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The association of uric acid with the risk of metabolic syndrome, arterial hypertension or diabetes in young subjects- An observational study

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ABSTRACT

Background: A growing number of studies are available to shed some light on the association between uric acid (UA) and cardiovascular diseases. However, there have been few studies to support a causal link between UA, metabolic syndrome (MetS), diabetes mellitus (DM) and hypertension (HTN) in young subjects.
Methods: From the Health Examination Registration System of Taiwanese military service during the period 2013–2015, there were 46,561 eligible participants who were 20 years old or older in our study. Different analytical steps of analysis were performed to examine the association between UA and cardiometabolic risk using logistic regression, receiver operating characteristic (ROC) curve analysis and Cox regression.
Results: For total population, serum UA had significant associations with the presence of MetS (OR = 2.08, 95% CI = 1.51–2.87), DM (OR = 2.59, 95% CI = 1.09–6.19) and HTN (OR = 1.49, 95% CI = 1.07–2.07) in the cross-sectional analysis. According to the cut-off values of UA calculating by the ROC curve analysis in each sex/age subgroup, the association between UA and incident adverse outcomes were analyzed in a longitudinal study. In male, higher UA significantly increased the risks for developing MetS in 30–40 years (HR = 1.12, 95% CI = 1.01–1.25), DM in < 30 years (HR = 2.75, 95% CI = 1.38–5.45) and HTN in all subgroups (HR = 1.17, 95% CI = 1.01–1.37; HR = 1.65, 95% CI = 1.08–2.53; HR = 1.72, 95% CI = 1.22–2.43). In females, a higher UA was significantly associated with an increased risk of incident MetS in > 40 years (HR = 2.99, 95% CI = 1.34–6.64), HTN in > 40 years (HR = 2.58, 95% CI = 1.02–6.55), and no increased risk of DM.
Conclusions: Our study concluded that serum UA is an important predictor for the risk of incident MetS, DM, and HTN in adults, especially in male population.

1. Introduction

Uric acid (UA) is a weak acid produced in the liver, muscles, and intestines [1]. Purines are the precursors of UA, and xanthine oxidoreductase is the enzyme responsible for UA production. Exogenous sources that can increase serum UA include fatty meat, organic meat and seafood [2]. Accumulating studies have proposed that high level of UA contributes to incidental adverse health outcomes [3].

Metabolic syndrome (MetS) represents a group of clinical and laboratory abnormalities. According to the National Cholesterol Education Program Adult Treatment Panel III Criteria, MetS is defined as a cluster of risk factors which is composed of central obesity, hypertension (HTN), dyslipidemia and insulin resistance [4]. Recently, the increasing prevalence of MetS is reported worldwide including Asian countries and Taiwan [5–7]. Components of MetS correlating to hyperuricemia were also reported in previous studies. In a recent study concerning the development of HTN, the serum UA was an imperative surrogate [8]. Nakanishi et al. demonstrated that the serum UA was positively correlated to impaired glucose tolerance [9]. In a cross-sectional study based on the U.S. population, hypertriglyceridemia carried

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the strongest association with hyperuricemia [10]. Adipose tissue has been proposed to be able to UA, and the production of UA is augmented in obesity [11].

To date, there had been some studies investigating the association between UA and MetS in different age groups. In adolescents aged between 10 and 15 years, UA was correlated with future MetS components and was a risk factor for developing MetS [12]. In terms of the elderly population, subjects with higher levels of UA had a higher likelihood for progressing to MetS [13]. Despite a large body of evidence of serum UA on MetS, little attention had been given to the adult population. Therefore, we included 46,561 eligible participants in the Taiwanese military service from 2013 to 2015 for an observational study performed by cross-sectional and longitudinal analysis. Our aim is to investigate the relationship between UA and the presence of MetS in the young adult population, and to determine cut-off values of UA in predicting incident MetS, DM and HTN.

2. Methods

2.1. Study design and participants

All data were obtained from the Health Examination Registration System, which consisted of the regular health examinations of the Taiwanese military service from 2013 to 2015. There were 46,561 eligible participants who aged 20 years old or older in our study. Study approval was conduct by the Institutional Review Board of Tri-Service General Hospital, Taiwan. According to the flow chart of the study in Fig. 1, the participants enrolled in the study were examined by different statistical analyses and excluded step-by-step in the following orders. First, participants with missing data were excluded ($n = 1351$). Second, we explored the association between UA and MetS by cross-sectional

