Association between Plasma Xanthine Oxidoreductase Activity and the Renal Function in a General Japanese Population: The Tohoku Medical Megabank Community-Based Cohort Study

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**Keywords**
Chronic kidney disease · Cystatin C · Estimated glomerular filtration rate

**Abstract**

**Introduction:** Xanthine oxidoreductase (XOR) has been identified as a critical source of reactive oxygen species in various pathophysiological conditions, including hypertension, endothelial dysfunction, and atherosclerosis. This study investigated the association between XOR and renal function in a general Japanese population.

**Methods:** The Iwate Tohoku Medical Megabank Organization pooled individual participant data from a community-based cohort study in Iwate prefecture. Chronic kidney disease (CKD) was estimated using the estimated glomerular filtration rate of cystatin C (eGFRcys). Individuals with a history of hyperuricemia or severe renal dysfunction (eGFRcys < 15 mL/min/1.73 m\textsuperscript{2} or undergoing dialysis) were excluded from the study. We performed a multinominal multivariate logistic analysis adjusted for age, blood pressure, uric acid, glycosylated hemoglobin A1c, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol to associate XOR activity and renal function.

**Results:** The present study included 4,248 participants (male/female: 1,373/2,875, age: 62.9 ± 11.7 years). When participants were divided according to XOR quartiles, blood pressure, body mass index, uric acid, low-density lipoprotein cholesterol, and glycated hemoglobin A1c were highest in the highest XOR quartile (all \(p < 0.001\)). The XOR activity was significantly higher in the subgroup with CKD stage G3 and G4 (G1 vs. G2 vs. G3-G4: 44.8 ± 40.5 vs. 52.0 ± 42.9 vs. 54.1 ± 43.9 pmol/h/mL, \(p = 0.02\)). The higher XOR ac-
Association between XOR and Renal Function in General Population

Introduction

Chronic kidney disease (CKD) has been reported to be strongly associated with cardiovascular disease (CVD) [1]. Our previous report showed that a decrease in the estimated glomerular filtration rate of cystatin C (eGFRcys) was closely associated with cardiovascular biomarkers, including highly sensitive troponin T- and N-terminal prohormone of brain natriuretic peptide, and a high Suita score, and found that it provides additional value in the assessment of CVD risk [2]. The high rates of CVD-related morbidity and mortality in CKD patients cannot be explained by classical CVD risk factors alone, including hypertension, smoking habits, diabetes, and hyperlipidemia [3]. An increase in oxidative stress has been a novel, nonclassical risk factor for CVD [4]. The xanthine oxidoreductase (XOR) activity is the sum of xanthine dehydrogenase and xanthine oxidase, which are both involved in the metabolic pathway of uric acid (UA) [5]. Both generate reactive oxygen species, such as superoxide (O2−) and hydrogen peroxide (H2O2) during the reaction and have been reported to be involved in vascular inflammation and, ultimately, in the development of atherosclerosis [6, 7]. Our previous report showed that high XOR activity was associated with a high risk of developing CVD in a general Japanese population [8]. XOR has been reported to be involved in vascular inflammation and, ultimately, in the development of atherosclerosis [6, 7]. It has been reported that XOR activity is higher in patients with CKD and patients undergoing dialysis [12]. However, there have been no previous investigations on the relationship between plasma XOR activity and renal function in the general population. This study aimed to determine the association between XOR activity and renal function in the Tohoku Medical Megabank Organization Community Cohort Study (TMM CommCohort Study).

Methods

Study Population

TMM CommCohort Study was a community-based adult cohort study of people living in the Iwate prefecture of East Japan [13]. Participants over 20 years of age, in some regions of the General Population Cohort, agreed to the Iwate Medical University Iwate Tohoku Medical Megabank Organization (IMM) survey between July 2013 and March 2016 and were enrolled. Participants were excluded from the present study if they had a history of hyperuricemia, severe renal dysfunction (eGFRcys < 15 mL/min/1.73 m² or were undergoing dialysis), or unavailability of data. A history of hyperuricemia was defined as a serum UA level higher than 6.8 mg/dL or a history of treatment [14].

Cohort Data Collection

The subjects completed a self-administered questionnaire that included age, sex, and medical history. Body mass index (BMI), systolic blood pressure, and diastolic blood pressure were also measured. Experienced nurses collected blood samples, and plasma samples were analyzed immediately or stored at −80°C until the analysis. Hypertension was diagnosed with systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and/or antihypertensive drugs [15]. Participants were diagnosed with diabetes in the presence of glycated hemoglobin (HbA1c) levels ≥ 6.5% and/or nonfasting blood glucose ≥ 200 mg/dL and/or the use of antidiabetic drugs such as insulin [16]. Participants were diagnosed with dyslipidemia in the presence of low-density lipoprotein (LDL) cholesterol above 140 mg/dL and/or taking antihyperlipidemic agents [17].

