The Predictive Factor for Future Renal Replacement Therapy among the Working Generation

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Objective: Many patients undergoing renal replacement therapy (RRT) have had the cause since the working generation, but it has often been unnoticed. To reduce RRT patients, early detection of high-risk subjects, lifestyle modification, and appropriate treatment are desired. We aimed to reveal the situation about high-risk cases for future RRT and rapid estimated glomerular filtration rate (eGFR) decline cases (over -3 mL/min/1.73m^2/year) among the working generation, and detect predictive factors for both groups.
Methods: We prospectively observed five-year consecutive health checkup data of the employees at a steelworks in Japan. The risk for future RRT was estimated using annual change of eGFR (ΔeGFR) and expected remaining lifetime for each subject.
Results: Among 959 subjects, we identified 75 high-risk cases for RRT (7.8%) and 46 rapid eGFR decline cases (4.8%). In logistic regression analyses, urine protein level by dipstick test was an independent predictive factor for both high-risk cases for RRT (odds ratio 2.04) and rapid eGFR decline cases (odds ratio 2.23).
Conclusion: A considerable number of high-risk subjects were latent even in active workers. It was suggested that urine protein level was a predictive factor for RRT risk regardless of whether eGFR was preserved among the working generation.

Key words; chronic kidney disease, ΔeGFR, predictive factor, proteinuria, occupational health checkup

INTRODUCTION

The number of chronic kidney disease (CKD) patients is estimated to be 13.3 million in Japan, and dialysis patients are still rising along with the increase of the elderly. According to the data provided by the Japanese Society for Dialysis Therapy (JSDT), the mode of age at dialysis initiation reached 75–79 years in male and 80–84 years in female in 2017 [1]. However, many causes of CKD are closely related to lifestyle since working generation. As the effect of treatment after progression of CKD is limited, high-risk cases for future end stage kidney disease (ESKD) needing renal replacement therapy (RRT) should be detected at an early phase, and lifestyle modification and appropriate treatment are desired in those cases. Although many epidemiological studies on CKD progression using health checkup data of National Health Insurance have reported in Japan, so far there have been few reports on occupational health checkup targeting only the working generation.

MATERIALS AND METHODS

Study purpose, design, and subjects

To reveal the situation about rapid estimated glomerular filtration rate (eGFR) decline cases and high-risk cases for future RRT, and detect those predictive factors, we prospectively observed the results of occupational health checkups for the employees (aged 40 to 61 in 2014) at a steelworks in Hyogo prefecture from 2014 to 2018. Only those who had received all five consecutive annual health checkups were included in the present study.

Study procedure

For evaluation of kidney function, serum creatinine value had been measured by enzymatic method and had indicated to two decimal places in the health checkup. We calculated eGFR value for each subject by Japanese equation for eGFR from serum creatinine [2] as follows.

eGFR (mL/min/1.73m^2) = 194 × serum creatinine $^{-1.094}$ × age $^{-0.287}$ (if female: × 0.739) [2]

And then, we calculated average annual change of eGFR (ΔeGFR) based on the slope of the regression line of eGFR values of five consecutive health checkup data. Faster than -3.0 mL/min/1.73m^2/year of ΔeGFR was defined as "rapid eGFR decline cases" in the present study. We also calculated predicted eGFR at the end of life (predicted end eGFR) for each subject using the data of the age, the eGFR value, and the ΔeGFR.

The formula is as follows.

Predicted end eGFR = eGFR + (life expectancy - age) × ΔeGFR

With regard to life expectancy, the data of Japanese in 2017, male 81.1 and female 87.3 years old, were

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used. We defined the cases whose predicted end eGFR values would be less than 5 mL/min/1.73m^2 as "high-risk cases for RRT" in this study. Finally, we analyzed the relation between "each data of health checkup" and "high-risk cases for RRT and rapid eGFR decline cases".

Furthermore, we revealed the proportion of high-risk cases for RRT, rapid eGFR decline cases, and the cases with cardiovascular disease (CVD) including new onset cases, for each category of CKD severity classification presented in "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" issued by the Japanese Society of Nephrology [3].

