Association of dipstick proteinuria with all-cause mortality in a large cohort of general population in Japan

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INTRODUCTION

Specific Health Check and Guidance (Tokutei-Kenshin) aimed to decrease the socio-economic burden related to obesity has been conducted since 2008 in Japan. In this nationwide general screening program, debates on selecting essential laboratory tests including chronic kidney disease (CKD) measures are continuing.

Currently, dipstick urine test but not serum creatinine is one of the mandatory laboratory examinations. Dipstick proteinuria is useful for predicting incidence of ESRD in general screening.

However, only a few paper published on the association of dipstick proteinuria with mortality.

AIM OF THE Study

We examined the association of dipstick proteinuria, from (-) to (3+ and over) on mortality among the participants of Tokutei-Kenshin.

Furthermore, the relationships between cancer death and CKD measures such as proteinuria and eGFR were also investigated

Methods

Screened Population

Specific Health Check and Guidance program, so-called Tokutei-Kenshin, was started on 2008 in Japan for adult population with age 40 to 74 years old. Details of this cohort have been published previously1. Furthermore; we identified death cases among the screened subjects up to the end of 2012.

In brief, databases included in this study were from 6 prefectures and ethical approval was obtained from the respective institute review board. Screening participants are eligible for public support for the standard health checks, such as measurement of height, weight, waist circumference, blood pressure, fasting blood glucose, hemoglobin A1c, triglyceride, serum high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, glutamyl oxaloacetic transaminase (GOT), glutamate pyruvate transaminase (GPT), gamma-glutamyl transpeptidase (GTP), hemoglobin, uric acid, serum creatinine, dipstick urine test for proteinuria, hematuria, and glycosuria. Proteinuria was coded as (-), (±), (1+), (2+), and (3+ and over) and positive proteinuria was defined as 1+ and over. Serum creatinine was measured using the enzymatic method. Glomerular filtration rate was calculated using the formula of the Japanese Society of Nephrology43 . Kidney function was categorized into 5 groups:≥90, 60-89, 45-59. 30-44, and <30 ml/min/1.73m^2.

Screened Population

Blood pressure was measured in all cohorts using a standard sphygmomanometer. Hypertension was defined as 140/90 mmHg and over or on antihypertensive medication. DM was defined as hemoglobin A1c≥ 6.1% (JDS) or on medication for DM. HbA1c in NGSP value is plus 0.4 to HbA1c JDS value.

National database of death certificate

Upon permission from the Ministry of Health and Welfare, we obtained the database of the death certificate between 2008 and 2012 (total registered were about 6 million). The dataset included sex, birthdate, place of death, data of death and causes of death by ICD-10. Database was solely used and managed by Chiho Iseki and the principal analyses to identify those died among screened subjects were completed by March 2015.

Outcomes

By using two registries, we identified candidates who died after participating at the screening in each district. Identifiers such as sex, birthdate, date of death and the place of death were used and confirmed at each center that has performed the screening

Statistical analysis

Data were analyzed with SAS/STAT software (version 6.03, SAS Institute, Tokyo, Japan) and JMP software (version 10, SAS Institute, Tokyo, Japan). One-factor analysis of variance (ANOVA) test and Chi-squared test were performed to compare the significance of discrete variables. Kaplan-Meier method and log-rank test was used to compare the cumulative probability. Cox-proportional hazard model analysis was done after adjusting for age, sex, BMI, eGFR, proteinuria, and other pertinent variables. Hazard ratio (HR) and 95% confidence interval (CI) were calculated. A P value of less than 0.05 was considered statistically significant in all analyses

Results

Demographics and clinical characteristics

Baseline characteristics by eGFR levels from a total of 295,297 screened subjects from 6 districts were summarized in Table 1. Prevalence of proteinuria increased from 4.3% in eGFR≥90 ml/min/1.73m^2 to 58.6% in eGFR<30 ml/min/1.73m^2. Measurement of serum creatinine was not mandatory, however it was available in 81% of the total cohort (N=239,274). The median eGFR was 73.8 ml/min/1.73m^2 and those with severely low eGFR of <15 ml/min/1.73m^2 was 241 (0.1%). Urine test for dipstick proteinuria was mandatory, but urine sample was not available in 544 (0.2% of the total) subjects. Proteinuria was positive in 5.3%. Baseline characteristics by dipstick proteinuria were summarized in Table 2. Mean values of eGFR decrease gradually from 74.5 ml/min/1.73m^2 in proteinuria (-) to 60.7 ml/min/1.73m^2 in proteinuria (3+ and over).

