*Original Article*

# Slower Decline of Glomerular Filtration Rate in the Japanese General Population: A Longitudinal 10-Year Follow-Up Study

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**The prevalence of stage 3 to 5 chronic kidney disease (CKD) in Japan (18.7%) is considerably higher than that in the United States (4.5%). This study investigated in the Japanese general population whether this higher prevalence of CKD might reflect to a progressive decline of renal function, and in turn to the increased risk of end-stage renal disease. A decline in renal function over 10 years was examined in 120,727 individuals aged 40 years or older who participated in the annual health examination program of the two periods over 10 years, 1988–1993 and 1998–2003. Renal function was assessed with estimated glomerular filtration rate (GFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation modified by a Japanese coefficient. The rate of GFR decline in the participants was 0.36 mL/min/1.73 m$^2$/year on average. In the male population aged 50–79, the mean rate of GFR decline was significantly higher in the presence of hypertension than in its absence. The rate of GFR decline was more than two times higher in participants with proteinuria than in those without proteinuria in both sexes. The rate was significantly higher in participants with an initial GFR <50 mL/min/1.73 m$^2$ among the groups younger than age 70 and in participants with an initial GFR <40 mL/min/1.73 m$^2$ in the group with age 70–79. Based on the slow rate of GFR decline, we concluded that the decline in renal function progresses slowly in the Japanese general population. Hypertension, proteinuria and lower GFR were found to be significant risk factors for a faster decline of GFR. (*Hypertens Res* 2008; 31: 433–441)**

***Key Words*: glomerular filtration rate, Modification of Diet in Renal Disease, equation, Japanese**

## Introduction

A current epidemic of chronic kidney disease (CKD) is a major health problem worldwide. In Japan, the number of new patients with end-stage renal disease (ESRD) has been increasing during the last three decades. In 2005, a total of 36,063 ESRD patients were introduced to dialysis therapy, most of whom were elderly (mean age of 66) (*1*).

Previously, we have confirmed that an accurate glomerular

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**Table 1. Study Participants**

| Prefecture of health-check program | Period of 10-year comparison | Sex | *n* | Total program participants (%) |
|---|---|---|---|---|
| Okinawa | 1993 and 2003 | Male | 11,324 | 38 |
| | | Female | 18,349 | 42 |
| Ibaraki | 1993 and 2003 | Male | 25,262 | 38 |
| | | Female | 60,723 | 45 |
| Hokkaido | 1991 and 2001 | Male | 395 | 46 |
| | | Female | 572 | 49 |
| Tokyo | 1992 and 2001 | Male | 1,928 | 26 |
| | | Female | 622 | 24 |
| Fukuoka | 1988 and 1998 | Male | 605 | N/A |
| | | Female | 951 | N/A |
| Total | | Male | 39,510 | |
| | | Female | 81,217 | |
| | | Total | 120,727 | |

N/A, not available.

filtration rate (GFR) is estimated from serum creatinine value for Japanese using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation modified by a Japanese-coefficient (*2*). When CKD was defined by GFR <60 mL/min/1.73 $m^2$ (CKD stage 3), prevalence of CKD in the Japanese general population was predicted to be 18.7% (about 19 million) based on a nationwide epidemiological study in 527,594 individuals aged 20 years and older (211,034 males and 316,560 females) who participated in a community-based, company-based or hospital-based annual health examination program conducted in 2000–2004 (*3*).

The prevalence of CKD is higher in Japanese population (19%) than in both Norwegian population of Nord-Trondelag county and US population (both about 10%). The prevalences of stage 3 and 4 CKD (GFR: 60–31 and 30–15 mL/min/1.73 $m^2$) were also higher in the Japanese general population than in populations of the countries the above (for Japan: 18.5% and 0.20% in 2000–2004 (*3*); for the US: 3.7% and 0.13% in 1999–2000 (*4*); and for Nord-Trondelag county, Norway: 4.2% and 0.16% in 1995–1997 (*5*), respectively). Eriksen *et al*. (*6*) reported in a longitudinal study that the mean change in the estimated rate of GFR decline over 10 years was 1.03 mL/min/1.73 $m^2$/year, and the renal function declined progressively in a relatively small population of patients in a hospital of Tromso, Norway. We predicted that the large Japanese population with lower GFR may have progressive decline in the renal function. In that case, we may have a large number of ESRD patients in Japan in the near future. Thus, the present study investigated the rate of decline in GFR in the Japanese general population over a period of 10 years using the data on serum creatinine, blood pressure and urinalysis of participants aged 40 years and older of the annual Japanese health examination program. The rate of GFR decline was estimated from a set of serum creatinine values obtained 10 years apart in 120,727 participants of the Japanese health examination program which was conducted over two periods, 1988–1993 and 1998–2003, in five prefectures.

Hypertension and proteinuria was evaluated as risk factors for accelerated decline of renal function in the study population, since these conditions are known to exacerbate CKD progression to end-stage renal disease.

