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Original Investigation

Association Between Aristolochic Acid and CKD: A Cross-sectional Survey in China

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Background: Long-term intake of herbs containing aristolochic acid (AA) has been reported to be associated with increased risk of chronic kidney disease (CKD), whereas population-based studies are limited.

Study Design: Cross-sectional study.

Setting & Participants: A national representative sample of 47,204 adults in China.

Predictor: Self-reported long-term use of medications containing AA.

Outcomes & Measurements: CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or the presence of albuminuria, defined as albumin-creatinine ratio >30 mg/g.

Results: 467 participants reported long-term AA intake, with a prevalence adjusting for a synthesized weight of 1.5% (95% CI, 1.2%-1.7%). After adjusting for age, sex, and other potential confounders, long-term AA intake was associated with eGFR <60 mL/min/1.73 m^2 and albuminuria, with ORs of 1.83 (95% CI, 1.22-2.74) and 1.39 (95% CI, 1.03-1.87), respectively. Further adjustment for intake of nonsteroidal anti-inflammatory drugs did not change ORs substantially. A positive association between accumulated time of AA intake and kidney disease also was observed, with fully adjusted ORs of 1.07 (95% CI, 1.03-1.12) per 6-month longer intake for eGFR <60 mL/min/1.73 m^2 and 1.04 (95% CI, 1.01-1.08) per 6-month longer intake for albuminuria.

Limitations: Self-reported intake of herbs containing AA; the AA content of the preparations by weight was unknown; single measurement of indicators of kidney damage.

Conclusions: Long-term intake of medications containing AA is prevalent in China and is associated with the presence of CKD.

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INDEX WORDS: Chronic kidney disease; aristolochic acid; China.

Chronic kidney disease (CKD) is an important public health issue that affects approximately 10.2%-13.1% of adults.[1,2] In a recent nationwide survey, the prevalence of CKD was reported to be 10.8%,[3] corresponding to 119.5 million adults with CKD in China.

Botanical medicines are widely used worldwide. According to data from the World Health Organization,[4] 75% of the world population, mostly in the developing world, depend on botanical medicines for their basic health care needs. Another study indicated that as many as 3 in 10 Americans used botanical remedies in a given year.[4] Aristolochic acid (AA)-containing Chinese herbs are widely used for the treatment of urinary, hepatitis, and cardiovascular diseases in China[5] and elsewhere in the world.[6] During the last 20 years, kidney injury related to herbs has been reported, including herbs containing AA. Since the first report of AA and kidney disease from Belgium,[7] there have been only a few regional studies showing that consumption of herbs containing AA is associated with the presence of kidney damage in the general population.[8-11] The present study aimed to investigate the cross-sectional association between CKD and consumption of certain herbs containing AA using data from a national representative sample of Chinese people 18 years or older.

METHODS

Study Participants

The sampling method has been described in detail elsewhere.[3] In brief, we used a multistage stratified sampling method to obtain a representative sample of people 18 years or older in the general

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population. Altogether, 50,550 people were invited to participate, of whom 47,204 completed the survey. Those participants were from 13 provinces located in different geographic regions of China (east, south, middle, north, northwest, and southwest). The ethics committee of Peking University First Hospital approved the study. All participants gave written informed consent before data collection.

Screening Protocol

All on-site screenings were done between September 2009 and September 2010. Data were collected in examination centers at local health stations or community clinics in participants' residential areas. All participants completed a questionnaire documenting sociodemographic status, personal and family health history, and lifestyle with the assistance of medical students, trained general practitioners, and nurses. Anthropometric measurements (eg, weight and height) were obtained. All study investigators and staff members completed a training program that taught the methods and process of the study.

Evaluation of Exposure to Herbs Containing AA

In the questionnaire, participants were asked about long-term intake of the 3 most commonly used pills or granules containing AA (Long Dan Xie Gan Wan, Pai Shi Ke Li/Pai Shi Chong Ji, and Guan Xin Su He Wan). These drugs often are used to treat hepatitis, urinary tract infection, vaginitis, and oral ulcer.[8] Mu Tong and Fang Ji (sometimes referred to as Fangchi), which are prescribed Chinese patent medications also known to contain AA, were included in the list of AA-containing pills/granules.

Long-term intake of AA-containing pills or granules (referred to hereafter simply as "long-term AA intake") was defined as at least twice a week and for longer than 2 months. The cumulative duration (in months) of lifetime intake was asked in the questionnaire.

Indicators of Kidney Damage and Other Covariates

Urinary albumin and creatinine were measured from a fresh morning spot urine sample or morning urine sample stored at 4°C for less than 1 week. Albuminuria was measured with immunoturbidimetric tests. Urinary creatinine was measured with the Jaffé kinetic method. Urinary albumin-creatinine ratio (ACR) was calculated. Participants with ACR >30 mg/g were defined as having albuminuria.

