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Renal glucosuria is not associated with atherosclerotic cardiovascular disease outcome in a general Japanese community

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ABSTRACT

Background and aims: Renal glucosuria is defined as the excretion of detectable amounts of glucose in the urine without diabetes or hyperglycemia. Few data exist regarding the prevalence of renal glucosuria and its clinical impact on atherosclerotic cardiovascular diseases.

Methods: This study included 47,842 subjects (16,913 men, 35.4%) aged ≥40 years who underwent the Japanese specific health checkup in Kanazawa City during 2014. We defined renal glucosuria as fulfillment of all of the following three criteria: 1) detectable glucosuria; 2) the absence of diabetes; 3) normal blood glucose (<110 mg/dl fasting, and <140 mg/dl non-fasting). The presence of renal glucosuria and of factors associated with atherosclerotic cardiovascular diseases, including coronary artery disease and stroke, was assessed.

Results: The criteria for renal glucosuria were met by 665 (1.4%) subjects. Significantly higher proportions of subjects with renal glucosuria exhibited coronary artery disease, stroke, or either outcome than those without (14.9% *vs.* 12.1%, $p = 0.0305$; 9.9% *vs.* 6.9%, $p = 0.00255$; 22.3% *vs.* 17.0%, $p = 4.0 \times 10^{-4}$, respectively), but multivariate logistic regression analyses revealed that renal glucosuria was not associated with coronary artery disease (odds ratio [OR] = 0.940, 95% confidence interval [CI] = 0.748−1.171, not significant), stroke (OR = 1.122, 95% CI = 0.853−1.453, not significant), or atherosclerotic cardiovascular diseases (OR = 1.122, 95% CI = 0.853−1.453, not significant).

Conclusions: These results indicate that the prevalence of renal glucosuria in the Japanese general population was 1.4%, and that renal glucosuria was not associated with atherosclerotic cardiovascular diseases *per se*.

1. Introduction

Renal glucosuria is the excretion of detectable amounts of glucose in the urine, while maintaining a normal blood glucose concentration [1]. Such a situation can be found in individuals with familial renal glucosuria associated with mutations in the sodium-glucose cotransporter 2 (SGLT2) coding gene, *SLC5A2* [2–4] or in patients receiving tenofovir for human immunodeficiency virus (HIV) infection [5]. Renal glucosuria could be caused either by lowering renal threshold for glucose and/or impaired renal tubule capacity for glucose reabsorption. It has been shown that the majority of the "patients" with renal glucosuria do not seem to develop significant clinical problems [6].

On the other hand, a recent clinical trial demonstrated that the beneficial effect of an SGLT2 inhibitor on cardiovascular disease inadvertently caused artificial glucosuria [7]. In this EMPA-REG OUTCOME trial, the major driver of the beneficial effect is considered as preventive effect of heart failure, rather than that of atherosclerotic cardiovascular diseases. Thus, it is still unclear whether an artificial glucosuria could affect atherosclerotic cardiovascular outcomes. Currently, little data exists regarding the prevalence of renal glucosuria and its clinical impact on atherosclerotic cardiovascular diseases in the general population. Accordingly, the current study investigated the prevalence of renal glucosuria and its impact on atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease (CAD) and stroke,

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among subjects who underwent the Japanese specific health checkup, to see if the presence of renal glucosuria might affect such atherosclerotic cardiovascular outcomes.

2. Materials and methods

2.1. Study subjects

This study included 47,842 subjects (16,913 men, 35.4%) aged 40 years or older who underwent the Japanese specific health checkup in 2014 at Kanazawa City, Japan, and for whom there were no missing data. Most of the subjects visited general practitioners in clinics in Kanazawa City, Japan. Data were collected and anonymized by the Kanazawa Medical Association.

2.2. Ethical considerations

This study was approved by the Ethics Committee of Kanazawa Medical Association (No. 16000003) and Kanazawa University (No. 2179-1). All procedures were followed in accordance with the ethical standards of the Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all subjects prior to inclusion in the study.

2.3. Data collected in the Japanese specific health checkup

The Japanese specific health checkup has been described previously [8–10]. Briefly, it is a healthcare strategy initiated by the Japanese Government in 2008 for the early diagnosis of, and intervention in, metabolic syndrome. Eligible participants visit a clinic and respond to a questionnaire regarding any past history of stroke, cardiac disease or kidney disease, lifestyle habits such as smoking, alcohol intake, walking, etc., and any medications for hypertension, diabetes, and dyslipidemia. Measurements include the standard medical checks, including measurement of height, weight, waist circumference, blood pressure, fasting and non-fasting blood glucose, hemoglobin A1c, triglycerides, total cholesterol, serum high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, serum creatinine, and the dipstick urine test for proteinuria, hematuria, and urinary glucose.

