Renal Failure, 32(10): 1137–1147, (2010)

ISSN 0886-022X print/1525-6049 online
DOI: 10.3109/0886022X.2010.516853

informa
healthcare

CLINICAL STUDY

Coffee, nutritional status, and renal artery resistive index

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Abstract

Background: The relationship between nutrition and atherosclerosis is known, even dissociated from protein malnutrition. Cardiovascular impact of several nutrients is known; among them the action of coffee is still debated and cardiovascular effect of caffeine has been investigated without definite results. *Objective*: The aim of this study is to investigate whether coffee habits, and/or quantity of coffee consumption, have any relationship with renal resistive index (RRI), a hallmark of arterial stiffness (AS). The relationship of AS with nutritional status assessed by body composition and serum albumin, insulin resistance (assessed by HOMA), and renal function assessed by glomerular filtration rate (GFR) is concurrently investigated. *Methods*: This study was done with 221 consecutive patients, without diabetes, cancer, liver, renal, and heart disease, referred for clinical noninvasive assessment and nutritional counseling: 124 essential hypertensive and 97 nonhypertensive patients were eligible. Personalized Mediterranean diet, physical activity increase, and smoking withdrawal counseling were provided. *Results*: By multiple linear regression, fat-free mass (FFM), HOMA (positive relationship), and number of cups of coffee/day (negative relationship) account for 17.2% of the variance to RRI. By odds ratios lower risk to increased RRI is associated with higher serum albumin, higher hemoglobin, and FFM; greater risk is associated with hypertension, insulin resistance (HOMA $\geq$ 3.0), and renal insufficiency (GFR $\leq$ 90); coffee, assessed by number of cups/day, reduces risk. *Conclusion*: Coffee use is inversely associated with RRI. Habitual coffee users have risk protection to higher RRI; lower serum albumin, insulin resistance, and renal insufficiency are associated with greater RRI.

Keywords: malnutrition, coffee, essential hypertension, ultrasound, renal resistive index, insulin resistance, HOMA-IR

INTRODUCTION

The relationship between nutrition and atherosclerosis is recognized, more in obesity than in malnutrition, and is usually linked to obesity-associated conditions. Among the factors studied, a possible favorable effect of caffeinated coffee consumption was envisaged: the relation between caffeinated coffee consumption and heart disease morbidity and mortality is of great interest given the extensive use of this beverage.[1]

Diabetes and/or insulin resistance, overweightness, arterial hypertension, cigarette smoking, and dyslipidemia are the most established risk factors for cardiovascular disease; nonetheless, malnutrition and/or chronic disorders along with low BMI, low diastolic blood pressure (BP), low total and HDL cholesterol, and high insulin sensitivity can predict cardiovascular mortality.[2,3]

Hypoalbuminemia is associated with chronic renal and vascular disease, even dissociating this effect from protein malnutrition; it is a composite marker that reflects malnutrition as well as increased acute-phase inflammation, that is, it is also a negative acute-phase reactant.[4] Traditional risk factors for hypertension[5] may have less importance in drug-treated hypertensive patients in comparison with untreated hypertensive patients,[6] and there are reasons for investigating different lifestyle and nutritional aspects.

Possible health hazards of coffee have been related to its main ingredient, caffeine. Activation of the sympathetic nervous system by coffee may enhance cardiovascular risk; however, it is unclear whether this effect of coffee is related to caffeine or other substance(s) also contained in decaffeinated coffee.[7] The cardiovascular impact of coffee remains debated because the underlying mechanisms of action are complex[8] and involve

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Received 27 May 2010; accepted 14 August 2010

several behavioral risk factors,[9] including its use during mental stress. Caffeine appears to affect BP through adenosine receptor inhibition and an increased release of select neurotransmitters. Caffeine levels peak 30–120 min after oral intake and caffeine's half-life is 3–6 h. Caffeine tolerance diminishes the acute effect of caffeine on BP, and hypertensive individuals are more susceptible to BP changes with caffeine administration and/or intake.[10]

Various components, including cigarette smoking and caffeine, are being increasingly investigated for the possible impact on arterial stiffness (AS) and wave reflection and on cardiovascular risk.[11,12] Caffeine consumption is a risk factor for heart failure, but its effects remain controversial.[13] However, in epidemiological studies, no evidence was found supporting an association between increased level of caffeine consumption and increased all-cause mortality or cardiovascular disease mortality.[14,15] Moreover, although the precise nature of the relation between coffee and BP is still epidemiologically unclear, most evidence suggests that regular intake of caffeinated coffee does not increase the risk of hypertension.[16] Also the unfavorable acute vascular effects of caffeine are controversial because the acute administration of caffeine augments endothelium-dependent vasodilatation in healthy young men through an increase in nitric oxide production.[17] Caffeine improves insulin sensitivity but increases plasma cholesterol levels and impairs renal function in models of obesity with the metabolic syndrome and hypertension.[18,19]

Cardiovascular effects of coffee consumption and notably the development of AS can be mediated also through insulin-resistance mechanisms.[20] AI, a hallmark of vascular aging, is assessed also by the renal resistive index (RRI), and a relationship between the ultrasound RRI, BP, and renal function response is recognized as a most powerful predictor of death during follow-up of patients with atherosclerotic renovascular disease.[21]

However, increased RRI may imply the presence of some type of underlying renal damage, including ischemic nephropathy,[22] and is useful for predicting long-term renal functions in renal transplant patients.[23] RRI, used as a hallmark of the progression of renal disease rather than as a marker of specific renal damage, can be increased by extrinsic factors such as kidney compression, breath holding during the Valsalva maneuver, and extreme bradycardia. RRI values are also correlated with extrarenal markers of vascular stiffness. RRI increases in diabetic nephropathy when the kidneys start to shrink and microalbuminuria occurs, and decreases with use of renin–angiotensin system inhibitors in diabetic nephropathy and hypertensive nephrosclerosis, helping to explain why these drugs are renoprotective.[24] Age and pulse pressure are independently associated with RRI,[25] and these factors must be taken into account.

