

The Evaluation of Coffee Therapy for Improvement of Renal Oxygenation (COFFEE) Study: A Mechanistic Pilot and Feasibility Study Evaluating Coffee's Effects on Intrarenal Hemodynamic Function and Renal Energetics



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INTRODUCTION

Coffee remains one of the most widely consumed beverages in the United States with an estimated 400 million cups ingested daily.¹ Extensive studies have revealed a wide variety of health benefits attributed to coffee consumption, and in a meta-analysis of 3 large prospective studies involving 208,501 adults, consumption of both caffeinated and decaffeinated coffee was associated with a lower risk of all-cause mortality.² One potential explanation for the survival benefit of coffee consumption is protection against kidney disease. Indeed, habitual coffee consumption was associated with a lower incidence of chronic kidney disease (CKD) in the Atherosclerosis in Communities study, a large population-based study of 14,209 older adults.³ Yet, the specific physiological effects of coffee on kidney function that may contribute to improvements in morbidity and mortality have not yet been elucidated.

Regular coffee contains multiple potential kidney-modifying compounds, including caffeine, a methylxanthine alkaloid which acts as an antagonist of the adenosine receptor,⁴ and polyphenol bioactive compounds, which serve as plant-based antioxidants.⁵ Caffeine has been found to modify kidney hemodynamics and natriuresis through factors including inhibition of proximal and distal tubule sodium reabsorption to promote free water and solute excretion and modification of the renin-angiotensin-aldosterone system.^{4,6} In response to sodium delivery to the distal tubule, caffeine has also been hypothesized to inhibit the tubuloglomerular feedback response and may maintain glomerular filtration rate (GFR) and renal plasma flow (RPF) while concurrently reducing consumption of renal oxygen (O₂). In conjunction with the beneficial effects of caffeine, bioactive compounds in coffee have also been found to improve oxidative stress and inflammation, known contributing factors for kidney injury.^{5,7} However, to date, there are no data

Table 1. Characteristics of participants in the COFFEE study at baseline

Characteristics	Baseline value
Age (yr)	18.5 ± 2.6
Type 1 diabetes duration (yr)	5.9 ± 2.2
Sex (female, %)	40
Race/ethnicity (%)	
Black non-Hispanic	0
Hispanic	0
White non-Hispanic	100
Fat mass (kg)	16.6 ± 7.0
Hemoglobin A1c (%)	8.4 ± 1.0
Caffeinated compound intake (units per wk)	
Regular coffee (6 oz)	2 (0–10)
Espresso beverage	0 (0–0)
Caffeinated soft drink (12 oz)	2 (0–3.5)
Black or green tea (6 oz)	0 (0–1)
Energy drink (12 oz)	0 (0–2)
Chocolate bar (8 oz)	2 (0–2)
Aspirin/paracetamol/caffeine (Excedrin)	0 (0–0)

Data are presented as mean ± SD or median (interquartile range) unless otherwise noted.

evaluating the influence of coffee-induced and/or caffeine-induced natriuresis on intrarenal hemodynamic function and renal energetics in youth-onset type 1 diabetes (T1D), a population at high risk for CKD. Youth with T1D were selected for this study as we have previously found that adolescents with T1D exhibit relative renal hypoxia when compared with healthy controls and this is associated with increased RPF, albuminuria, and insulin resistance,⁸ thus making youth with T1D an ideal focus for therapeutic strategies targeting intraglomerular hemodynamic dysfunction and renal hypoxia as precursors for future DKD.

In the Evaluation of Coffee Therapy for Improvement of Renal Oxygenation (COFFEE) Study (NCT03878277), a study of 10 youths aged 12 to 21 years with T1D, we aimed to assess the effects of a confirmed 7-day course of a single daily Starbucks Cold Brew (325 ml, 175 mg caffeine) coffee on intraglomerular hemodynamic function by RPF and GFR and renal oxygenation by kidney functional magnetic resonance imaging (Supplementary Methods^{S1–S23}). We hypothesized in this open-label, pilot, and feasibility trial that daily coffee consumption would improve renal oxygenation without changes in GFR and RPF.

