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# Gender differences in the association between hyperuricemia and diabetic kidney disease in community elderly patients

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ABSTRACT

*Aims:* To investigate gender differences of the associations between hyperuricemia and diabetic kidney disease (DKD) in elderly patients with type 2 diabetes mellitus (T2DM) based on electronic health records (EHR).
*Methods:* A total of 20,207 older diabetic patients (mean age 71 ± 7 years) were investigated based on the EHR from 2012 to 2013 in the Minhang District of Shanghai-China. The status of hyperuricemia, albuminuric DKD and the odds ratios of DKD relative to hyperuricemia were analyzed among 8541 men and 11,666 women.
*Results:* The overall rate of hyperuricemia was 20.5% (males: 17.2%, females: 23.0%) and that of albuminuric DKD was 36.2% (males: 32.2%, female: 39.1%) in these diabetic patients. Hyperuricemia was independently associated with increased risk of reduced renal function and albuminuria ($p < 0.001$) in both genders. After adjustment of traditional DKD risk factors, hyperuricemia had a stronger association with albuminuric DKD in males (OR 1.67, 95% CI: 1.48–1.88) than in females (OR 1.23, 95% CI: 1.12–1.35).
*Conclusions:* This study showed an independent association of hyperuricemia with albuminuric DKD that was stronger in elderly males for the first time in China based on EHR. The level of uric acid should be monitored and managed in older diabetic patients.



## 1. Introduction

Diabetic kidney disease (DKD) is one of the most frequent micro-vascular complications of diabetic patients and has been reported to be the main reason leading to end-stage renal disease (ESRD) in developed countries (Tuttle et al., 2014). Moreover, diabetic patients with kidney damage have a high risk of coronary disease, stroke and peripheral arterial disease (Lewis & Maxwell, 2014). Although information from Chinese Renal Data System revealed that glomerular disease is still the most common cause of ESRD (Liu, 2013), the increased number of older people coupled with the high prevalence of type 2 diabetes mellitus (T2DM) in China will impose a high burden on the prevalence of ESRD now and in the future, but the awareness is still low among patients and health-care providers (Cao, Li, Yang, Liu, & Li, 2012). Thus, the early detection and prevention of both diabetes and chronic kidney disease (CKD) in older people are important issues facing the health care system in China.

It was suggested that persistent proteinuria and/or low estimated glomerular filtration rate (eGFR < 60 m/min/1.73 $m^2$) in patients with diabetes was the diagnostic assumption of DKD (KDOQI, 2007). During the natural course of DKD, diabetic patients begin with microalbuminuria and progress to overt proteinuria and then to clinically-evident renal dysfunction (KDOQI, 2007). Albuminuria can be regarded as an initial sign of DKD. Since diabetes is a common condition, coincidence with nondiabetic CKD in clinic is relatively frequent. Renal impairment can occur in the absence of albuminuria in people with diabetes, so-called normoalbuminuria renal impairment (Doggen et al., 2013). Previous studies have identified many risk factors for DKD, such as hyperglycemia, hypertension, and dyslipidemia (Bhalla et al., 2013; Harjutsalo & Groop, 2014). However, clinical trials suggested that intensive control of blood glucose and blood pressure and regulation of blood lipids had limited protective effects on delaying the progression of renal function decline and improving cardiovascular outcomes (Slinin et al., 2012).

Uric acid is the end product of purine metabolism in humans, and studies have shown that elevated serum uric acid or hyperuricemia is strongly associated with renal dysfunction in both the general population (Ponte et al., 2013; Ryoo, Choi, Oh, & Kim, 2013; Toda, Ishizaka, Tani, & Yamakado, 2014) and patients with T2DM in various countries (Behradmanesh, Horestani, Baradaran, & Nasri, 2013; Bonakdaran, Hami, & Shakeri, 2011; Cai, Han, & Ji, 2011; Chen, Ding,

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Fu, Yu, & Ma, 2014; Chuengsamarn, Rattanamongkolgul, & Jirawatnotai, 2014; Kim et al., 2014; Zoppini et al., 2012). For patients with T2DM, studies have shown that higher serum uric acid concentrations were associated with a greater probability of albuminuria, incidence of impaired GFR, or CKD (either decreased kidney function or albuminuria) (Behradmanesh et al., 2013; Bonakdaran et al., 2011; Cai et al., 2011; Chen et al., 2014a; Chuengsamarn et al., 2014; Kim et al., 2014; Sheikhbahaei, Fotouhi, Hafezi-Nejad, Nakhjavani, & Esteghamati, 2014; Zoppini et al., 2012). Moreover, recent studies revealed that hyperuricemia was an independent predictor of both micro- and macro-vascular complications and mortality in T2DM patients, especially in Asian populations (Xu et al., 2013). However, these relationships were observed in hospital outpatient clinics or hospitalized patients; the gender and age differences were not considered in detail. Different methods of estimating GFR were used. The role of uric acid in the development of DKD did not get much attention in community studies.