## Methods

### Study Population

In this study, we obtained the data on 290,268 individuals (107,145 males and, 183,123 females) aged 40 years and older who participated in the annual health examination program of 5 different prefectures of Japan (Hokkaido, Ibaraki, Tokyo, Fukuoka, and Okinawa) during the period between 1988 and 1993 (Table 1). Of those, 120,727 adult participants (41% of the total; 39,510 males and 81,217 females) who had two serum creatinine values measured at an interval of 10 years were included in the present study. When proteinuria was defined as a urinary protein level of 1+ or more (about ≥30 mg/dL) in the dipstick test using a spontaneously and freshly voided urine sample, 2,054 patients (1.7%) had proteinuria among 117,865 participants whose urinary protein was measured. When hypertension was defined as a mean blood pressure of 106 mmHg or more measured in the sitting position, 16,722 patients (13.9%) had hypertension among 120,727 participants whose blood pressure was measured. All the participants were kept anonymous and the study was conducted according to the Japanese law of privacy protection.

### Calibration of Serum Creatinine Values

Although the Jaffe method was generally used for creatinine assay before 2000, the enzymatic method is currently used in many laboratories in Japan. In the present study, creatinine was measured by the Jaffe method in the earlier annual health

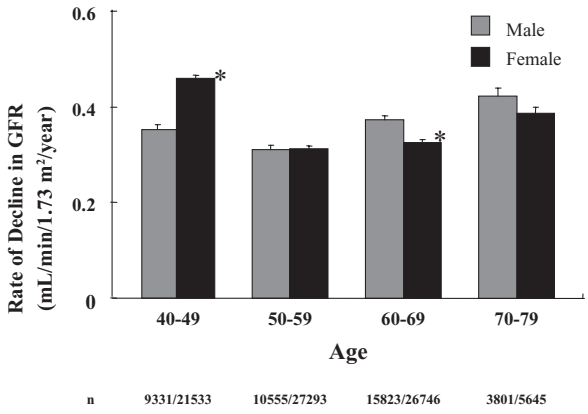



**Fig. 1.** *Difference in the rate of decline in GFR between male and female participants in each age group. The rates of decline in GFR were calculated from 39,510 males and 81,217 females. Data are shown as the means±SEM. *p< 0.001 vs. male.*

examination program and was measured by the enzymatic method in the later program. The mean creatinine values of the general population measured by the Jaffe method were higher than those obtained by the enzymatic method, but the degree of difference between the two measurements was roughly constant across the age groups. We previously conducted a nationwide epidemiological study to predict the prevalence of CKD in the Japanese general population, based on a survey of participants in an annual health examination program run by community, company and hospital (*3*). The serum creatinine values of each laboratory were calibrated in the central laboratory. To use the surveyed serum creatinine values from different laboratories in different years in the present study, the values were aligned to the gender-specific and age-specific mean creatinine values in the previous study noted above and calibrated to the values of the central laboratory measured by the Jaffe method. We calculated the mean creatinine value for the subjects with age ranging from 40 to 79 years in each laboratory by either method. The mean difference in creatinine values was corrected in each laboratory on a year- and gender-basis.

### GFR Estimation with the Japanese-Coefficient–Modified MDRD Study Equation

The GFR of each participant was calculated from the serum creatinine value (S-Cr) and the age using the Japanese-coefficient–modified MDRD Study equation as follows.

$$\text{GFR (mL/min/1.73 m}^2) = 0.881 \times 186 \times \text{Age}^{-0.203} \times \text{S-Cr}^{-1.154} \text{ (if female} \times 0.742)$$

The rate of GFR decline over 10 years were calculated for each group of participants with initial GFR of five categories (30–39, 40–49, 50–59, 60–69, >70 mL/min/1.73 m$^2$). When analyzed using two successive measurements, the values will, on average, tend to be closer to the mean on the second measurement (the so-called regression effect). When we compared the rate of GFR decline in one GFR category with that in another GFR category, the regression effect on the rate of GFR decline was corrected by the following equation:

$$\text{Corrected rate of decline in GFR} = \text{GFR}_2 - \text{GFR}_1 + (1 - b) \times (\text{GFR}_1 - \text{mean GFR}_1)$$

Where $GFR_1$ is the initial GFR value of the subject, $GFR_2$ is the final GFR value of the subject, mean $GFR_1$ is the mean of the initial GFR values in the study population, and $b$ is the slope of the regression line in the study population (with final GFR on the $Y$ axis and initial GFR on the $X$ axis).

### Statistics

Data were expressed as the number of participants or percentage (%) of the study population. The rate of GFR decline was expressed as the mean±SEM. The rates of GFR decline were compared among three or more cases by Scheffé's multiple comparison method after analysis of variance (ANOVA) or between two cases by Student's $t$-test. Values of $p<0.05$ were considered statistically significant.

## Results

### Prevalence of CKD (GFR <60 mL/min/1.73 m$^2$) in Participants in the Annual Health Examination Program

Among the 120,727 participants (39,510 males and 81,217 females), 42.72%, 35.91%, 17.80%, 3.29%, 0.26% and 0.01% had initial values of GFR >70, 69–60, 59–50, 49–40, 39–30, and <30 mL/min/1.73 m$^2$, respectively. In the study population, the prevalence of CKD stage 3 was 21.34% of the total participants and that of CKD stage 4 and 5 together was 0.01% of the total participants.