Definition

As for diagnosis at baseline in 2014, hypertension was defined as systolic blood pressure higher than 140 mmHg or taking antihypertensive. Diabetes was defined as fasting blood glucose higher than 126 mg/dL, hemoglobin A1c (HbA1c) above 6.5%, or taking antidiabetics. Dyslipidemia was defined as serum low density lipoprotein (LDL) cholesterol higher than 140 mg/dL or taking lipid lowering medication. Overweight and underweight were defined as body mass index (BMI) higher than 25.0 kg/m^2 and less than 18.5 kg/m^2, respectively. As for the data during the observation period (between 2014 and 2018), such as systolic blood pressure, HbA1c, serum LDL cholesterol, and BMI, the average value of five consecutive health checkup data was used. Urine protein was evaluated in five levels as -, ±, 1+, 2+, and 3+ by dipstick urine test, and ± or higher was considered positive in this study. During the observation period, the highest value of urine protein in each subject was used for analysis.

Statistical analysis

We used the computer software application IBM SPSS Statistics 23 (IBM Corp. USA) for all statistical analyses. For continuous variables the significance of differences between two groups was analyzed using Student's T test. For categorical variables it was analyzed using Chi-square test. When the number of cases in any group was five or less, it was analyzed using Fisher's exact test. For multivariate analysis, logistic regression test was performed. A p value of less than 0.05 was considered to be statistically significant.

Compliance with ethical standards
Human and Animal Rights

All procedures performed in the present study involving human participants were in accordance with the ethical standards of the Institutional Review Board of Hyogo University (IRB approval number 13016) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by the author.

Informed Consent

Since the present study is a prospective observational study using only the data of health checkup excluding personal identification information, it does not involve invasion or intervention. The data could be linked to personal information on the company side, but not on researcher's side. Therefore, document or verbal consent from each study subject is not required. By posting documents at three conspicuous places at the site of health checkup in Kobe Steel, Ltd. Kakogawa Works (Kakogawa, Hyogo, Japan), we notified study subjects of study content so that they could easily understand it, and guaranteed opportunities for them to refuse it (opt out). If there was an offer that they would not want to be a subject of the study, since it was possible to match the data with individuals, only at the company side, we quickly asked the company to exclude the subject's data and did not use their data in this study.

RESULTS

Among 959 subjects who had been annually observed from 2014 to 2018, there were 63 cases (6.6%) of CKD stages G3–G5 and 29 cases (3.0%) of proteinuria with above 60 mL/min/1.73m^2 of eGFR at baseline in 2014. There were 364 cases (38.0%) of hypertension, 81 cases (8.4%) of diabetes, 388 cases of dyslipidemia (40.5%), and 316 cases of overweight (33.0%) at baseline.

We identified as many as 75 high-risk cases for RRT (7.8%). In comparison between high-risk cases for RRT and the others at the beginning of the observation, there were statistically significant differences in proteinuria ($p = 0.006$) and overweight ($p = 0.046$) (Table 1), but only the level of urine protein was an independent predictive factor (odds ratio 2.04, 95% confidence interval 1.18–3.52) in logistic regression analysis (Table 2). In those comparison during the observation period, there were statistically significant differences in proteinuria ($p = 0.002$) and above 25.0 kg/m^2 of average BMI ($p = 0.03$) (Table 3), but only the level of urine protein was an independent predictive factor (odds ratio 1.85, 95% confidence interval 1.35–2.54) in logistic regression analysis (Table 4).

We also identified 46 rapid eGFR decline cases (4.8%) among those 959 subjects. In comparison between rapid eGFR decline cases and the others during the observation period, there were statistically significant differences in proteinuria ($p < 0.001$) and average HbA1c ≥ 7.0% ($p = 0.002$) (Table 5), and both were independent predictive factors (odds ratio 2.23, 95% confidence interval 1.58–3.15 in the level of urine protein, odds ratio 3.06, 95% confidence interval 1.17–8.03 in average HbA1c ≥ 7.0%) in logistic regression analysis (Table 6).

