeine on the inflammatory response or the fact that the trials were varied markedly with respect to study design and the individual markers considered as outcomes.

The only trial that reported a favorable effect of caffeine on proinflammatory markers (Shechter et al., 2011) selected the participants on the basis of the absence of coronary heart disease and assessed CRP levels. Their mean age was 53 years and their level of physical activity was not reported. On the other hand, the other two caffeine studies that assessed CRP comprised

participants who were younger and healthy, and no change was found in the serum levels of this protein (Alexopoulos et al., 2008, Bloomer et al., 2013).

IL-6 was the most frequently assessed proinflammatory marker in caffeine trials. Despite the heterogeneous design of the studies, there seemed to be a dose-response effect. Three out of five trials described increased serum IL-6 levels in response to caffeine and involved administration of higher doses of caffeine (Walker et al., 2007, Tauler et al., 2013, Tauler et al., 2016). Additionally, these studies involved recreational athletes and IL-6 was assessed after a session of exercise and administration of carbohydrate. On the other hand, the two trials that reported neutral effects of caffeine involved the administration of lower doses of caffeine to subjects not described as recreational athletes (Alexopoulos et al., 2008, Ramakers et al., 2011). Interestingly, Tauler et al (2013) and Tauler et al (2015) also described increased levels of the anti-inflammatory cytokine IL-10 in response to caffeine, pointing to the complex effect of caffeine on the inflammatory response in the clinical setting.

A limitation of this systematic review was that the included trials varied with respect to several aspects, such as methodological design and baseline metabolic status of the participants. Therefore, we could not assess the effects of coffee or caffeine on inflammatory markers according to body mass index categories or other metabolic parameters. In addition, there were limited data to define whether coffee type or the method used to prepare it affects inflammatory markers serum levels.

In conclusion, coffee administration over several weeks had a predominant anti-inflammatory effect assessed by serum markers, but caffeine had no clear short-term effect on inflammatory

response. These data suggest that an anti-inflammatory action of coffee consumption may be involved in the protective effect of this beverage on type 2 diabetes risk, and further studies are needed to address whether caffeine or other coffee components underlie this effect.

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Table 1. Clinical trials comparing coffee intervention and control in relation to serum inflammatory markers.

Source	Country	Study design	Metabolic health status (N)	Sex	Age in years (mean, SD)	Intervention	Duration	Washout (start)	Washout (between)	Time between intervention and sample collection	Results
Strong quality											
Gavrieli et al., 2011	Greece	Crossover randomized clinical trial	Healthy overweight (16)	Male (16)	27.8 (5.2)	1) One cup (200 mL) of instant caffeinated coffee with 3 mg caffeine/kg BW	2 weeks	3 days	1 week	30, 60, 90, 120, 150 and 180 min after coffee consumption	Caffeinated coffee vs control
						2) One cup (200 mL) of instant decaffeinated coffee with 3 mg caffeine/kg BW					↔ adiponectin, IL-6 and IL-18 Decaffeinated coffee vs control
											↔ adiponectin, IL-6 and IL-18
Wedick et al., 2011	US	Randomized clinical trial	Healthy overweight (45)	Male (16)Female (29)	40.6 (13.1)	1) 5 cups/d (each prepared with pre-weighed 2g portions of instant caffeinated coffee in 177 mL of water)	8 weeks	2 weeks	-	After fasting (≥ 12 h) following 8 week intervention	Caffeinated coffee vs control
Moderate quality						2) 5 cups/d (each prepared with pre-weighed 2g portions of instant decaffeinated coffee in 177 mL of water)					↑ adiponectin and IL-6
											↔ CRP and fetuin-A
											Decaffeinated coffee vs control
											↓ fetuin-A
											↔ adiponectin, CRP and IL-6
Kempf et al., 2010	Germany	Clinical trial	Overweight and obesity (47)	Male (11 Female (36)	54.0 (9.0)	2nd month: 4 cups (150 mL each) of filtered coffee/d (50 g coffee/d) 3rd month: 8 cups (150	12 weeks	4 weeks	-	After an overnight fast (≥ 8 h) following 12 week intervention	4 cups vs control
											↔ IL-18, 8-isoprostane, adiponectin, L-6, IL-1RA and CRP 8 cups vs