### Mean Rate of Decline in GFR

The rates of GFR decline over 10 years were similar among the age groups: 0.35, 0.31, 0.37, and 0.42 mL/min/1.73 m$^2$/year in males, and 0.41, 0.31, 0.32 and 0.39 mL/min/1.73 m$^2$/year in females for the age groups of 40–49, 50–59, 60–69 and 70–79 years, respectively (Fig. 1). The overall rate of GFR decline in the study population was 0.36 mL/min/1.73 m$^2$/year.

### Rate of GFR Decline in Hypertensive Patients

Hypertension occurred in 17.8% of males and 11.9% of females in the study population. In the presence of hypertension, GFR declined with significantly higher rate; the rate was higher in the group ≥106 mmHg than in the group <96

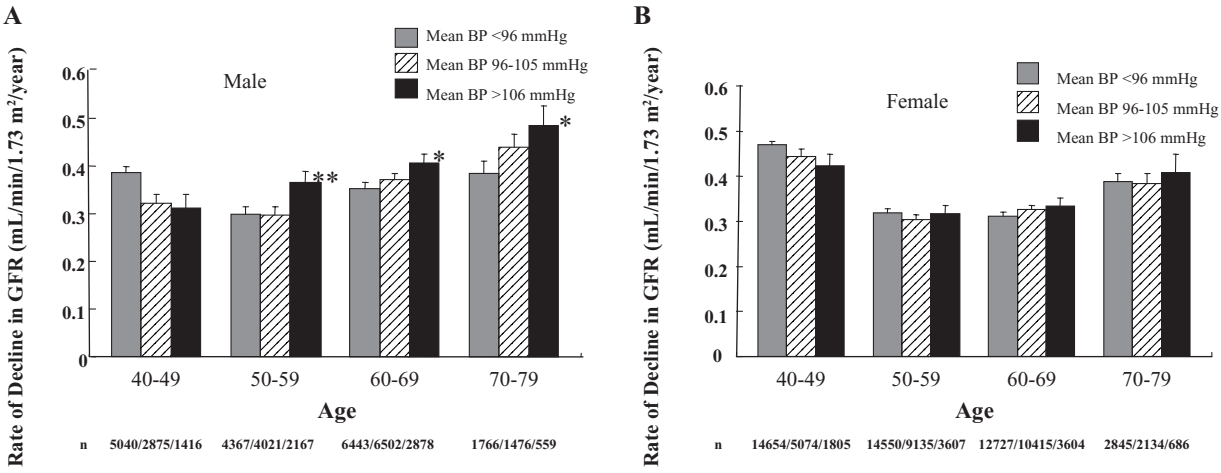



**Fig. 2.** *A: Difference in the rate of decline in GFR in male participants with a mean blood pressure of below 96 mmHg, 96 to 105 mmHg, or above 105 mmHg in each age group (n = 39,510). B: Difference in the rate of decline in GFR in female participants with a mean blood pressure of below 96 mmHg, 96 to 105 mmHg, or above 105 mmHg in each age group (n = 81,217). Data are shown as the means ± SEM. *p < 0.05, **p < 0.01 vs. BP < 96 mmHg.*

mmHg in the male groups aged 50 years and older (Fig. 2A). In female, the rate of GFR decline was slightly higher but not significantly in hypertensive patients than in normotensive participants in the age groups older than 60 years (Fig. 2B).

## The Rate of Decline in GFR in Patients with Proteinuria

In the overall study population, proteinuria occurred in 2.6% of the males and 1.3% of the females. Patients with proteinuria had a twofold higher mean rate of GFR decline compared with patients without proteinuria in all the age groups in both males and females (Fig. 3), demonstrating that proteinuria accelerated the rate of a decline in renal function and was a strong risk factor for a decline in renal function.

## The Impact of Initial GFR on the Rate of Decline in GFR

Initial GFR influenced the rate of GFR decline in both sexes. The lowest rate of GFR decline was in individuals with an initial GFR of 60–69 mL/min/1.73 $m^2$. In the age group of 40–49, the rates were 0.34±0.02 mL/min/1.73 $m^2$/year in males and 0.45±0.01 mL/min/1.73 $m^2$/year in females. When the rate was used as a reference point, the rate of GFR decline significantly increased in the group with an initial GFR of 30–39 mL/min/1.73 $m^2$ and was 10-fold higher (3.28±0.72 mL/min/year) in males and 4-fold higher (1.94±0.47 mL/min/year) in females (Fig. 4A). The mean rates were significantly higher in the groups with an initial GFR < 50 mL/min/1.73 $m^2$.

In the age group of 50–59, the rate of GFR decline was higher in the group with an initial GFR of 30–39 mL/min/1.73 $m^2$, 3 times higher (0.91±0.43 mL/min/year) in male and 6 times higher (1.34±0.24 mL/min/year) in female, compared with the rate in the group of an initial GFR of 60–69 mL/min/1.73 $m^2$ (0.31±0.01 mL/min/1.73 $m^2$/year in males and 0.24±0.01 mL/min/1.73 $m^2$/year in female) (Fig. 4B). The mean rate of decline in GFR was greater in the group with an initial GFR < 50 mL/min/1.73 $m^2$.

