Serum Uric Acid and Pulse Wave Velocity Among Healthy Adults: Baseline Data From the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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BACKGROUND
We aimed to evaluate a possible association between serum uric acid (SUA) levels and carotid-to-femoral pulse wave velocity (cf-PWV) among healthy participants of the ELSA-Brasil.

METHODS
We excluded subjects using antihypertensive medication, diuretics, allopurinol, binge drinkers, body mass index (BMI) >35 kg/m², and those with history of cardiovascular diseases (CVD). In a cross-sectional and sex-specific analysis, linear regression models were built having cf-PWV as dependent variable and SUA as independent variable. Multiple adjustments were subsequently made for age, heart rate and blood pressure, BMI, and fasting glucose levels as covariates. Product interaction terms were built to test interaction between SUA and other covariates.

RESULTS
We analyzed 1,875 men and 1,713 women (mean ages, 48.9±8.4 and 50.2±8.7 years, respectively). SUA was linearly associated with cf-PWV in men (P = 0.01) and in women (P = 0.01). After full adjustment, the association remained significant for men (P = 0.01) and no longer significant for women (P = 0.10). Fully adjusted linear coefficients β (95% CI) were 0.06 (0.015; 0.112) and 0.04 (−0.01; 0.12) in men and women, respectively. Significant interaction between SUA and age (P = 0.02) fasting glucose (P < 0.01) and BMI (P = 0.02) was found only for women.

CONCLUSION
In an apparently healthy population, SUA was significantly associated to cf-PWV in men but not in women.

Keywords: aortic stiffness; blood pressure; gender; hypertension; pulse wave velocity; uric acid.

doi:10.1093/ajh/hpu298

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Initially submitted October 16, 2014; date of first revision November 16, 2014; accepted for publication December 15, 2014; online publication January 21, 2015.

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did not find any association between uric acid and high cf-PWV.

These contrasting results might be an indicative of conflicting data related to different populations, sampling methods, and different PWV measurement devices used in previous studies. Moreover, these studies were carried out on Asian and European populations and aortic stiffness seems to be higher in Blacks living in Angola, South Africa, Brazil, and the United States. In order to verify the link “uric acid–pulse wave velocity” in a population with heterogeneous ethnic background encompassing White, Brown, and Black participants and to help clarify the possible association between SUA and cf-PWV, we chose to address this question in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

METHODS

Study subjects

ELSA-Brasil is a multicenter prospective cohort study enrolling 15,105 civil servants aged 35–74 years (54% women) from 6 cities of Brazil (Belo Horizonte, Porto Alegre Rio de Janeiro, Salvador, São Paulo e Vitória) which aims to investigate factors associated to the development and progression of CVD and diabetes. We applied a cross-sectional analysis using baseline data of ELSA-Brasil collected from 2008 to 2010. For the purpose of this study, we excluded subjects using antihypertensive medication, diuretics, allopurinol, binge drinkers (men ≥ 210 g alcohol/week; women ≥ 140 g alcohol/week), BMI > 35 kg/m², and those with history of CVDs. Hence, this analysis was based on data collected in 3,588 participants (1,875 men and 1,713 women).

Laboratory measurements

After an overnight fasting, blood sample was collected in all participants and uric acid was determined enzymatically by the uricase method. Blood glucose was determined enzymatically by the hexokinase method. Total cholesterol, high-density cholesterol (HDL cholesterol) and triglycerides were determined by the enzymatic colorimetric method. Low-density cholesterol (LDL cholesterol) was calculated using the Friedewald equation and filtration glomerular rate was calculated as the mean heart rate. The strategies for the collection, processing, transportation, and quality control of blood and urine tests in the ELSA-Brasil are described in detail elsewhere.

Cf-PWV measurements

Cf-PWV was measured with an automatic and validated device (Complior, Artech Medicale, France) with the participant lying down in a room with controlled temperature (20 °C–24 °C). Before cf-PWV measurement, blood pressure was measured in the supine position with an automatic device (Omron 705 CP, Japan) at the nondominant arm. The distance from the sternum manubrium to the right femoral pulse was measured with a standardized inelastic tape without correction for abdomen curvature. The pulse sensors were placed on the right carotid and femoral arteries, allowing visualization of the pulse wave on a computer screen. Software registered only the pulse waves with good quality. Cf-PWV is calculated by dividing the distance from the suprasternal notch to the femoral pulse by the time lag between the carotid and femoral pulses. The cf-PWV of each participant was calculated as the arithmetic average obtained in 10 consecutive cardiac cycles in regular heart rhythm. cf-PWV is influenced not only by the stiffness of large arteries (e.g., aorta), but also by the pressure inside the artery in the moment of the exam, which determines recruitment of elastic and collagen fibers. Therefore, cf-PWV obtained in ELSA-Brasil was adjusted by the BP measured immediately before the exam in the logistic models. For the quality control, all cf-PWV tests were recorded in the 6 sites and sent to a centralized Reading Center responsible to validate exams of all ELSA-Brasil participants.