Death risk by eGFR and dipstick proteinuria

Death risk by eGFR level was summarized in Table 3. Risk of death was lowest among those with eGFR 60 to 89 ml/min/1.73m^2. Survival curves by eGFR are shown in Figure 1. Death risk by dipstick proteinuria was summarized in Table 4. Higher the proteinuria, risk of death increased. Even with dipstick (+/-) proteinuria, the risk of death increased significantly: the hazard risk 1.301 (95% confidence interval, 1.145-1.478, P<0.001). Survival curves by dipstick proteinuria are shown in Figure 2. Death risk was further estimated with the combination of dipstick proteinuria and eGFR level. (Table 5) Survival curves by this combination are shown in Figure 3.

Causes of death

The leading cause of death was neoplasm, but the fraction was decreased as lowering eGFR and increasing proteinuria. On the contrarily, the fraction of death due to CVD increase with lowering eGFR and increasing proteinuria. Leading cause of death was neoplasm in subjects with eGFR≥60 and proteinuria (-), however it was lowest among subjects with eGFR<60 and proteinuria (+). Causes of death were not different between men and women. Death due to neoplasm was significantly increased among elderly subjects.

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Conflict of interest

The authors have declared that no conflict of interest exists

Table 1. Characteristics of screened subjects (N=295,297) by eGFR.

eGFR level, ml/min/1.73m^2	≥90	60-89	45-59	30-44	<30	P for trend
Number of subject	38,190	163,313	33,702	3,340	729	
Age, years	60.1±8.8	63.4±8.6	66.7±6.1	68.4±5.1	66.9±7.0	<0.001
Men, %	29.2	41.4	50.4	54.9	49.9	<0.001
Body height, cm	155.5±8.6	157.1±8.5	157.8±8.3	157.3±8.5	156.8±8.5	<0.001
Body weight, kg	56.0±10.6	57.6±10.5	59.4±10.2	60.6±10.7	58.8±10.6	<0.001
Body mass index, kg/m^2	23.1±3.5	23.3±3.3	23.8±3.2	24.4±3.5	23.9±3.6	<0.001
Waist circumference, cm	83.8±9.7	84.4±9.1	85.8±8.8	87.4±9.4	86.2±10.0	<0.001
Systolic blood pressure, mmHg	127.5±17.7	128.4±17.6	130.8±17.5	133.0±17.6	135.3±18.5	<0.001
Diastolic blood pressure, mmHg	75.6±11.0	76.2±10.7	77.2±10.7	77.0±11.2	76.3±11.6	<0.001
AST, U/L	24.3±13.6	24.1±11.9	24.5±10.2	24.9±13.2	21.9±8.9	<0.001
GPT, U/L	23.0±16.8	22.0±14.8	21.7±13.2	21.4±14.5	18.4±11.6	<0.001
Γ-GTP, U/L	40.1±57.0	36.2±45.1	35.7±41.5	38.4±49.4	34.3±43.1	<0.001
Triglyceride, mg/dL	118.5±92.9	118.7±79.8	125.6±77.6	140.4±84.1	149.2±126.2	<0.001
HDL-cholesterol, mg/dL	63.0±15.8	61.6±15.9	59.2±15.6	55.4±15.0	54.2±16.1	<0.001
LDL-cholesterol, mg/dL	124.3±31.5	125.6±30.3	126.7±30.2	122.5±31.6	117.4±35.2	<0.001
Fasting blood glucose, mg/dL	99.4±26.9	97.0±19.2	97.7±18.1	100.6±23.2	102.2±31.9	<0.001
Hemoglobin, g/dL	13.3±1.5	13.6±1.4	13.7±1.4	13.2±1.7	11.6±1.6	<0.001
HbA1c, %	5.4±0.9	5.3±0.6	5.4±0.6	5.5±0.8	5.5±0.8	<0.001
Serum creatinine, mg/dL	0.53±0.08	0.71±0.11	0.94±0.13	1.26±0.21	3.34±2.59	<0.001
Uric Acid, mg/dL	4.7±1.3	5.2±1.3	6.0±1.4	6.7±1.6	6.5±2.4	<0.001
Proteinuria, ≥1+ (%)	4.3	4.5	8.5	25.5	58.6	<0.001
Hematuria, ≥1+ (%)	17.2	17.3	18.5	21.3	26.8	<0.001
Glycosuria, ≥1+ (%)	3.3	1.7	1.6	3.3	7.9	<0.001
Lifestyle						
Smoking, %	16.9	13.4	9.7	10.3	10.9	<0.001
Drinking, %	43.0	44.6	43.4	38.4	35.2	<0.001
Walking, %	49.4	52.5	55.3	53.4	49.1	<0.001
Exercise, %	35.8	44.5	52.4	50.1	39.1	<0.001
Medication						
Hypotensives, %	21.4	25.9	37.0	60.1	72.8	<0.001
Lipid Lowering, %	11.4	13.0	17.0	25.3	26.1	<0.001
Diabetes Mellitus, %	5.2	4.3	5.8	12.3	18.4	<0.001
Past History						
Stroke, %	2.2	3.0	5.2	9.6	11.2	<0.001
Heart Disease, %	3.8	5.5	8.8	13.8	15.9	<0.001
Kidney Disease, %	0.6	0.6	1.2	4.5	28.5	<0.001