In the age group of 60–69, the rate of GFR decline increased with decreased initial GFR. The significant increase in the rate was 3 times higher in the group with initial value of GFR 30–39 mL/min/1.73 $m^2$ (0.98±0.18 mL/min/year) in male and 4 times higher (1.18±0.13 mL/min/year) in female compared with that in the group of GFR 60–69 mL/min/1.73 $m^2$ (0.31±0.01 mL/min/1.73 $m^2$/year in male and 0.26±0.01 mL/min/1.73 $m^2$/year in female) as shown in Fig. 4C. The mean rate of GFR decline was greater in those with an initial GFR of < 50 mL/min/1.73 $m^2$.

In the age group of 70–79, the mean rate of GFR decline also increased along with the decreased initial GFR. The rate was higher (1.24±0.25 mL/min/year in males and 0.82±0.09 mL/min/year in females; both 3-fold increases) in those with an initial GFR of 30–39 mL/min/1.73 $m^2$ than in those with an initial GFR of 60–69 mL/min/1.73 $m^2$ (0.36±0.03 mL/min/1.73 $m^2$/year in males and 0.29±0.02 mL/min/1.73 $m^2$/year in females) (Fig. 4D). The GFR reduction rate was accelerated in those with an initial GFR of < 40 mL/min/1.73 $m^2$.

A simulation of the GFR decline in relation to age is shown in Fig. 5. A significantly greater rate of GFR decline was observed in subjects with an initial GFR of < 50 mL/min/1.73 $m^2$ in the age group of younger than 70 years and in those with an initial GFR < 40 mL/min/1.73 $m^2$ in the age group of 70–79.

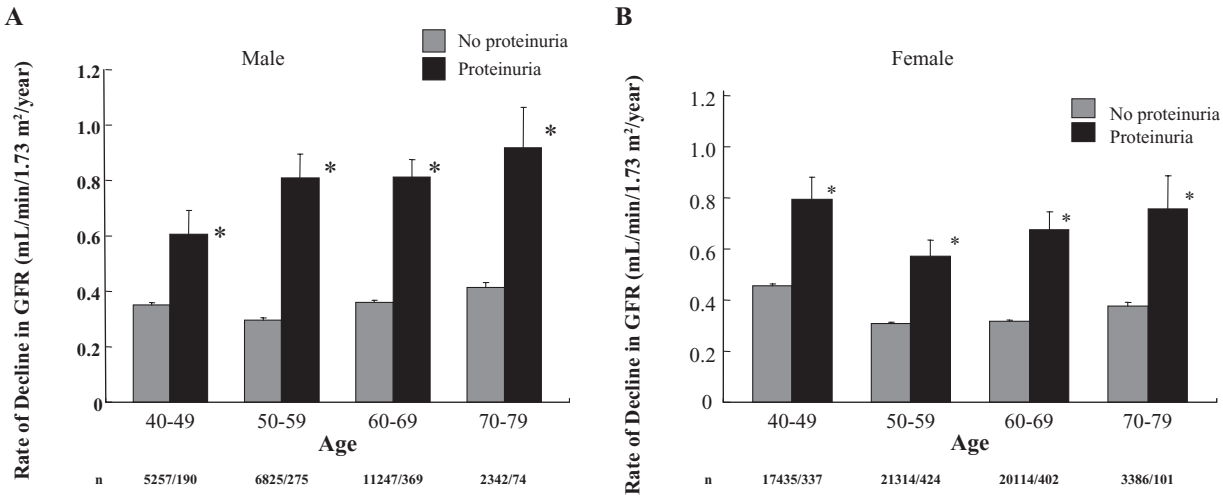



**Fig. 3.** *A: Effects of proteinuria on the rate of decline in GFR were evaluated in male participants with proteinuria (n = 985) or without proteinuria (n = 37,444). B: Effects of proteinuria on the rate of decline in GFR were evaluated in female participants with proteinuria (n = 1,069) or without proteinuria (n = 78,367). Data are shown as the means ± SEM. *p < 0.0001 vs. no proteinuria group.*

## Discussion

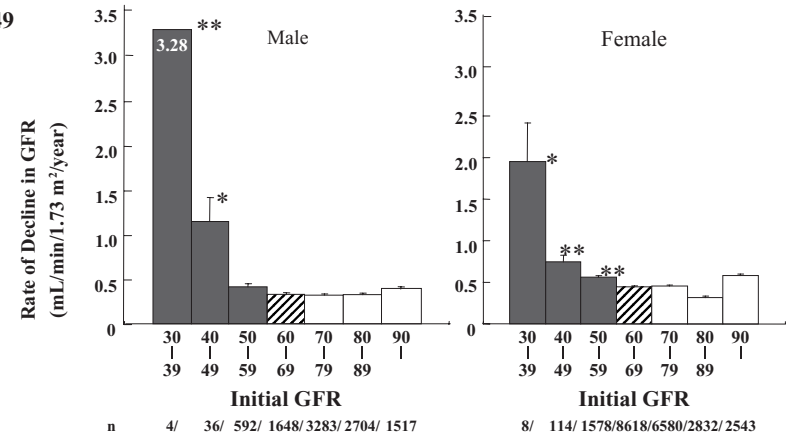
The rate of decline in GFR over 10 years in the Japanese general population was estimated in a large-scale longitudinal study of participants aged 40–79 years. The rate of GFR decline was found to be 0.36 mL/min/1.73 $m^2$/year. Accelerated GFR decline occurred in the presence of proteinuria in both sexes in any age, and in the presence of hypertension in men with age 50 and older in marginal extent. The rate of GFR decline over 10 years was affected by the initial GFR in different manner in different age groups. Accelerated decline in GFR occurred over the following 10 years when the initial GFR was < 50 mL/min/1.73 $m^2$ in the group with age younger than 70, while accelerated GFR decline occurred with the initial GFR < 40 mL/min/1.73 $m^2$ in the group with age 70–79.

