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Associations of fibroblast growth factor 23 with urate metabolism in patients with chronic kidney disease

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ABSTRACT

Objective. In patients with preserved kidney function, a positive association of fibroblast growth factor 23 (FGF23) with serum uric acid (SUA) has been reported; however, the relationship in overall chronic kidney disease (CKD) patients has not been investigated. No report has examined the relationship between FGF23 and uric acid clearance (CUA). The aim of the present study was to determine whether FGF23 is independently associated with urate metabolism in patients with CKD stages 1–5.

Materials and methods. In this cross-sectional study, 537 CKD patients were enrolled. SUA, CUA, FGF23, parathyroid hormone (PTH), and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) were measured. Multivariable linear regression analysis was applied to determine independent factors associated with SUA or CUA.

Results. In all patients, both SUA and CUA were independently associated with male sex, use of diuretics, use of uric acid-lowering agents, estimated glomerular filtration rate, and log FGF23 ($\beta = 0.29$, $P < 0.01$ for SUA; $\beta = -0.11$, $P < 0.01$ for CUA), but not with log PTH or log $1,25(OH)_2D$. Dyslipidemia and diabetes were also independent factors for SUA and CUA, respectively. In multivariable analyses by sex, log FGF23 was associated with SUA in both sexes ($\beta = 0.32$, $P < 0.01$ in males *vs.* $\beta = 0.20$, $P = 0.02$ in females). Conversely, log FGF23 was

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FGF, fibroblast growth factor; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone; SUA, serum uric acid; CUA, uric acid clearance; UEUA, urinary excretion of uric acid; FEUA, fractional excretion of uric acid; FEPi, fractional excretion of phosphate; FENa, fractional excretion of sodium; URAT, urate transporter; NHERF, sodium-hydrogen exchanger regulatory factor; Npt, sodium-phosphate cotransporters; ABCG, ATP-binding cassette sub-family G member; ARB, angiotensin II receptor blockers; PDZK1, PDZ domain containing 1; 25(OH)D, 25-hydroxyvitamin D.

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independently associated with CUA in males (β = −0.15, P < 0.01), but not in females (β = −0.09, P = 0.17).

Conclusions. FGF23 was independently associated with urate metabolism in this population of CKD patients. FGF23 might also have a stronger association with urate metabolism in males compared with females.

1. Introduction

Serum uric acid (SUA) is the end product of purine metabolism in humans, as humans lack the hepatic urate oxidase, uricase, which converts uric acid to allantoin, unlike the majority of mammals. Almost all serum urate is filtered through glomeruli, while urate reabsorption and secretion are carried out at proximal tubules, and approximately 90% is reabsorbed into the blood. Approximately 90% of hyperuricemia is caused by urate underexcretion from the kidneys [1], while increased renal urate excretion results in hypouricemia. Furthermore, as approximately two-thirds of SUA is excreted through the kidneys, chronic kidney disease (CKD) patients develop hyperuricemia as the glomerular filtration rate declines [2]. These findings suggest that renal urate handling plays a key role in determining SUA levels [3]. Several proteins involved in urate transport have been identified, including a urate-anion exchanger localized at the apical membrane of proximal tubules, urate transporter 1 (URAT1) [4]. These urate transporters have been recognized as key regulators for renal urate handling.

Fibroblast growth factor 23 (FGF23) is a 251 amino acid protein secreted by osteocytes in adults [5]. FGF23 binds to FGF receptor and its cofactor, klotho. FGF23 increases urinary phosphate excretion by reducing the expression of sodium-phosphate cotransporters type 2a (Npt2a) and 2c at the apical membrane of proximal tubules and decreases dietary phosphorus absorption through the inhibition of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) synthesis by suppressing 1α-hydroxylase activity [6–12]. FGF23 functions as an important regulator that maintains serum phosphorus levels within the normal range in patients with CKD [13].

Previous studies have demonstrated that higher SUA levels are associated with higher parathyroid hormone (PTH) [14–17] and lower $1,25(OH)_2D$ levels [18,19] in people without CKD. FGF23 was also independently associated with SUA in people with preserved kidney function [20–22]. However, no studies have examined the relationship between SUA and FGF23 in CKD patients. In addition, the association between uric acid clearance (CUA) and FGF23 has not been investigated. Therefore, the aim of the present study was to determine whether FGF23 is independently associated with urate metabolism factors such as SUA and CUA in patients with CKD stages 1–5.

2. Patients and Methods

2.1. Patient Selection and Study Design

A total of 606 patients were admitted to our hospital for the evaluation and education of CKD between June 2009 and January 2016. Patients with no available data for blood and urine samples and who experienced acute exacerbation of kidney function were excluded (n = 69). The remaining 537 were enrolled in this cross-sectional study. All patients provided written informed consent to the protocol, which was approved by the Ethics Committee of the National Hospital Organization Kyushu Medical Center, and the study was registered in the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN, #000,020,652).

2.2. Clinical and Biochemical Assessment

After admission, all patients were provided a diet containing low salt and protein. Blood samples were obtained in the early morning after an overnight fast, and serum creatinine (SCr), SUA, serum phosphorus, intact PTH, $1,25(OH)_2D$, and intact FGF23 levels were evaluated. Intact FGF23 levels were measured using an FGF23 ELISA kit (Kainos Laboratories, Tokyo, Japan). The assay for intact FGF23 has a lower limit of detection of 3 pg/mL and intra-assay and inter-assay coefficients of variation (CVs) of less than 10%. Intact PTH levels were measured by electrochemiluminescence immunoassay (Elecsys PTH; Roche Diagnostics, Mannheim, Germany). The detection limit of the assay was 1.20 pg/mL. The intra-assay CV was less than 2.8% and inter-assay CV was less than 3.4%. A radioimmunoassay was used to measure $1,25(OH)_2D$ (Immunodiagnostic Systems, Boldon, UK). The lower detection limit was 2.1 pg/mL and the intra- and inter-assay CVs were less than 15%.

From 24-h collected urine samples, CUA (mL/min/1.73 m^2), urinary excretion of uric acid (UEUA) (mg/kg/h), fractional excretion of uric acid (FEUA) (%), fractional excretion of phosphate (FEPi) (%), and fractional excretion of sodium (FENa) (%) were examined. Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) was calculated using the new Japanese equation: $eGFR = 194 \times SCr^{-1.094} \times age^{-0.287} \times 0.739$ (if female) [23].

All enrolled patients were interviewed and clinically examined at presentation. Their medical histories and outpatient records were evaluated in detail. Demographic information (age and sex), medication history, alcohol drinking history, and atherosclerotic risk factors (hypertension, history of smoking, dyslipidemia, and diabetes mellitus) at presentation were recorded for each patient. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or the current use of antihypertensive drugs. Dyslipidemia was defined as plasma triglycerides ≥150 mg/dL, plasma low-density lipoprotein cholesterol ≥140 mg/dL, plasma high-density lipoprotein cholesterol <40 mg/dL, or the use of lipid-lowering drugs based on a history of dyslipidemia. Diabetes mellitus was defined as previous or current plasma fasting glucose