Mean ± SD

Table 2. Characteristics of screened subjects (N=295,297) by dipstick proteinuria.

Dipstick Proteinuria	(-)	(+/-)	(1+)	(2+)	(3+ and over)	P for trend
Number of subject	257,040	21,981	10,802	3,753	1,177	
Age, years	63.5±8.3	63.7±8.7	64.5±8.3	65.1±7.9	65.1±7.9	<0.001
Men, %	38.8	48.4	55.3	63.0	62.9	<0.001
Body height, cm	156.8±8.5	157.9±8.6	158.3±8.6	158.7±8.7	158.4±8.8	<0.001
Body weight, kg	57.2±10.3	59.4±10.9	61.3±11.4	63.2±11.7	63.6±13.0	<0.001
Body mass index, kg/m^2	23.2 ±3.2	23.8±3.5	24.4±3.8	25.0±3.9	25.3±4.3	<0.001
Waist circumference, cm	84.0±9.0	85.6±9.4	87.1±9.8	88.6±9.9	88.7±11.1	<0.001
Systolic blood pressure, mmHg	128.3±17.3	130.6±17.9	135.1±18.6	139.2±19.0	139.3±19.6	<0.001
Diastolic blood pressure, mmHg	76.2±10.7	77.2±11.0	79.4±11.5	81.0±11.9	80.2±11.6	<0.001
AST, U/L	24.1±11.0	25.1±14.7	26.4±15.3	28.2±25.4	26.8±19.4	<0.001
GPT, U/L	21.7±14.1	23.5±17.3	25.0±19.1	26.4±17.8	24.8±17.7	<0.001
Γ-GTP, U/L	35.2±43.3	41.9±55.9	48.4±66.7	58.0±83.3	54.3±83.7	<0.001
Triglyceride, mg/dL	118.6±78.6	125.4±90.2	137.7±100.1	153.7±114.6	164.7±119.3	<0.001
HDL-cholesterol, mg/dL	61.8±15.9	60.1±15.9	58.5±16.5	56.6±15.8	56.2±16.7	<0.001
LDL-cholesterol, mg/dL	125.7±30.4	124.4±31.2	124.9±32.3	124.5±33.4	127.6±36.7	<0.001
Fasting blood glucose, mg/dL	96.7±18.5	100.3±24.3	106.8±33.0	113.1±39.0	117.0±42.9	<0.001
Hemoglobin, g/dL	13.6±1.4	13.7±1.5	13.9±1.7	13.9±1.8	13.8±1.8	<0.001
HbA1c, %	5.3±0.6	5.4±0.8	5.6±1.1	5.8±1.3	6.0±1.4	<0.001
Serum creatinine, mg/dL	0.72±0.20	0.75±0.26	0.81±0.37	0.99±0.81	1.13±0.92	<0.001
eGFR, ml/min/1.73m^2	74.5±14.8	73.4±16.2	70.5±18.6	64.4±21.3	60.7±25.0	<0.001
Uric Acid, mg/dL	5.2±1.4	5.4±1.4	5.7±1.5	6.1±1.7	6.3±1.6	<0.001
Hematuria, ≥1+ (%)	16.0	22.3	28.9	32.2	59.5	<0.001
Glycosuria, ≥1+ (%)	1.7	2.9	6.4	9.4	14.8	<0.001
Lifestyle						
Smoking, %	13.0	16.2	19.0	20.3	20.5	<0.001
Drinking, %	43.7	47.5	49.0	49.9	45.8	<0.001
Walking, %	51.4	51.8	48.8	51.1	48.0	0.008
Exercise, %	43.7	44.8	42.8	42.8	42.7	0.009
Medication						
Hypotensives, %	26.3	33.8	42.5	55.2	59.5	<0.001
Lipid Lowering, %	14.0	15.1	17.0	20.6	23.4	<0.001
Diabetes Mellitus, %	4.2	6.2	10.3	16.3	23.0	<0.001
Past History						
Stroke, %	3.1	3.9	5.2	7.3	8.0	<0.001
Heart Disease, %	5.6	6.6	8.5	10.0	11.2	<0.001
Kidney Disease, %	0.8	0.6	1.8	4.5	5.9	<0.001

