Serum Creatinine Level Underestimates Hypertensive Renal Involvement in Elderly Patients with Essential Hypertension

Yuji Shigematsu, Mareomi Hamada, Go Hiasa, Osamu Sasaki, Tomoaki Ohtsuka, Hidetoshi Hashida, Shuntaro Ikeda, Makoto Suzuki, Yuji Hara, and Kunio Hiwada

It is well recognized that serum creatinine level provides a quick general assessment of renal function. However, we frequently encounter elderly hypertensive patients with renal involvement whose serum creatinine levels are within normal limits. The aim of this study was thus to determine whether serum creatinine level is a sensitive indicator of renal function in elderly hypertensive patients. Study groups were classified according to age: 82 elderly patients (aged 65 yr or older) and 98 middle-aged patients (aged 40–65 yr) with essential hypertension. To assess hypertensive renal involvement, serum creatinine and serum uric acid levels were measured. We also measured the left ventricular mass (LVM) index by using echocardiography as a marker of hypertensive target organ damage. There was no age-related difference in the LVM index, but the serum creatinine level in elderly hypertensive patients was significantly lower than that in middle-aged hypertensive patients. There was no significant difference in serum uric acid level between the two groups. In addition, the LVM index was correlated with the serum uric acid level ($r=0.46$, $p=0.0001$) but not with the serum creatinine level in elderly hypertensive patients. In middle-aged hypertensive patients, the LVM index was related to both serum uric acid level ($r=0.41$, $p=0.007$) and serum creatinine level ($r=0.43$, $p=0.003$). In conclusion, serum creatinine level may underestimate hypertensive renal involvement in elderly hypertensive patients. In contrast, serum uric acid level may be a sensitive indicator of hypertensive target organ damage irrespective of age. (*Hypertens Res* 1999; 22: 297–301)

Key Words: essential hypertension, age, serum creatinine, serum uric acid, left ventricular hypertrophy

The kidneys are one of the major target organs affected by hypertension. It is also well recognized that serum creatinine level provides a quick general assessment of renal function. However, we frequently encounter elderly hypertensive patients with renal involvement whose serum creatinine levels are within normal limits. On the other hand, it has been reported that hyperuricemia observed in untreated essential hypertensive patients may reflect a decrease in renal blood flow and early hypertensive nephrosclerosis (1). High serum uric acid levels and low urinary uric acid levels are also associated with insulin resistance (2).

In essential hypertension, echocardiographically determined left ventricular hypertrophy (LVH) is known to be an independent risk factor of future cardiovascular complications (3–6). Furthermore, we have shown that LVH and structural remodeling of the heart progress in parallel with hypertensive renal involvement (7, 8). However, these data are derived from all age groups rather than from a specific geriatric population.

Accordingly, the purpose of the present study

was to determine whether serum creatinine level is a sensitive indicator of hypertensive renal involvement in elderly patients with hypertension. We also studied the clinical significance of serum uric acid level for the assessment of hypertensive target organ damage in essential hypertension.

Methods

Study Population

One hundred and eighty consecutive patients (98 men and 82 women) with uncomplicated essential hypertension were enrolled in the study. Patients were excluded who had a pre-existing cardiac disease, a pre-existing medical illnesses, such as diabetes mellitus, or M-mode echocardiograms inadequate for clearly detecting the internal lines of the interventricular septum and left ventricular posterior wall. All subjects gave their informed consent prior to participation in the present study.

In all hypertensive patients, a complete medical history and physical examination and appropriate laboratory evaluation failed to reveal a secondary

From the Second Department of Internal Medicine, Ehime University School of Medicine, Ehime, Japan.

Address for Reprints: Yuji Shigematsu, M.D., The Second Department of Internal Medicine, Ehime University School of Medicine, Shigenobu-cho, Onsen-gun, Ehime 791-0295, Japan.

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Table 1. Baseline Characteristics in Study Subgroups

Characteristics	Elderly HT (n=82)	Middle-aged HT (n=98)
Men/Women	41/41	57/41
Age (yr)	69±4	52±7*
Body mass index (kg/m ²)	24.3±2.4	24.4±3.3
Duration of hypertension (yr)	15.3±10.5	11.2±9.8*
Systolic blood pressure (mmHg)	167±14	171±19
Diastolic blood pressure (mmHg)	90±12	99±14*
Left ventricular mass index (g/m ²)	113±30	114±30
Relative wall thickness	0.39±0.08	0.40±0.08
Total cholesterol (mg/dl)	212±34	203±44
HDL cholesterol (mg/dl)	45±14	42±12

Values are mean±SD. * $p<0.01$ vs. Elderly HT. HT: hypertension, HDL: high density lipoprotein.

cause for the hypertension. Study groups were classified according to age: 82 elderly patients with hypertension (aged 65 yr or older) and 98 middle-aged patients with hypertension (aged 40-65 yr). None of the patients had ever received any anti-hypertensive therapy at the time of the initial diagnostic evaluation.