Malnutrition can be defined as the imbalance between intake and requirement, which results in altered metabolism, impaired function, and loss of body mass.[26] It includes both protein–energy malnutrition and inadequate micronutrient status and is defined by the association of low serum markers of malnutrition, including serum albumin and cholesterol, together with indicators of decreased fat mass (FM) and fat-free mass (FFM).[26] The determination of the FFM, extracellular water (ECW), and intracellular water (ICW) in healthy subjects and in patients with stable water and electrolytes balance is possible by validated Bioimpedance assessment (BIA) equation, age-, sex-, and race-adjusted. These measurements are useful for determining hydration and lean mass body content; longitudinal follow-up of body composition by BIA is possible in subjects with BMI 16–34 kg/m without abnormal hydration.[27]

The aim of this study is to investigate whether coffee habits, and/or quantity of coffee consumption, have any relationship with RRI. The relationship of RRI with nutritional status, assessed by BIA body composition and serum albumin, insulin resistance (assessed by HOMA), and renal function assessed by glomerular filtration rate (GFR) is concurrently investigated.

PATIENTS AND METHODS

This study was carried out with 221 consecutive patients referred to our day hospital for clinical non-invasive assessment and nutritional counseling. Patients with diseases other than hypertension were considered ineligible according to the exclusion criteria detailed below. The overall study design is reported in Figure 1. Local ethical committee permission was obtained. The subjects gave their informed consent also with regard to personal data management.

A total of 124 consecutive essential hypertension (EH) patients, already treated with a satisfactory pharmacological response for at least 2 years, were included in this study. Arterial hypertension was defined as >140 mmHg of systolic and >90 mmHg of diastolic BP, according to the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Responders were conventionally defined as patients with arterial BP regularly below 140/90 mmHg. Moreover, 97 nonhypertensive patients were also considered eligible according to the same criteria.

Patients with congestive heart failure, renal failure (creatinine clearance below 75 mL/min/1.73 m^2), and oncological disease, thyroid disease, alcohol abuse above 20 g/die, and severe liver disease were preliminarily excluded. Arrhythmias influence the pulse wave pattern, so measurements made in the presence of premature beats and patients with atrial fibrillation were excluded. Patients with any history of diabetes mellitus, established by a fasting glucose level ≥126 mg/dL or a HbA1c ≥ 6.5%, or those under treatment for

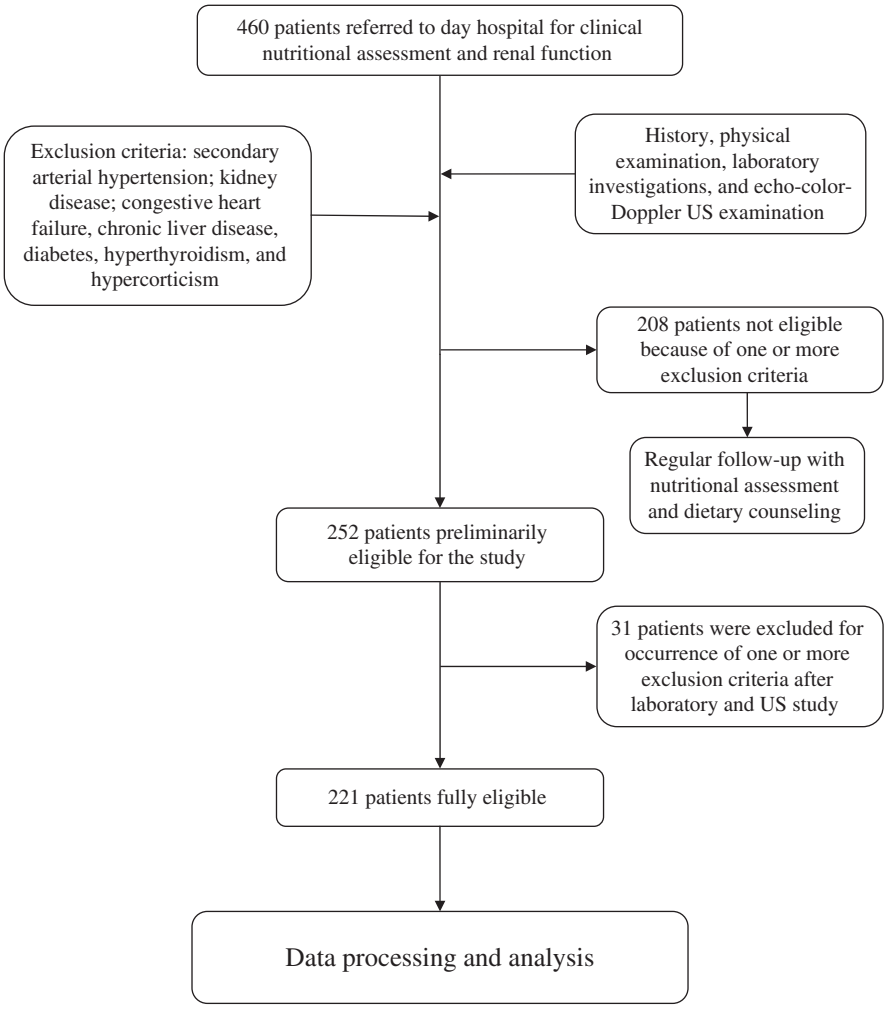

Figure 1. Overall study design.

other conditions, apart from well-controlled arterial hypertension, were not considered eligible for this study.

Daily users of Coca-Cola and tea were preliminarily excluded if an estimated daily intake of caffeine with these beverages above 100 mg (the content of a cup of coffee) was reported; in this regard, measurements were estimated according to current dietary content tables.

