Environ Health Prev Med (2011) 16:191–195
DOI 10.1007/s12199-010-0183-9

SHORT COMMUNICATION

The relation between estimated glomerular filtration rate and proteinuria in Okayama Prefecture, Japan

Nobuyuki Miyatake · Kenichi Shikata · Hirofumi Makino · Takeyuki Numata

Received: 17 June 2010 / Accepted: 23 September 2010 / Published online: 15 October 2010
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Abstract
Objective We investigated the link between renal function as evaluated by estimated glomerular filtration rate (eGFR) and proteinuria in Okayama Prefecture, Japan.
Subjects and methods A total of 11030 Japanese subjects, aged between 20 and 79 years, were recruited in a cross-sectional clinical investigation study. eGFR was calculated using serum creatinine, age, and sex. Proteinuria was measured by using urine strip devices.
Results Age-related variations in eGFR were noted. Two hundred sixteen men (6.2%) and 316 women (4.2%) were diagnosed with trace positive (±) and 140 men (4.0%) and 130 women (1.7%) were diagnosed with positive (+≤) proteinuria. eGFR in subjects with +≤ proteinuria was significantly lower than that in subjects without proteinuria, in both sexes.
Conclusion The present study indicates that proteinuria might be an important marker in the etiology of lower eGFR in Okayama Prefecture, Japan.

Keywords Estimated glomerular filtration rate (eGFR) · Proteinuria · Prevalence

N. Miyatake (✉)
Department of Hygiene, Faculty of Medicine,
Kagawa University, Miki,
Kagawa 761-0793, Japan
e-mail: miyarin@med.kagawa-u.ac.jp

K. Shikata · H. Makino
Department of Medicine and Clinical Science,
Okayama University Graduate School of Medicine,
Dentistry, and Pharmaceutical Sciences,
Okayama 700-8558, Japan

T. Numata
Okayama Southern Institute of Health,
Okayama Health Foundation, Okayama 700-0952, Japan

Introduction

Chronic kidney disease (CKD) has become an important public health challenge in Japan, and it is a major risk factor for end-stage renal disease, cardiovascular disease, and premature death [1, 2]. Identifying and taking care of risk factors for early CKD may be the best approach to prevent and delay adverse outcomes from happening prematurely [1]. The Japanese Society of Nephrology recently established an equation for estimating glomerular filtration rate (GFR) from serum creatinine (Cr) and age for the Japanese general population [3]. The new equation provides reasonably accurate estimated GFR (eGFR) values for clinical practice and epidemiological study. Imai et al. [4] reported that approximately 13.3 million people were predicted to have CKD in 2005.

We have previously shown that eGFR in men with abdominal obesity and in women with hypertension was significantly lower than in those without such conditions in a cross-sectional study [5]. In addition, decreased systolic blood pressure was closely linked to improved eGFR in 53 Japanese healthy women in a 1-year follow-up study using the new equation for the Japanese [6].

It is well known that proteinuria promotes renal dysfunction. However, the link between proteinuria and eGFR calculated with the new equation remains to be investigated. Therefore, we evaluated eGFR and its relation to prevalence of proteinuria in a large sample of Japanese population in Okayama Prefecture, Japan.

Subjects and methods

Subjects

We used data of 11030 Japanese subjects from a database of 16383 people at Okayama Southern Institute of Health in Okayama Prefecture, Japan, aged between 20 and 79 years in a cross-sectional study (Table 1). All subjects met the following criteria: (1) he or she had received an annual health checkup from June 1999 to May 2008 at Okayama Southern Institute of Health; (2) he or she had received Cr, urine examination, and anthropometric measurements as part of their annual health checkups; and (3) he or she provided us with written informed consent. Ethical approval for the study was obtained from the Ethical Committee of Okayama Health Foundation (2010-9).

Anthropometric measurements

Anthropometric parameters were evaluated by using the respective parameters such as height, body weight, body mass index (BMI), and abdominal circumference. BMI was calculated as weight/[height]^2 (kg/m^2). Abdominal circumference was measured at the umbilical level of a standing subject after normal expiration [7].

Blood sampling and assays

We measured overnight-fasting serum levels of Cr [3] (enzymatic method). eGFR was calculated using the following equation: eGFR (ml/min/1.73 m^2) = $194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if woman) [3]. Reduced eGFR was defined as eGFR <60 ml/min/1.73 m^2.

Urine examination

Urine samples were collected from the second morning urine (before 10 a.m.) and examined within 1 h. Urine examination was performed using urine strip tests (Bayer, Tokyo, Japan). The reagent strip was dipped directly into the urine sample. Just after dipping, the sample was graded as: −, negative; ±, trace positive; +, positive (30 mg/dl); 2+, positive (100 mg/dl); 3+, positive (300 mg/dl); or 4+, positive (1000 mg/dl) by comparison with a standard color chart found on the container's label [8].