Average ΔeGFR values in high-risk cases for RRT and the others were -3.4 mL/min/1.73m^2/year and 0.4 mL/min/1.73m^2/year, respectively.

The proportions of high-risk cases for RRT and rapid eGFR decline cases for each baseline age group are shown in Table 7. The proportion of high-risk cases for RRT tended to be higher in younger age group, though there was no statistically significant difference ($R^2 = 0.73$, $p = 0.07$). While, the proportion of rapid eGFR decline cases did not correlated with the age group at all ($R^2 = 0.06$, $p = 0.70$).

In the present study, in any comparison, there was no statistically significant difference in smoking habit, weight gain of over 10 kg from the age of 20, past history of CVD, and new onset of CVD.

Among 63 cases of CKD stages G3–G5, average ΔeGFR were -2.0 mL/min/1.73m^2/year in those with proteinuria ($N = 6$) and 0.1 mL/min/1.73m^2/year in

Table 1 Baseline data of high-risk cases for future renal replacement therapy and the others.

	High risk cases (N = 75)	The others (N = 884)	P value
Male	97.3%	94.8%	0.33
Age (year)	48.8 (± 7.5)	50.9 (± 7.6)	0.02*
S-Cr (mg/dL)	0.91 (± 0.34)	0.84 (± 0.13)	0.08
eGFR (mL/min/1.73m^2)	75.1 (± 16.1)	76.6 (± 11.6)	0.44
Proteinuria (N, %)	7 (9.3%)	28 (3.2%)	0.006*
3 +	0	0	
2 +	1	1	
1 +	2	6	
±	4	21	
SBP (mmHg)	134.0 (± 17.7)	132.9 (± 18.5)	0.60
HbA1c (%)	5.7 (± 1.2)	5.5 (± 0.6)	0.31
S-LDL chol (mg/dL)	124.9 (± 33.2)	128.3 (± 29.5)	0.35
BMI (kg/m^2)	24.4 (± 3.9)	23.9 (± 3.5)	0.31
Hypertension	48.0%	37.1%	0.06
Diabetes	10.7%	8.3%	0.47
Dyslipidemia	37.3%	40.7%	0.57
Overweight	42.7%	32.1%	0.046*
Underweight	4.0%	2.3%	0.19
Past CVD history	4.0%	4.0%	1.00
Weight gain (≥ 10kg)	40.0%	33.5%	0.25
Smoking history	69.3%	66.9%	0.66

S-Cr: serum creatinine; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; HbA1c: hemoglobin A1c; S-LDL-chol: serum low density lipoprotein cholesterol; BMI: body mass index; CVD: cardiovascular disease
*p < 0.05

Table 2 Comparison of baseline data between high-risk cases for future renal replacement therapy and the others by logistic regression analysis.

	P value	Odds ratio	95% CI
Male	0.28	3.05	0.41–22.73
Urine protein level	0.01*	2.04	1.18–3.52
Hypertension	0.21	1.38	0.83–2.28
Overweight	0.18	1.42	0.86–2.35

95% CI: 95% confidence interval
*p < 0.05

Table 3 The data during the observation period of high-risk cases for future renal replacement therapy and the others.

	High risk cases (N = 75)	The others (N = 884)	P value
ΔeGFR (mL/min/1.73m^2/year)	-3.4 (± 1.2)	0.4 (± 1.6)	< 0.001*
Final S-Cr (mg/dL)	1.25 (± 1.47)	0.82 (± 0.13)	0.01*
Final eGFR (mL/min/1.73m^2)	61.5(± 16.4)	77.5 (± 12.6)	< 0.001*
Proteinuria (N, %)	16 (21.3%)	88 (10.0%)	0.002*
3 +	1	0	
2 +	3	6	
1 +	5	21	
±	7	61	
Average SBP (mmHg)	135.3 (± 15.2)	134.2 (± 16.3)	0.60
Average HbA1c (%)	5.7 (± 0.9)	5.6 (± 0.6)	0.45
Average S-LDL chol	126.2 (± 24.3)	126.2 (± 26.1)	0.99
Average BMI (kg/m^2)	24.6 (± 3.8)	24.1 (± 3.5)	0.20
Average SBP ≥ 140 mmHg	36.0%	33.1%	0.62
Average HbA1c ≥ 7.0 %	6.7%	4.0%	0.23
Average S-LDL chol ≥ 140 mg/dL	28.0%	31.1%	0.58
Average BMI ≥ 25.0 kg/m^2	46.7%	35.1%	0.03*
New onset CVD	2.7%	1.5%	0.33
Current smoker	33.3%	37.6%	0.47