Coffee habits were defined according to the absolute number of coffee cups (only espresso coffee), and also graded as 1 (0 cup of coffee/day), 2 (1–2 cups of coffee/day), and 3 (≥3 cups of coffee/day). Smoking was quantified as number of cigarettes/day and also on a yes–no-previous smoker-status basis, according to present habit.

Routine laboratory included virus hepatitis (HAV, HBV, and HCV) and cancer markers (AFP, CEA, Ca 125, Ca 15-3), fT3, fT4, TSH, antithyroglobulin, and antithyroperoxidase antibodies (TPOAb), PTH, AST, ALT, γ-glutamyl transpeptidase (γ-GT), ferritin, total protein, and albumin. Normal albumin and hemoglobin are defined within the range of the 25th to 75th percentile, and are derived from measurements of all eligible patients of this study.

Renal function is estimated by the MDRD formula in mL/min/1.73 m^2: $170 \times \text{creatinine}^{-0.999} \times \text{age}^{-0.176} \times \text{urea}^{-0.170} \times \text{albumin}^{0.318} \times 0.762$ if female (all participants are white and no correction is required for colored people), according also to Clinical Practice Guidelines for Chronic Kidney Disease KDOQI; GFR ≥ 90 is assumed as normal renal function.

Weight (BW) was measured in light clothing, without shoes, in kilogram, and height (H) was measured in meters, using a scale-integrated stadiometer. Body mass index (BMI) was calculated as BW/H^2 and patients were categorized as normal weight (<25.0 kg/m^2), overweight (≥25.0 and ≤29.9 kg/m^2), and obese (>30.0 kg/m^2). The obesity was classified into grade I (30.0–34.9 kg/m^2), grade II (35.0–39.9 kg/m^2), and grade III (>40.0 kg/m^2). Waist–hip ratio was also assessed.

As a general clinical conduct, all patients self-measured their own BP three times a day throughout this study (in the morning before drug intake, in the afternoon, and in the late evening) for a 3-day period, before every monthly scheduled visit (self-BP measurements – SBPM),

registering their self-measurements on a form: the prevailing SBPM value was determined from the average of the nine measurements. Both conventional office BP measurements and SBPM were always performed on the nondominant arm, with the subject in sitting position, after at least 5 minutes of rest, using the same type of fully automated oscillometric device for arm BPM (Visomat Comfort II – Roche Diagnostics Italia, Monza, Italy) validated by the German Hypertension Society and by the Italian Ministry of Health and according to the International Protocol of the European Society of Hypertension.

No extensive pharmacological washout is arranged because of the inclusion criteria that encompass adequate therapeutic response. Lower salt/lower calories personalized Mediterranean diet (Dietosystem® – Milan, Italy), physical activity increase, and smoking withdrawal counseling were provided. Mediterranean diet prescribed is characterized by a high intake of vegetables, legumes, fruits and nuts, and cereals, a high intake of olive oil and a low or no intake of saturated lipids, a moderately high intake of fish, a low-to-moderate intake of dairy products mostly in the form of cheese or yogurt), and a low intake of meat and poultry. Physical activity was encouraged in the form of walking using the "10,000 steps a day" suggestion. A portable electronic pedometer (*step counter*) was also given as motivational tool, because its use is associated with significant increases in physical activity and significant decreases in BMI and BP.

Medication is adjusted according to a stepwise treatment schedule after each visit, and included an angiotensin II-receptor blocker, losartan (50 mg, with possible and transient increase to 100 mg/day) in all patients. A calcium-channel blocker (felodipine 5–10 mg) or, more occasionally, a beta-blocker (atenolol, 12.5–50 mg) is administered, as adjunctive or substitute therapy, when the angiotensin II-receptor antagonist is no longer effective. All patients have their drugs early in the morning; laboratory assays and ultrasound study are performed after 24 hours of complete drug withdrawal and before any drug assumption. All patients fast for more than 12 hours before blood collection (coffee and alcohol were totally excluded in this withdrawal period from 1.00 pm of the preceding day), without any special dietary or fluid restriction. Thereafter, in the morning (8.00–9.30 am), ultrasound examination is performed after 30 minutes rest and the BP (systolic and diastolic) and pulse rate are measured and recorded. Afterward, 10 mL of blood is collected from the median antecubital vein into a plain tube for biochemistry tests.

Ultrasound examination is performed by the same echographist to reduce inter-observer variability. The physician is unaware of clinical details of any patients at the time of the procedure; a GE echo-color-Doppler equipment (GE Logiq 5 Expert US, manufactured by GE Medical Systems, Milwaukee, WI, USA), high resolution, with real-time sectional scan transducers was used. Renal color-Doppler echography is performed assessing intra-parenchymal renal artery mean velocity (mVRA) and intra-parenchymal renal artery RI ([peak systolic velocity – end diastolic velocity]/peak systolic velocity).[28,29] After recording pulse and BP, the first measurement is the size of the left and right kidney. For orientation purposes, perfusion in the whole of the left and right kidneys is then checked using color duplex ultrasonography and the main trunk of the renal artery is displayed. If duplex ultrasonography does not reveal any abnormalities in size or perfusion, three measurements for each kidney are taken by pulsed Doppler within 5 min, in the vicinity of the interlobar artery. RRI is calculated as the average value of all measurements taken. RRI threshold is defined by the 75th percentile derived by measurements of all eligible patients of this study.

