The influence of green coffee bean extract supplementation on blood glucose levels: A systematic review and dose-response meta-analysis of randomized controlled trials

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The influence of Green Coffee Bean Extract Supplementation on Blood Glucose Levels: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Abstract

Aims

Studies regarding the influence of Green Coffee Extract (GCE) on blood glucose levels are conflicting. Thus, we sought to conduct a meta-analysis and systematic review of all available randomized controlled trials (RCTs) to quantify the effects of GCE and CGA intervention on blood glucose and insulin levels.

Methods

We performed systematic online searches in Scopus, Web of science, and PubMed databases, from inception to July 2019. Data were combined analyzed using a random effects model (Der Simonian-Laird method), and reported as weighted mean differences (WMD). Ten trials reported the influences of GCE on FBS and insulin, and were subsequently entered into the meta-analysis.

Results

Combined results highlighted that FBS was significantly altered after GCE consumption (WMD: -1.791mg/dl,95% CI:-3.404,-0.177), with no significant heterogeneity among the studies (I^2=35.0%,p=0.128). However, overall results demonstrated that GCE administration did not result in any significant alteration in insulin levels (WMD: -0.925 μU/ml,95% CI:-1.915,0.064), with significant heterogeneity found across studies (I^2 =87.9 %). In sub-group analysis, insulin levels were significantly reduced when GCE was supplemented in dosages of ≥400 mg/day (WMD:-1.942mg/dl,95%CI:-1.184,-0.975;I^2 =0.0%).

Conclusion

The results of present study support the use of GCE for the enhancement of blood glucose, whilst sub-group analysis highlighted significant improvements in insulin levels when GCE is supplemented in doses ≥400mg/d.

Keywords: Green coffee, insulin, FBS, blood glucose

Introduction

Contemporary evidence suggests that high blood glucose concentration is associated with chronic disease onset in patients with prediabetes or diabetes (Rizza, 2010; Standl, Schnell, & Ceriello, 2011). Therefore, reducing elevated blood glucose concentrations is a principal aim in the amelioration and management of chronic metabolic disorders (Rizza, 2010). Postprandial hyperglycemia is a prominent risk factor for metabolic syndrome (Adeyemi et al., 2017); although medicinal therapeutic strategies, such as insulin and hypoglycemic drugs, have accomplished some success in treatment, pharmacological interventions possess well-known adverse side effects (Scheen, 2005). Thus, recent investigations have focused on nonpharmacologic approaches to reduce blood glucose levels (Chikwere & Annan, 2016; Iddrisu, Oduro, Tandoh, & Annan, 2015; O'Keefe, Gheewala, & O'Keefe, 2008).

One of the most frequently consumed beverages in the world is coffee (Shang, Li, & Jiang, 2016). It is a major source of bioactive components, including phenolic acids, methylxanthines, and particularly polyphenol compounds, that are well-known as protective agents against numerous chronic degenerative diseases (Esquivel & Jiménez, 2012; Gaafar, El-Ghamery, & Mahmuod, 2013). Various epidemiological and in vivo (experimental) examinations have demonstrated an inverse relationship between coffee ingestion and risk of several glycemic indicators of diabetes mellitus (DM) (Greenberg, Boozer, & Geliebter, 2006; Tanaka et al., 2009), and a positive link between coffee ingestion and insulin sensitivity (Agardh et al., 2004). The key polyphenol