To measure estimated glomerular filtration rate (eGFR), blood was collected by venipuncture after an overnight fast of at least 10 hours. Serum creatinine was measured by the same methods as was urinary creatinine. eGFR was calculated with an equation developed using data from Chinese patients with CKD[12]: eGFR (mL/min/1.73 m^2) = $175 \times SCr\ (mg/dL)^{-1.234} \times age\ (in\ years)^{-0.179} \times 0.79$ (if female), where SCr is serum creatinine. Reduced kidney function was defined as eGFR <60 mL/min/1.73 m^2.

Hematuria of 1+ or greater by urinary routine test was verified by microscopic examination of urinary sediment within 2 hours. Participants with red blood cells of 3 or more per high-power field were defined as having hematuria.

Blood pressure was measured 3 times at 5-minute intervals by sphygmomanometer. The mean value of the 3 readings was calculated unless the difference between the readings was >10 mm Hg, in which case the mean value of the 2 closest measurements was used. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, any use of antihypertensive medication in the past 2 weeks, or self-reported history of hypertension. Fasting blood glucose was measured enzymatically with a glucose oxidase method. Diabetes was defined as fasting plasma glucose level ≥7.0 mmol/L, by hypoglycemic agents despite fasting plasma glucose level, or self-reported history of diabetes. Serum total, low-density lipoprotein, and high-density lipoprotein cholesterol; triglycerides; and uric acid were measured with commercially available reagents. Laboratories used a timed–end point colorimetric method to measure low- and high-density lipoprotein cholesterol.

Statistical Analysis

Data are presented as proportions for categorical variables (eg, sex and hypertension) and mean ± standard deviation for continuous variables, except for ACR, which is presented as median [interquartile range]. Relevant characteristics were described and compared between participants reporting long-term AA intake and their age- and sex-matched participants without a self-reported history of long-term AA use (using a ratio of 1:2). Comparisons were made using *t* test or Wilcoxon rank sum test for continuous variables and Fisher exact test for binary variables.

Synthesized weights, which were calculated by the product of sampling weight, nonresponse weight, and population weight, were used to estimate the prevalence of long-term AA intake.

We analyzed the association between self-reported long-term AA use and the presence of kidney damage using logistic regression models. Crude and multivariable adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Covariates included in the multivariable logistic regression models were age (per 10-year interval), sex, history of cardiovascular disease (yes vs no), hypertension (yes vs no), diabetes (yes vs no), rural versus urban residents, education (high school or higher vs less than high school), current smoker (yes vs no), alcohol intake (habitual drinker, nonhabitual drinker, and nondrinker), self-reported hepatitis B virus infection (yes vs no), long-term use of nonsteroidal anti-inflammatory drugs (yes vs no), body mass index (categories of <18.5, 18.5-23.9 [reference], 24.0-27.9, and ≥28.0 kg/m^2), hyperuricemia (defined as uric acid >7.1 mg/dL for males and >6.1 mg/dL for females), plasma triglyceride level (continuous), plasma low-density lipoprotein cholesterol level (continuous), and plasma high-density lipoprotein cholesterol level (continuous). Body mass index was calculated as measured weight in kilograms divided by the square of measured height in meters.

We used EpiData software (version 3.1; EpiData Association) for data entry and management. All *P* values are 2 sided, and $P < 0.05$ was considered significant. Analyses were performed with SUDAAN (version 10; RTI Int) and SAS (version 9.1; SAS Institute Inc).

RESULTS

Altogether, 467 participants reported long-term AA intake, with an adjusted prevalence of 1.5% (95% CI, 1.2%-1.7%). General characteristics of participants reporting long-term AA intake are listed in Table 1. Those participants had higher percentages of self-reported hepatitis B virus infection, long-term use of nonsteroidal anti-inflammatory drugs, history of cardiovascular disease, and hypertension compared with age- and sex-matched controls. Percentages with eGFR <60 mL/min/1.73 m^2 only, albuminuria only, and both were 4.5%, 10.9%, and 2.6%, respectively.

After adjusting for age and sex, long-term AA intake was associated with eGFR <60 mL/min/1.73 m^2 and albuminuria, with ORs of 2.20 (95% CI, 1.51-3.12) and 1.67 (95% CI, 1.27-2.20), respectively (Table 2). Adjusting for other covariates attenuated the ORs, which were 1.83 (95% CI, 1.22-2.74) and 1.39 (95% CI, 1.03-1.87) for eGFR <60 mL/min/1.73 m^2 and albuminuria, respec-