Insulin resistance is assessed by homeostasis model-insulin resistance index (HOMA-IR),[30] according to the following formulas: "(fasting insulin value × fasting blood sugar level)/405"; this is equivalent to the HOMA-formula: HOMA = (fasting serum insulin (mU/mL) × fasting plasma glucose (mM/L))/22.5. HOMA correlates with the IR index measured by the hyperinsulinemic euglycemic clamp method, even though it has a suboptimal reproducibility, reflecting day-to-day variability.[4,5] Two thresholds for insulin resistance are conventionally considered as HOMA > 1.7 according to the likelihood ratios for 11-year incident cardiovascular disease, and as HOMA > 3.0 according to the Likelihood ratios for 7-year incident diabetes mellitus type 2.[31]

BIA of body composition is performed by a single-frequency BIA device 50 kHz and 800 mA (model BIA 101 RJL; Akern, Firenze, Italy) according to the standard tetrapolar technique; to avoid artifacts, the electrodes are placed on the feet, ankles, hands, and wrists. The body composition is calculated from BIA measurements (resistance and reactance) and anthropometric variables [body weight (BW) and height (H)], using the software provided by Akern/RJL Systems. This predictive model allows for the calculation of total body water (TBW), body FM and FFM, body cell mass (BCM), and ECW; all measurements are expressed in kilograms and in relative percentages.[28] Normal FFM (or lean mass), assumed as an index of normal nutrition, is defined within the range of the 25th to 75th percentile, and is derived by measurements of all eligible patients of this study.

Echo-color-Doppler echocardiography, chest X-ray and electrocardiogram, and other laboratory or instrumental examination, as suitable, are performed as well within the overall clinical evaluation and considered only for the eligibility criteria assessment.

Statistical analysis

Descriptive results of continuous variables are expressed as averages (± standard deviation). HOMA, albumin, hemoglobin, obesity, arterial hypertension, mild-borderline renal insufficiency, and coffee habits are assessed also as odds ratios (OR) with 95% confidence intervals (CI) versus increased renal RRI. Correlation analysis of RRI and, respectively, of quantity of coffee cups versus all considered measurement is performed by Spearman's and Pearson's statistics according to the type of variables. Multiple linear regression is used to find predictor(s) to RRI among the considered variables. Two sided p-value < 0.05 is considered statistically significant. All analyses are performed using SPSS 14.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Anthropometric and biochemical characteristics of the subjects are shown in Table 1. The average of the number of cups of coffee/day is 2.47 ± 1.26 among coffee users. In the comparison of differences between coffee versus no-coffee users, the two groups were fully comparable, and the only differences were lower cholesterol and hemoglobin. A subsequent comparison (Table 2) of hypertensive versus normal BP patients is done: the significant differences observed are greater BP, RRI, HOMA, and LDL cholesterol in hypertensive patients.

The comparison between coffee versus no-coffee users is given also separately in hypertensive and in normal BP patients (Table 3). There are significant differences only in hypertensive patients: coffee users have lower ECW and RRI and higher hemoglobin; no difference is present in normal BP patients, apart from a slightly but not significantly lower HOMA among coffee users.

By correlation analysis, correlations of RRI are significantly positive versus age ($r = 0.586$; $p < 0.0001$), BUN ($r = 0.314$; $p < 0.001$), FFM ($r = 0.236$; $p = 0.003$), ECW ($r = 0.199$, $p < 0.001$), HOMA ($r = 0.169$; $p = 0.014$), pulse pressure ($r = 0.257$; $p < 0.001$), and significantly negative versus serum albumin ($r = –0.160$; $p = 0.019$), hemoglobin ($r = –0.225$; $p < 0.001$), and number of coffee cups ($r = –0.241$; $p < 0.0001$) (Table 4).

Correlation analysis of number of coffee cups versus all considered measurement is also performed (Table 4). The correlations of number of cups of coffee are significantly positive versus BMI ($r = 0.191$; $p < 0.001$), versus albumin ($r = 0.130$; $p < 0.05$), versus LDL Cholesterol ($r = 0.196$; $p < 0.01$), versus hemoglobin ($r = 0.291$; $p < 0.0001$). Correlations of number of cups of coffee are significantly negative versus age ($r = –0.243$;

Table 1. Characteristic of study population and differences between coffee versus no-coffee users.

	Total (n = 221)	Coffee users (n = 176)	No-coffee users (n = 45)	p
Women (n)	125 (56.6%)	96	29	0.232
Hypertension (n)	124 (56.1%)	101	23	0.449
Obese (n)	69 (31.2%)	54	15	0.732
Insulin resistance patients (n)	137 (61.9%)	109	28	0.971
Age (y)	58.43 ± 10.48	57.94 ± 9.97	60.36 ± 12.21	0.169
Number of cigarettes/day	10.89 ± 15.10	11.43 ± 15.15	8.76 ± 14.91	0.290
Systolic blood pressure (mmHg)	126.04 ± 4.80	126.59 ± 13.91	123.89 ± 17.90	0.276
Diastolic blood pressure (mmHg)	78.96 ± 9.81	79.52 ± 9.81	76.78 ± 9.60	0.095
Pulse pressure (mmHg)	47.08 ± 10.93	47.07 ± 9.98	47.11 ± 14.20	0.984
BMI (kg/m^2)	27.80 ± 4.52	27.97 ± 4.32	27.12 ± 5.25	0.258
Fat-free mass (%)	64.18 ± 14.40	64.72 ± 14.46	62.29 ± 14.21	0.374
Fat mass (%)	41.10 ± 14.70	41.24 ± 14.63	40.62 ± 15.14	0.826
FFM/FM ratio	2.67 ± 1.32	2.75 ± 1.36	2.40 ± 1.12	0.159
ECW (%)	41.40 ± 4.86	40.90 ± 4.10	43.11 ± 6.68	0.016
ICW (%)	58.60 ± 4.86	59.10 ± 4.10	56.89 ± 6.68	0.016
Blood glucose (mg/dL)	93.67 ± 11.53	93.99 ± 11.34	92.33 ± 12.35	0.423
Insulin (μIU/mL)	10.44 ± 6.60	10.13 ± 6.00	11.66 ± 8.55	0.167
HOMA-IR	2.71 ± 2.30	2.64 ± 2.18	3.03 ± 2.72	0.309
Blood urea nitrogen (mg/dL)	19.52 ± 5.56	19.26 ± 5.16	20.58 ± 6.90	0.157
Creatinine (mg/dL)	0.87 ± 0.21	0.87 ± 0.19	0.85 ± 0.27	0.672
GFR	76.31 ± 17.79	75.96 ± 15.40	77.67 ± 25.25	0.566
Total cholesterol (mg/dL)	201.15 ± 41.15	204.39 ± 40.06	188.47 ± 43.34	0.020
HDL cholesterol (mg/dL)	52.52 ± 15.97	52.58 ± 15.97	52.27 ± 16.12	0.907
Triglycerides (mg/dL)	121.07 ± 60.34	120.51 ± 59.26	123.29 ± 65.03	0.783
LDL cholesterol (mg/dL)	124.54 ± 35.19	127.88 ± 34.42	111.54 ± 35.51	0.005
Albumin (g/dL)	4.60 ± 0.42	4.62 ± 0.37	4.55 ± 0.56	0.370
Hemoglobin (g/dL)	13.96 ± 1.74	14.18 ± 1.67	13.13 ± 1.76	<0.0001
RRI	0.63 ± 0.06	0.62 ± 0.05	0.64 ± 0.07	0.029