RESULTS

Baseline Characteristics

COFFEE participants had a mean age ± SD of 18.5 ± 2.6 years with a T1D duration of 5.9 ± 2.2 years and a mean hemoglobin A1c of 8.4 ± 1.0% (Table 1). The participants were predominantly male (60%), and all identified as White/non-Hispanic.

Table 2. Characteristics of participants in the COFFEE study pre-coffee and post-coffee therapy

Characteristics	Pretherapy (n = 10)	Post-therapy (n = 10)	P value
BMI (kg/m ²)	22.5 ± 4.1	23.0 ± 4.3	0.77
Weight (kg)	67.4 ± 14.4	68.4 ± 14.2	0.08
SBP (mm Hg)	116 ± 5	121 ± 11	0.25
DBP (mm Hg)	77 ± 10	73 ± 14	0.19
Serum creatinine (μmol/l)	70.7 ± 21.2	70.7 ± 19.5	0.68
Cystatin C (mg/l)	0.82 ± 0.18	0.84 ± 0.19	0.92
Hematocrit (%)	43.3 ± 2.8	42.4 ± 2.5	0.48
UACR (mg/mmol)	0.45 (0.34–0.68)	0.45 (0.45–0.68)	0.37
GFR (ml/min)	195 ± 28	196 ± 48	0.97
RPF (ml/min)	785 ± 95	781 ± 40	0.69
Cortex R2* (s ⁻¹)	20.2 ± 1.4	20.0 ± 1.9	0.59
Medulla R2* (s ⁻¹)	27.1 ± 3.2	27.1 ± 3.4	0.98
Whole kidney R2* (s ⁻¹)	22.4 ± 1.5	22.5 ± 2.1	0.93
FSOC (cortex) (s ⁻¹)	1.41 ± 0.78	0.69 ± 0.65	0.11
FSOC (medulla) (s ⁻¹)	6.30 ± 2.19	5.68 ± 2.76	0.67
FSOC (whole kidney) (s ⁻¹)	3.04 ± 0.97	2.67 ± 1.46	0.61
Renal blood flow by 3D pCASL (right) (ml/100 g/min)	181 ± 40	182 ± 37	0.97
Renal blood flow by 3D pCASL (left) (ml/100 g/min)	189 ± 30	182 ± 43	0.14

BMI, body mass index; DBP, diastolic blood pressure; 3D pCASL, 3-dimensional pseudocontinuous arterial spin labeling; FSOC, furosemide-suppressible oxygen consumption = R2* (baseline) – R2* (post-furosemide); GFR, glomerular filtration rate; R2*, the transverse magnetization decay time proportional to the tissue content of deoxyhemoglobin; RPF, renal plasma flow; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

Data are presented as mean ± SD or median (interquartile range) unless otherwise noted.

Pre-Coffee and Post-Coffee Outcomes

Participant weight, systolic blood pressure, and diastolic blood pressure did not differ significantly after a 1-week course of coffee consumption (Table 2). Serum creatinine, cystatin C, hematocrit, and urine albumin-to-creatinine ratio also remained similar across the 2 time points. Gold standard measures of GFR by iohexol clearance and of RPF by *p*-aminohippurate clearance did not differ significantly before and after coffee consumption. Kidney blood oxygen level-dependent magnetic resonance imaging revealed no significant changes between the baseline and follow-up visits for the cortex, medulla, or whole kidney R2* (fractional oxygenation), furosemide-suppressible oxygen consumption, or 3-dimensional pseudocontinuous arterial spin labeling on the right or left (perfusion).