compound in coffee beans is regarded to be Chlorogenic Acid (CGA), given that numerous favorable health effects are derived from it (Ong, Hsu, & Tan, 2012). In fact, CGA is recognized as a family a esters formed from quinic acid and cinnamic acids, especially p-coumaric, ferulic and caffeic acids, that posses several biological features, such as antioxidant, anti-bacterial, and anti-carcinogenic characteristics (M. Clifford, 1985). Green Coffee Extract (GCE) has a high amount of polyphenol compounds and is a rich source of CGA (M. N. Clifford, 1999); indeed, recent human studies have revealed that GCE and CGA supplementation can yield reductions in insulin resistance and blood glucose concentrations (Thom, 2007). Various mechanisms have been posited for the impact of GCE/CGA on glucose metabolism, however, the precise mechanism remains unclear. One proposed mechanism is a reduction in the process of intestinal glucose uptake by regulating levels of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-I (GLP-I), which elevates insulin secretion after oral glucose ingestion (Johnston, Clifford, & Morgan, 2003). In addition, CGA, by decreasing glucose-6-phosphatase enzyme activity, can reduce the process of gluconeogenesis and glycogenolysis, respectively (Hemmerle et al., 1997). However, the exact effect of GCE and CGA on glycemic indicators levels is largely unclear, and previous clinical trials have reported controversial results; indeed, several studies have shown GCE supplementation leads to decrements in blood glucose and insulin concentrations (Hanieh Roshan, Omid Nikpayam, Meghdad Sedaghat, & Golbon Sohrab, 2018; Satoko Soga, Noriyasu Ota, & Akira Shimotoyodome, 2013), whilst contrastingly, some trials do not support these results (Satoko Fukagawa et al., 2017; Takuya Watanabe et al., 2006). Thus, we sought to conduct a meta-analysis and systematic review of all available randomized controlled trials (RCTs) to quantify the effects of GCE and CGA intervention on blood glucose and insulin levels.

Methods

This article was carried out in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis guidelines (Guyatt et al., 2008; McInnes et al., 2018). This study was not prospectively registered.

Search strategy

We performed systematic online searches in the online databases, Scopus, Web of science, and PubMed, from inception to July 2019. The following search words were used: "green coffee" OR "chlorogenic acid" OR "green coffee extract" AND "clinical trials " OR "double-blind method OR "cross-over studies" OR "single-blind method" OR RCT OR "random allocation" OR "intervention studies" OR "controlled trial" OR "intervention" OR "randomized" OR "randomised" OR "randomly" "random" OR "assignment" OR "placebo". We also reviewed the reference lists of previous reviews to detect potentially eligible publications.

Eligibility criteria

Two authors independently implemented the initial examination. Any discrepancy was resolved by conversation and consensus by the lead author. To be eligible, studies had to meet the ollowing criteria: (1) Population: adult subjects more than 18 years. (2) Intervention: green coffee extract supplementation. (3) Comparison: placebo group. (4) Primary outcomes: articles that report adequate information (mean and SD) on baseline and final study of FBS or insulin in both GCE and placebo groups. The most recent data were used for duplicates. Comments, reviews, letters, experimental study, and animal studies were excluded. Trials with unobtainable data were also excluded.

Data extraction

Two investigators individually executed the information extraction using a standard excel sheet. Any discrepancy was resolved by consensus with the lead author. Subsequently, the following information was extracted from each trial: publication year, the first author, mean and SD of FBS

or insulin levels, intervention versus comparison, doses for GCE, treatment period (week). We also emailed the corresponding authors to acquire the data, if required.

Quality assessment

We applied the Cochrane risk of bias tool to evaluate the quality of eligible publications (J. P. Higgins et al., 2011). This assessment tool comprises of random sequence generation, allocation concealment, blinding of subjects, personnel-to-study protocol, blinding of results assessment, incomplete outcomes data, selective reporting, and other bias. The trials were assortment as high risk, low risk, and unclear risk of bias based on the reported items. Trials with more than one key criterion was recorded as possessing a high risk of bias, those without all items were regarded as possessing a low risk of bias. Otherwise, they were defined as having an unclear risk of bias.