Sociodemographic and anthropometric variables

Other variables included in our analysis were age, sex, education (elementary, high-school, college); smoking status (never, former, and current), age (years), and self-reported ethnicity (White, Brown, Black, Asian, and Native). Height and weight were measured and BMI was calculated dividing body weight to the squared height in meters (kg/m²). Waist circumference (cm) was measured using standardized procedure. Blood pressure was obtained in the sitting position after a minimum rest period of 5 min. Three consecutive readings were obtained in each participant after 1 min interval each. The mean of the 2 last measurements was defined as the casual blood pressure. Heart rate was measured 3 times in the supine position. The mean of the 2 last measurements was defined as the mean heart rate.

Statistical analysis

Categorical variables are reported as percentages and continuous variables as means and standard deviations unless stated otherwise. Statistical normality was checked with the Kolmogorov–Smirnov test. Age-adjusted correlation was tested between uric acid and cf-PWV.

Normality, linearity, and homoscedasticity assumptions of the linear model were checked. We tested the linear association between SUA and PWV by building sex-specific multilinear regression models using PWV continuously as a dependent variable and SUA as independent variable. Adjustments were subsequently made by age, blood pressure measured at the time of cf-PWV measurement, body mass index, and fasting glucose.

As cf-PWV is known to increase with age and blood pressure, our first model was adjusted for age and blood pressure measured immediately before the cf-PWV measure. Further adjustments were made including fasting glucose and heart rate as covariates. Product interaction terms were built to test interaction between SUA and other covariates. A 2-tailed level of significance was set at 5%. Analyses were carried out using the SPSS 20.0 statistical package.
RESULTS

We analyzed 1,875 men and 1,713 women (mean ages, 48.9 ± 8.4; 50.2 ± 8.7 years respectively). As predicted, SUA values were higher in men than in women (6.2 ± 1.2 mg/dl vs. 4.53 ± 0.9 mg/dl). Mean PWV also differed among genders (9.06 ± 1.41 m/s vs. 8.4 ± 1.30 m/s for men and women, respectively) justifying a sex-specific analysis. Age-adjusted Pearson correlation between SUA and cf-PWV showed coefficients of $r = 0.089$ for men ($P = 0.01$) and $r = 0.073$ for women ($P = 0.01$).

Pulse wave velocity measurements (m/s) by SUA units (mg/dl) are shown in Table 1. Univariate analysis showed significant linear association between SUA and PWV for men and women ($P = 0.01$ for both genders). After adjustment for age, blood pressure, and heart rate the linear association lost significance for men ($P = 0.06$) and remained significant in women ($P = 0.01$). After further adjustments for BMI and glucose levels the association was positive and significant for men ($P = 0.01$). Linear coefficient showed that there is a difference of 0.06 (0.015; 0.112) m/s in men cf-PWV by unit in SUA (mg/dl). Nonsignificant interaction between SUA and age, blood pressure, BMI, or fasting glucose was found for men. For women, we found significant interaction between SUA and age ($P = 0.02$) fasting glucose ($P = 0.01$) and BMI ($P = 0.02$).

DISCUSSION

We found linear association between SUA and cf-PWV beyond the natural required adjustments for age and blood pressure at the time of CF-PWV measurement in men on a healthy multiethnic population. Our main findings suggest a different association of SUA and cf-PWV between genders.

Some previous studies have addressed the association between uric acid and cf-PWV. Vlachopoulos et al. evaluated 1,225 newly diagnosed hypertensive patients treated with medication, and renal failure. After adjustment for age, sex, BMI, total cholesterol, triglycerides, fasting glucose, and smoking status. Liang et al. evaluated a population of 1,283 women and 2,389 men drawn from a community based health examination with an exclusion criteria of cardiovascular disease, diabetes mellitus, or hyperlipidemia treated with medication, and renal failure. After adjustment for age, sex, BMI, total cholesterol, triglyceride, HDL-C, LDL-C, blood pressure, heart rate, and fasting glucose, they found SUA was associated with elevated aortic arterial stiffness in Chinese adults, independent of traditional cardiovascular risk factors.

Contrarily, in the 619 men and women participants of the Brisighella Heart Study, who were not taking antihypertensive, antidiabetic, lipid-lowering and uric acid-lowering drugs with mean age of 53.3 years, no significant association between SUA and cf-PWV was found after adjustment for age. Potential mechanisms for the effect of aortic stiffness to cardiovascular risk factors are accredited to breaks in elastin fibers, accumulation of collagen, fibrosis, inflammation, medial smooth muscle necrosis, and medial calcifications. On the other hand, experimental studies have shown that uric acid may favor microvascular disease stimulating vascular smooth muscle cell proliferation in vitro, with the production of proinflammatory, prooxidative, and vasoconstrictive substances. Therefore, possible explanation for Filtration rate, waist measurement, us-C-reactive protein, and use of diuretics. No association was found for men. Again, in a sample of 1,276 Korean individuals with a frequency of almost 25% of metabolic syndrome, no association was found between quartiles of uric acid and heart-femoral and brachial-ankle cf-PWV for females and males separately.