The rate of GFR decline, 0.36 mL/min/1.73 $m^2$/year, in the present study was slower than the rates of 0.75–1.0 mL/min/1.73 $m^2$/year in the longitudinal studies of the United States (*7*) and Norway (*6*). GFR declined at a similar rate in males and females in any age groups. Iseki *et al*. (*8*) reported that the rate of GFR decline was 0.19 mL/min/1.73 $m^2$/years in Japanese in a longitudinal study of the screenings between 1983 and 1993, although the GFR was estimated by the original 4-variable MDRD Study equation without calibration of serum creatinine values.

We found that hypertension and proteinuria affected the rate of decline in renal function. In the presence of hypertension, the GFR decline significantly accelerated only in male participants aged 50 years and older. Subjects with proteinuria had an approximately two-fold higher rate of GFR decline than those without proteinuria in both males and females of all age groups. In comparison with the group having an initial GFR of 60–69 mL/min/1.73 $m^2$, the groups with a lower initial GFR had a significantly higher rate of GFR decline in all age groups, suggesting that the lower the GFR the faster the decline of renal function. The initial GFR to produce significantly sharper decline in GFR was different in each age group; the GFR was < 50 mL/min/1.73 $m^2$ in the age groups 40–69, and it was < 40 mL/min/1.73 $m^2$ in the older group of age 70–79, suggesting that the decline in kidney function starts accelerating at a lower GFR in the elderly. In the present study, we demonstrated that a risk for fast decline in renal function starts at relatively higher initial GFR in younger patients than elderly patients. It is a particular importance that the findings were made in the present longitudinal study of 10-year follow-up with more than 120,000 participants who represented the Japanese general population. Figure 5 shows estimation of the GFR decline according to the aging.

In contrast to our findings, many studies have demonstrated that elderly subjects had a sharper decline in GFR than younger subjects. The mean rate of GFR decline was found to be 0.42 mL/min/1.73 $m^2$/year in males and 0.39 mL/min/1.73 $m^2$/year in females in the age group of 70–79 in Japanese, whereas the rate was higher approximately 1 mL/min/year in a normal elderly US population (*9–11*). The results of small study of the Baltimore Longitudinal Study on Aging also supported the findings, where an average GFR decline was 0.75 mL/min/year in men as evaluated with creatinine clearance (*7*). Similarly, in a longitudinal community-based study of a 2-year follow up of the elderly Canadians, Hemmelgarn *et al*. reported that the rate of GFR decline was 0.8 mL/min/1.73 $m^2$/year in women and 1.4 mL/min/1.73 $m^2$/year in men in age

**A: Age Group 40–49**

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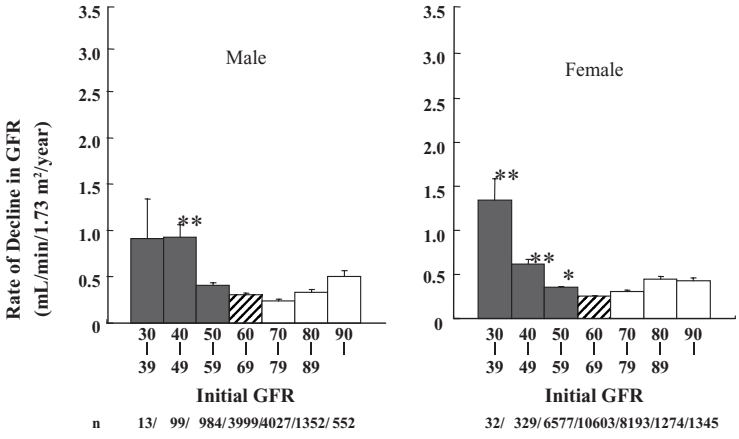
**B: Age Group 50–59**

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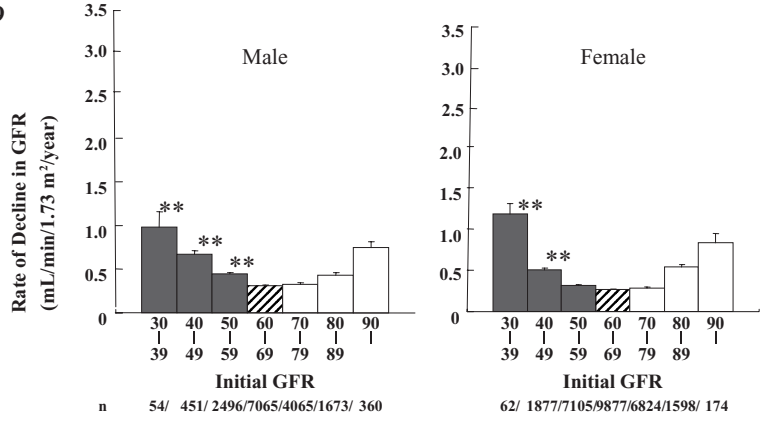
**C: Age Group 60–69**