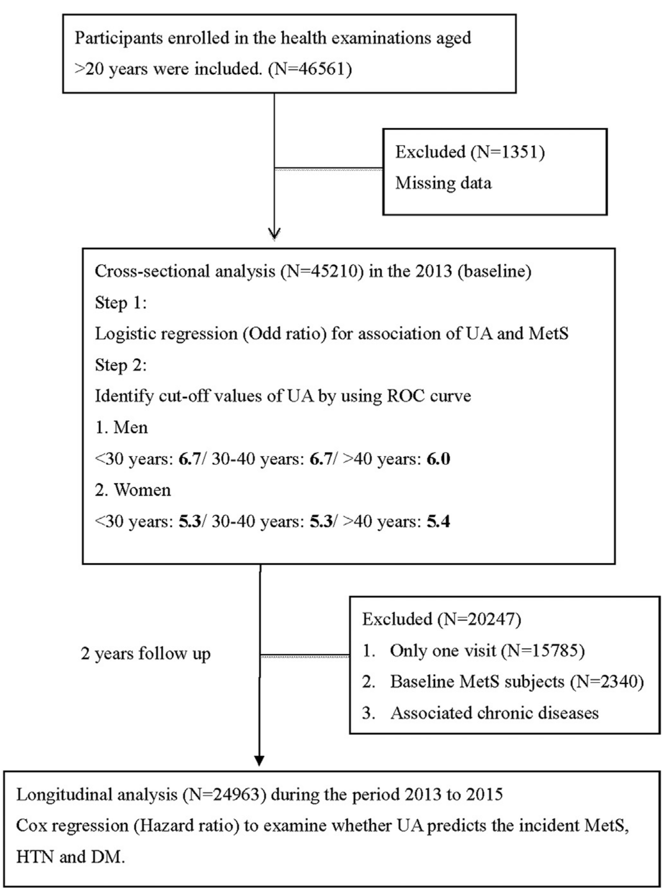

Fig. 1. Flow chart which represented the steps of analysis performed in the study.

analysis for baseline information in 2013. Next, we identified the cut-off values of UA by using ROC curve analysis. After excluding the participants who had only one visit in the health examination, those with chronic diseases (such as DM, HTN, and cardiovascular disorders) and those with MetS in the 2 years follow up ($n = 20,247$), longitudinal analyses during the period 2013 to 2015 were performed to examine whether UA predicted incident MetS, HTN and DM at the final stage.

2.2. Measurement of serum uric acid

The level of serum UA was measured by using the Beckman Coulter AU5800 (Beckman Coulter Inc., Brea CA, USA). Details concerning data quality control have been published elsewhere.

2.3. Criteria of MetS

According to the Modified National Cholesterol Education Program-Adult Treatment Panel III criteria, MetS was defined if an individual manifested 3 or more of the following components: (1) waist circumference > 90 cm for male participants and > 80 cm for female participants; (2) triglyceride ≧ 150 mg/dL; (3) HDL-C < 40 mg/dL for male participants and < 50 mg/dL for female participants; (4) systolic blood pressure ≧130 mmHG or diastolic blood pressure ≧ 80 mmHg, use of antihypertensive medication or a past history of HTN; and (5) fasting plasma glucose ≧ 100 mg/dL, a past history of diabetes status, or use of antidiabetic agents [4].

2.4. Definition of Type 2 DM

Type 2 DM was defined according to the American Diabetes Association criteria as follows: fasting plasma glucose ≥ 126 mg/dL; hemoglobin A1c test ≥ 6.5%; Random plasma glucose ≥ 200 mg/dL; past history of diabetes status, or use of antidiabetic agents [14].

2.5. Definition of HTN

Based on the guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the management of hypertension, HTN was defined if the blood pressure was higher than 140/90 mmHg or subjects were taking antihypertensive agents [15].

2.6. Covariates measurement

The regular health examinations included standard evaluations of physical and mental health, comprehensive biochemistry tests, and anthropometric measurements. The body mass index (BMI) was obtained based on the formula in which the weight of the subject in kilograms is divided by the square of the height in meters (kg/m^2). The waist circumference was measured at the mid-level between the iliac crest and the lower border of the 12th rib while the subject stood with feet 25–30 cm apart. Hemodynamic status included systolic blood pressure (SBP) and diastolic blood pressure (DBP) estimated when the participants was seated. Biochemical analysis was conducted by drawing blood samples from subjects after fasting for at least 8 h. The fasting plasma glucose (FPG) was detected using a glucose oxidase method. Serum levels of lipid profiles such as total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were measured using an enzymatic colorimetric method.

2.7. Statistical analysis

All statistical estimations were performed using by the Statistical Package for the Social Sciences, version18.0 (SPSS Inc., Chicago, IL, USA) for Windows. Student's *t*-test and Pearson's chi-square tests were performed to examine the differences between the age groups in terms of demographic information and laboratory data. A two-sided P-value