Mean ± SD

Table 3. Results of the multivariate Cox analyses on the risk of death by eGFR level: Hazard ratio (95% confidence interval, CI) was calculated after adjusting for sex, age, body mass index, dipstick proteinuria, comorbid condition (DM, hypertension, and dyslipidemia), past history (stroke, heart disease, and kidney disease), and lifestyle (smoking, drinking, walking, and exercise). Serum creatinine was available in 81% of the total cohort (N=239,274).

eGFR level	Participants	Death	Death rate, %	Hazard Ratio	95% CI	P value
≥90	38,183	434	1.1	reference		
60 to 89	163,320	1,778	1.1	0.756	0.676-0.847	<0.001
45 to 59	33,690	518	1.5	0.897	0.780-1.031	ns.
30 to 44	3,352	115	3.4	1.494	1.185-1.883	0.001
<30	729	40	5.5	1.803	1.211-2.685	0.001
Total	239,274	2,885	1.2			

eGFR, ml/min/1.73m^2.CI denotes confidence interval. ns., not significant.

Table 4. Results of the multivariate Cox analyses on the risk of death by dipstick proteinuria: Hazard ratio (95% confidence interval, CI) was calculated after adjusting for sex, age, body mass index, eGFR level, comorbid condition (DM, hypertension, and dyslipidemia), past history (stroke, heart disease, and kidney disease), and lifestyle (smoking, drinking, walking, and exercise). Urine sample was not available in 544 (0.2% of the total).

Proteinuria	Participants	Death	Death rate, %	Hazard Ratio	95% CI	P value
(-)	257,040	2,939	1.1	reference		
(+/-)	21,981	352	1.6	1.301	1.145-1.478	<0.001
(1+)	10,802	249	2.3	1.474	1.252-1.735	<0.001
(2+)	3,753	152	4.1	2.030	1.639-2.513	<0.001
(≥3+)	1,177	55	4.7	1.873	1.301-2.696	0.001
Total	294,753	3,747	1.3			

CI denotes confidence interval

Table 5. Results of the multivariate Cox analyses on the risk of death by combination of dipstick proteinuria and eGFR: Hazard ratio (95% confidence interval, CI) was calculated after adjusting for sex, age, body mass index, comorbid condition (DM, hypertension, and dyslipidemia), past history (stroke, heart disease, and kidney disease), and lifestyle (smoking, drinking, walking, and exercise). Proteinuria (+) denotes dipstick (1+ and over).