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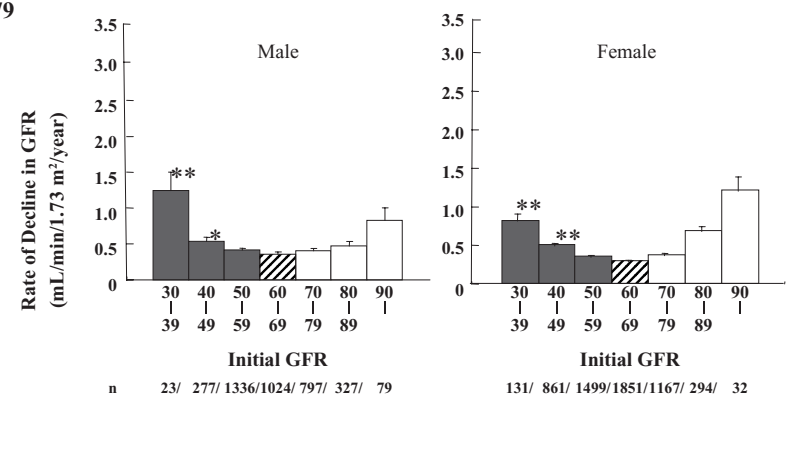
**D: Age Group 70–79**

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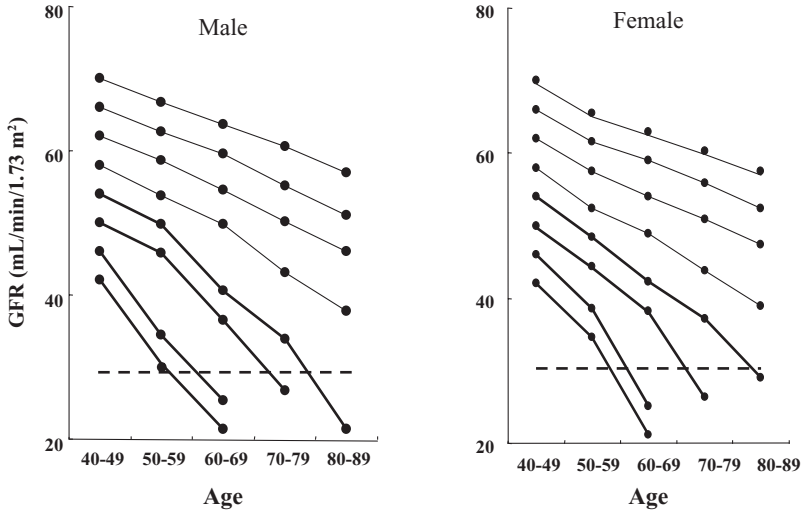


**Fig. 5.** *Estimation of the decline in GFR. The predicted GFR is illustrated in males and females. Thick solid lines show individuals who have an increased risk of sharp decline in GFR, potentially progressing to end-stage renal disease.*

group 66 years or older (about age 76 on average) without diabetes (*10*). However, these studies had critical disadvantages, because the study was conducted with a cross-sectional design (*9*) or with small number of subjects (*7*), and the loss of kidney function was analyzed using dichotomous outcomes (*10*) or evaluated based on creatinine clearance (*7*). Alternatively, GFR in the elderly individuals with longevity may slowly decline according to the aging, while the elderly with diseases may die early before the second measurement of serum creatinine 10 years later. A prospective study is required to answer the question.

In the present study, the highest rate of GFR decline was found among the subjects with an initial GFR of 30–39 mL/min/1.73 $m^2$. The maximal rate was much higher in the age group 40–49 than in the age groups 50 and older in both males and females. We may be underestimating the rate of GFR decline in study subjects with a lower initial GFR because some of the study subjects may already be introduced to renal replacement therapy by the time of the later health examination program of 10 years later and may be excluded from the study.

Furthermore, patients with CKD had a significantly slower decline of GFR in the Japanese cohort of our study than in the US cohort of a previous study; the rate of GFR decline in the MDRD Study was higher 7.8 mL/min/1.73 $m^2$/year (2.6 mL/min/1.73 $m^2$/4 months) in the patients with an average GFR of 38.6 mL/min/1.73 $m^2$, and 4.0 mL/min/1.73 $m^2$/year in the patients with the GFR of 18.5 mL/min/1.73 $m^2$ (*11*). In a 25-year follow-up study of a US population, Ishani *et al*. reported that men with high risk of heart disease and GFR $<60$ mL/min/1.73 $m^2$ but without kidney disease had significantly higher hazard ratio of 3.85 for a risk of ESRD (*12*). Taken together, these results indicate that a risk of progressive CKD and ESRD can be associated with different GFR values in different ethnic populations.

