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Original article

Association between serum uric acid concentrations and grip strength: Is there effect modification by age?

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SUMMARY

Background: Given that some of the deleterious effects of uric acid (UA) on health are greater in younger than in older subjects, and that age is strongly associated with skeletal muscle composition and function, this study tested the hypothesis that the association between UA and muscle strength differs by age.
Methods: Cross-sectional analysis with 3595 individuals who participated in NHANES 2011–2012. Serum uric acid was determined by the uricase-peroxidase technique. Grip strength was calculated as the average of the best measure obtained in each hand with a Takei digital grip strength dynamometer. Linear regression models were adjusted for the main confounders.
Results: In individuals aged 20–40 years, the beta coefficients (95% CI) of muscle strength as dependent variable and UA as independent variable comparing the second and third to the lowest tertile of UA were −0.45 kg (−1.46; 0.57) and −2.36 kg (−3.27; −1.44), respectively, p-linear trend ≤0.01. By contrast, in subjects aged 40–60 years the corresponding beta coefficients were 0.21 kg (−1.00; 1.42) and −0.45 kg (−2.10; 1.20), p-linear trend: 0.60; and for subjects ≥60 years they were 0.58 kg (−3.27; 1.65) and 1.57 kg (0.63; 2.50), p-linear trend <0.01. These results held after numerous sensitivity analyses.
Conclusion: The association between UA and muscle strength differed depending on age: while a negative link was observed in adults aged 20–40 years, this relationship disappeared later in life, and was reversed after the age of 60. Future research should evaluate if uric acid targets for individuals with hyperuricemia should consider patients age and muscle strength.

1. Introduction

Muscle strength is a requisite for good physical function that decreases progressively with age [1,2]. It is a strong predictor of cause-specific and all-cause mortality in middle-aged [3,4] and older adults [3,5–7], with decreased muscle strength leading to increased mortality risk. Recent evidence also suggests that decreased muscle strength during adolescence is associated with the future risk of cardiovascular disease [8,9]. Additionally, muscle strength has been negatively associated with the prevalence [10] and incidence [10] of obesity, the prevalence [11] and incidence [12] of the metabolic syndrome, and the risk of hypertension among pre-hypertensive middle-aged adults [13], as well as with the prevalence [14] and incidence [14] of insulin resistance among older adults.

Uric acid (UA) is the end product of purine and nucleic acid metabolism. Evidence for a relationship between UA and muscle strength is limited to older adults [15–17]. For example, in a cross-sectional survey of individuals aged 50–74 years in China, grip strength increased across increasing serum UA tertiles [15]. Moreover, investigators from the InCHIANTI study first described a positive cross-sectional link between serum UA concentrations and muscle strength among individuals aged ≥65 years [16]. They also showed a positive association between baseline UA concentrations and muscle strength in a sub-sample of individuals with a mean baseline age of 76 years, who were followed for up to 3 years [16]. More recently, results from the Seniors-ENRICA study, with 2198 older adults aged ≥60 followed during a mean 3.5-year period, have shown a negative association between baseline UA levels and risk of muscle weakness [17]. Finally, in a cohort of hemodialysis patients in Israel with a mean age of 68.6 years, UA concentrations positively correlated with handgrip strength values [18]. However,

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the protective effect of UA on the aged muscle is apparently inconsistent with its role as a risk factor for numerous chronic conditions, including cardiovascular disease [19], hypertension [20], diabetes [21], or the metabolic syndrome [22].

Given the evidence that some of the deleterious effects of UA on health, such as hypertension [23] or the metabolic syndrome [24], are stronger in younger than older subjects, and that age is strongly associated with skeletal muscle composition and function [1,2], we hypothesized that the effects of UA on the muscle could differ by age groups. To assess this hypothesis, we evaluated and compared the association between serum UA concentrations and grip strength among young [20–39], middle-aged [40–59] and older (≥60 years) adults who participated in the 2011–2012 National Health and Nutrition Examination Survey (NHANES).

2. Methods

2.1. Study design and population

NHANES is a multistage probability-sampling survey designed to assess the health and nutritional status of the noninstitutionalized population of the United States. Details on the design and data collection procedures can be accessed online [25]. Participation rates during the 2011–2012 wave ranged from 71.0% among individuals aged 30–39 years to 56.1% among those aged ≥70 years. NHANES data collection protocols are approved by the National Center for Health Statistics ethics review board. Informed consent is obtained from all participants.

The present study has been limited to participants ≥20 years with complete grip strength assessment, complete data on body measurements (including arm circumference), and available serum uric acid determinations (n = 4184). Given that the study was conducted among community-dwelling individuals, the disease frequency increases with age and approximately reflects that distribution in the general US population.