Note: BMI, body mass index; ECW, extracellular water; FFM, fat-free mass; FM, fat mass; GFR, glomerular filtration rate; HDL, high-density lipoprotein; ICW, intracellular water; LDL, low-density lipoprotein; RRI, renal resistive index.

Table 2. Differences between hypertensive versus normal blood pressure patients.

	Hypertensive patients (n = 124)	Normal BP patients (n = 97)	p
Age (y)	59.37 ± 11.54	57.24 ± 8.86	0.133
Cups of coffee/day (n)	1.92 ± 1.33	2.03 ± 1.69	0.584
Number of cigarettes/day	12.00 ± 15.47	9.46 ± 14.57	0.216
SBP (mmHg)	131.09 ± 14.91	119.59 ± 11.94	<0.0001
DBP (mmHg)	81.41 ± 9.89	75.82 ± 8.80	<0.0001
Pulse pressure (mmHg)	49.68 ± 11.29	43.76 ± 9.52	<0.0001
BMI (kg/m^2)	28.32 ± 4.03	27.13 ± 5.03	0.054
ECW (%)	41.33 ± 4.12	41.50 ± 5.72	0.827
ICW (%)	58.67 ± 4.11	58.50 ± 5.72	0.829
FFM/FM ratio	2.62 ± 1.41	2.73 ± 1.19	0.587
Blood glucose (mg/dL)	94.33 ± 11.57	92.87 ± 11.50	0.373
Insulin (μIU/mL)	11.45 ± 7.25	9.15 ± 5.43	0.010
HOMA-IR	3.07 ± 2.57	2.26 ± 1.81	0.009
BUN (mg/dL)	19.77 ± 5.56	19.21 ± 5.59	0.457
Creatinine (mg/dL)	0.87 ± 0.20	0.86 ± 0.22	0.775
GFR	75.99 ± 18.68	76.72 ± 16.68	0.765
Total cholesterol (mg/dL)	197.35 ± 42.48	206.01 ± 39.06	0.121
HDL cholesterol (mg/dL)	52.25 ± 14.78	52.86 ± 17.44	0.780
Triglycerides (mg/dL)	124.94 ± 55.65	116.12 ± 65.81	0.282
LDL cholesterol (mg/dL)	120.11 ± 36.22	130.26 ± 33.13	0.034
Albumin (g/dL)	4.65 ± 0.44	4.55 ± 0.38	0.086
Hemoglobin (g/dL)	13.96 ± 1.77	13.97 ± 1.70	0.975
RRI	0.63 ± 0.06	0.62 ± 0.05	0.043

Note: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FFM, fat-free mass; FM, fat mass; ECW, extracellular water; ICW, intracellular water; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RRI, renal resistive index.

Table 3. Differences between coffee versus no-coffee users in hypertensive and normal blood pressure patients.

