MAYO CLINIC

ORIGINAL ARTICLE

Associations of Urinary Caffeine and Caffeine Metabolites With Arterial Stiffness in a Large Population-Based Study

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Abstract

Objective: To assess the influence of caffeine on arterial stiffness by exploring the association of urinary excretion of caffeine and its related metabolites with pulse pressure (PP) and pulse wave velocity (PWV).

Participants and Methods: Families were randomly selected from the general population of 3 Swiss cities from November 25, 2009, through April 4, 2013. Pulse pressure was defined as the difference between the systolic and diastolic blood pressures obtained by 24-hour ambulatory monitoring. Carotid-femoral PWV was determined by applanation tonometry. Urinary caffeine, paraxanthine, theophylline, and theobromine excretions were measured in 24-hour urine collections. Multivariate linear and logistic mixed models were used to explore the associations of quartiles of urinary caffeine and metabolite excretions with PP, high PP, and PWV.

Results: We included 863 participants with a mean ± SD age of 47.1±17.6 years, 24-hour PP of 41.9±9.2 mm Hg, and PWV of 8.0±2.3 m/s. Mean (SE) brachial PP decreased from 43.5 (0.5) to 40.5 (0.6) mm Hg from the lowest to the highest quartiles of 24-hour urinary caffeine excretion ($P<.001$). The odds ratio (95% CI) of high PP decreased linearly from 1.0 to 0.52 (0.31-0.89), 0.38 (0.22-0.65), and 0.31 (0.18-0.55) from the lowest to the highest quartile of 24-hour urinary caffeine excretion ($P<.001$). Mean (SE) PWV in the highest caffeine excretion quartile was significantly lower than in the lowest quartile (7.8 [0.1] vs 8.1 [0.1] m/s; $P=.03$). Similar associations were found for paraxanthine and theophylline, whereas no associations were found with theobromine.

Conclusion: Urinary caffeine, paraxanthine, and theophylline excretions were associated with decreased parameters of arterial stiffness, suggesting a protective effect of caffeine intake beyond its blood pressure–lowering effect.

 ■ Mayo Clin Proc. 2018;■■(■):1-11

Aortic stiffness is as a major risk factor for all-cause mortality,[1] cardiovascular disease (CVD),[2] and hypertension.[3] Several mechanisms including vascular growth factor dysregulation, calcification, elastin degradation, inflammation, and immune responses are presumably involved in aortic wall stiffening as well as the release of vasoactive factors by the endothelium.[3,4]

Diet may also influence arterial stiffness: increased arterial stiffness is associated with higher fat, sucrose, and sodium intake and lower potassium intake.[5] Limited evidence suggested that caffeine intake acutely increases arterial stiffness[5-8] but that tolerance develops.[9,10] The long-term effect of caffeinated beverage consumption on arterial stiffness is less clear.[11] Previous studies on the long-term effect of caffeine have been limited by the use of self-reported caffeine intake, which has substantial margin of error.[12,13] The urinary excretion of caffeine and caffeine metabolites is a valid measure of its intake.[14] Caffeine, more than 70% of which is provided by coffee consumption,[15] is metabolized by the liver CYP1A2 enzyme into paraxanthine (about 80%), theobromine (about 12%), and theophylline (about 4%). Caffeine and caffeine

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metabolites are methylxanthines that have diuretic and natriuretic properties, have sympathomimetic effects, and are smooth muscle relaxants.[9] Theobromine acts as a vasodilator by inhibition of phosphodiesterase.[16] Recent evidence suggests that long-term intake of caffeinated beverages could be associated with lower cardiovascular mortality and blood pressure (BP).[17-19]

Both pulse pressure (PP) and pulse wave velocity (PWV) are complementary methods to assess arterial stiffness.[20] Brachial ambulatory systolic BP is negatively associated with the urinary excretion of caffeine and caffeine metabolites,[17] but no studies have explored the association of arterial stiffness with urinary excretion of caffeine and caffeine metabolites independent of BP. We therefore analyzed the associations between arterial stiffness—determined by PP and PWV—with 24-hour urinary excretion of caffeine and caffeine metabolites in a general adult population.

PARTICIPANTS AND METHODS

The Swiss Kidney Project on Genes in Hypertension (SKIPOGH) is a multicenter family- and population-based cohort focusing on the genetic and nongenetic determinants of BP and renal function. The SKIPOGH is part of an international family-based study, the European Project on Genes in Hypertension, using the same validated methods.[21-23] Briefly, the SKIPOGH recruited participants in 3 different parts of Switzerland: Bern, Geneva, and the city of Lausanne. Recruitment was conducted from November 25, 2009, through April 4, 2013. The index case was the person used for the initial selection, and then the family members of the index case were asked to participate. In Bern, the selection was made randomly using the cantonal phone directory. The index cases were randomly selected from 2 population-based studies in Lausanne and Geneva: the CoLaus[24] and Bus Santé studies,[25] respectively. The study was approved by the institutional ethics committees of the 3 participating university hospitals. All study participants provided written informed consent. The study population included 1128 participants belonging to 273 nuclear families.

A detailed health questionnaire was completed at home. After an overnight fast, participants attended the study centers and had all the clinical examinations and blood sample collections in the morning. They also collected their urine over a 24-hour period. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Antihypertensive and lipid-lowering treatments were based on self-reported drug intake. Hypertension was defined as a systolic and/or diastolic office BP measurement of 140/90 mm Hg or higher or taking an antihypertensive agent. Diabetes mellitus was based on self-reported diagnosis, taking antidiabetic drugs, or a fasting glucose level of 7.0 mmol/L or higher. Smoking was defined as active smoking only. Physical activity was coded as 1 (yes) or 0 (no) based on the participant's answer to the following question: "Do you practice any sports activities on a regular basis?" Current alcohol and oral contraceptive use were self-reported.

Standard clinical laboratory methods were used to measure 24-hour urinary volume and sodium, potassium, and creatinine excretions. We used the Chronic Kidney Disease Epidemiology Collaboration formula to estimate glomerular filtration rate (GFR).[26] Standard laboratory methods were used to measure lipids.

Ambulatory BP

We used validated Diasys Integra devices (Novacor S.A.) to measure 24-hour ambulatory BP.[27] Measurements were taken every 15 minutes during the day and every 30 minutes during the night (from 10 PM to 7 AM). Invalid values were defined as systolic BP greater than 280 mm Hg or less than 60 mm Hg, diastolic BP greater than 200 mm Hg or less than 40 mm Hg, heart rate greater than 200 beats/min or less than 40 beats/min, or diastolic BP > systolic BP.[28] The median number of 24-hour measurements was 68.5 (range, 18-100). Mean BP was computed as [(2 × mean 24-hour diastolic BP) + mean 24-hour systolic BP]/3.

Arterial Stiffness

Pulse Pressure. Pulse pressure was considered as the difference between systolic and diastolic 24-hour BP for both brachial and central PP. Central PP was computed using the central systolic and diastolic BP derived from the