ΔeGFR: The change of estimated glomerular filtration rate; Final S-Cr: serum creatinine at the end of the observation; Final eGFR: estimated glomerular filtration rate at the end of the observation; SBP: systolic blood pressure; HbA1c: hemoglobin A1c; S-LDL chol: serum low density lipoprotein cholesterol; BMI: body mass index; CVD: cardiovascular disease
Proteinuria: The highest value of urine protein in each subject was used.
*p < 0.05

Table 4 Comparison of the data during the observation period between high-risk cases for future renal replacement therapy and the others by logistic regression analysis.

	P value	Odds ratio	95% CI
Male	0.31	2.84	0.38–21.28
Urine protein level	< 0.001*	1.85	1.35–2.54
Average BMI ≥ 25.0 kg/m^2	0.12	1.48	0.91–2.43

95% CI: 95% confidence interval; BMI: body mass index
*p < 0.05

Table 5 The data of rapid eGFR decline cases and the others.

	Rapid eGFR decline (N = 46)	The others (N = 913)	P value
At baseline (2014)			
Male	97.8%	94.9%	0.72
Age (year)	52.1 (± 7.3)	50.7 (± 7.6)	0.24
Baseline S-Cr (mg/dL)	0.88 (± 0.39)	0.85 (± 0.13)	0.63
Baseline eGFR (mL/min/1.73m^2)	78.2 (± 16.6)	76.4 (± 11.8)	0.48
Baseline proteinuria (N, %)	6 (13.0%)	29 (3.2%)	< 0.001*
3 +	0	0	
2 +	1	1	
1 +	2	6	
±	3	22	
SBP (mmHg)	133.5 (± 17.9)	132.9 (± 18.5)	0.85
HbA1c (%)	5.9 (± 1.4)	5.5 (± 0.6)	0.12
S-LDL chol (mg/dL)	122.7 (± 35.1)	128.3 (± 29.5)	0.21
BMI (kg/m^2)	24.2 (± 4.0)	24.0 (± 3.5)	0.63
Hypertension	45.7%	37.6%	0.27
Diabetes	17.4%	8.0%	0.03*
Dyslipidemia	39.1%	40.5%	0.85
Overweight	37.8%	33.6%	0.56
Underweight	3.4%	3.6%	1.00
Past CVD history	2.2%	4.1%	1.00
Weight gain (≥ 10kg)	34.8%	34.0%	0.91
Smoking history	78.3%	66.5%	0.10
During the observation (2014–2018)			
Proteinuria	12 (26.1%)	92 (10.1%)	< 0.001*
3 +	1	0	
2 +	3	6	
1 +	4	22	
±	4	64	
Average SBP (mmHg)	133.7 (± 14.3)	134.3 (± 16.3)	0.78
Average HbA1c (%)	5.9 (± 1.1)	5.6 (± 0.6)	0.11
Average S-LDL chol	125.2 (± 28.6)	126.3 (± 25.8)	0.79
Average BMI (kg/m^2)	24.5 (± 3.8)	24.1 (± 3.5)	0.51
Average SBP ≥ 140 mmHg	32.6%	33.4%	0.91
Average HbA1c ≥ 7.0%	13.0%	3.7%	0.002*
Average S-LDL chol ≥ 140 mg/dL	28.3%	31.0%	0.70
Average BMI ≥ 25.0 kg/m^2	39.1%	35.8%	0.67
New onset CVD	2.2%	1.5%	0.73
Current smoker	45.7%	36.8%	0.23
At the end of the observation (2018)			
Final S-Cr (mg/dL)	1.34 (± 1.86)	0.83 (± 0.15)	0.07
Final eGFR (mL/min/1.73m^2)	61.5 (± 17.6)	77.0 (± 13.0)	< 0.001*
High risk of RRT	93.5%	3.5%	< 0.001*