	Hypertensive patients (n = 124)			Normal BP patients (n = 97)		
	Coffee users (n = 101)	No-coffee users (n = 23)	p	Coffee users (n = 75)	No-coffee users (n = 22)	p
Age (y)	58.68 ± 10.83	62.39 ± 14.11	0.165	56.95 ± 8.64	58.23 ± 9.73	0.554
Number of cigarettes/day	12.60 ± 15.11	9.35 ± 17.08	0.365	9.85 ± 15.15	8.14 ± 12.62	0.629
SBP (mmHg)	131.63 ± 13.77	128.70 ± 19.32	0.396	119.80 ± 10.95	118.86 ± 15.11	0.748
DBP (mmHg)	81.83 ± 9.99	79.57 ± 9.40	0.323	76.40 ± 8.68	73.86 ± 9.12	0.236
Pulse pressure (mmHg)	49.80 ± 10.10	49.13 ± 15.79	0.798	43.40 ± 8.59	45.00 ± 12.34	0.491
BMI (kg/m^2)	28.59 ± 3.77	27.11 ± 4.93	0.113	27.14 ± 4.87	27.12 ± 5.68	0.987
ECW (%)	40.76 ± 4.02	43.34 ± 3.90	0.013	41.10 ± 4.24	42.84 ± 9.21	0.290
ICW (%)	59.24 ± 4.02	56.67 ± 3.90	0.013	58.90 ± 4.24	57.16 ± 9.21	0.290
Fat-free mass (%)	64.42 ± 13.83	59.02 ± 15.30	0.135	65.12 ± 15.38	66.38 ± 11.93	0.763
Fat mass (%)	41.42 ± 13.92	43.08 ± 15.41	0.646	41.00 ± 15.64	37.55 ± 14.69	0.435
FFM/FM ratio	2.74 ± 1.51	2.19 ± 0.89	0.120	2.75 ± 1.16	2.66 ± 1.34	0.781
Blood glucose (mg/dL)	95.79 ± 11.61	87.85 ± 9.06	0.005	91.76 ± 10.66	97.05 ± 13.77	0.074
Insulin (μIU/mL)	11.19 ± 6.96	12.62 ± 8.49	0.395	8.71 ± 4.00	10.65 ± 8.69	0.141
HOMA-IR	3.06 ± 2.62	3.13 ± 2.39	0.906	2.07 ± 1.18	2.92 ± 3.07	0.051
BUN (mg/dL)	19.60 ± 5.78	20.54 ± 4.47	0.464	18.80 ± 4.17	20.61 ± 8.88	0.182
Creatinine (mg/dL)	0.88 ± 0.20	0.82 ± 0.21	0.214	0.85 ± 0.18	0.89 ± 0.32	0.532
GFR	75.73 ± 15.61	77.15 ± 29.00	0.743	76.27 ± 15.20	78.22 ± 21.32	0.633
Total cholesterol (mg/dL)	202.17 ± 41.05	176.17 ± 43.04	0.008	207.39 ± 38.75	201.32 ± 40.69	0.525
HDL cholesterol (mg/dL)	51.85 ± 13.96	54.00 ± 18.23	0.532	53.56 ± 18.40	50.45 ± 13.76	0.465
Triglycerides (mg/dL)	127.50 ± 56.79	113.70 ± 49.95	0.285	111.08 ± 61.56	133.32 ± 77.73	0.165
LDL cholesterol (mg/dL)	124.82 ± 35.27	99.43 ± 33.67	0.002	132.06 ± 33.01	124.20 ± 33.56	0.331
Albumin (g/dL)	4.66 ± 0.38	4.58 ± 0.65	0.401	4.55 ± 0.36	4.53 ± 0.47	0.791
Hemoglobin (g/dL)	14.27 ± 1.65	12.59 ± 1.68	<0.0001	14.05 ± 1.71	13.70 ± 1.70	0.396
RRI	0.63 ± 0.06	0.66 ± 0.07	0.027	0.62 ± 0.05	0.62 ± 0.06	0.630

Note: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FFM, fat-free mass; FM, fat mass; ECW, extracellular water; ICW, intracellular water; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RRI, renal resistive index.

Table 4. Pearson's correlation.

	Cups of coffee/day	RRI	Pulse pressure	HOMA	BUN	ECW%
Age (years)	–0.243***	0.586***	0.296***	0.040	0.346***	0.172**
Cups of coffee/day (*n*)	–	–0.241***	–0.025	–0.060	–0.173**	–0.251***
Number of cigarettes/day	0.115	–0.016	0.058	0.139*	–0.020	–0.023
SBP (mmHg)	–0.017	0.117	0.749***	0.058	–0.016	–0.112
DBP (mmHg)	0.002	–0.111	0.016	0.063	–0.118	–0.127
Pulse pressure (mmHg)	–0.025	0.257***	–	0.022	0.084	–0.035
BMI (kg/m^2)	0.191**	–0.082	0.058	0.369***	–0.031	–0.135
FFM/FM ratio	0.065	–0.167**	–0.146	–0.188**	–0.083	–0.362***
ECW (%)	–0.251***	0.199**	–0.035	–0.020	0.083	–
ICW (%)	0.251***	–0.199**	0.035	0.020	–0.083	–1.000**
Blood glucose (mg/dL)	0.007	0.273***	0.095	0.545***	0.146*	–0.097
Insulin (μIU/mL)	–0.047	0.124	0.011	0.939***	0.038	–0.015
HOMA-IR	–0.057	0.169**	0.022	–	0.081	–0.020
BUN (mg/dL)	–0.173**	0.312***	0.084	0.080	–	0.083
Creatinine (mg/dL)	–0.018	–0.008	0.094	–0.049	0.431***	–0.062
GFR	0.094	–0.060	–0.059	0.095	–0.443***	–0.028
Total cholesterol (mg/dL)	0.121	–0.168**	0.066	–0.025	–0.152*	–0.158*
HDL cholesterol (mg/dL)	–0.066	–0.069	–0.052	–0.268***	–0.096	–0.077
Triglycerides (mg/dL)	–0.072	0.057	0.093	0.302***	0.046	–0.038
LDL cholesterol (mg/dL)	0.196**	–0.181**	0.067	–0.014	–0.148*	–0.134
Albumin (g/dL)	0.130	–0.160**	–0.074	0.094	0.099	–0.068
Hemoglobin (g/dL)	0.291***	–0.225***	0.007	0.007	–0.209**	–0.298***
RRI	–0.241***	–	0.257***	0.169**	0.314**	0.199*

Note: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FFM, fat-free mass; FM, fat mass; ECW, extracellular water; ICW, intracellular water; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RRI, renal resistive index.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

$p < 0.0001$), BUN ($r = –0,173$; $p < 0.01$), ECW ($r = –0.251$; $p < 0.001$), and versus RRI ($r = –0.241$; $p < 0.0001$): lower degrees of RRI are present in heavier coffee users (Figure 2).

By multiple regression analysis, age adjusted, to eliminate this confounding factor, RRI is significantly explained by FFM, HOMA, and number of coffee cups/day; the model accounts for 17.2% of the variance (Table 5).