						mL each) of filtered coffee/d (83,33 g coffee/d)					control ↓ IL -18 and 8-isoprostane ↑ adiponectin ↔ IL-6, IL-1RA and CRP
Ohnaka et al., 2012	Japan	Randomized clinical trial	Overweight with mild-to-moderate fasting hyperglycemia (45)	Male (45)	52.7 (7.9)	1) 5 cups/d (each prepared with 1.2-1.3 g of instant caffeinated coffee in 100 mL of water – 6-6.5 g/day)	16 weeks	2 weeks	-	After an overnight fast (≥ 10 h) following 16 week intervention	Caffeinated coffee vs control
						2) 5 cups/d (each prepared with 1.2-1.3 g of instant decaffeinated coffee in 100 mL of water – 6-6.5 g/day)					↔ CRP, total adiponectin and HMW adiponectin Decaffeinated coffee vs control ↔ CRP, total adiponectin and HMW adiponectin

BW: body weight; CRP: C-reactive protein; HMW: high molecular weight; IL: interleukin; IL-1RA: IL-1 receptor antagonist.

Table 2. Clinical trials comparing caffeine intervention and control in relation to serum inflammatory markers.

Source	Country	Study design	Metabolic health status (N)	Sex	Age in years (mean, SD)	Intervention	Duration	Washout (start)	Time between intervention and sample collection	Results
Strong quality										
Alexopoulos et al., 2008	Greece	Cross-over randomized clinical trial	Healthy overweight (14)	Male (9) Female (5)	30 (3.0)	1) 6 g of green tea	120 min	>48 h	30, 90 and 120 min after caffeine consumption	After caffeine consumption vs control
Moderate quality						2) 125 mg of caffeine				↔ hs-CRP, IL-6 and IL-1B
Walker et al., 2007	United Kingdom	Cross-over randomized clinical trial		Male	22 (1.0)	Before exercise (60 min): 6 mg/kg of caffeine with 2 mL/kg of water Just before exercise: 5 mL/kg of a 6% CHO solution** (in the CAF/CHO and PLA/CHO trials) During exercise (every 15 minutes during 120 minutes of training): 2 mL/kg of a 6% CHO solution Just after exercise: 5 mL/kg of a 6% CHO solution	1) Resting for 60 min	60 h (before each intervention)	After an overnight fast (10-12 h) following intervention	1) Co-ingestion of CAF/CHO significantly attenuated IL-6 responses that occurred after ingestion of CAF alone (CAF/PLA)
							2) Cycling for 120 min			2) Plasma IL-6: significantly ↑above resting values after exercise, with values remaining significantly ↑than rest at 1 h after exercise ($P < 0.01$)
							3) Resting for 60 min			3) Plasma IL-6 significantly increased after exercise on CAF/PLA compared with both CAF/CHO and PLA/CHO
Ramakers et al., 2011	The Netherlands	Randomized clinical trial	Healthy overweight (20)	Male	22.5 (21-24.5)	2 ng/kg *E. coli* LPS with caffeine pretreatment (4 mg/kg BW)	8 h	48h	30, 60, 120 min, 240 and 480 min after caffeine consumption	Caffeine vs control
										↔ TNF- α, IL-6, IL-10, and IL1-RA
Shechter et al., 2011	Israel	Cross-over randomized clinical trial	Without coronary artery disease (40)	Male (33) Female (7)	53 (6.0)	200 mg of caffeine	60 min	48 h	1 hour after caffeine consumption	Caffeine vs control
										↓ CRP
										↔ adiponectin
Bloomer et al., 2013	US	Randomized clinical trial	Healthy (50)	Male	23.0 (1.3)	1st week: 250 mg	12 weeks	48h	After an overnight	Caffeine vs control

						caffeine /d 2nd-12th weeks: 500 mg caffeine/d			fast (8 h) following intervention	↔ CRP
Tauler et al., 2013	Spain	Clinical trial	Recreational athletes (33)	Male	40 (6.7)	6 mg of caffeine/kg BW	180 min + race time (not specified)	48 h	After an overnight fast (12 h) following the day of intervention	Caffeine vs control ↑ IL-6 and IL-10
Tauler et al., 2015	Spain	Randomized clinical trial	Recreational athletes (28)	Male	36.7 (6.2)	6 mg of caffeine/kg BW	180 min + race time (not specified)	48h	After an overnight fast (12 h) following the day of intervention	Caffeine vs control ↑ IL-6, IL 10 ↔ IL-12 p 40

** CHO drink: 150 mL of low-calorie lemon cordial, 850 mL of water, and dextrose monohydrate (6.6% w/v) per liter of solution. BW: body weight; CRP: C-reactive protein; hs-CRP: highly sensitive CRP; IL: interleukin; TNF- α: tumor necrosis factor alpha.