In the present study, hypertension defined by a mean arterial blood pressure $\geq 106$ mmHg was a marginal risk factor for faster decline in renal function in men but not in women. Similar observation was reported in the Multiple Risk Factor Intervention Trial (MRFIT) with a 16-year follow-up, where hypertension was a risk for developing ESRD in men in the US population (*13*). In a large community-based epidemiological study of 98,759 subjects with a 17-year follow-up in Okinawa, Japan, hypertension was the risk factor in both men and women (*14*). Furthermore, Yamagata *et al*. recently reported that hypertension defined by a blood pressure of 140/

**Fig. 4.** *The rate of decline in GFR was compared among the groups categorized with initial GFR. White columns indicate tentative values of decline rate because the individuals with higher initial eGFR were underestimated their GFR and may often be reduced the value in the second measurement by the effect of regression to the means. A: Rate of decline in GFR in age group 40–49 in males and females. The average GFR at age 40–49 was 77±10 mL/min/1.73 $m^2$ in male (n=9,331) and 74±11 mL/min/1.73 $m^2$ in females (n=21,533). B: Rate of decline in GFR in age group 50–59 in males and females. The average GFR at age 50–59 was 72±11 mL/min/1.73 $m^2$ in males (n=10,555) and 69±10 mL/min/1.73 $m^2$ in females (n=27,293). C: Rate of decline in GFR in age group 60–69 in males and females. The average GFR at age 60–69 was 77±10 mL/min/1.73 $m^2$ in males (n=15,823) and 74±11 mL/min/1.73 $m^2$ in females (n=26,746). D: Rate of decline in GFR in age group 70–79 in males and females. The average GFR at age 70–99 years old was 64±11 mL/min/1.73 $m^2$ in males (n=3,801) and 61±11 mL/min/1.73 $m^2$ in females (n=5,645). Data are shown as the means±SEM. *p<0.01, **p<0.001 vs. initial GFR 60–69 mL/min/1.73 $m^2$.*

90 mmHg or higher was an independent risk for developing CKD in a 10-year follow-up study of a general population in Japan (*15*). In a study of 504 African-American and 218 Caucasian men between 1976 and 1999, hypertension was a strong risk factor for early decline in kidney function; hypertensive patients (BP ≥160/95 mmHg) had a 5 times greater decline in GFR, (2.67 mL/min/1.73 $m^2$/year) compared with patients with blood pressure <140/90 mmHg (*16*).

The effect of hypertension on the rate in GFR decline in the elderly is controversial. In a longitudinal study, Eriksen *et al*. (*6*) showed that creatinine clearance declined more rapidly with age in hypertensive elderly than in normotensive elderly, where the rate of GFR decline was 0.92±0.32 mL/min/year in hypertensives, *vs*. 0.75±0.12 mL/min/year in normotensives. In contrast, another cross-sectional study reported that values of GFR measured by inulin clearance were not different between elderly hypertensives and elderly normotensives (*17*).

Being male has been reported to have a negative effect on the progression of CKD (*18*). Eriksen *et al*. reported that the rate of GFR decline was lower in female than in male patients with CKD 3 (male *vs*. female: 1.39 *vs*. 0.88 mL/min/1.73 $m^2$/year) (*6*).

In hypertensive males whose mean blood pressure were over 106 mmHg, GFR declined with significantly faster rate at age 50 and older, while the rate of GFR decline was not affected by the blood pressure at age 40–49. The systemic vascular lesion caused by hypertension may influence the rate of GFR decline after age 50 and older. A previous study reported that the mean common carotid intima-media thickness (IMT) increased in a linear manner with age in healthy subject, and the increase was more significant in the subjects with age 50 and older than in subjects with younger age (*19*). The carotid IMT was greater in patients with CKD than healthy controls at age 50 and older; however, the IMT in the patients was not different from that of healthy controls at age 40–49 (*20*). These results may support our results that the impact of hypertension on renal function may become apparent after age 50.

The prevalence of overt proteinuria was higher 2.6% in this study compared to 1.4% in the NHANES III in male (2.6% *vs*. 1.4%), but the incidence was similar between the two studies in female (1.3% *vs*. 1.5%) (*21*). In studies on diabetic patients, proteinuria including microalbuminuria has been shown to increase a risk for progression of renal disease (*22*). A higher risk for ESRD has also been demonstrated in patients with proteinuria in two large cohort studies with long-term follow-up. The hazard ratio of developing ESRD in patients with proteinuria was 3.1 in a sub-analysis of the MRFIT study with a 25-year follow-up of a total of 12,866 men, and was 3.09 in a study in Okinawa, Japan (*23*). Yamagata *et al*. also presented evidence that proteinuria is a risk factor for developing stage 3 CKD in the Japanese general population (*15*).

When creatinine is measured by the enzymatic method, estimated GFR (eGFR) is generally calculated by the isotope dilution mass spectrometry (IDMS)–traceable creatinine based 4-variable MDRD (IDMS-MDRD) Study equation (*24*). In the present study, we did not use the IDMS-MDRD Study equation with the Japanese Society of Nephrology–Chronic Kidney Disease Initiatives (JSN-CKDI) coefficient, although the modified equation is recommended for Japanese by the Japanese Society of Nephrology (*25*). The creatinine measurements in the participating laboratories were made by the Jaffe method in early 1990s, and some laboratories changed to the enzymatic method after 2000. Since most of the serum creatinine values in the present study were measured by Jaffe method, it was necessary to use the modified original MDRD Study equation with the Japanese coefficient which was created using values measured by the Jaffe method. The serum creatinine values measured by the enzymatic method were converted to the value obtained by the Jaffe method.