Odds ratios to higher RRI risk are shown in Figure 3: higher risk of increased renal AS, defined according to the 75th percentile RRI threshold, that is, ≥0.65, is

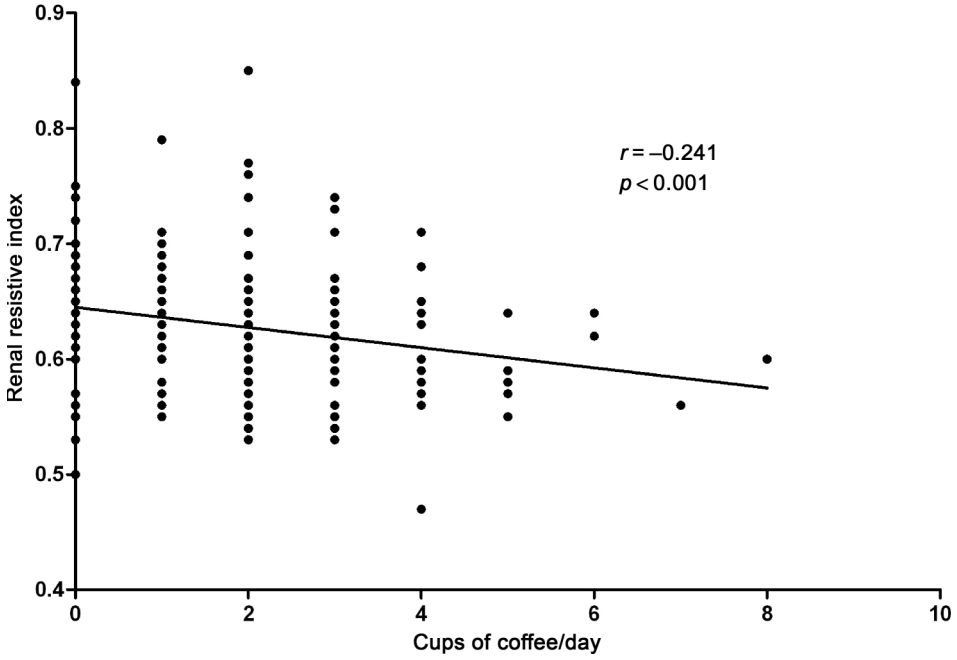

Figure 2. Relationship of renal resistive index versus number of coffee cups/day.

Table 5. Multiple linear regression to RRI.

	RRI						
Predictors	*R*	R^2	R^2 Change	*F*	Significance	β	*p*
	0.414	0.172	0.172	5.147	<0.0001		
Cups of coffee/day (*n*)						−0.182	0.025
Fat-free mass (%)						−0.144	0.063
GFR						−0.024	0.752
Albumin (g/dL)						−0.173	0.029
Hemoglobin (g/dL)						−0.176	0.034
HOMA						0.158	0.038

Note: GFR, glomerular filtration rate; RRI, renal resistive index.
Note: Weighted least-squares regression – Weighted by age.

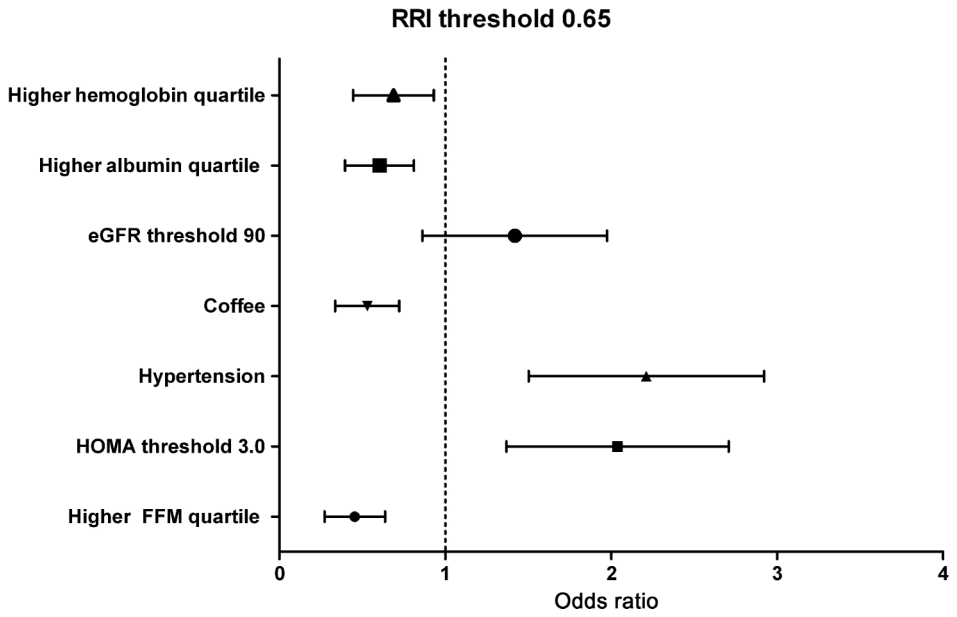

Figure 3. Odds ratios to increased RRI. Higher albumin, FFM, and hemoglobin quartile groups, along with coffee consumers, have a lower risk of increased RRI. Renal insufficiency, arterial hypertension, and insulin resistance have a greater risk of increased RRI.

associated with lower serum albumin, lower hemoglobin, lower FFM percentage and hypertension, and greater insulin resistance (HOMA ≥ 3.0) and renal insufficiency (GFR ≤ 90); coffee habit appears to be a protective factor (OR 0.459; CI 0.236–0.894).

DISCUSSION

From our results, increased RRI is associated with higher degrees of insulin resistance, mild renal insufficiency, lower lean mass, and lower serum albumin; a significant inverse relationship of RRI with the number of coffee cups habitually taken is present (Figure 2). This could indicate a favorable response of renal arteries to chronic coffee consumption. Because this study involves early-stage CKD patients, our results imply and suggest that the mechanism of vascular repair is likely to be adequately functional. Thus, lasting coffee use may conceivably stimulate the pathway of vascular repair by which it may minimize the process of vascular disease.

No insulin resistance difference was observed between coffee users versus nonusers (Table 1), and no correlation of coffee intake and HOMA was found (Table 4). Relationship of BUN and RRI seemingly reflects the physiological response of renal arterial blood flow resistance to lower ECW content, that is, to proportionally greater dehydration: conversely, greater ECW is associated with greater RRI (Table 4). BUN was not managed as a nutritional biomarker, in our study, also because no relationship of BUN with FFM/FM, a positive nutritional index, is observed. Moreover, patients with protein malnutrition and significant liver disease are not present in our study, according to our eligibility criteria, and cannot account for relatively low BUN measurements.