Table 3. Clinical trials comparing serum inflammatory markers before and after coffee intervention.

Source	Country	Study design	Metabolic health status (N)	Sex	Age in years (mean, SD)	Intervention	Duration	Washout (start)	Washout (between)	Time between intervention and sample collection	Results
Strong quality											
Saito et al., 2011	Japan	Cross-over randomized clinical trial	Healthy (19)	Male (8) Female (11)	22.3 (1.7)	3 cups (150 mL each)/d 1) Coffee (18 g/d) 2) Green tea (6 g/day)	2 weeks	8 days	7 days	Early morning following 2 week intervention	Baseline vs coffee ↑ adiponectin Baseline vs tea ↔ adiponectin
Kempf et al., 2015	Germany	Randomized clinical trial	Overweight (114)	Male (39) Female (75)	49.3 (12.2)	Average of 4 to 5 cups (125 mL each)/d 1) Pads of medium-roasted coffee (M-coffee) (30-37.5 g coffee/d) 2) Pads of dark-roasted coffee (D-coffee) (30-37.5 g coffee/d)	12 weeks	4 weeks	-	After an overnight fast (8 h) following 12 week intervention	Baseline vs M-coffee ↑ adiponectin ↔ CRP Baseline vs D-coffee ↔ adiponectin ↔ CRP
Riedel et al., 2014	Austria	Cross-over randomized clinical trial	Healthy (84)	Male (46) Female (38)	25.6 (5.8)	3 cups (250 mL each)/d 1) Pads of medium roast coffee (45 g coffee/d) 2) Pads of dark roast coffee (45 g coffee/d) * 5--8 wk: first coffee intervention period (MB and SB) * 13--16 wk: second coffee intervention period (MB and SB)	20 weeks	1-4 weeks	1) 9--12 weeks: second wash-out period 2) 17--20 weeks: third wash-out period	After an overnight fast (12 h) following 20 week intervention	Washout vs medium roast coffee ↔ adiponectin Washout vs dark roast coffee ↔ adiponectin
Moderate quality											
Correa et al., 2013	Brazil	Cross-over randomized clinical trial	Healthy overweight (20)	Male (6) Female (14)	49.0 (9.0)	3 or 4 cups (150 mL each)/d 1) Medium light roast (MLR) paper-filtered coffee (45-60 g of coffee/d) 2) Medium roast (MR) paper-	9 weeks 4 wk: MRL 4 wk: MR	1 week	-	After an overnight fast (8 h) following 9 week intervention	Baseline vs MRL ↔ hs-CRP, IL-1b, IL-6, TNF-α Baseline vs MR ↔ hs-CRP,

						filtered coffee (45-60 g of coffee/d)					IL-1b, IL-6, TNF-α

BW: body weight; CRP: C-reactive protein; hs-CRP: highly sensitive CRP; IL: interleukin, TNF- α: tumor necrosis factor alpha.

Table 4. Summary of results from clinical trials addressing the effects of coffee or caffeine on serum inflammatory markers.

