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Short Report

Low serum creatinine is a type 2 diabetes risk factor in men and women: The Yuport Health Checkup Center cohort study

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ABSTRACT

Aim. – Type 2 diabetes (T2D) is a risk factor for muscle loss and subsequent frailty. The reverse association, however, may also happen. This study examined whether serum creatinine level, an indicator of muscle mass, predicted diabetes development. In addition, a role for body mass index (BMI) as an effect modifier of creatinine levels was evaluated.
Methods. – This cohort study included 9667 subjects without diabetes or hypertension and with normal creatinine levels at baseline. Multiple-adjusted hazard ratios (HRs) for associations between baseline creatinine and diabetes development were estimated using the Cox proportional-hazards model. Stratified analyses based on BMI were also performed.
Results. – During the follow-up period (mean: 5.6 years), 287 (5.5%) men and 115 (2.3%) women developed T2D. HR in men with serum creatinine $\leq$ 0.7 mg/dL compared with 0.9–1.2 mg/dL was 1.40 (95% CI: 1.05–1.87) after adjusting for age, BMI, blood pressure and fasting plasma glucose at baseline, whereas the adjusted HR in women with creatinine $\leq$ 0.5 mg/dL compared with 0.7–1.1 mg/dL was 1.69 (95% CI: 1.04–2.76). In a subgroup analysis stratified by BMI, interactions between BMI and baseline creatinine levels for T2D were statistically significant in women with the lowest creatinine levels ($P = 0.08$ for interaction).
Conclusion. – Low serum creatinine levels, a surrogate marker of muscle mass, predict T2D development in both genders, even after excluding the effect of diabetic and prediabetic glomerular hyperfiltration. BMI modified the association between creatinine and diabetes development in women.

Introduction

Type 2 diabetes (T2D) is a risk factor for muscle loss and subsequent frailty [1]. Reduced insulin signalling leads to decreased protein synthesis and increased protein degradation, which can ultimately lead to reduced muscle mass [2]. The reverse association, however, may also be found between muscle loss and diabetes. Skeletal muscle is a major target organ of insulin action. Therefore, decreased skeletal muscle mass can potentially generate insulin resistance, a risk factor for T2D [3,4]. Indeed, Moon [4] reported that sarcopenia (muscle loss due to ageing) may be an early predictor of diabetes and susceptibility to the metabolic syndrome in the non-obese population.

Creatinine levels reflect the amount of muscle in the body [5] when the kidneys and liver are functioning "normally" and protein intake is also normal. As an indicator of low muscle mass, low serum creatinine levels may be associated with diabetes. Yet, to date, only one prospective study [6] has identified lower levels of serum creatinine as a risk factor of T2D in Japanese men, while there have been no studies in women.

Elevated serum creatinine levels are an indicator of renal failure, which is also a major complication of diabetes. However, during early stages of the disease, serum creatinine may decrease because of osmotic diuresis (hyperfiltration) due to T2D and hypertension [7]. In addition, the prevalence of glomerular hyperfiltration is increased with increasing stages of prediabetes and prehypertension [8]. Thus, when examining the causal

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association between creatinine and diabetes, those with diabetes and hypertension need to be excluded while taking into account the effect of normal-range higher plasma glucose levels and blood pressure at baseline.

The present cohort study targeted individuals free of diabetes and with normal creatinine levels and examined the association between creatinine and T2D development. In general, as women have less muscle mass than men, the men and women in our cohort were analyzed separately. In addition, body mass index (BMI), which quantifies the amount of tissue mass, is associated with impaired glucose tolerance, an association observed in both low-weight and obese individuals [9]. For this reason, subanalyses were also included to evaluate the creatinine–diabetes association classified according to BMI.

Materials and methods

Study participants

The present study included 11,129 participants from a health-screening programme offered at the Yuport Medical Checkup Center in Tokyo [10]. The 4-year baseline period was set from 1998, and the 4-year follow-up period from 2002, so ending in 2006. If participants underwent more than one checkup during the baseline period, only the first was used as baseline data. If subjects underwent more than one checkup during the follow-up period, all of their data were used to diagnose T2D. The enrollment process of the study participants is shown in Fig. S1 (see supplementary material associated with this article online). At an early stage of diabetes or even in the prediabetes stage, serum creatinine levels may be decreased because of a hyperfiltrative status of the kidneys, an effect that is reportedly augmented by high blood pressure [7]. Thus, the study excluded 708 people with T2D [fasting plasma glucose (FPG) $\geq$ 7.0 mmol/L, haemoglobin A_{1c} (HbA_{1c}) $\geq$ 6.5% (47.5 mmol/mol) and/or known diabetes] and 324 people with a history of hypertension at baseline. To eliminate those with kidney dysfunction, 34 subjects with creatinine levels outside of the normal reference range ($\geq$ 1.3 mg/dL for men and $\geq$ 1.2 mg/dL for women) were also excluded. The upper reference range ($\geq$ 1.3 mg/dL) used here was more restrictive than that of a past study in men ($>$ 2.0 mg/dL) [6]. Also excluded was one individual who had chronic kidney disease that was $\geq$ stage 4 (estimated glomerular filtration rate $<$ 30 mL/min/1.73 m^2, after adjusting for body surface area). In addition, 395 people with a follow-up duration of $<$ 2 years between baseline and follow-up checkup were also excluded. Ultimately, 9667 subjects were enrolled. Blood samples were obtained following overnight fasting and assessed at the Center's laboratory.