Proteinuria	eGFR	Participants	Death	Death rate, %	Hazard Ratio	95% CI	P value
(-)	≥60	192,142	2,008	1.0	reference		
(-)	<60	33,549	513	1.5	1.212	1.063-1.377	0.004
(+)	≥60	8,993	185	2.1	1.502	1.233-1.813	<0.001
(+)	<60	4,104	154	3.8	2.050	1.623-2.555	<0.001

eGFR, ml/min/1.73m^2.CI denotes confidence interval. N.s., not significant. CI denotes confidence interval

Results

Fig.1. Relationship between baseline eGFR and mortality.

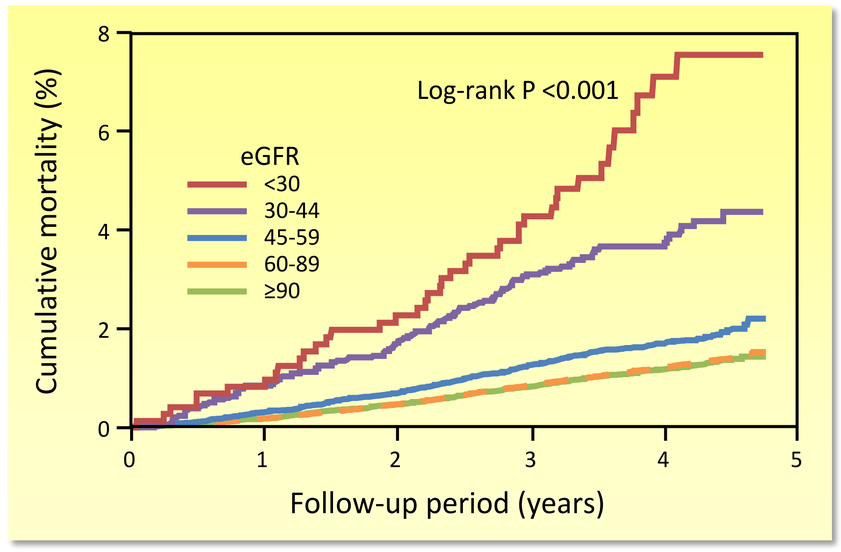


Fig.2. Relationship between baseline dipstick proteinuria and mortality.

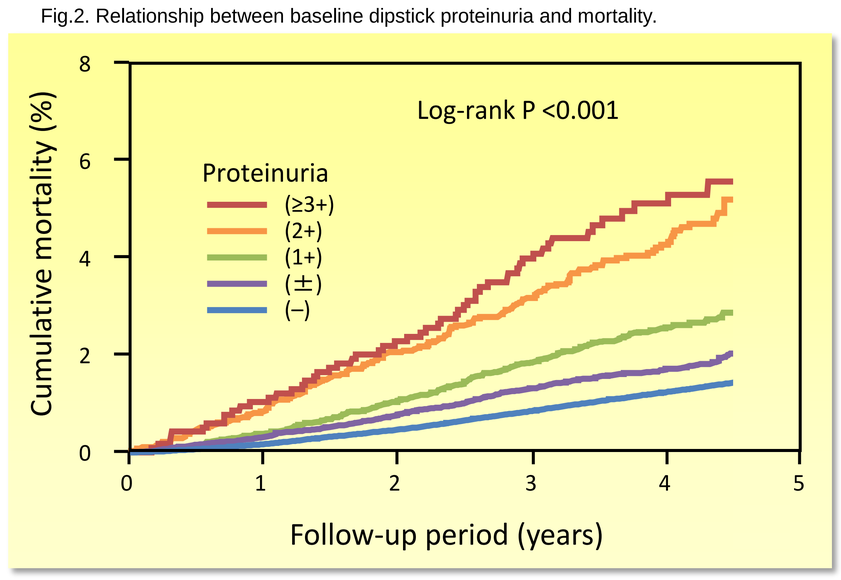
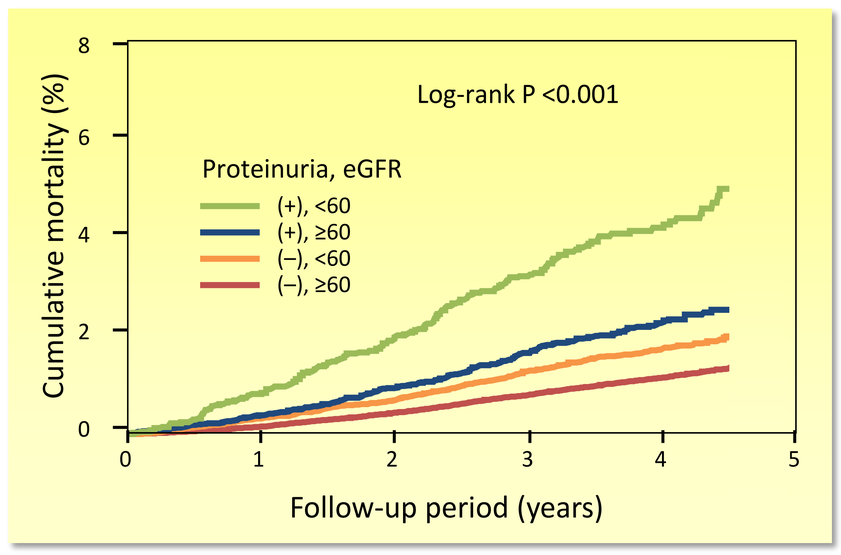