Statistical methods

We combined data using the generic inverse variance approach, with random effects model (using DerSimonian-Laird approach), and reported as weighted mean differences (WMDs) with 95% confidence intervals (CIs). We used Stata program (Stata Corp. College Station, Texas, USA) for primary analyses, sensitivity analyses, and publication bias and dose response analyses. We used standard calculations to obtain the mean and SD when data was expressed in a different format (J. Higgins, 2011; Hozo, Djulbegovic, & Hozo, 2005). For instance, if the SD of the change was not expressed in the trials, we derived it using the following formula: SD differences = square root $[(SD_{baseline}^{2}+SD_{end}^{2}) - (2\times R\times SD_{baseline}\times SD_{end})]$. We assessed heterogeneity across studies by the Cochran Q statistic and quantified using the I^2 statistic. We explored sources of heterogeneity by stratified analyses and sensitivity analyses, in which each study was excluded separately, and the overall effect size re-estimated. Publication bias was measured by means of Egger's tests and visual calculation of funnel plots (Egger, Smith, Schneider, & Minder, 1997). the 'trim and fill'

method was applied to assess the number of omitted publications due to publication bias (Palmer, Peters, Sutton, & Moreno, 2008).

Results

Study selection

The initial database search yielded 831 records; following elimination of duplictes,646 publications remained. In the next step, all articles' abstract and titles were screened, which resulted in 24 papers for full-manuscript examination. Ultimately, 10 publications were included in this study. Of the 10 eligible articles, all 10 trials reported the influences of GCE on FBS (S. Fukagawa et al., 2017; Haidari, Samadi, Mohammadshahi, Jalali, & Engali, 2017; Kim et al., 2012; Ochiai et al., 2004; Park, Kim, Lee, & Lee, 2010; H. Roshan, O. Nikpayam, M. Sedaghat, & G. Sohrab, 2018; Shahmohammadi, Hosseini, Hajiani, Malehi, & Alipour, 2017; S. Soga, N. Ota, & A. Shimotoyodome, 2013; Suzuki et al., 2019; T. Watanabe et al., 2006), and 5 trials reported on insulin (S. Fukagawa et al., 2017; Haidari et al., 2017; Park et al., 2010; H. Roshan et al., 2018; Shahmohammadi et al., 2017) (**Figure 1**).

Characteristics of the eligible trials

The characteristics of the eligible trials are detailed in Table 1. Included papers were published between 2004 and 2019., and were conducted in different countries; including, three in the Iran (Haidari et al., 2017; H. Roshan et al., 2018; Shahmohammadi et al., 2017), five in Japan (S. Fukagawa et al., 2017; Ochiai et al., 2004; S. Soga et al., 2013; Suzuki et al., 2019; T. Watanabe et al., 2006), and two in Korea (Kim et al., 2012; Park et al., 2010). The treatment duration varied between 2 and 16 weeks, whilst daily administrated dosage of GCE ranged from 100 to 1000 mg. Studies were conducted on both genders (H. Roshan et al., 2018; Shahmohammadi et al., 2017; T. Watanabe et al., 2006), on men (Ochiai et al., 2004; S. Soga et al., 2013; Suzuki et al., 2019), and on women-only (S. Fukagawa et al., 2017; Haidari et al., 2017; Kim et al., 2012; Park et al., 2010).

The participant number in the studies ranged from 16 to 64, whilst the study population in eligible publications consisted of; adults with mild hypertension (T. Watanabe et al., 2006), adults with the metabolic syndrome (H. Roshan et al., 2018) and adults with NAFLD (Non-Alcoholic Fatty Liver Disease) (Shahmohammadi et al., 2017), adults who were classified as obese or overweight (Haidari et al., 2017; Kim et al., 2012; Park et al., 2010), or healthy individuals (S. Fukagawa et al., 2017; Ochiai et al., 2004; S. Soga et al., 2013; Suzuki et al., 2019).

Quality assessment of eligible studies

Risk of bias and methodological quality of eligible trials are reported in **Supplemental Table 1.** Breifly, trials indicated acceptable quality for key items; hilst incomplete outcome data (S. Fukagawa et al., 2017; Haidari et al., 2017) and allocation concealment items (Haidari et al., 2017) were the main sources of bias.