Systolic and diastolic BP correlations versus HOMA and RRI are likely blunted by the pharmacological treatment, despite the 24 h wash-out, whereas correlation of pulse pressure to RRI is still significant, suggesting that this measurement is a more consistent hallmark of increased renal artery resistance.

Also considering the need to take into account different factors, an integrated multifactorial model, derived from our data, explains the degree of RRI by FFM percentage, HOMA, and the number of coffee cups. RRI is lower in subjects with greater FFM, that is, with increased protein and lower adipose cell content. This finding addresses a better nutritional state, suggested also by higher albumin and hemoglobin as explaining factors of lower RRI. The role of the quantity of daily cups of coffee is seemingly relevant and of benefit, that is, subjects who are greater coffee users have lower RRI.

Possible beneficial effects of coffee on blood vessels have been reported by several studies: however, a satisfactory explanation of this clinical-epidemiological observation is not available.[1,14–16] There are many putative mechanisms explaining how coffee consumption may protect against hypertension. Among the underlying biological mechanisms, most research has been devoted to the BP-raising effects of caffeine. However, there are many other substances in coffee, such as polyphenols, soluble fibers, and potassium, which could exert beneficial cardiovascular effects. Although the precise nature of the relation between coffee and BP is still unclear, most evidence suggests that regular intake of caffeinated coffee does not increase the risk of hypertension.[16]

AS and wave reflection can indicate different aspects of vascular status in otherwise healthy subjects[32] and in hypertensive patients[25]; atherosclerosis is a process that does not affect the arterial bed uniformly but has a variable local distribution and is frequently superimposed on stiffened vessels.[33] It is known that lifestyle interventions, such as those achieving modest weight loss and even only physical exercise without weight changes, are associated AS changes and with improvements in insulin sensitivity and lipid profile[34,35]: impaired insulin sensitivity may be involved in the development of renal dysfunction at an early stage, before the onset of diabetes or prediabetic glucose elevations.[36] This can have several implications for current hypertension guidelines.[37]

Long-term consumption of beverages containing caffeine such as coffee and green tea is associated with a reduced risk of type 2 diabetes mellitus; in healthy subjects daily caffeine intake reduces insulin sensitivity[38]; the vascular repair mechanism is adequately functional in the early stage of CKD.[39,40] In experimental models, caffeine attenuated the endotoxin-induced release of cytokines and augmented endotoxin-induced increases in plasma catecholamines and PRA: caffeine, most likely through the interaction with adenosine receptors and interference with anti-inflammatory and/or glomerular hemodynamic effects of adenosine, augments proteinuria and stimulates some of the key proliferative mechanisms involved in glomerular remodeling and sclerosis.[41] Adenosine is an endogenous nucleoside with potent vasodilatory capacities: its mechanisms of action, however, remain elusive. Adenosine induces vasodilatation in the human hypertensive kidney and this effect is mediated by the adenosine receptor.[42] Nitric oxide plays, at most, a minor part in the adenosine-induced vasodilatation. Furthermore, renin secretion is not affected by adenosine and caffeine inhibition of adenosine deaminase lowers BP and may provide beneficial effects in older hypertensives with cardiovascular protection.[43] Cardiovascular effects of adenosine can be modulated by genetic factors (e.g., a single nucleotide polymorphism in the gene encoding for adenosine monophosphate deaminase), by metabolic factors (e.g., by the plasma homocysteine concentration), and by drugs, such as caffeine, dipyridamole, and methotrexate.[44] Moreover, purinergic and adrenergic components of the neurogenic response of small arteries differ between vessels from different vascular beds, and even between vessels from different levels within the same vascular bed, and may contribute to the regional specificity of sympathetic control of blood vessels.[45]

A potential limitation of our study is related to the fact that most of the hypertensive patients were on angiotensin-receptor blockers. However, the 24-h complete pharmacological washout at the moment of US and laboratory examination should reduce a protracted effect, if any, beyond the 2 h of half-life of the drug. Caffeine alters the renal plasma flow dose–response to short-term Ang II infusion in salt-replete subjects and may cause renal vasoconstriction by increasing renin release and endogenous tissue Ang II levels. Increased tissue Ang II levels would lead to the downregulation of vascular Ang II receptors and desensitization to the effects of exogenous Ang II.[19] Moreover, caffeine (despite improving insulin sensitivity) exacerbates renal failure in an obese, diabetic animal model.[46] Despite these preliminary concerns, we find similar results when challenging differences of the studied measurements both in hypertensive-treated patients and in the group with normal BP. A reasonable interpretation is that the 24-h pharmacological washout may be sufficient to eliminate the most relevant effects of renal artery circulation.

In our study we do not find any correlation between systolic and/or diastolic BP and RRI, conceivably because of the pharmacological normalization of high BP; nonetheless, the relationship of pulse pressure with RRI suggests that renal damage can develop, even in the absence of significant EH, when there is an enhanced and pulsed transmission of systemic BP to renal microvasculature.[40] The conceptual view of CKD treatment at an early stage can take also advantage of the clinical nutritional information of this study. We envisage that approaches addressed at the change of lifestyle/environmental factors could be favorable for renal artery responsiveness under relatively stressful conditions, for example, in arterial hypertension and in conditions with increased pulse pressure.

CONCLUSION

Coffee use is inversely associated with the degree of RRI. Habitual coffee users appear to have some risk protection with regard to increased RRI, whereas lower serum albumin, insulin resistance, and renal insufficiency are associated with a greater RRI.

The concurrent effect of coffee habits and nutritional state could be important also in the evaluation and reliability of clinical trials with drugs and/or therapeutic regimens addressed to modify artery stiffness and/or metabolic profiles.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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