Lower Serum Creatinine Is a New Risk Factor of Type 2 Diabetes

The Kansai Healthcare Study

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OBJECTIVE — Because skeletal muscle is one of the target tissues for insulin, skeletal muscle mass might be associated with type 2 diabetes. Serum creatinine is a possible surrogate marker of skeletal muscle mass. The purpose of this study was to determine whether serum creatinine level is associated with type 2 diabetes.

RESEARCH DESIGN AND METHODS — The study participants were nondiabetic Japanese men (n = 8,570) aged 40–55 years at entry. Type 2 diabetes was diagnosed if fasting plasma glucose was ≥126 mg/dl or if participants were taking oral hypoglycemic medication or insulin.

RESULTS — During the 4-year follow-up period, 877 men developed type 2 diabetes. Lower serum creatinine was associated with an increased risk of type 2 diabetes. The multiple-adjusted odds ratio for those who had serum creatinine levels between 0.40 and 0.60 mg/dl was 1.91 (95% CI 1.44–2.54) compared with those who had levels between 0.71 and 0.80 mg/dl.

CONCLUSIONS — Lower serum creatinine increased the risk of type 2 diabetes.

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Although skeletal muscle is one of the major target organs of insulin (1–3), to our knowledge, no prospective study has investigated the association between total skeletal muscle mass and type 2 diabetes. Serum creatinine is primarily a metabolite of creatine, almost all of which is located in skeletal muscle. Because the amount of creatine per unit of skeletal muscle mass is consistent and the breakdown rate of creatine is also consistent, plasma creatinine concentration is very stable and a direct reflection of skeletal muscle mass (4). If skeletal muscle mass is associated with type 2 diabetes, consequently, serum creatinine might also be associated with type 2 diabetes. Considering this hypothesis, we examined the prospective relationship between serum creatinine and type 2 diabetes in Japanese men.

RESEARCH DESIGN AND METHODS

The Kansai Healthcare Study is an ongoing cohort investigation designed to examine the risk factors for cardiometabolic diseases. The details of this study have been described previously (5). The protocol for this research was reviewed by the human subjects review committee at Osaka City University.

For the current analysis, study participants consisted of 11,063 Japanese men aged 40–55 years at entry who had fasting plasma glucose levels <126 mg/dl and serum creatinine levels <2.0 mg/dl and were not taking oral hypoglycemic medication or insulin. Follow-up examinations were conducted annually, and the follow-up period was 4 years. A total of 2,493 men were excluded because of loss to follow-up. The analytic cohort consisted of 8,570 men.

Blood samples were drawn after an overnight 12-h fast. Serum creatinine was mainly measured by an enzymatic method using a Hitachi 7350 automatic chemistry analyzer (Hitachi, Tokyo, Japan). Serum creatinine was also measured by the Jaffe method in 1,770 participants. We recalibrated the Jaffe method to the enzymatic method using the following formula: serum creatinine (mg/dl, enzymatic method) = 1.02 × serum creatinine (mg/dl, Jaffe method) − 0.25 (r = 0.9996). The normal range of serum creatinine by the enzymatic method was 0.6–1.1 mg/dl. BMI was calculated as the weight in kilograms divided by the square of height in meters.

Questionnaires about physical activity included the duration of the walk to work and leisure-time physical activity. Participants were classified as engaging in regular leisure-time physical activity at least once weekly or less than once weekly. Validation of the aforementioned questionnaires has been described in detail previously (5). Regarding smoking habits, participants were classified as nonsmokers, past smokers, or current smokers. Questions about alcohol intake included the weekly frequency of alcohol consumption and the usual amount of alcohol consumed on a daily basis. Alcohol intake was converted to total alcohol consumption (in grams of ethanol per day) using standard Japanese tables.

Type 2 diabetes at baseline and at the follow-up examination was diagnosed if the fasting plasma glucose level was ≥126 mg/dl or if participants were taking oral hypoglycemic medication or insulin (6).

We used multiple logistic regression analysis to estimate the odds ratio for the incidence of type 2 diabetes in relation to baseline variables. We calculated the 95% CI for each odds ratio, and P values were two tailed. Statistical analyses were per-

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Table 1—*Baseline characteristics according to serum creatinine levels and multivariate logistic regression models of the incidence of type 2 diabetes*