Meta-analysis results

Impact of green coffee extract administration on FBS

Ten arms, with 363 subjects (case=179, and control=184), described FBS as an outcome measure. Overall results demonstrated that FBS was significantly altered after green coffee extract consumption (WMD: -1.791mg/dl, 95% CI: -3.404, -0.177, p = 0.030), with no significant heterogeneity across the trials (I^2 = 35.0%, p = 0.128) (**Figure2**). In subgroup analyses, FBS was significantly reduced in the subgroup in green coffee extract supplementation dosages of <400 mg/day (WMD: -1.21 mg/dl, 95% CI: -2.40, -0.02, p<0.001; I^2 = 1.7 %). In addition, in treatment durations ≤ 8weeks (WMD: -1.94 mg/dl, 95% CI: -3.82, -0.06), there was a greater reduction in FBS compared with treatment durations > 8 weeks(WMD: -0.99 mg/dl, 95% CI: -5.77, 3.88) **(Supplemental Figure 1)**.. However, the number of studies in some subgroups was low, and the results should, therefore, be interpreted with caution.

(Supplemental Figure 1).

Impact of green coffee extract administration on insulin levels

Five arms, with 243 subjects (case=119, and control=124), reported IN as an outcome measure. Pooled results revealed that green coffee extract administration did not result in any significant modification in insulin (WMD: -0.925 μU/ml, 95% CI: -1.915, 0.064, p = 0.067). We observed significant heterogeneity among trials (I^2 = 87.9 %, p<0.001) (**Figure2**). Results of the subgroup analyses showed that green coffee extract dosage (mg/day) was a source of heterogeneity. In sub-group analysis, insulin levels were significantly reduced in green coffee extract supplementation dosages of ≥400 mg/day (WMD: -1.942 mg/dl, 95% CI: -1.184, -0.975, p<0.001; I^2 = 0.0 %, p = 0.492) **(Supplemental Figure 1)**.

Non-linear dose-responses relationship between dose of green coffee extract and treatment duration and outcomes

Figure 4 depicts the results of the non-linear dose-response meta-analysis. The results highlighted that green coffee extract intake significantly alters FBS based on follow up duration (Coef. = -1.84, p= 0.016) or green coffee dosage (Coef. = -2.90, p= 0.044).

Sensitivity analysis

To ascertain the influence of each single trial on the meta-analyses, we excluded each arm from overall effect size, step by step. No significant impact of any individual study was observed on the coverall effect sizes of FBS, and insulin levels **(Supplemental Figure 2)**.

Publication bias

Visual inspection of funnel plot established no evidence of publication bias in the present study (**Figure5**). Egger's linear regression test also confirmed the funnel plot conclusion (FBS: p=0.160, and IN: p= 0.887).

Discussion

Contemporary evidence suggests that high blood glucose concentrations in humans are inextricably linked with chronic disease onset in patients with prediabetes or diabetes (Rizza, 2010; Standl et al., 2011), and as such, reducing or managing blood glucose concentrations represents an overarching aim in the amelioration and management of chronic metabolic disorders (Rizza, 2010). Traditional medicinal, therapeutic strategies, such as insulin and hypoglycemic drugs have achieved some success in managing high blood glucose, however, pharmacological interventions have well-known, adverse side effects (Scheen, 2005). Recently, bioactive phytochemicals of coffee have gained eminence because of their biological properties, including; anti-inflammatory and antioxidant activities (Godos et al., 2014), augmented insulin sensitivity and fatty acid oxidation, and modulation of glucose utilization and absorption (Sudeep, Venkatakrishna, Patel, & Shyamprasad, 2016). Whilst recently, Gorji et al, in a comprehensive meta-analysis, supported the use of GCE for the enhancement of obesity indices, with stratified analysis highlighting more enhancements in participants with a baseline BMI ≥25kg/m^2 (Gorji et al., 2019). However, regarding the effect of GCE and CGA on glycemic indicators levels, there remains a dearth of consensus. Several studies have shown GCE supplementation decreased blood glucose and insulin concentrations (Hanieh Roshan et al., 2018; Satoko Soga et al., 2013), whilst contrastingly, an equivalent number of trials did not support such assertions (Satoko Fukagawa et al., 2017; Takuya Watanabe et al., 2006). Moreover, previously published reviews have few studies, and did not evaluate the effects of CGA and GCE supplementation on blood glucose and insulin levels in a dose response model (Faraji, 2018; Nikpayam et al., 2019). Thus, our aim was to perform a dose-responses meta-analysis and systematic review of all published RCTs to quantify the effects of CGA and GCE supplementation on blood glucose and insulin levels In accord with the aforementioned aim, overall results specified that GCE did not result in any significant alteration in IN, however, sub-group analysis highlighted that IN was significantly reduced when GCE was supplemented in dosages ≥400 mg/day. In addition, we found that, overall, FBS was significantly