Blood pressure was measured in triplicate by a single physician who was expert in the evaluation of hypertension, with an appropriate arm cuff and a mercury sphygmomanometer after 5 minutes' rest in the sitting position. The arithmetic mean of the last two measurements was calculated. Korotkoff phase V was taken for diastolic blood pressure. Hypertension was defined as systolic blood pressure equal to or greater than 140 mmHg and/or diastolic blood pressure equal to or greater than 90 mmHg (9).

Renal Function

Creatinine was analyzed by Jaffe's method (normal range of serum creatinine for our laboratory, 0.5-1.2 mg/dl). Uric acid was analyzed by the uricase-peroxidase method (normal range for our laboratory, 2.7-8.0 mg/dl). The 24 h urine collections for creatinine clearance in hypertensive patients were supervised by the nursing staff. The 24 h creatinine clearance was taken as an index of glomerular filtration rate and also was corrected for body surface area. Measurements of serum creatinine, urinary creatinine, serum uric acid, total cholesterol and high density lipoprotein (HDL) cholesterol were carried out using an automatic analyzer (model TBA-60S, Toshiba Inc., Tokyo).

Echocardiographic Measurement

Two-dimensionally guided M-mode echocardiography was performed by standard methods as previously described (7, 10), using an SSD-9000 echocardiograph with a 3.5 MHz transducer (Aloka Inc., Tokyo). Left ventricular internal dimension (LVID) and interventricular septal and posterior wall thickness (IVST and PWT) were measured at end-diastole and end-systole, according to the American Society of Echocardiography guidelines (11), and used for all purposes except determination of left ventricular mass. Left ventricular mass (LVM) was

calculated at end-diastole by using Penn convention (12). LVM index was measured as follows: LVM index = LVM/body surface area. Relative wall thickness (RWT) was also measured as follows (13): $RWT = 2 \times (PWTd/LVIDd)$, where d is end-diastole.

Statistical Analysis

All values are expressed as mean±SD. The statistical evaluation was performed by unpaired Student's *t* test. In addition, the serum creatinine level was assessed by ANCOVA with age as a covariate. Univariate correlation was analyzed using Pearson's correlation coefficient. Results were considered significant at the probability level of (p) < 0.05.

Results

Baseline Characteristics

There were no significant differences in body mass index, total cholesterol or HDL cholesterol levels between the two hypertensive groups (Table 1). The duration of hypertension was shorter in middle-aged hypertensive patients. Although office systolic blood pressure did not differ significantly, office diastolic blood pressure in elderly hypertensive patients was lower than that in middle-aged hypertensive patients. The LVM index and relative wall thickness did not differ significantly between the two hypertensive groups.

Renal Function

As shown in Fig. 1 and Table 2, serum creatinine level was higher in middle-aged hypertensive patients than in elderly hypertensive patients. However, there were no significant differences in the serum creatinine level after eliminating the effects of age. The 24 h creatinine clearance in elderly hypertensive patients was significantly lower than that in middle-aged hypertensive patients. In addition, the 24 h creatinine clearance decreased with advancing age ($r=0.38$, $p<0.0001$). The serum uric acid level did not differ significantly between the two hypertensive groups.

Fig. 1. These bar graphs show the comparison of serum creatinine level (left) and 24 h creatinine clearance (right) between elderly and middle-aged hypertensive patients. HT indicates hypertension.

Table 2. Renal Function in Study Subgroups

Characteristic	Elderly HT (n=82)	Middle-aged HT (n=98)
Serum creatinine level (mg/dl)		
Unadjusted	0.84 ± 0.24	0.94 ± 0.32*
Adjusted for age	0.82 ± 0.42	0.96 ± 0.40
24 h Creatinine clearance (ml/min)	77.9 ± 24.0	88.3 ± 26.1†
Serum uric acid level (mg/dl)		
Men	6.32 ± 1.23	6.81 ± 1.33
Women	5.52 ± 0.91	5.23 ± 1.18

Values are mean ± SD. * $p < 0.05$, † $p < 0.01$ vs. Elderly HT. HT: hypertension.

Table 3. Relations of Left Ventricular Mass Index to Serum Creatinine Level and Serum Uric Acid Level

Characteristic	Left ventricular mass index (g/m ²)	
	<i>r</i>	<i>p</i>
Serum creatinine level (mg/dl)		
Elderly HT	0.16	0.148
Middle-aged HT	0.43	0.003
Serum uric acid level (mg/dl)		
Elderly HT	0.46	0.0001
Middle-aged HT	0.41	0.007

HT: hypertension.

Correlations between Renal Function and LVM Index

In total hypertensive patients, both serum creatinine level ($r = 0.31$, $p < 0.001$) and serum uric acid level ($r = 0.43$, $p < 0.0001$) were significantly related to LVM index. However, as shown in Table 3, serum creatinine level was not significantly related to LVM index in elderly hypertensive patients. In contrast, there was a significant correlation between serum creatinine level and LVM index in middle-aged

hypertensive patients. The serum uric acid level and LVM index were significantly correlated both in elderly and in middle-aged hypertensive patients.