			Effect on inflammatory marker				
Source	Type of coffee preparation used in the intervention	Duration	TNF-α	IL-6	CRP	Adiponectin	Other
Coffee							
Gavrieli et al 2011	Instant caffeinated coffee	2 wk	-	↔	-	↔	↔ IL-18
	Instant decaffeinated coffee	2 wk	-	↔	-	↔	↔ IL-18
Wedick et al., 2011	Instant caffeinated coffee	8 wk	-	↑	↔	↑	
	Instant decaffeinated coffee	8 wk	-	↔	↔	↔	
Kempf et al., 2010	Filtered coffee (4 cups)	12 wk	-	↔	↔	↔	↔ 8-isoprostane
							↔ ILR-1A
	Filtered coffee (8 cups)	12 wk	-	↔	↔	↔	↓ 8-isoprostane
							↔ ILR-1A
Ohnaka et al., 2012	Instant caffeinated coffee	16 wk	-	-	↔	↔	
	Instant decaffeinated coffee	16 wk	-	-	↔	↔	
Saito et al., 2011	Ground coffee (not specified)	2 wk	-	-	-	↑	
Correa et al., 2013	Medium light roast paper-filtered coffee	9 wk	↔	↔	↔	-	↔ IL-1B
	Medium roast paper-filtered coffee	9 wk	↔	↔	↔	-	↔ IL-1B
Kempf et al., 2015	Espresso medium-roast coffee	12 wk	-	-	↔	↑	
	Espresso dark-roast coffee	12 wk	-	-	↔	↔	
Riedel et al., 2014	Espresso medium-roast coffee	20 wk	-	-	-	↔	
	Espresso dark-roast coffee	20 wk	-	-	-	↔	
Caffeine							
Alexopoulos et al., 2008		120 min	-	↔	↔	-	↔ IL-1B
Walker et al., 2007		8 h	-	↓	-	-	
Ramakers et al., 2011		8 h	↔	↔	-	-	↔ IL-1RA
Shechter et al., 2011		60 min	-	-	↓	↔	↔ IL-10
Bloomer et al., 2013		12 wk	-	-	↔	-	
Tauler et al., 2013		180 min	-	↑	-	-	↑ IL-10
Tauler et al., 2015		180 min	-	↑	-	-	↑ IL-10 ↔ IL-12 p40

CRP: C-reactive protein; IL: interleukin; TNF- α: tumor necrosis factor alpha.

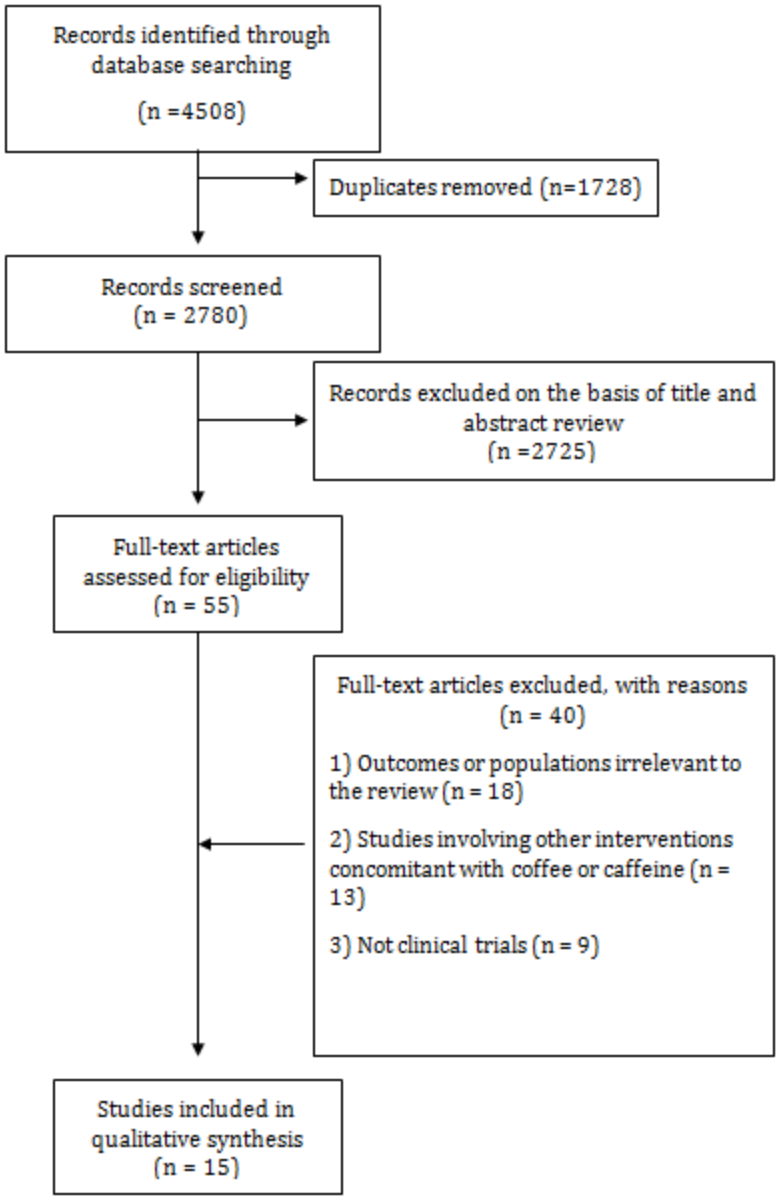

Figure 1: Flowchart of selection of studies.