Measurements of XOR Activity

Recently, a protocol for measuring plasma XOR activity has been established [18–20]. Plasma XOR activity was measured using frozen samples that were maintained at −80°C until the assay time. Small molecules (e.g., hypoxanthine, xanthine, and UA) were removed from plasma samples and mixed in Tris buffer with (13C2, 15N2)-xanthine and NAD+ substrates and (13C3, 15N3)-UA as an internal standard. After incubating each mixture, it was dried and ultrafiltered and then analyzed by LC/TSQ-Quantum triple quadrupole mass spectrometer using a Nanospace SI-2 LC system (Shiseido Co., Ltd., Tokyo, Japan) and a TQMS (Thermo-Fisher Scientific, Bremen, Germany). As previously reported, we have performed a highly sensitive analysis of XOR activity [18, 20]. The calibration curve for (13C2, 15N2) UA showed linearity in the range of 4–4,000 nM (r² > 0.995), with a lower limit of quantification of 4 nM. The lower limit of detection for XOR activity was 6.67 pmol/h/mL, and the intra-assay and inter-assay coefficients of variation for human plasma XOR activity were 6.5% and 9.1%, respectively [20].

Measurements of eGFR

The present study followed the guidelines and used the recommended cystatin C to assess the renal function in the present study [21]. The present study measured renal function using eGFRcys. The eGFRcys is calculated as follows: eGFRcys = 104 × serum cystatin C 1.019 × 0.996 × age (× 0.929 for women) − 8 mL/min/1.73 m² [22]. All participants were divided into six subgroups according to CKD stage as follows: G1 (eGFR 90 or more mL/min/1.73 m²),
G2 (eGFR 60–89 mL/min/1.73 m²), G3a (eGFR 45–59 mL/min/1.73 m²), G3b (eGFR 30–44 mL/min/1.73 m²), G4 (eGFR 15–29 mL/min/1.73 m²), and G5 (eGFR 14 or less mL/min/1.73 m²) [21].

### Statistical Analysis

The distribution of XOR activity was checked and classified into quartiles. Basic characteristics were compared among the XOR quartile groups using an analysis of variance (ANOVA) for normally distributed variables, and the Kruskal-Wallis test was used for skewed variables. The χ² test was used to analyze between the XOR quartile groups for categorical variables. The correlation between two variables was assessed using Pearson’s correlation coefficient. The XOR activity was logarithmically transformed before performing Pearson’s correlation coefficient analysis. To determine the association between XOR activity and renal function, multinominal logistic regression analysis was performed with XOR quartile as the dependent variable and eGFR (ml/min/1.73 m²) as the independent variable. In a further analysis, the CKD stage (G1, G2, and G3 and G4) was used as the dependent variable and XOR activity (pmol/h/mL) as the independent variable. In multivariate adjusted model, the odds ratios and 95% confidence intervals were calculated adjusting for age, sex, BMI, diabetes, dyslipidemia, stroke, BP, UA, HbA1c, LDL cholesterol, and HbA1c were highest in the highest XOR quartile group (all p < 0.001) (Table 1). In contrast, HDL cholesterol and eGFRcys were lowest in the highest XOR quartile (all p < 0.001) (Table 1).

### Association between Quartiles of XOR Activity and eGFRcys

There was a weak negative statistical correlation between the XOR activity and eGFR in a general population according to Pearson’s correlation coefficient analysis (r = −0.25, p < 0.001). There was an inverse association between quartiles of XOR activity and eGFRcys. In the multivariate model, the odds ratios (95% confidence intervals) per 1 mL/min/1.73m² in eGFRcys with the lowest XOR activity quartile (Q1) as a reference were 0.91 (0.82–0.97) in the Q2, 0.81 (0.73–0.88) in Q3, and 0.82 (0.70–
0.93) in Q4 (online Suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000527654).

**Association between CKD Stage and XOR Activity**

The XOR activity in patients with CKD stage G3-G4 was higher than those with stage G1 and G2 (G1 vs. G2 vs. G3-G4: 44.8 ± 40.5 vs. 52.0 ± 42.9 vs. 54.1 ± 43.9 pmol/h/mL, p = 0.02). The higher XOR activity was significantly associated with an increase of CKD stage: the odd ratios (95% confidence intervals) per 1 pmol/h/mL increase in XOR activity with CKD stage G1 as a reference were 1.37 (1.13–1.73) in G2 and 1.51 (1.30–1.84) in G3-G4 (Table 2). Subgroup analyses revealed a statistical relationship between the CKD stage and XOR activity in subgroups according to age, sex, and the presence of a history of diabetes mellitus, and hypertension (online Suppl. table 2). However, no statistical relationship was observed between the CKD stage and XOR activity in the subgroups with heart disease (online Suppl. table 2). The general linear model analysis showed there was no significant interaction in the CKD stage between XOR activity and age, sex, history of heart disease, diabetes mellitus, or hypertension (p value for interaction: age, 0.33; sex, 0.67; a history of diabetes mellitus, 0.29; hypertension, 0.81; and heart disease, 0.54).