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Comparison of parameters was performed by one-way analysis of variance (ANOVA), Scheffe's F test, and logistic regression analysis, with $p < 0.05$ considered statistically significant. Statistical analysis was performed using StatView 5.0 (SAS Institute Inc., Cary, NC, USA).

Results

The clinical profile of the subjects is summarized in Table 1. eGFR was 85.3 ± 18.6 ml/min/1.73 m^2 in men and 91.2 ± 22.6 ml/min/1.73 m^2 in women. eGFR classified by age group is summarized in Table 2. eGFR decreased significantly with age in subjects over 30 years old, and eGFR in the eighth decade was similar to that in the seventh decade for both sexes. A total of 253 men (7.3%) and 417 women (5.5%) were diagnosed with reduced eGFR. Prevalence of subjects with reduced eGFR increased with age.

We evaluated prevalence of proteinuria; 216 men (6.2%) and 316 women (4.2%) were diagnosed with ±, while 140 men (4.0%) and 130 women (1.7%) were diagnosed with +≤ proteinuria (Table 2). Prevalence of

Table 1 Clinical profile of the Japanese subjects

	Men (n = 3467)			Women (n = 7563)		
	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
Age (years)	43.1 ± 13.9	20	79	42.4 ± 14.0	20	79
Height (cm)	169.0 ± 6.2	143.7	187.6	156.3 ± 5.7	134.9	179.3
Body weight (kg)	70.2 ± 11.5	39.1	142.4	55.1 ± 9.0	32.1	116.9
BMI (kg/m^2)	24.6 ± 3.6	13.6	45.4	22.6 ± 3.6	12.9	48.7
Abdominal circumference (cm)	84.2 ± 10.1	58.0	132.1	72.1 ± 9.6	43.3	123.6
Cr (mg/dl)	0.83 ± 0.15	0.39	1.90	0.60 ± 0.16	0.20	6.8
eGFR (ml/min/1.73 m^2)	85.3 ± 18.6	27.8	191.3	91.2 ± 22.6	7.0	260.0

BMI body mass index, *Cr* creatinine, *eGFR* estimated glomerular filtration rate

Table 2 Changes in eGFR and proteinuria, classified by age group

Age (years)	Number of subjects	eGFR Mean ± SD	Number of subjects with reduced eGFR	%	Proteinuria (−)	%	(±)	%	(+≤)	%
Men										
20–29	714	99.8 ± 16.9	0	0.0	648	90.7	47	6.6	19	2.7
30–39	850	89.8 ± 16.3[a]	11	1.3	766	90.1	54	6.5	30	3.5
40–49	724	81.9 ± 15.3[a,b]	45	6.2	645	89.1	54	7.5	25	3.5
50–59	633	77.9 ± 16.1[a,b,c]	63	10.0	570	90.0	31	4.9	32	5.1
60–69	441	73.1 ± 15.8[a,b,c,d]	102	23.1	393	89.1	25	5.7	23	5.2
70–79	105	68.1 ± 14.5[a,b,c,d]	32	30.5	89	84.7	5	4.8	11	10.5
Total	3467	85.3 ± 18.6	253	7.3	3111	89.7	216	6.2	140	4.0
Women										
20–29	1832	106.7 ± 21.9	10	0.5	1697	92.6	101	5.5	34	1.9
30–39	1703	96.8 ± 20.3[a]	29	1.7	1608	94.4	70	4.1	25	1.5
40–49	1483	87.6 ± 19.0[a,b]	66	4.5	1396	94.1	60	4.0	27	1.8
50–59	1459	81.2 ± 18.7[a,b,c]	141	9.7	1386	95.0	51	3.5	22	1.5
60–69	921	75.5 ± 16.4[a,b,cd]	133	14.4	875	95.0	28	3.0	18	2.0
70–79	165	70.8 ± 16.3[a,b,c,d]	38	23.0	155	93.9	6	3.6	4	2.4
Total	7563	91.2 ± 22.6	417	5.5	7117	94.1	316	4.2	130	1.7

eGFR estimated glomerular filtration rate

[a] $p < 0.05$ versus age 20–29 years

[b] $p < 0.05$ versus age 30–39 years

[c] $p < 0.05$ versus age 40–49 years

[d] $p < 0.05$ versus age 50–59 years

+≤ proteinuria was highest in the eighth decade for both sexes.

We evaluated the relationship between eGFR and proteinuria (Table 3). Prevalence of proteinuria was closely linked to reduced eGFR. eGFR in subjects with +≤ proteinuria was significantly lower than that in subjects without proteinuria, for both sexes. Twenty-one men (15.0%) and 21 women (16.2%) in subjects with +≤ proteinuria were diagnosed as having reduced eGFR (Table 3).

