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# Coffee polyphenol consumption improves postprandial hyperglycemia associated with impaired vascular endothelial function in healthy male adults

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ABSTRACT

Epidemiological studies indicate that habitual coffee consumption lowers the risk of diabetes and cardiovascular diseases. Postprandial hyperglycemia is a direct and independent risk factor for cardiovascular diseases. We previously demonstrated that coffee polyphenol ingestion increased secretion of Glucagon-like peptide 1 (GLP-1), which has been shown to exhibit anti-diabetic and cardiovascular effects. We hypothesized coffee polyphenol consumption may improve postprandial hyperglycemia and vascular endothelial function by increasing GLP-1 release and/or reducing oxidative stress. To examine this hypothesis, we conducted a randomized, acute, crossover, intervention study in healthy male adults, measuring blood parameters and flow-mediated dilation (FMD) after ingestion of a meal with or without coffee polyphenol extract (CPE). Nineteen subjects consumed a test meal with either a placebo- or CPE-containing beverage. Blood biomarkers and FMD were measured at fasting and up to 180 minutes postprandially. The CPE beverage led to a significantly lower peak postprandial increase in blood glucose and diacron-reactive oxygen metabolite, and significantly higher postprandial FMD than the placebo beverage. Postprandial blood GLP-1 increase tended to be higher after ingestion of the CPE beverage, compared with placebo. Subclass analysis revealed that the CPE beverage significantly improved postprandial blood GLP-1 response and reduced blood glucose increase in the subjects with a lower insulinogenic index. Correlation analysis showed postprandial FMD was negatively associated with blood glucose increase after ingestion of the CPE beverage. In conclusion, these results suggest that coffee polyphenol consumption improves postprandial hyperglycemia and vascular endothelial function, which is associated with increased GLP-1 secretion and decreased oxidative stress in healthy humans.



*Abbreviations:* AUC, area under the curve; CGA, chlorogenic acid; CPE, coffee polyphenol extract; dROM, diacron-reactive oxygen metabolites; FMD, flow mediated dilation; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

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## 1. Introduction

Coffee, one of the most popular beverages throughout the world, has been consumed for thousands of years due to its flavor and physiological effects. Many studies have demonstrated the potential health benefits of daily coffee consumption. Previous epidemiological studies have reported that an increase in daily consumption of coffee was associated with a reduced risk of metabolic syndrome [1–3], diabetes [4], and death due to cardiovascular diseases [5]. Similar findings were also true for decaffeinated coffee consumption [6]. However, the active components responsible for the reduced risk of these diseases with daily coffee consumption have not yet been fully elucidated [7].

Coffee is one of the major sources of dietary polyphenols. A recent study by Fukushima et al. showed that coffee contributed to 50% of the daily polyphenol consumption in the Japanese population [8]. The health benefits of daily coffee consumption may be associated with its polyphenol content, which leads to various physiological effects [9]. Caffeic acid and its quinic acid ester (chlorogenic acid [CGA]) have been identified as the most abundant polyphenols in coffee; a single cup of coffee contains 70 to 350 mg of CGAs [10]. Our previous study demonstrated that dietary supplementation with coffee polyphenols improved energy metabolism and reduced body fat, and these effects were probably due to enhanced fat catabolism in the liver [11]. We also demonstrated that the daily ingestion of CGAs increased fat catabolism in healthy humans [12,13]. However, the relationship between daily ingestion of CGAs and diabetes or blood glucose and cardiovascular diseases remain unknown.

We previously demonstrated that coffee polyphenol ingestion stimulated secretion of Glucagon-like peptide 1 (GLP-1), in both human enteroendocrine cells and mice [14]. GLP-1 is a gut-derived hormone that stimulates the glucose-induced secretion of insulin from pancreatic $\beta$ cells. Prolonged activation of GLP-1 signaling has been shown to attenuate diabetes in animals and humans. Therefore, use of GLP-1 secretagogues may be a practicable option for patients to control their blood glucose levels [15]. In addition, recent studies have suggested multiple direct cardiovascular effects of increased GLP-1 signaling [16]. A growing amount of evidence has demonstrated the beneficial effects of GLP-1 on vascular endothelial cells [17–19]. A recent study has demonstrated that improvement of vascular endothelial function restores impaired glucose tolerance by ameliorating insulin resistance in skeletal muscle [20]. Whereas dietary supplementation with GLP-1 stimulators may offer potential benefits for the treatment of diabetes and the maintenance of vascular health, food-derived GLP-1 modulators have not yet been examined in detail.

Habitual coffee polyphenol ingestion improves vascular endothelial function [21], which is impaired in diabetes, as well as hypertension and the early stages of cardiovascular diseases. However, the acute effect of coffee polyphenol ingestion on endothelial function still remains to be clarified. Kawano et al. demonstrated that vascular endothelial function measured by flow-mediated dilation (FMD) was decreased after glucose ingestion, with concomitant increase in oxidative stress markers [22]. In addition, ingestion of antioxidants attenuated postprandial endothelial dysfunction [23]. Postprandial hyperglycemia is a direct and independent risk factor for coronary heart disease [24], and endothelial dysfunction has been identified as an important contributor to this state. Thus, we focused on endothelial dysfunction and hyperglycemia after meal ingestion.

Taking these previous findings together, we hypothesized that coffee polyphenol consumption may improve postprandial hyperglycemia and vascular endothelial function by stimulating postprandial GLP-1 release and/or reducing oxidative stress in healthy humans. To test this hypothesis, we examined the acute effects of a single intake of coffee polyphenols on postprandial blood glucose and peripheral endothelial function, in a single-blind, randomized, placebo-controlled, crossover trial in healthy male adults.

## 2. Methods and materials

### 2.1. Materials

Coffee polyphenol extract (CPE) was prepared from roasted coffee beans (Vietnam Robusta, Brazil; L value = 25 for each) by hot water extraction followed by activated carbon filtration for this study. Chlorogenic acids (CQAs) mainly include the following 9 compounds: 5-CQA as the most abundant component, 3-CQA, 4-CQA, 3,4-diCQA, 3,5-diCQA, 4,5-diCQA, 3-FQA, 4-FQA, and 5-FQA. The polyphenol composition of CPE was measured by high-performance liquid chromatography. The composition of CQAs in CPE was 72.4% CQA (total 3-CQA, 4-CQA, and 5-CQA), 19.3% feruloylquinic acid (3-FQA, 4-FQA, and 5-FQA), and 8.3% dicaffeoylquinic acid (3,4-diCQA, 3,5-diCQA, and 4,5-diCQA).

### 2.2. Test beverages

The beverages were taste- and flavor-matched (coffee-flavored) and differed only in polyphenol content. The CPE beverage (185 mL) contained 355 mg of CQAs. The placebo beverage did not contain CQAs. Each beverage contained 54.9 mg of caffeine.

### 2.3. Subjects

A statistical power analysis was performed for sample size estimation (n = 19) based on data from a preliminary pilot study (subjects, n = 9; significance, $\alpha = .05$, power, $1 - \beta = 0.83$). Thirty-five people were recruited for eligibility screening through an in-house mail system, and 20 subjects were enrolled in the study. One subject was excluded from analyses due to insulin resistance. Nineteen healthy Japanese men (BMI 21.8 ± 2.3) aged 24 to 53 (38.1 ± 8.4) years were analyzed in this study (Fig. 1). Three subjects were smokers. None of the subjects took medication; had lifestyle interventions, allergies, hypersensitivity to caffeine or coffee; or partook in heavy alcohol use. The Human Ethics Committee of Kao Corporation approved the study protocol. All subjects provided written informed consent. The present study was