Dipstick urine tests were coded as negative, plus and minus, 1 plus, 2 plus, 3 plus, and 4 plus. Serum creatinine was measured using the enzymatic method. The glomerular filtration rate was calculated using the formula of the Japanese Society of Nephrology [11]. Blood samples were analyzed within 24 h of sampling using an automated clinical chemical analyzer. Blood analyses were conducted at local, rather than central, laboratories. Although the methods used for blood analyses were not calibrated between laboratories, the analyses were performed according to the methods for laboratory tests recommended by the Japan Society of Clinical Chemistry, which have been widely adopted by laboratories across Japan [12]. Hypertension was defined as blood pressure $\geq$ 140/90 mmHg or by the subject taking hypotensive medication. Diabetes was defined as hemoglobin A1c $\geq$ 6.5% or taking hypoglycemic medication. The presence of chronic kidney disease (CKD) was defined according to the CKD classification and based on the estimated glomerular filtration rate (eGFR) and dipstick proteinuria findings [13]. Stroke included ischemic stroke as well as hemorrhagic stroke. We defined ASCVD as the presence of CAD or stroke, both defined by the medical questionnaires.

2.4. Definition of renal glucosuria

We defined renal glucosuria as fulfillment of all of the following three criteria: 1) detectable glucosuria (1 plus, 2 plus, 3 plus, or 4 plus); 2) the absence of diabetes; 3) normal blood glucose (<110 mg/dl fasting, and <140 mg/dl non-fasting).

2.5. Evaluations

We assessed the prevalence of renal glucosuria among the subjects, and the factors associated with CAD, stroke, and ASCVD.

2.6. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or median (1st and 3rd quartiles), and categorical variables are expressed as number and percentage. Differences in the baseline characteristics between groups were evaluated using Student's *t*-test for parametric data and the Mann–Whitney *U* test for non-parametric data. Categorical variables were compared using the Chi-square test or Fisher's exact test. The prognostic value of each factor was first evaluated by univariate logistic regression analysis. The factors with $p < 0.05$ in the univariate analysis were entered into a multivariate logistic regression model to identify the independent predictors. A p-value < 0.05 was considered statistically significant, and all tests were two-tailed. The analyses were performed with R statistical software.

3. Results

3.1. Characteristics of study subjects

Clinical characteristics of study subjects are shown in Table 1. As expected, the subjects with CAD, stroke, or ASCVD were older and more likely to be male, with a higher body mass index (BMI), and larger waist circumference. They were more likely to have CKD, hypertension, diabetes, and renal glucosuria. In contrast, the proportion of subjects currently smoking was lower among those with CAD, stroke, or ASCVD, probably due to the non-smoking guidance. The subjects with CAD, stroke, or ASCVD had lower LDL cholesterol levels, and a higher proportion were undergoing lipid-lowering therapy, although their triglyceride levels were nevertheless higher, and their HDL cholesterol levels were lower.

3.2. Characteristics of the subjects with renal glucosuria

A comparison of the clinical characteristics of the subjects with and without renal glucosuria is shown in Table 2. The subjects with renal glucosuria were older, with a smaller BMI and lower waist circumference. They were more likely to smoke, and to have CKD, hypertension, CAD, stroke, or ASCVD. The subjects with renal glucosuria had lower LDL cholesterol levels, despite the proportion of subjects on lipid-lowering therapy being lower in those subjects. There were no significant differences between the groups in triglyceride level or uric acid level.

3.3. Factors associated with CAD, stroke, and ASCVD

3.3.1. Renal glucosuria

We investigated the factors associated with CAD, including the presence of renal glucosuria (Table 3). Univariate logistic regression analysis demonstrated that age, being male, BMI, waist circumference, triglycerides, HDL cholesterol, LDL cholesterol, current smoking, CKD, hypertension, diabetes, and glucosuria were all significantly associated with CAD. Multivariate logistic regression analysis showed that the presence of glucosuria was not an independent risk factor for CAD (odds ratio [OR] = 0.940, 95% confidence interval [CI] 0.748–1.171, NS). In contrast, the other traditional risk factors were each independently associated with

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