The study was approved by the review board of the Yuport Medical Checkup Center and the participants' written informed consent for anonymous participation in epidemiological research was obtained at every evaluation.

Diagnosis of type 2 diabetes

T2D was diagnosed when the subject met at least one of the following criteria:

- FPG $\geq$ 7.0 mmol/L;
- HbA_{1c} $\geq$ 6.5%;
- diagnosis of diabetes by a physician.

Details of the FPG and HbA_{1c} analyses have been described elsewhere [10].

Creatinine

Creatinine levels were measured using enzymatic methods (reagents supplied by Mitsubishi Kagaku Iatron Inc., Tokyo, Japan). All study participants were classified into three subcategories according to tertiles of creatinine. For men, the categories were $\leq$ 0.7 mg/dL, 0.8 mg/dL and 0.9–1.2 mg/dL; for women, the categories were $\leq$ 0.5 mg/dL, 0.6 mg/dL and 0.7–1.1 mg/dL.

Statistical analysis

First, means $\pm$ standard deviations (SDs) were calculated for baseline characteristics. Next, crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for associations between baseline creatinine levels and T2D were estimated, using the Cox proportional-hazards model with follow-up years as the time scale. HRs were also adjusted for age, BMI, systolic blood pressure and baseline FPG as individual parameters; the latter two variables were added to robustly exclude the effect of prediabetes glomerular hyperfiltration. Next, to determine whether BMI modified the effects of reduced creatinine levels with respect to diabetes risk, the statistical interaction between BMI and creatinine was evaluated at a significance level of 0.10 by including an interaction term in the model [11]. The effects, stratified by BMI, were then analyzed using median BMI scores as cut-off values (23.32 kg/m^2 for men, 21.92 kg/m^2 for women) and SPSS version 22.0 J software (IBM Corp., Armonk, NY, USA). A P value $<$ 0.05 was considered statistically significant. In addition, baseline creatinine levels were modelled with a penalized spline term on a continuous variable (per 0.1-mg/dL increment), using the "coxph" function in the "survival" package and plotted with the spline against HRs, using the "plotHR" function in the "Greg" package of R version 3.3.2 software (R Foundation for Statistical Computing, Vienna, Austria). Smoothness (degree of freedom) was chosen from the term with two to four degrees of freedom, based on minimizing the Akaike information criterion.

As a further supplementary analysis, given that recent epidemiological studies have often employed age as the time scale [12], our analysis also estimated HRs accordingly.

Results

Table 1 presents the baseline characteristics and crude and adjusted HRs of diabetes incidence by baseline creatinine levels. During a mean follow-up period of 5.6 years, T2D was newly identified in 287 (5.5%) men and 115 (2.3%) women. Mean creatinine levels were 0.8 (SD: 0.1) mg/dL for men and 0.6 (SD: 0.1) mg/dL for women. The lowest creatinine levels among the study participants were 0.4 mg/dL and 0.3 mg/dL in men and women, respectively. BMIs were lower among those with lower creatinine levels in both genders.

Compared with participants with higher creatinine levels (reference), the HRs for diabetes were higher in participants with intermediate and low creatinine levels, even after adjusting for age, BMI, systolic blood pressure and baseline FPG. The adjusted HR in men with serum creatinine levels $\leq$ 0.7 mg/dL compared with 0.9–1.2 mg/dL was 1.40 (95% CI: 1.05–1.87) and the adjusted HR in women with creatinine levels $\leq$ 0.5 mg/dL compared with 0.7–1.1 mg/dL was 1.69 (95% CI: 1.04–2.76). Also, the HRs of study participants with low serum creatinine levels were higher than those with intermediate serum creatinine levels. In the BMI stratified analysis, the interaction terms between BMI and baseline creatinine levels for diabetes were statistically significant in women with the lowest creatinine levels (P = 0.08 for interaction). When baseline creatinine was modelled on a continuous variable, a reverse J-shaped curvilinear association was observed in men. In

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