eGFR: estimated glomerular filtration rate; S-Cr: serum creatinine; SBP: systolic blood pressure; HbA1c: hemoglobin A1c; S-LDL-chol: serum low density lipoprotein cholesterol; BMI: body mass index; CVD: cardiovascular disease; RRT: renal replacement therapy
Proteinuria: The highest value of urine protein in each subject was used.
*p < 0.05

Table 6 Comparison of the data during the observation period between rapid eGFR decline cases and the others by logistic regression analysis.

	P value	Odds ratio	95% CI
Male	0.51	1.96	0.26–14.71
Urine protein level	< 0.001*	2.23	1.58–3.15
Average HbA1c ≥ 7.0 %	0.02*	3.06	1.17–8.03

eGFR: estimated glomerular filtration rate; 95% CI: 95% confidence interval; HbA1c: hemoglobin A1c
*p < 0.05

Table 7 The proportions of high-risk cases for future renal replacement therapy and rapid eGFR decline cases for each age group.

Age		High risk cases	Rapid eGFR decline
40–44	(N = 311)	10.6%	3.9%
45–49	(N = 128)	7.8%	3.1%
50–54	(N = 90)	5.6%	4.4%
55–59	(N = 300)	7.7%	7.3%
60–61	(N = 130)	3.1%	3.1%
Correlation with age group		$R^2 = 0.73$ p = 0.07	$R^2 = 0.06$ p = 0.70

eGFR: estimated glomerular filtration rate; Age: the age at baseline (2014)
R^2: coefficient of determination

Table 8 Average change of eGFR, high-risk cases for renal replacement therapy, and the cases with cardiovascular disease for each category of CKD severity classification.

	CKD stage	Total cases	Average ΔeGFR (mL/min/1.73m²/year)	High risk for RRT	New onset CVD	Total CVD cases
Green	G1A1, G2A1	867	0.2	62 (7.2%)	11 (1.3%)	37 (4.3%)
Yellow	G1A2, G2A2, G3aA1	78	0.3	8 (10.3%)	2 (2.6%)	11 (14.1%)
Orange	G1A3, G2A3, G3aA2, G3bA1	8	-1.1	3 (37.5%)	0 (0%)	0 (0%)
Red	Others	6	-2.0	2 (33.3%)	2 (33.3%)	2 (33.3%)

CKD: chronic kidney disease; ΔeGFR: The change of estimated glomerular filtration rate; RRT: renal replacement therapy; CVD: cardiovascular disease

those without proteinuria (N = 57) (p = 0.03). As for CKD severity classification, in order from most severe category to mild category, the severity was expressed as red (CKD stages G1A1, G2A1), orange (G1A2, G2A2, G3aA1), yellow (G1A3, G2A3, G3aA2, G3bA1), and green (the other stages) [3]. Average ΔeGFR values were -2.0, -1.1, 0.3, and 0.2 mL/min/1.73m²/year, and the proportion of high-risk cases for RRT were 33.3%, 37.5%, 10.3%, and 7.2% in red, orange, yellow, and green categories, respectively (Table 8). Prevalence rate of CVD including new onset CVD during the observation period was 33.3%, 0%, 14.1%, and 4.3% in each category (Table 8).

Among 81 cases of diabetes, 18 cases (22.2%) had proteinuria, and four cases (6.3%) showed rapid eGFR decline regardless of without proteinuria.

DISCUSSION

We prospectively observed 959 employees at a steelworks for five consecutive years. Despite targeting only active workers, there were a considerable number of potential high-risk cases for future ESKD needing RRT. But many of them may not have been aware of the risk because 89.3% of them had higher than 60 mL/min/1.73m² of eGFR at baseline. In fact, among high-risk cases for RRT, the rate of the subjects who had regularly followed up by internists was only 49.3%.