Fig.3. Relationship between the combination of baseline dipstick proteinuria and eGFR on mortality.



Strength of the present study

Subjects are participants of the large nation-wide screening program. Both clinical and laboratory tests performed using standard set of examination and therefore the quality of data was reliable. Also, a uniform questionnaire regarding lifestyle-related variables was required; therefore future research is possible based on current status of general Japanese population. Identification of death case was made using National Death Certificate database and confirmed in each district.

Limitations of the study

#1. Results were based on cross-sectional data. Data of dipstick proteinuria and eGFR may fluctuate in repeated measurements. Currently, changes in eGFR (30 to 40% in 2 years) have been proposed as a surrogate marker of CKD progression and therefore could be used another risk factor of death. Effects of changes in dipstick proteinuria on mortality remained to be studied. Recently, albuminuria changes showed significant association with subsequent risk of ESRD and mortality.

#2. This screening program is voluntary one and is self-selected. Therefore, we believe only a few people with self-evident illness have participated. By using the longitudinal data of the screening, we could further investigate the role of dipstick proteinuria on cancer incidence.

#3. There are obvious regional differences in incidence and prevalence of CVD and ESRD. In this study, we obtained only 6 out of 47 districts from north to south. Therefore, the database may not be representative of whole Japan. In this regard, we are expecting the growth of database after negotiating with each stake-holder.

#4. Participants of this screening were restricted to middle to old (40 to 74 years) person. In this age range, cancer mortality is high even though the relative risk of cancer death becomes lower. The policy to restrict age range was based on the assumption that the benefits of early detection of obesity and metabolic syndrome is greater than the cost of screening. Thereafter, candidates are entitled to the management program for lifestyle related diseases such as DM, hypertension, dyslipidemia, CVD, and probably CKD. Actually, we reported favorable lifestyle changes to non-smoking, healthy weights, adequate alcohol drinking, physical activity and healthy eating habit were associated with low incidence of proteinuria. We also observed that intensive care, involving regular monitoring of BMI and lifestyle, and when appropriate, intervention by dietitians and general practitioners, led to improved renal outcomes among patients with stage 3 CKD, compared to standard care. In Norway, CKD prevalence remained stable despite modest increases in DM and obesity, probably explained with marked improvements in blood pressure, lipid levels, and physical activity. However, the cost of general screening which was largely covered by Japanese government is not clear.

#5. We used ICD-10 codes from death certificate. Misclassification is inevitable in particular with aged and multi-comorbid patients. It would be worth to study the relationship between dipstick proteinuria on the incidence of neoplasm. But, we may need through baseline work-ups for cancer and longer follow-up.

Conclusions

The present study showed the significance of CKD measures both dipstick proteinuria and eGFR on mortality among general screening participants in Japan.

Our results support the strategy which has been used commonly for general screening.

Dipstick urine test is simple and cheap to predict both ESRD incidence and mortality; therefore preferable for prevention of CKD and ESRD in developing countries.

However, the frequency of proteinuria screening is still debatable.