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Discovery and validation of serum creatinine variability as novel biomarker for predicting onset of albuminuria in Type 2 diabetes mellitus

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ABSTRACT

Aim: We aim to study association serum creatinine(cr) variability and albuminuria progression.

Methods: We conducted a retrospective cohort study on patients with Type 2 Diabetes Mellitus at a Diabetes Centre in Singapore ("discovery cohort"). Outcome is worsening of urinary albumin-to-creatinine(ACR) across stages. Cr variability was expressed as adjusted cr-intrapersonal standard deviation(SD) and coefficient-of-variation(cr-CV). A separate cohort was used for validating association between cr variability and albuminuria progression ("validation cohort").

Results: Over median follow-up of 4.2 years, 38.4% of 636 patients had albuminuria progression in the discovery cohort. Increasing log-transformed adjusted cr-intrapersonal SD and cr-CV were significantly associated with albuminuria progression: HRs 1.43 (95%CI 1.11–1.85) and 1.44 (1.11–1.87) respectively in the discovery cohort, and HRs 1.94 (1.09–3.45) and 1.91 (1.05–3.45) respectively in the validation cohort. When stratified by baseline urinary ACR, higher cr variability was significantly associated with albuminuria progression in patients with normoalbuminuria but not microalbuminuria.

Conclusions: Cr variability independently predicts albuminuria onset. This is evident in patients with normoalbuminuria, suggesting that higher cr variability could herald albuminuria onset.

1. Introduction

Kidney disease is a major complication of Type 2 Diabetes Mellitus (T2DM), affecting 25–40% of individuals with T2DM [1]. Of note, Asians have a higher tendency to develop diabetic kidney disease (DKD) than other ethnicities such as Caucasians [2]. Given the substantial morbidity, mortality and economic costs imposed by DKD, it is imperative to identify

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the risk factors of DKD onset and progression in order to support prevention efforts. There is accumulating literature on risk factors predictive of chronic kidney disease progression. These included age, gender, body mass index, systolic blood pressure, serum creatinine, urinary albumin-to-creatinine ratio (uACR), estimated glomerular filtration rate and even novel biomarkers [3].

Baseline serum GFR has long been recognized as a risk factor of kidney disease progression in T2DM. However, baseline GFR reveals little information on the functional reserve of the kidney. Functional renal mass can differ in different individuals even though their baseline GFR can be similar [4]. In the presence of reduced residual renal mass, more stress is exerted on the remaining nephrons. This in turn leads to hyperfiltration and kidney disease progression [4]. There is a need to look beyond baseline renal function to gain deeper insights into the progression of kidney disease.

It was observed that reported patients with higher serum creatinine fluctuation during admission experienced a higher risk of mortality post discharge compared to those with more fluctuation [5]. One possible explanation was that rapid fluctuations in the GFR are reflective of acute kidney injury (AKI). Patients with AKI have a higher death risk during inpatient hospitalization and in the first year post hospital discharge [5,6].

To date, the role of stability of renal function on progression of chronic kidney disease remains under-explored. We therefore aim to study the association between serum creatinine variability over long-term and onset and progression of albuminuria in T2DM.

2. Materials and methods

2.1. Study population

We conducted a retrospective cohort study on patients with T2DM who enrolled at a Diabetes Centre in a regional hospital in Singapore in 2002–2014 (“discovery cohort”). The exclusion criteria were: less than 21 years of age, pregnancy, active infections, active cancer, autoimmune disease, presence of other suspected causes of kidney disease (e.g. urinary tract infection, polycystic kidney disease, haematuria or history of glomerulonephritis). For the purpose of analysis, subjects were included if they had at least two years of follow-up for serum creatinine, absence of macroalbuminuria indicated by urinary albumin-to-creatinine ratio (ACR) >300 mg/g at baseline, at least two measurements of urinary ACR, four or more measurements of serum creatinine, and a follow-up period for urinary ACR of at least one month after the last serum creatinine measurement. There were altogether 636 patients eligible for the analysis. See Supplementary Fig. 1 for the flowchart.

2.2. Data collection

Clinical and demographic information were obtained from a standard questionnaire or extracted from patient’s medical records. Trained nurses measured Blood pressure (BP) using a standard sphygmomanometer using an appropriate cuff size in the sitting position after a resting period of at least 10 min. One random day spot urine sample for ACR was collected for each patient at baseline and through follow-ups. Follow-up urinary ACR was collected on a yearly basis or more frequently if the ACR was high. Blood and spot urine samples were collected and sent to the hospital laboratory accredited by the College of the American Pathologists (CAP). Serum creatinine was quantitated with enzymatic colorimetric test (Roche cobas® c 501); Haemoglobin A1c (HbA1c) with Tinaquant Haemoglobin A1c Gen.3 (Roche cobas® c 501); and urinary albumin with immunoturibidmimetric assay (Roche cobas® c 501). Measurements were taken at recruitment and at multiple time points during follow-up. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation formula [7].

A separate cohort was also used for validating the association between serum creatinine variability and kidney disease progression. This comprised adult subjects attending the Diabetes Centre in the same regional hospital or a primary-care polyclinic in 2011–2016. The patients were included in the analysis if they had no macroalbuminuria at baseline, at least two urinary ACR measurements, at least four measurements of serum creatinine, and the last follow-up urinary ACR measurement taken after the last serum creatinine measurement. A total of 199 subjects met the inclusion criteria. See Supplementary Fig. 2 for the flowchart. Trained nurses measured BP using a standard sphygmomanometer using an appropriate cuff size in the sitting position after a resting period of at least 10 min. Two BP readings were taken and the average BP was derived. Clinical and laboratory measurements were taken at multiple time points till February 2016. One random day urine sample for ACR was taken at baseline and follow-ups on yearly basis or more frequently if the ACR was high. Blood and urine samples were quantitated at the same hospital laboratory using assays similar to those for the DN cohort. The study was approved by the National Healthcare Group Domain Specific Review Board in Singapore. All participants provided written informed consent.

2.3. Outcome definition

The following stages of diabetic nephropathy were graded as follows: normoalbuminuria, microalbuminuria and macroalbuminuria indicated by uACR < 30 mg/g, 30–299 mg/g and ≥300 mg/g respectively. Patients who experienced worsening of these stages – from normo- to micro- or macroalbuminuria, or from micro- to macroalbuminuria were considered as having albuminuria progression (“progressors”). Those who did not experience worsening of these stages were “non-progressors”.

2.4. Calculation of serum creatinine variability

The median number of serum creatinine measurements was 6.0 (IQR 5.0–8.0) in the discovery cohort and 5.0 (4.0–5.0) in the validation cohort.

Intrapersonal mean and standard deviation (SD) of serum creatinine were calculated for each patient. Serum creatinine