In the general population women have a longer life expectancy than men. It is suggested that the progression rate of many renal diseases is affected by sex. A large meta-analysis of nondiabetic kidney disease revealed that men had more rapid decline compared to women (Neugarten, Acharya, & Silbiger, 2000). Some studies revealed that the prevalence of hyperuricemia was significantly higher in males than in females before the age of 60 years, and that the difference was reversed after 70 years (Bhole, de Vera, Rahman, Krishnan, & Choi, 2010; Liu et al., 2014; Zhang, Lou, Meng, & Ren, 2011). A recent meta-analysis revealed that the serum uric acid level was independently associated with CKD in middle-aged adults but not in elderly adults (Zhu, Liu, Han, Xu, & Ran, 2014). The Pathways Study in the U.S. found that older women with diabetes had higher risk of advanced DKD and prevalence of common DKD risk factors compared to men although hyperuricemia was not considered in this study (Yu, Lyles, Bent-Shaw, & Young, 2012). How hyperuricemia affects DKD status in Chinese older patients is still unclear.

The adoption and use of electronic health record (EHR) have increased in China's hospitals and communities. The Minhang District of Shanghai is now a model for establishing and utilizing the information on EHR systems in China. Analyzing routinely recorded clinical data from the system has become feasible. Thus, the purpose of this study was to determine the gender differences in the relationship between hyperuricemia and DKD in older diabetic patients of a large community based on EHR of the Minhang District, Shanghai, China.

## 2. Methods

### 2.1. Subjects

The Minhang District located in the southwest part of Shanghai covers an area of 372 $km^2$ with a population of approximately 2,508,000 (2012). There are 13 community health centers and 5 district-hospitals in the Minhang District. The information system that focused on chronic disease control and management for the entire district was established by the Health Planning Committee of Shanghai and Center for Disease Prevention and Control (CDC) in Minhang District of Shanghai in 2007. All community health centers used the same EHR system, and the community-hospital-integrated diabetes management program was established based on this system.

The program screened for diabetes in each community health center and conducted various forms of follow-up visits and disease management according to diabetic patients' situations. The system included Type 1 diabetes, Type 2 diabetes, impaired glucose tolerance, and impaired fasting glucose patients. Among them, over 90% were T2DM patients, and more than 80% were over 60 years old. In the system, each patient owned a health card with a unique personal identification number, which contained all clinical and laboratory data. For this observational study, data were extracted in 2013 from the EHR, including 13 community care centers in the Minhang district of Shanghai.

The data between October 1, 2012 and September 30, 2013 were extracted from the EHR for all 55,533 patients involved in diabetes management. After excluding patients who had incomplete data regarding serum creatinine, urinary albumin to creatinine ratio (ACR), and standard Hemoglobin A1c (HbA1c) (n = 24,491), or who were under the age of 60 years (n = 6021), 25,021 cases of elderly patients diagnosed with Type 2 diabetes [International Classification of Diseases (ICD)-10 codes E10–E14] were eligible for analysis. After further exclusion of those with missing data on serum uric acid levels (n = 4814), we rendered a final sample of 20,207 elderly diabetic patients for further analyses.

The study protocol was approved by the ethics review committee of the No.5 Hospital of Shanghai, Fudan University, Shanghai, China, and adhered to the Declaration of Helsinki. All eligible participants provided their written informed consent.

### 2.2. Data collection

Patient factors, including age, gender, and duration of diabetes, were collected in each community clinic. Trained investigators collected data on anthropometric indices (standing height, body weight, and waist circumference) according to the recommendations by the World Health Organization (Molarius, Seidell, Sans, Tuomilehto, & Kuulasmaa, 1999). Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of the height (in meters). Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported diagnosis of hypertension and use of antihypertensive medication.

Serum fasting blood glucose was measured enzymatically via the glucose oxidase method. Diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/L and/or 2-h postprandial plasma glucose ≥11.1 mmol/L, by the use of hypoglycemic agents despite fasting plasma glucose, or any self-reported history of diabetes. Standard methods were used in the 13 community health centers for blood sample storage and analysis. The intra- and inter-variation of data results were checked periodically by the Minhang CDC. Serum total cholesterol, low density lipoprotein cholesterol (LDL_C), high density lipoprotein cholesterol (HDL_C), triglycerides, and serum uric acid were measured with auto-analyzer (COBAS INTEGRA 400 Plus, Roche, Basel, Switzerland). Serum creatinine was measured by Jaffe's kinetic method. HbA1c was measured using standard high performance liquid chromatography (HPLC).

Urinary albumin and creatinine were measured using a morning urine sample. Urinary creatinine was measured using the same method as that for serum creatinine, and albuminuria was measured by immunoturbidimetric methods. The urinary albumin-to-creatinine ratio (ACR, milligram per gram) was calculated.

### 2.3. Outcome measurements

Participants were diagnosed with hyperuricemia if their serum uric acid level was > 420 μmol/L in men or > 360 μmol/L in women. Albuminuria categories were based on ACR: A1 < 30 mg/g (normal to mildly increased), A2 30–300 mg/g (moderately increased), and A3 > 300 mg/g (severely increased).

Renal function was defined on the basis of estimated glomerular filtration rate (eGFR), calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation, $eGFR(ml/min/1.73\ m^2) = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times$ [1.018 if female] and × [1.159 if black], where Scr is serum creatinine (mg/dl), $\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is −0.329 for females and −0.411 for males; min indicates the minimum of Scr/$\kappa$ or 1, and max indicates the maximum of Scr/$\kappa$ or 1 (Levey et al., 2009). CKD was classified into