reduced following GCE consumption, and responded in a non-linear fashion with GCE dosage and treatment duration, respectively.

Coffee is a major source of bioactive components, including methylxanthines, phenolic acids, and, in particular, polyphenol compounds (Esquivel & Jiménez, 2012; Gaafar et al., 2013). Chlorogenic acids (ester of caffeic acid and quinic acid) is the glycosylated derivate forms of polyphenol, the major polyphenol exist in coffee. Polyphenols have repeatedly been shown to combat non-communicable diseases related with oxidative stress and its incumbent complications (Manach, Scalbert, Morand, Rémésy, & Jiménez, 2004). There exists agglomerative evidence that coffee can elicit positive changes in metabolic syndromes such as type 2 diabetes, obesity, and insulin-resistance (Dickson et al., 2015; Ding, Bhupathiraju, Chen, van Dam, & Hu, 2014; Ho et al., 2012; Salamat et al., 2019). Numerous different pharmacological publications regarding GCE reported that the chlorogenic acids constituent in GCE can regulate hypertension, glucose metabolism, and vasoreactivity (Blum, Lemaire, & Lafay, 2007; Kozuma, Tsuchiya, Kohori, Hase, & Tokimitsu, 2005). Indeed, in the current meta analyses we demonstrated that FBS is significantly reduced following GCE consumption, and the response is not dependent on dosage or duration of treatment. Previous results suggest that any protective impacts of coffee are unlikely to be specially attributable to caffeine, but rather, as speculated earlier, they likely involve a broader range of chemical constituents, such as magnesium(Haytowitz et al., 2011), lignans (Milder, Arts, van de Putte, Venema, & Hollman, 2005) and chlorogenic acids (M. N. Clifford, 1999). The impacts of these coffee constituents on glucose metabolism and insulin sensitivity from both animal studies and in vitro experiments have been extensively reviewed (Van Dam, 2006), and, indeed, in the current study, we found that IN was significantly reduced when GCE was supplemented in dosages ≥400 mg/day.