**Discussion**

This study investigated the association between XOR activity and CKD stage in 4,248 IMM participants. The number of participants in the present study is the largest among previously reported cohort studies regarding XOR activity in general populations worldwide. The present study showed that XOR activity was negatively associated with eGFRcys in IMM participants. In addition, the XOR activity in participants with CKD stage G3 and G4 was higher than those with stage G1 or G2.

When participants were divided according to their XOR quartile, the present study showed that some baseline characteristics, including age, BP, BMI, UA, LDL cholesterol, and HbA1c, were highest in the highest XOR quartile.
quartile. Our previous study demonstrated that XOR activity was independently associated with the presence of diabetes and dyslipidemia [8]. XOR activity was also positively correlated with UA and HbA1c levels [8]. It has been reported that XOR activity is positively correlated with HbA1c in diabetic patients [23]. In addition, XOR activity was associated with dyslipidemia in a general Japanese population study [24]. Elevated XOR activity is responsible for forming UA from hypoxanthine and xanthine, which leads to superoxide and ROS production [25, 26]. It is well known that ROS production in the vessel wall is involved in the progression of atherosclerosis [27]. Therefore, these observations suggested that classical CV risk factors, such as aging, diabetes, and dyslipidemia, may upregulate XOR activity and then induce ROS production.

An important result of the present study was identifying a negative association between XOR activity and eGFRcys. In addition, XOR activity in participants with CKD stage G3 and G4 was higher than those with stage G1 or G2. It has been reported that XOR induces the renin-angiotensin system in tissues and promotes a positive feedback loop activation leading to organ damage and nephro sclerosis [28]. Furthermore, according to this report, therapy with XOR inhibitors effectively improves the survival rate of dialysis patients [28]. An experimental model demonstrated that in response to tissue necrosis caused by tissue hypoxia, ROS generation by NADPH oxidase activation and XOR activation occur concurrently, followed by progression to the renal fibrosis pathway [29]. Therefore, XOR inhibition can reduce the oxidative stress related to organ damage from renal failure. A positive correlation between XOR activity and serum creatinine levels in CKD patients has been reported [30]. There was a negative correlation between XOR activity and eGFR in patients with chronic heart failure [31]. The present study also showed a negative statistical correlation between XOR activity and eGFR in a general population.

It has been reported that XOR activity was positively correlated with HbA1c in patients with diabetes. Short-term carbohydrate-restricted treatment (2 weeks of inpatient treatment) reduced plasma XOR activity, suggesting that diabetes may play an important role in regulating XOR activity [32]. Indeed, the present study showed that the HbA1c levels were highest in patients with the highest XOR quartile, which is in line with the report’s findings mentioned above (Table 2) [32].

GFR is more frequently estimated using the serum creatinine level in clinical practice. Recent guidelines for CKD suggest the use of cystatin C to validate the diagnosis of CKD in patients who are currently considered to have CKD based solely on a creatinine-based eGFR of less than 60 mL per minute per 1.73 m², without albuminuria or other markers of age, sex, or muscle mass [21].

**Limitations**

The present study had several limitations. First, the XOR activity and other covariates were only measured at baseline because this was a cross-sectional study. Second, the present study evaluated whether each participant had a medical history using self-reported answers rather than a clinical examination. A future prospective study is needed to determine whether XOR activity is an independent predictor of the long-term outcomes of renal dysfunction.
Conclusion

The present study concluded that high XOR activity was associated with the severity of CKD in a general Japanese population after excluding patients with a history of hyperuricemia or severe renal dysfunction. The present study suggests that the upregulation of XOR activity may be involved in advanced renal dysfunction. We plan to conduct further prospective studies to investigate this association.

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Statement of Ethics

Following the Declaration of Helsinki (1991), written informed consent was obtained from each subject. This study was approved by the Ethics Committee of Iwate Medical University (HG2018-004).

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Conflict of Interest Statement

This study was carried out in collaboration with Sanwa Kagaku Kenkyusho Co., Ltd (Tokyo, Japan). XOR activity was measured at the laboratory. The company had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Author Contributions

Satoru Taguchi, Takahito Nasu, Fumitaka Tanaka, Koichi Asahi, Yoshihiro Morino, Kenji Sobue, Makoto Sasaki, Mamoru Satoh, and Atsushi Shimizu were involved in study design and data interpretation. Satoru Taguchi, Takahito Nasu, Mamoru Satoh, Yuka Kotozaki, Kozo Tanno, Hideki Ohmomo, Hiroto Kikuchi, Takamasa Kobayashi, and Atsushi Shimizu were involved in the data analysis. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

Data Availability Statement

Data sharing does not apply to this article due to restrictions on privacy or ethical. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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