In comparison between high-risk cases for RRT and the others in logistic regression analysis, only the level of urine protein was an independent predictive factor both at baseline and during the observation period. It was suggested that with each increase in urine protein level, future RRT risk increased 2.04 times at baseline and 1.85 times during the observation period, but to confirm the relation further studies are required because the numbers of higher levels of urine protein were very small in this study. There was no difference in eGFR at baseline between the two groups. It was speculated that the level of urine protein was more important rather than eGFR value itself to predict the risk among the working generation. The risk for future RRT can be estimated by present eGFR value, ΔeGFR, and expected remaining lifetime. Compared to the elderly, since expected remaining lifetime was very long in the working generation, it was considered that ΔeGFR rather than eGFR value greatly contributed to kidney prognosis. From the results we considered that, in addition to being the cause and the consequence of decreased kidney function, proteinuria was the most significant factor affecting ΔeGFR. In general, many of the cases with preserved eGFR and proteinuria may not visit physicians, but we should let them know that a considerable number of high-risk cases for RRT were latent among them.

With regard to rapid eGFR decline, it was reported that in patients with type 2 diabetes where yearly eGFR decline rate was over 7.5%, renal prognosis may have been poor [4]. While, in Japanese general population, decline in eGFR was 0.36 mL/min/1.73m²/year [5]. Past studies suggested that eGFR decline rates of approximately 0.3 to 1 mL/min/1.73m²/year among participants without proteinuria or comorbidity and the rates of approximately two to three times higher among participants with proteinuria or comorbidity [6]. Therefore, in the present study, faster than -3.0 mL/min/1.73m²/year of ΔeGFR was defined as "rapid eGFR decline cases". In comparison between rapid eGFR decline cases and the others in logistic regression analysis, the level of urine protein during the observation period was an independent predictive factor. It was suggested that with each increase in urine protein level, the risk for rapid eGFR decline increased 2.23 times, but the numbers of higher levels of urine protein were very small as same as the result regarding the risk for future RRT. Baseline diabetes and above 7.0% of average HbA1c during the observation period

were also independent predictive factors.

Among rapid eGFR decline cases, 93.5% of them fell into the category of high-risk cases for future RRT probably due to the long expected remaining lifetime among the working generation because the prediction formula for high-risk cases for RRT used in this study included subject's age. The proportion of high-risk cases for RRT tended to be higher in younger age group (but not statistically significant difference), while the proportion of rapid eGFR decline cases did not correlated with the age group at all. For the reason stated earlier, the risk was evaluated to be higher as the baseline age was younger and the expected remaining lifetime was longer, even for comparable ΔeGFR.

In this study, there were statistically significant differences in the proportion of overweight cases between high-risk cases for RRT and the others both at baseline and during the observation period, but overweight was not determined as an independent predictive factor in logistic regression analysis. Since overweight was strongly related to hypertension ($p < 0.001$), HbA1c ($p < 0.001$), serum LDL cholesterol ($P = 0.002$), and eGFR ($p = 0.005$) at baseline and average systolic blood pressure ($p < 0.001$), average HbA1c ($p < 0.001$), the presence of proteinuria ($p = 0.01$), and average serum LDL cholesterol ($p = 0.02$) during the observation period, overweight was considered to be a complex finding of various factors associated with CKD progression. While, when the set of proteinuria or overweight was used in screening for high-risk cases for RRT, about half of them could be detected (sensitivity 49.3% and specificity 66.4%). In this way, though it is uncertain whether overweight is a risk factor for CKD progression, overweight may be a useful indicator in screening for high-risk cases for RRT.