DISCUSSION

Coffee consumption is highly prevalent in both youth and young adults, yet our knowledge of its underlying physiological effects remains limited. In the Atherosclerosis in Communities study, attenuation of CKD risk was found in adults without diabetes who consumed higher amounts of coffee daily,³ and we hypothesized that this may be secondary to coffee-induced

improvements in kidney oxygenation with maintenance of GFR and RPF. Yet, in an exploratory analysis from the COFFEE pilot and feasibility study, consumption of a single, daily, cold-brew coffee in a small group of young persons with T1D with habitual caffeine intake did not significantly affect intraglomerular hemodynamic function or kidney oxygen availability.

To best of our knowledge, ours is the first study to evaluate the impact of coffee consumption on intraglomerular hemodynamic function and kidney energetics in T1D. From the results of this pilot study, we may conclude that either our small sample size has diminished our power too considerably to see a potential significant difference over time or the mechanisms whereby coffee mediates the cardiorenal protective effects observed in epidemiologic studies may be independent of the effects of coffee on intraglomerular hemodynamics and kidney energetics. Additional predisposing factors for the development of kidney injury, such as elevated age, acute illness, or baseline CKD, which were absent in our current cohort, may be also necessary to fully identify the kidney protective effects of coffee.

Strengths of COFFEE include its prospective interventional study design and the collection of gold standard measures of GFR and RPF by iohexol and *p*-aminohippurate clearance techniques, while maintaining steady-state glycemic concentrations to avoid glycemic variability and mimic the typical hyperglycemic milieu of T1D. COFFEE used state-of-the-art multiparametric kidney magnetic resonance imaging assessments for kidney oxygenation and perfusion as well. Notably, measurements of kidney oxygenation and perfusion by blood oxygen level-dependent magnetic resonance imaging and pseudocontinuous arterial spin labeling have been effectively used in populations with and without diabetes or with varying degrees of CKD and have consistently revealed associations between low oxygenation and kidney function decline.⁹

Limitations of COFFEE include the small sample size, as it was designed as a pilot, and the homogeneous non-Hispanic White race/ethnicity (a common finding in T1D studies in Colorado, USA) and younger age demographic, with less potential for age-related kidney dysfunction. Accordingly, further research is necessary before rejecting modification of renal bioenergetics and hemodynamics as potential protective mechanisms of coffee consumption. It is notable that individuals in the COFFEE study had a baseline diagnosis of T1D, which places them at higher risk for kidney injury than their peers without diabetes because of factors including chronic poor glycemic control, acute hyperglycemic events, dehydration, and potential

diabetic ketoacidosis,^{S24} and therefore have greater potential for improvement in response to coffee consumption.

In conclusion, although we did not identify significant changes over time in GFR, RPF, or renal perfusion or oxygenation in response to a short treatment course of daily coffee in this small pilot and feasibility study involving youth with T1D, further large-scale studies in youth and adults with and without diabetes are necessary to better understand and optimize the long-term beneficial effects of habitual coffee consumption on cardiorenal protection.

DISCLOSURE

PB has reported acting as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, LG Chem, Sanofi, Novo Nordisk, and Horizon Pharma and serving on the advisory boards of AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and XORTX. CRP has reported serving as a member of the advisory board of and owning equity in RenalytixAI and as a consultant for Genfit and Novartis. All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

KLT analyzed and interpreted the data and wrote the manuscript. CV collected, analyzed, and interpreted the data. LPL assisted with MRI postprocessing and analyses. CMR, CS, EAH, ES, LMS, JC, and MEG analyzed and interpreted the data. PP developed the magnetic resonance imaging protocols, postprocessing, and analyses. CRP designed the study, analyzed and interpreted the data, and contributed to discussion. PB designed the study, collected the data, analyzed and interpreted the data, and contributed to discussion. All coauthors reviewed and edited the manuscript. PB is the guarantor of this work and, as such, has full access to the data sets and takes responsibility for the integrity of the data and the accuracy of the data analysis.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplementary Methods.](#)

[Supplementary References.](#)

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