2.2. Study variables

Serum uric acid was determined by the uricase-peroxidase technique [26].

Grip strength was measured in the MEC by trained examiners, using a Takei digital grip strength dynamometer. Each hand was tested three times, and the highest reading from each was used to calculate the average maximum grip strength, expressed in kg.

We also used data on variables which are related to age, UA or muscle strength. Specifically, we used socio-demographic data (sex, age, education, race/ethnicity) and information on lifestyles (smoking, alcohol consumption, physical activity and sedentary behavior). Serum cotinine was determined by an ID HPLC-API-MS/MS [27]. Non-smokers with serum cotinine concentrations above the limit of detection and below 10 ng/mL were considered exposed to secondhand smoke, while participants who reported smoking or had serum cotinine concentrations ≥10 ng/mL were considered active smokers. Individuals were deemed as never drinkers if they had never consumed ≥12 drinks in any one year. Ever drinkers were classified into former or current drinkers according to their consumption of alcohol during the last year (< or ≥12 drinks, respectively). Physical activity was ascertained with the Global Physical Activity Questionnaire, that collects information on vigorous and moderate activities at work, transportation and leisure time. Total physical activity was expressed as metabolic equivalents (METs)/hour/week and estimated by multiplying the hours per week spent at each activity by its MET. Sedentary behavior was defined as the number of hours/day spent watching TV.

Total energy and protein intake were calculated based on two 24-h dietary recall interviews. The first interview was administered in the Mobile Examination Center and the second was conducted by telephone 3–10 days later. Average values between the two dietary recall interviews are used in the analyses. Participants were asked about their diet quality using the question "*In general, how healthy is your diet?*"

Weight and height were collected according to standardized procedures, and used to estimate the body mass index (BMI) as the weight in kg divided by the squared height in m. For this purpose, participants were asked to wear a disposable shirt, pants and slipper. The arm circumference was measured with the subject standing and with the right arm hanging loosely and relaxed, half the distance from the acromion to the olecranon processes. Blood pressure was measured three times with the participant seated for 5 min.

Participants also reported their status for the following medical conditions: cardiovascular disease (congestive heart failure, coronary heart disease, stroke), diabetes, hypertension, cancer and osteo-articular disease (osteoarthritis, rheumatoid arthritis, osteoporosis). Hypertension was defined as an average systolic blood pressure ≥140 mm Hg, an average diastolic blood pressure ≥90 mm Hg, a self-reported physician diagnosis of hypertension or hypertension medication. Plasma glucose was measured using an enzyme hexokinase method [28]. Participants with fasting serum glucose ≥126 mg/dL, with a self-reported diagnosis of diabetes or under treatment with insulin or oral antidiabetic drugs were considered to suffer from diabetes.

Serum albumin was estimated by the Bromocresol Purple method [26]. Urinary albumin was determined with a solid phase fluorescence immunoassay and urine creatinine with the Roche/Hitachi Modular P. Chemistry Analyzer [26]. The urine albumin–creatinine ratio (ACR) was calculated dividing urine albumin (μg/mL) by urine creatinine (mg/dL), while the estimated glomerular filtration rate (eGFR) was determined using the CKD-EPI equation.

2.3. Statistical analysis

From the initial sample of 4184 participants, we excluded the following individuals with missing information: 161 on education, 279 on alcohol consumption, 127 on protein consumption, and 22 on other potential confounders. Thus, the final analytical sample comprised 3595 individuals.

The first analyses explored differences in participant characteristics by sex-specific tertiles of UA, using chi-square tests for categorical variables and ANOVA tests for continuous variables.

To assess the main study association, three multiple linear regression models with progressive levels of adjustment were fitted. In all these models the main independent variable was serum UA (categorized into sex-specific tertiles) and the dependent variable was muscle strength. Model 1 was adjusted for sex and age; model 2 was additionally adjusted for BMI, ethnicity and educational level; while model 3 was additionally adjusted for tobacco smoke exposure, alcohol consumption, physical activity, sedentary behavior, total protein intake, diet quality, arm circumference, comorbid conditions, serum albumin and measures of kidney function (eGFR and the ACR). In order to evaluate differential associations by age groups, an interaction term between UA tertiles and three pre-defined age groups (20–39, 40–59, ≥60) was included in all three models; also, the final analyses were stratified by age.

To account for potential non-linearities, UA concentrations were modeled using restricted cubic splines with knots at the 10th, 50th, and 90th percentile of its distribution in each specific age-group.

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