		Serum creatinine (mg/dl)				
	Total	0.40–0.60	0.61–0.70	0.71–0.80	0.81–0.90	0.91–1.60
n	8,570	699	2,101	3,046	1,837	887
Age (years)	47.8 ± 4.2	48.1 ± 4.0	47.7 ± 4.2	47.7 ± 4.2	47.7 ± 4.1	48.0 ± 4.1
Height (cm)	168.9 ± 5.6	167.6 ± 5.7	168.6 ± 5.7	169.1 ± 5.5	169.2 ± 5.4	169.4 ± 5.6
Weight (kg)	66.8 ± 9.4	63.9 ± 9.2	65.3 ± 9.7	67.0 ± 9.0	68.1 ± 9.1	69.6 ± 9.3
BMI (kg/m^2)	23.4 ± 2.9	22.7 ± 2.9	23.0 ± 3.0	23.4 ± 2.8	23.8 ± 2.7	24.2 ± 2.9
Fasting plasma glucose (mg/dl)	97.6 ± 9.5	97.7 ± 9.8	97.3 ± 9.4	97.6 ± 9.5	97.8 ± 9.2	98.1 ± 9.5
Daily alcohol consumption (g ethanol)	25.2 ± 21.9	29.0 ± 24.2	27.4 ± 22.6	25.2 ± 21.7	23.7 ± 21.3	20.2 ± 19.5
Drinking habit categories						
Nondrinkers	15.5	14.7	13.3	15.6	16.8	18.6
Light drinkers	19.3	15.6	18.0	18.9	20.4	24.5
Moderate drinkers	35.0	33.9	35.6	34.4	35.3	36.1
Heavy drinkers	30.1	35.8	33.1	31.1	27.5	20.9
Smoking habit						
Nonsmokers	21.5	12.7	18.2	21.3	24.9	29.5
Past smokers	22.4	14.3	17.8	22.7	27.1	29.2
Current smokers	56.1	73.0	64.0	56.0	48.0	41.3
Walk to work						
0–10 min	19.8	18.0	18.2	18.9	22.0	23.3
11–20 min	52.4	52.1	52.2	54.6	49.0	52.2
≥21 min	27.9	29.9	29.6	26.5	29.0	24.5
Regular leisure-time physical activity	18.1	10.0	15.8	17.9	21.7	23.1
Family history of diabetes	12.9	12.7	12.6	12.9	13.6	12.1
Incidence of type 2 diabetes	877 (10.2)	103 (14.7)	223 (10.6)	283 (9.3)	176 (9.6)	92 (10.4)
Total model						
Crude odds ratio (95% CI)		1.69 (1.32–2.15)	1.16 (0.96–1.40)	1.00	1.04 (0.85–1.26)	1.13 (0.88–1.45)
Multiple-adjusted odds ratio (95% CI)*		1.91 (1.44–2.54)	1.32 (1.07–1.63)	1.00	1.04 (0.83–1.30)	1.01 (0.76–1.35)
Stratified analysis according to median BMI						
BMI ≤23.31 kg/m^2	4,286					
Crude odds ratio (95% CI)		1.90 (1.31–2.76)	1.27 (0.94–1.71)	1.00	1.11 (0.79–1.57)	0.99 (0.61–1.62)
Multiple-adjusted odds ratio (95% CI)*		1.96 (1.28–2.98)	1.37 (0.98–1.91)	1.00	1.13 (0.78–1.65)	0.91 (0.53–1.56)
BMI >23.31 kg/m^2	4,284					
Crude odds ratio (95% CI)		1.78 (1.28–2.46)	1.20 (0.94–1.52)	1.00	0.95 (0.75–1.22)	1.06 (0.79–1.42)
Multiple-adjusted odds ratio (95% CI)*		1.85 (1.26–2.73)	1.29 (0.98–1.71)	1.00	0.99 (0.75–1.32)	1.05 (0.75–1.48)

Data are means ± SD, %, or *n* (%) unless otherwise indicated. In multiple logistic regression analysis, age, daily alcohol consumption, fasting plasma glucose, and serum creatinine showed a nonlinear association with the incidence of type 2 diabetes in all models. Therefore, we fit the models by using these variables categorized for easy understanding. *The multiple logistic regression model was adjusted for age (40–44, 45–49, or 50–55 years), BMI, fasting plasma glucose (<100, 100–109, or 110–125 mg/dl), daily alcohol consumption (nondrinkers, light drinkers [0.1–16.3 g ethanol/day], moderate drinkers [16.4–42.6 g ethanol/day], or heavy drinkers [42.7–115.0 g ethanol/day]), smoking habit (nonsmokers, past smokers, or current smokers), the duration of the walk to work (0–10, 11–20, or ≥21 min), regular leisure-time physical activity, and family history of diabetes.

formed using SPSS version 16.0 (SPSS, Chicago, IL).

RESULTS — During the 4-year follow-up period, 877 men developed type 2 diabetes. The characteristics of the study population are summarized in Table 1. The lowest category of serum creatinine levels (0.40–0.60 mg/dl) was associated with an increased risk of type 2 diabetes in multiple-adjusted models (Table 1). To assess whether body build modified the association between the low serum creatinine and the risk of type 2 diabetes, we stratified participants according to the median BMI (Table 1). In both groups, the lowest category of serum creatinine levels was associated with an increased risk of type 2 diabetes. No significant first-order interaction between serum creatinine and the other variables was observed.

CONCLUSIONS — Asians and Asian Americans have been reported to have a lower prevalence of obesity than Caucasians but a higher percentage of body fat at the same BMI (7,8). These reports suggest that Asians and Asian Americans might have a lower percentage of total

skeletal muscle mass than Caucasians at the same BMI level (7,8). Our results might explain in part how the pathogenesis of type 2 diabetes renders Asian Americans and Japanese at high risk for type 2 diabetes.

This study did not elucidate the reason why lower serum creatinine independently increased the risk of type 2 diabetes. As we hypothesized, lower serum creatinine might reflect a lower volume of skeletal muscle. Skeletal muscle is a major target tissue of insulin, and its insulin resistance leads to the development of type 2 diabetes (1–3). A lower volume of skeletal muscle would mean fewer target sites for insulin, and this may explain in part the pathogenesis of type 2 diabetes associated with lower serum creatine. Because all participants in our cohort were current employees of the same company and were not malnourished, it is hardly conceivable that the association between lower serum creatinine and the risk of diabetes is due to any dietary deficiency.

The present study had some limitations: First, other confounding variables such as fasting plasma insulin, dietary factors, and waist circumference might explain the association observed between serum creatinine and the incidence of type 2 diabetes. Second, because all participants were registered employees of the same company and members of a single ethnic group, our results may not be representative of the general population but may apply to Japanese-American men and also possibly other Asian-American and native Asian men. Our results may differ in women because of their lower levels of skeletal muscle mass.

In conclusion, lower serum creatinine was associated with an increased risk of type 2 diabetes. Because resistance training has been reported to be associated with skeletal muscle hypertrophy (9), it may be beneficial for subjects at high risk of type 2 diabetes due to low serum creatinine. To confirm these findings, further research on these associations is needed.

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