We also compared the relationship between eGFR and proteinuria as classified by age group (Table 3). eGFR in women with ± proteinuria in their third and fifth decades was significantly lower than that in women without proteinuria. In addition, eGFR in women with +≤ proteinuria in their third and seventh decades was also significantly lower than that in women without proteinuria. In other age groups, eGFR in subjects with proteinuria was also lower than that in subjects without proteinuria, but not significantly so. On logistic regression analysis, there was significant difference in eGFR after adjusting for age in women ($p < 0.0001$). However, significant difference of eGFR was not noted after adjusting for age in men ($p = 0.0960$).

Discussion

In this study, we explored eGFR and its relation to proteinuria. eGFR was closely linked to proteinuria, especially in women of Okayama Prefecture in Japan.

It is well known that prevalence of proteinuria increases with age, and its rate among Japanese is reported to be 3.2% by Imai et al. [4]. eGFR also decreases with age [9]. Regarding the link between eGFR and age, in the large sample of another Japanese cohort, the rate of decrease of eGFR was 0.36 ml/min/1.73 m^2/year [9]. In this study, we also found that prevalence of proteinuria was highest in the eighth decade, and eGFR decreased with age on cross-sectional analysis.

Several studies have documented the relationship between proteinuria and end-stage renal disease [9, 10]. Imai et al. reported that the rate of decrease of eGFR, using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation modified by a Japanese coefficient, was more than two times higher in participants with proteinuria than in those without it [9]. Iseki et al. [10] also reported that they identified a strong, graded relationship between end-stage renal disease and positive dipstick urinalysis for proteinuria (adjusted odds ratio 2.71).

Table 3 Relationship between eGFR and proteinuria, classified by age group

Age (years)	Proteinuria		
	(−)	(±)	(+≤)
Men			
20–29	100.0 ± 16.9	98.3 ± 18.2	94.9 ± 15.6
30–39	90.4 ± 16.1	85.3 ± 17.5	84.4 ± 16.0
40–49	82.0 ± 15.2	81.1 ± 14.5	81.0 ± 18.9
50–59	77.7 ± 15.5	84.3 ± 19.7	76.9 ± 20.9
60–69	73.0 ± 15.1	75.9 ± 24.1	70.9 ± 16.3
70–79	69.1 ± 12.8	63.7 ± 24.7	61.2 ± 21.0
Total	85.5 ± 18.4	85.3 ± 19.8	79.5 ± 19.9[a,b]
Number of subjects with reduced eGFR (%)	216 (6.9)	16 (7.4)	21 (15.0)
Women			
20–29	107.3 ± 21.9	101.0 ± 20.9[a]	94.1 ± 19.9[a]
30–39	96.8 ± 20.2	98.1 ± 20.6	92.9 ± 21.2
40–49	88.0 ± 19.1	80.4 ± 15.6[a]	85.6 ± 16.2
50–59	81.3 ± 18.7	77.9 ± 19.4	76.8 ± 18.6
60–69	75.8 ± 15.9	72.2 ± 22.2	62.5 ± 25.2[a]
70–79	71.2 ± 16.5	64.8 ± 11.8	62.3 ± 8.3
Total	91.4 ± 22.6	89.5 ± 22.7	83.8 ± 22.6[a]
Number of subjects with reduced eGFR (%)	374 (5.3)	22 (7.0)	21 (16.2)

Mean ± SD

[a] $p < 0.05$ versus (−)

[b] $p < 0.05$ versus (±)

In addition, macroalbuminuria was a better risk marker than low eGFR or erythrocyturia to identify individuals at risk for accelerated GFR loss in population screening with 4-year follow-up [11]. Therefore, proteinuria is a strong, independent predictor of end-stage renal disease. Our study also showed that eGFR in subjects with +≤ proteinuria was significantly lower than that in subjects without proteinuria. Prevalence of subjects with reduced eGFR among subjects with proteinuria was also higher than that in subjects without it. About 15% were diagnosed with reduced eGFR among subjects with +≤ proteinuria. However, the significant relationships between eGFR and proteinuria were attenuated by separate analysis by age group classification and logistic regression analysis. The small sample size of subjects with proteinuria may have affected these results.

Potential limitations still remain in our study. First of all, the cross-sectional study design we used makes it difficult to infer association between proteinuria and eGFR. Secondly, we are yet to prove directly the mechanism of the link between proteinuria and eGFR. Thirdly, although we had reported the clinical impact of some factors on eGFR [5, 6], we are yet to evaluate these factors, including hemoglobin A1c. However, our findings are applicable to clinical and public health practice settings. In conclusion, prevalence of proteinuria is associated with lower eGFR, especially in women, in Okayama Prefecture, Japan. Further prospective studies are necessary to investigate the link between eGFR and proteinuria in the Japanese population in general.

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