Our study has the advantages of large sample size and 10-year longitudinal follow-up. However, it also has several limitations. First, the data of this study were derived from health examination program run by community and hospital. Approximately 40% of the total participants of the first health examination program participated in the program 10 years later. Since a set of serum creatinine measurements over 10 years was required for evaluation of the rate of GFR decline, a survival bias may have been exist in the study. Additional bias may have arisen from patients with serious diseases who had already been examined in hospital visits and thus would not have participated in the health examination program. Second, although the two sets of creatinine values measured 10 years apart were measured in the same individuals in the same laboratories, the values of the serum creatinine may have drifted. We calibrated the value of serum creatinine for each laboratory based on the values in the central laboratory each year for either gender. Third, although we have adjusted the effect of regression to means, residual effects may be present. Fourth, systolic blood pressure is a stronger risk for ESRD than diastolic blood pressure (*13*).The risk of blood pressure should therefore be analyzed separately for systolic and diastolic blood pressure rather than by using the mean blood pressure. However, these data were not available in the present study.

In conclusion, the average rate of GFR decline in the Japanese general population was 0.36 mL/min/1.73 $m^2$/year, considerably slower compared with that of the Caucasian general population. Hypertension was a marginal risk factor for a faster decline in renal function in men, and proteinuria was a risk factor in both men and women. Patients younger than age 70 are at risk when they have GFR less than 50 mL/min/1.73 $m^2$, while patients aged 70–79 are at risk when their GFR is less than 40 mL/min/1.73 $m^2$. From the results, we are proposing the current definition for CKD, a GFR less than 60 mL/min/1.73 $m^2$, to be re-evaluated for the Japanese population.

## References


1. Japanese Society for Dialysis Therapy: An Overview of Regular Dialysis Treatment in Japan as of Dec. 31, 2005. Tokyo, Japanese Society of Dialysis Therapy, 2006, 39 pp.
2. Imai E, Horio M, Nitta K, *et al*: Estimation of glomerular filtration rate by the MDRD equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007; **11**: 41–50.
3. Imai E, Horio M, Iseki K, *et al*: Prevalence of chronic kidney disease (CKD) in Japanese population predicted by MDRD equation modified by a Japanese coefficient. *Clin Exp Nephrol* 2007; **11**: 156–163.
4. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003; **41**: 1–12.
5. Hallan S, Coresh J, Astor B, *et al*: International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 2006; **17**: 2275–2284.
6. Eriksen B, Ingebretsen O: The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006; **69**: 375–382.
7. Lindeman R, Tobin J, Shock N: Longitudinal studies on the rate decline in renal function with age. *J Am Geriatr Soc* 1985; **33**: 278–285.
8. Iseki K, Iseki C, Ikeyama Y, Kinjo K, Takishita S: Risk nof developing low glomerular filtration rate or elevated serum creatinine in s screened cohort in Okinawa, Japan. *Hypertens Res* 2007; **30**: 167–174.
9. Epstein M: Aging and kidney. *Physician* 1985; **31**: 123.
10. Hemmelgarn B, Zhang J, Manns B, *et al*: Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int* 2006; **69**: 2155–2161.
11. Klahr S, Levey A, Beck G, *et al*: The effect of dietary protein restriction and blood-pressure control on the progression of chronic renal failure. *N Engl J Med* 1994; **330**: 877–884.
12. Ishani A, Grandits G, Grimm R, *et al*: Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. *J Am Soc Nephrol* 2006; **17**: 1444–1452.
13. Klag M, Whelton P, Randall B: Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996; **334**: 13–18.
14. Tozawa M, Iseki K, Iseki C, Kinjo K, Ikeyama Y, Takishita S: Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension* 2003; **41**: 1341–1345.
15. Yamagata K, Ishida K, Sairenchi T, *et al*: Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 2007; **71**: 159–166.
16. Vupputuri S, Francis M, Eberhardt M, *et al*: Effect of blood pressure on early decline in kidney function among hypertensive men. *Hypertension* 2003; **42**: 1144–1149.
17. Fliser D, Franek E, Joest M, Block S, Mutschler E, Ritz E: Renal function in the elderly: impact of hypertension and cardiac function. *Kidney Int* 1997; **51**: 1196–1204.
18. Naugarten J, Acharya A, Silbiger SR: Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol* 2000; **11**: 319–329.
19. Homma S, Hirose N, Ishida H, Ishii T, Araki G: Carotid plaque and intima-media thickness assessed by b-mode ultrasonography in subjects ranging from young adults to centenarians. *Stroke* 2001; **32**: 830–835.
20. Shoji T, Emoto M, Tabata T, *et al*: Advanced atherosclerosis in predialysis patients with chronic renal failure. *Kidney Int* 2002; **61**: 2187–2192.
21. Jones C, Francis M, Eberhardt M, *et al*: Microalbuminuria in the US population: Third national hralth and nutrition examination survey. *Am J Kidney Dis* 2002; **39**: 445–459.
22. Selby J, FitzSimmons S, Newman J, Katz P, Sepe S, Showstack J: The natural history and epidemiology of diabetic nephropathy. Implications for prevention and control. *JAMA* 1990; **263**: 1954–1960.
23. Iseki K, Ikeyama Y, Iseki C, Takishita S: Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 2003; **63**: 1468–1474.
24. Levey AS, Coresh J, Greene T, *et al*: Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247–254.
25. Imai E, Horio M, Nitta K, *et al*: Modification of the MDRD Study equation for Japan. *Am J Kidney Dis* 2007; **50**: 927–937.