Mechanistic action

Diets abundant in polyphenols may be conducive to the prevention of numerous diseases or comorbidities related with oxidative stress, such as coronary heart disease and various cancers (Adlercreutz & Mazur, 1997; Tijburg, Mattern, Folts, Weisgerber, & Katan, 1997). Green coffee extract has been demonstrated efficient of scavenging free radicals *in vitro*, whilst yielding increases in the antioxidant ability of plasma, *in vivo* (Blum et al., 2007; Monteiro, Farah, Perrone, Trugo, & Donangelo, 2007). Moreover, there is empirical data available to suggest that GCE, might mediate intestinal glucose absorption (Bidel, Hu, Sundvall, Kaprio, & Tuomilehto, 2006; Lopez-Garcia et al., 2006). This biological activity may present a basis for putatively elucidation its impacts on FBS and IN, where GCE would have a protective impact against diabetes via modifications in gastrointestinal hormone secretion (Greenberg et al., 2006). Additionally, the mechanism by which blood glucose may be declined by chlorogenic acids is reputedly via its stimulation of AMP-activated protein kinase (AMPK). Stimulation of AMPK contributes to the improvement of GLUT4 translocation to the plasma membrane, amplifying transportation of glucose to the cells, leading to peripheral glucose disposal (Ong et al., 2012). With particular reference to chlorogenic acids, which are highly abundant in GCE, they are, independently, asserted to elicit positive effects on type 1 diabetes, blood glucose and insulin sensitivity via their antioxidant properties(M. N. Clifford, 1999), effects on soft tissue mineral composition through action as a metal chelator (de Sotillo & Hadley, 2002), decreasing of hepatic glucose output through inhibition of glucose-6-phosphatase (Arion et al., 1997; Herling et al., 1999), and declining of intestinal glucose uptake through inhibition of glucose-6-phosphate translocase 1 and other mechanisms, and a subsequent elevate in GLP-1 (McCarty, 2005). Given the putative mechanisms above, it is conceivable that the significant alterations to IN are only manifest in dosages >400mg/d because modifications in gastrointestinal hormone secretion might only be viable at higher quantities (Greenberg et al., 2006). Furthermore, some evidence suggests that GCE could mediate intestinal glucose absorption, however, this might only yield noticeable changes in

higher quantities (Bidel, Hu, Sundvall, Kaprio, & Tuomilehto, 2006; Lopez-Garcia et al., 2006). Notwithstanding, however, the above explanation for the dose-response found in this study is speculative, and clearly necessitates detailed, mechanistic work.

Strength and limitations

The most important strength of this study was that this meta-analysis reported a comprehensive overview of the impact of GCE on blood glucose as manifest in human-based RCTs; and specified the potential to treat or manage blood glucose dysfunction or disease, this is valuable endeavor. The evidence base, previous to present meta-analysis, was distinctly lacking in consensus, and thus, immediately required a quantitative assessment, summative, which we have reported. Indeed, systematic reviews and meta-analyses are at the top in the hierarchy of the clinical evidence (Colato). We revealed that there is adequate evidence for GCE administration to elicit positive impacts on FBS, and insulin levels (when consumed in doses ≥400mg/d). A Further strength of the present study is the assimilation of the heterogeneous sample of individuals, with a range of ages and ethnicities. We were also able to stratify analyses across both duration of intervention and dose, therein providing foresight into expected results based on such data, and of particular interest is that FBS responded in a non-linear fashion.

Notwithstanding, the present study has some limitations. The analyses enabled a larger number of trials and individuals to be included for meta-analyses, however could possibly impact mechanism of effectiveness and action, and thus warrants further investigation. Furthermore, due to lack of rigorous regulation, there is a distinct need for the manufacturers of GCE products to prove efficacy, safety and quality of a marketed product, particularly given such concerns are less strongly enforced than in the pharmaceutical sector (Williamson), which may have influenced the emergence of significant heterogeneity among included studies. Moreover, many available products might be ineffective, and thus require more detailed examination (Williamson).

Conclusion

The results of the present meta-analysis study confirm the use of GCE administration for the enhancement of blood glucose, where FBS was improved, and sub-group analysis highlighted improvement in insulin levels when consumed is doses ≥400mg/d. We have highlighted the positive impact elicited by GCE intervention for some clinically relevant variables (FBS and insulin levels), however, it is manifested that more, well-controlled and randomized trials are required to support the veracity of our findings, and importantly, and, in particular, explicate the mechanism in population and health status sub-groups. Furthermore, there is the possibility that studies discussed in the present review article have not been performed in accordance with a recent consensus document providing a perspective in best practice in pharmacological research on bioactive preparations from plants (Heinrich et al).

Conflict of Interest

None of the authors have any conflicts of interest related to this article.

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