The relation between obesity and CKD has not been concluded yet. In large-scale longitudinal studies, BMI was related to the development of CKD [7], and higher BMI were associated with rapid eGFR decline [8]. Hsu CY *et al*. reported that overweight was a significant risk factor for ESKD (adjusted relative risk 1.87, 95% confidence interval 1.64–2.14) [9]. On the other hand, there were several reports that obesity without metabolic syndrome did not increase the risk for ESKD [10, 11]. And underweight may also be associated with poor kidney prognosis through malnutrition. In the present study, as the elderly were not included, the proportion of overweight was 33.0% and underweight was 2.4%, which was more overweight cases and less underweight cases compared to the data of across Japan (overweight 30.7% in male and 21.9% in female, underweight 4.0% in male and 10.3% in female) [12]. Overall, the lower negative impact of underweight may have resulted in a greater risk of overweight in this study. In addition, most of previous studies on obesity and CKD were reported overseas, but it was considered that the effect of obesity on CKD in Japanese may have been different from western people with different physique.

Additionally, it was shown that CKD patients with metabolic syndrome had been at increased risk for ESKD [10, 11]. The health checkup data used in this study did not include abdominal circumference, serum high density lipoprotein (HDL) cholesterol, and triglyceride, so we could not confirm whether each subject was metabolic syndrome. Therefore, it could not be denied that not only overweight itself but also metabolic syndrome had affected the results in this study. In the working generation, to confirm whether overweight itself is a risk factor for RRT in CKD patients of Japanese, further investigation is required.

With regard to CKD severity classification, though the predicted risk for RRT and the incidence rate of CVD tended to correlate with the severity presented in "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" [3], we could not discuss it because the numbers of cases in some categories were very small in the present study.

The prevalence rate of diabetes at baseline was 8.4%, which was lower than the national average rate in Japanese, because the elderly was not included and postprandial hyperglycemia was not counted in this study. In the observational study on type 2 diabetes of Japanese, it was reported that the proportion of microalbuminuria, overt albuminuria with below 2.0 mg/dL of serum creatinine were 31.6% and 7.4%, respectively [13]. In the present study, only 22.2% of diabetic cases had proteinuria, but it seemed that a substantial number of mild albuminuria was missed because dipstick urine test had been used to detect proteinuria.

Meanwhile, in recent decades, it has been noted that "rapid eGFR decliner", whose kidney function declines rapidly without proteinuria, is existing among diabetic patients [14]. In the observational study on type 1 diabetes, it was reported that in 9% of the patients without albuminuria eGFR declined more than 3.3%/year [15]. Among US adults with diabetes from 1988 to 2014, the prevalence of reduced eGFR increased, though the prevalence of albuminuria declined [16]. Regarding of the pathogenesis, the possibility of involvement of renal atherosclerosis and lipid toxicity was suggested [17]. Also in the present study, we identified rapid eGFR decline cases in 6.3% of diabetic cases without proteinuria. To avoid missing such cases, risk assessment for future RRT using ΔeGFR is necessary.

In conclusion, a considerable number of high-risk cases for future RRT were latent even in active workers. Many of them may have tended not to be aware of the risk, and about half of them had not visited internists regularly. Therefore, to assess potential risk, the use of ΔeGFR seems essential. However, eGFR value calculated using serum creatinine value often fluctuate by slight change in circulating plasma volume etc. In this study, to reduce such error as much as possible, we determined ΔeGFR using the slope of the regression line of five consecutive eGFR values. To evaluate ΔeGFR more accurately, further validation on the calculation method for it is needed. Since long-term observation of eGFR over several years is required for ΔeGFR estimation, the set of proteinuria or overweight may be useful in simple screening for the high-risk cases. In the cases with increase of urine protein even if active workers with preserved eGFR, sufficient attention should be paid.

In this study, we had tried to analyze the relation between ΔeGFR and various clinical indicators, such as systolic blood pressure, serum LDL cholesterol, and HbA1c, for each level of each indicator. But we could not conclude it because most of subjects with abnormal findings had visited medical facilities regularly with appropriate advice by industrial physicians of the com-

pany, and thus the number of poorly managed cases was extremely small. For example, all diabetic patients with HbA1c 7.0% or more, had visited internists regularly, and average HbA1c value of all diabetic patients was as very good as 6.6%.

As limitations of this study, we should mention that the data was from single workplace, and most subjects were males (95.0%).

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CONFLICT OF INTEREST

The author has declared that no conflict of interest exists.

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