Discussion

Our results indicate that serum creatinine level may underestimate hypertensive renal involvement in elderly hypertensive patients. In contrast, serum uric acid level may sensitively reflect hypertensive target organ damage irrespective of age.

It has been well established that the heart and kidneys are the major target organs of hypertension. Several studies (7, 8, 14) have shown that hypertensive renal involvement varies in parallel with the degree of LVH in essential hypertension. LVH is a potent sign of generalized preclinical hypertensive disease (15). However, these data are derived from all age groups rather than a specific geriatric population. In the present study, we found a significant correlation between LVM index and serum creatinine level in middle-aged hypertensive patients. However, there was no significant correlation between these two parameters in elderly hypertensive patients. An important clinical point should be emphasized from the results of our study.

Apparently normal serum creatinine level in uncomplicated elderly hypertensive patients may frequently represent preclinical hypertensive renal involvement. Thus, adjustments of dosage of medications may be necessary in elderly hypertensive patients with apparently normal serum creatinine level.

In a clinical setting, serum creatinine level is the most commonly used marker of renal function. The traditional method for measurement of serum creatinine level utilizes Jaffe's reaction, which is a colorimetric assay based on the formation of a complex between creatinine and alkaline picrate (16). Unfortunately, a number of substances normally found in serum contribute to the colorimetric reaction, thus falsely increasing the observed serum creatinine level (16). Furthermore, creatinine is produced non-enzymatically from creatine and phosphocreatinine in skeletal muscle. Since these compounds are found almost exclusively in skeletal muscle, creatinine is produced in proportion to the skeletal muscle mass (17). These factors, together with the variable degree of tubular creatinine secretion, preclude the use of serum creatinine levels as an accurate index of glomerular filtration rate.

The effect of aging on glomerular filtration rate as measured by creatinine clearance has been well documented (18, 19). In healthy normotensive subjects, the creatinine clearance may decline from 140 ml/min per 1.73 m² at the age of 30 to 97 ml/min per 1.73 m² at the age of 90 with a mean decline of 0.75 ml/min per yr (18). These observations agree with our finding that the creatinine clearance in elderly hypertensive patients was significantly lower than that in middle-aged hypertensive patients. In contrast, serum creatinine level in elderly hypertensive patients was significantly lower than that in middle-aged hypertensive patients even in the presence of an identical LVM index.

In our previous study, we reported that age significantly affected both LVM index and LV geometry (20). Echocardiographic studies have also shown that the left ventricular wall thickness and LVM significantly increase with advancing age in healthy normotensive subjects (21, 22). However, in the present study on otherwise healthy hypertensive patients, we detected no differences in LVM index or LV geometry between middle-aged and elderly hypertensive patients. Furthermore, there was no significant difference in serum creatinine level between middle-aged and elderly hypertensive patients after eliminating the effects of age. As indicated above, endogenous creatinine production from muscle is decreased with aging, and thus overestimation of renal function can result from the finding of a low serum creatinine level in elderly patients.

In the early stage of hypertension, the serum uric acid level increases as renal blood flow decreases without affecting the glomerular filtration rate (1). Furthermore, there is increasing evidence that hyperuricemia is associated with a multimetabolic syndrome (23) in which insulin-mediated renal hemodynamic abnormalities lead to hypertensive renal damage (24). Facchini *et al* (2) have suggested that resistance to insulin-mediated glucose uptake

and or the compensatory hyperinsulinemia associated with a multimetabolic syndrome decrease urinary uric acid clearance, with a subsequent increase in serum uric acid level. Recently, Alderman *et al* (25) demonstrated a positive association between sex-adjusted rates of coronary-heart disease and diuretic-induced increases in serum uric acid within a large cohort of treated hypertensive patients. However, despite the wealth of evidence that serum uric acid level is associated with a number of metabolic abnormalities, the relationship between serum uric acid level and the severity of hypertension is not yet fully understood. In the present study, there was a significant correlation between LVM index and serum uric acid level in not only middle-aged but also elderly hypertensive patients. These findings add further support to the concept that serum uric acid level is a sensitive indicator of hypertensive target organ damage irrespective of age.

The present study has several limitations. First, not only LVM index, but also age shows consistent and strong relations to the incidence of cardiovascular events in both sexes (5). Furthermore, as mentioned above, the left ventricular wall thickness and LVM significantly increased with advancing age in healthy normotensive subjects (21, 22). Therefore, it is speculated that the clinical significance of the LVM index may differ between middle-aged and elderly hypertensive patients. Another limitation is gender difference. The normal ranges of some parameters, such as LVM index and serum uric acid level, differ between men and women. Although our two hypertensive groups were of the same gender, we can't completely exclude the influence of gender difference on the present study.

In conclusion, serum creatinine level may not reflect hypertensive renal involvement in elderly hypertensive patients. In contrast, the strong positive association between serum uric acid level and LVM index in middle-aged and elderly hypertensive patients suggests a clinical significance of serum uric acid level for the assessment of hypertensive target organ damage irrespective of age.

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