Possible reasons for the discrepancy between our data and the literature could be due to PWV adjustment by sex and not a sex-specific analysis. Potential bias may also be secondary to the inclusion of patients taking medications that could introduce potential bias due to inclusion of participants taking medications that could affect both the dependent and the independent variables. Moreover differently from our studied population, some studies recruited participants within clinical relevant conditions.

Results from studies in apparently healthy populations are not clear either. Ishizaka et al. evaluated brachial-ankle cf-PWV in 982 men and women and found a positive association for both genders analyzing uric acid quartiles and after multivariate adjustment for age, total and HDL cholesterol, systolic blood pressure, triglycerides, fasting glucose, and smoking status. On the other hand, experimental studies have shown that uric acid may favor microvascular disease stimulating vascular smooth muscle cell proliferation in vitro, with the production of proinflammatory, prooxidative, and vasoconstrictive substances. Therefore, possible explanation for

| Table 1. Linear association between serum uric acid with pulse wave velocity by genders |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                    | Men ($n = 1,865$) |                | Women ($n = 1,713$) |                |
|                                    | $\beta$           | CI (95%)        | $P$              | $\beta$           | CI (95%)        | $P$              |
| Univariate                        | 0.07              | (0.03, 0.13)    | <0.01            | 0.14              | (0.13, 0.26)    | <0.01            |
| Adjusted for age                  | 0.36              | (0.05, 0.67)    | <0.01            | 0.38              | (0.05, 0.07)    | <0.01            |
| Plus blood pressure and heart rate| 0.04              | (–0.003, 0.089) | 0.06             | 0.07              | (0.013, 0.125)  | 0.01             |
| Fully adjusted                    | 0.06              | (0.015, 0.112)  | 0.01             | 0.04              | (–0.01, 0.12)   | 0.10             |

Fully adjusted model: age, blood pressure, and heart rate measured before pulse wave velocity measurement, body mass index, and fasting glucose. Results are presented as difference in cf-PWV unit by each serum uric acid unit (mg/dl).

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the association found in some studies is that uric acid could regulate critical proinflammatory pathways in smooth muscle cell suggesting that it might have a role in the vascular changes.28

As cf-PWV increases with age and it is influenced by sympathetic and parasympathetic activity,25 we adjusted our model to age, blood pressure, and heart rate measured in supine position immediately before the cf-PWV recording. Moreover, as SUA has been associated with fasting blood glucose and incident type 2 diabetes, we also adjusted our multivariate model for fasting blood glucose. As previous studies looked at the association between SUA and blood pressure found positive results that could be confounded by BMI,6 we therefore included BMI in our adjustments without material changes in results. Although some authors have adjusted their analysis for other covariables, we chose to exclude those participants from the sample as possible confounders.

Interestingly, most of the studies reporting positive cross-sectional associations between SUA and arterial stiffness were conducted among Asian populations.8,9,13,14 This highlights the importance of our study among a large healthy non-Asian population.

Our study has some strengths and limitations that merit consideration. We present data of CF-PWV of a well-defined population. Our study was powered to analyze SUA levels and cf-PWV in a sex-specific analysis even after exclusion of potential confounders to the association studied as use of antihypertensive, allopurinol, higher BMI, and binge drinkers. Nevertheless, due to the cross-sectional nature of the design we were not able to clear the possible pathway between SUA and cf-PWV.

In conclusion, our findings support that in an apparently healthy and multiethnic population SUA was significantly associated with PWV in men independently of age, blood pressure, heart rate, BMI, and fasting blood glucose. Future prospective studies using data from ELSA-Brasil would clarify about a causal relationship and bring more information about possible mechanisms that can explain the association between SUA and gender-related differences.

ACKNOWLEDGMENTS

We would also like to acknowledge the participation of the 15,105 individuals recruited for this study without which this study and those based on the ELSA-Brasil cohort would not have been possible. C.P.B., I.M.B., and P.A.L. contributed to the conception of the study, study design, data collection, data analysis, interpretation, and writing the manuscript. J.G.M. and R.S.C. contributed to data collection, analysis, interpretation, and critically reviewed the manuscript. The ELSA-Brasil baseline study was supported by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology and CNPq-National Research Council (grants # 01 06 0010.00 RS, 01 06 0212.00 BA, 01 06 0300.00 ES, 01 06 0278.00 MG, 01 06 0115.00 SP, 01 06 0071.00 RJ).

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES


