High-Normal Serum Creatinine Concentration Is a Predictor of Cardiovascular Risk in Essential Hypertension

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Background: Determination of serum creatinine concentration is recommended in all patients with hypertension as a marker of target organ damage. However, the possibility that creatinine values within the reference range might contribute to stratification of cardiovascular risk in essential hypertension has never been tested.

Patients and Methods: In the setting of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale Study, for up to 11 years (mean, 4 years) we followed up 1829 white patients with hypertension (mean±SD age, 51±12 years; 53% men; office blood pressure, 157/98 mm Hg) free of cardiovascular events and with normal pretreatment creatinine levels (men, 136 µmol/L [1.5 mg/dL]; women, 120 µmol/L [1.4 mg/dL]) who also underwent 24-hour blood pressure monitoring and electrocardiography before therapy.

Results: During follow-up, there were 175 fatal or non-fatal major cardiovascular morbid events (2.4 per 100 patient-years). Event rate increased progressively from the first to the fourth sex-specific quartiles of creatinine distribution (1.5, 2.3, 2.3, and 3.5 per 100 patient-years; P = .003 by log-rank test). After adjustment (in a multivariate Cox model) for age, sex, diabetes, cholesterol, smoking, left ventricular hypertrophy, and 24-hour pulse and mean blood pressures (P<.05 for all), creatinine concentration was an independent adverse predictor of cardiovascular morbid events (P = .01). The observed excess risk was 1.30 (95% confidence interval, 1.07-1.59) for a 20-µmol/L (0.23-mg/dL) increase in creatinine concentration.

Conclusions: A serum creatinine value within the reference range is a predictor of cardiovascular morbidity in white patients with essential hypertension. Its prognostic value persists after adjustment for several powerful confounders, including average 24-hour blood pressure and left ventricular hypertrophy.

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The kidney is a main target of organ damage in hypertension, and long-term exposure to elevations in blood pressure (BP), even within the normotensive range, can induce early renal damage. Current expert guidelines for the management of hypertension recommend determination of the serum creatinine concentration in all patients with hypertension as a marker of target organ damage. In the Joint National Committee VI guidelines, a frankly elevated creatinine concentration or the presence of proteinuria is considered a sign of organ damage, and a creatinine level of 106 to 178 µmol/L (1.2-2.0 mg/dL) is a major tool for risk stratification according to the World Health Organization—International Society of Hypertension guidelines. Nevertheless, few data exist about the prognostic value of normal or minimally elevated creatinine levels in hypertension. Despite the fact that renal hemodynamic values become abnormal even in the early stages of hypertension, the glomerular filtration rate is usually not significantly reduced until late in the course of the disease, and an elevated serum creatinine level is therefore a late sign of renal damage in essential hypertension. Although not an ideal marker for renal function, an increased serum creatinine level is strongly predictive of the subsequent development of end-stage renal disease. Moreover, frankly elevated serum creatinine values predict a poor prognosis in patients with hypertension, and mild elevations in serum creatinine levels were associated with an increased all-cause mortality rate in population-based samples of elderly patients and in patients with heart failure.

Thus, to our knowledge, the prognostic significance of serum creatinine levels in the upper-normal range has not been...
PATIENTS AND METHODS

The Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) Study is a prospective registry of complications and deaths in white adults with essential hypertension. The study design and procedures have been reported previously.\textsuperscript{17,19} Patients with hypertension were referred to 1 of 3 participating medical centers (Perugia General Hospital, Città della Pieve Civic Hospital, and Castiglione del Lago Civic Hospital) for baseline evaluation by a group of general practitioners practicing in Umbria in central Italy. A total of 1829 patients with complete follow-up data enrolled between January 1, 1988, and December 31, 1996, and all were included in the present analysis. All study patients fulfilled the following criteria: (1) office systolic BP of 140 mm Hg or higher, diastolic BP of 90 mm Hg or higher, or both on 3 or more visits at 1-week intervals; (2) no previous treatment for hypertension (70% of patients) or withdrawal from antihypertensive drug therapy 4 weeks or more before the study (30% of patients); (3) no clinical or laboratory evidence of heart failure, coronary heart disease, previous stroke, valvular defects or secondary causes of hypertension, or important concomitant disease; (4) 1 or more valid BP measurements per hour during 24 hours; and (5) normal serum creatinine levels (men, $<$1.36 mmol/L $<$1.5 mg/dL; women, $<$1.20 mmol/L $<$1.4 mg/dL). These cut-off points represent the 95th percentile of the distribution of serum creatinine in a population of 3241 healthy white individuals from the Framingham Heart Study.\textsuperscript{20} All patients gave informed consent to participate in the study.

Investigated to date in patients with hypertension. In the present study, we investigated the relation between serum creatinine concentration and subsequent risk for cardiovascular morbid events in patients with essential hypertension and normal levels of serum creatinine.

Table 1 shows the main clinical characteristics of the study population with and without cardiovascular events during follow-up. Patients who will develop an event were older, had a longer duration of hypertension, and were more frequently men and diabetic. In addition, serum cholesterol and serum creatinine levels, prevalence of left ventricular hypertrophy and proteinuria, and BP values (office and ambulatory) were higher in patients who will vs will not develop a cardiovascular event. The prevalence of smoking and body mass index did not differ between the groups.

During follow-up of 4.0 ± 2.0 years (range, 1.0-10.8 years), there were 175 new cardiovascular morbid events (2.37 events per 100 patient-years) at the cardiac (n=84), cerebrovascular (n=75), or peripheral vascular (n=16) level. Specifically, there were 33 patients with myocardial infarction, 8 with sudden cardiac death, 3 with cardiac death from other causes, 21 with unstable angina, 6 with coronary revascularization procedures, 13 with heart failure that required hospitalization, 56 with stroke, 19 with transient cerebral ischemia, and 16 with new-onset aortoiliac occlusive disease. During follow-up, we also registered 75 deaths from all causes (0.96 events per 100 patient-years), of which 36 were from cardiovascular causes (3 fatal myocardial infarctions, 12 sudden cardiac deaths, 11 other cardiac deaths, and 10 fatal strokes).

The rate of total (fatal plus nonfatal) cardiovascular events was 1.47, 2.30, 2.27, and 3.52 per 100 patient-years in the first, second, third, and fourth sex-specific quartiles of creatinine distribution, respectively (Figure 1). Event-free survival curves in the 4 quartiles of creatinine distribution differed significantly (P < .003 by log-rank test) (Figure 2). The cumulative cardiovascular event rate for the highest quartile was greater than 50% at 11 years compared with a cumulative rate of less than 20% for the lowest quartile. Event rate was intermediate in the second and third quartiles.

Results of multivariate survival analysis are shown in Table 2. The association between serum creatinine level and subsequent cardiovascular morbidity was maintained after adjustment for the confounding effects of age, sex, smoking, diabetes, cholesterol level, left ventricular hypertrophy, proteinuria, office and 24-hour ambulatory BP values, treatment status, body mass index, and family history of early-onset coronary heart disease. The observed excess risk was 1.30 (95% confidence interval [CI], 1.07-1.59; \( P = .01 \)) for each 20-µmol/L (0.23-mg/dL) increase in creatinine concentration. The prognostic impact of creatinine level remained significant also when multivariate analysis was restricted to the sub-

BASELINE MEASUREMENTS

Office BP was measured by physicians in the medical centers with a mercury sphygmomanometer after patients sat for 10 minutes or longer. The average of 3 or more measurements at 2 or more sessions was considered for the analysis. Ambulatory BP was recorded with an oscillometric device (models 90202 and 90207, SpaceLabs, Redmond, Wash) that was set to take a reading every 15 minutes throughout 24 hours. Normal daily activities were allowed and encouraged, and patients were told to keep their nondominant arm still and relaxed to the side during measurements. Reading, editing, and analysis of data were performed as previously described.\textsuperscript{17,18} Serum creatinine concentration was measured in an autoanalyzer (Technicon, Tarrytown, NY) by means of an automated technique measuring dialyzable Jaffe chromogen,\textsuperscript{21} and the presence of proteinuria was assessed by standard dipstick examination of an early-morning spot urine sample. To maximize the diagnostic sensitivity of electrocardiography, left ventricular hypertrophy was defined by a multifactorial criterion (S wave in V3 + R wave in aVL $>$2.4 mV in men or $>$2.0 mV in women, typical left ventricular strain, or Romhilt-Estes score $>$5) with significantly higher sensitivity, accuracy, and prognostic value than several other more widely used standard criteria.\textsuperscript{22,23}

FOLLOW-UP PROCEDURES AND END POINT EVALUATION

All patients were followed up by their family physicians, in cooperation with the outpatient clinic of the referring

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hospital, and treated with the aim of reducing office BP to less than 140/90 mm Hg using standard lifestyle and pharmacological measures. Most patients continue to be periodically referred to our institutions for BP control and other diagnostic procedures. Diuretics, β-adrennergic blocking agents, angiotensin-converting enzyme inhibitors, calcium channel blockers, and α-blocking agents, alone or in various combinations, were the most frequently prescribed antihypertensive drugs. Contacts with family physicians and telephone interviews were periodically undertaken to determine the incidence of major cardiovascular complications of hypertension. For patients who developed cardiovascular morbid events, we reviewed in conference hospital record forms and other available original source documents. Cardiovascular events included new-onset coronary artery disease (myocardial infarction, unstable angina with documentation of ischemic electrocardiographic changes, sudden cardiac death, or coronary revascularization procedure), stroke, transient cerebral ischemic attack, symptomatic aortoiliac occlusive disease verified by angiography, and congestive heart failure that required hospitalization. The international standard criteria used to diagnose cardiovascular events in the PIUMA Study have been reported previously.17,19

STATISTICAL ANALYSIS

Parametric data are reported as mean±SD. Standard descriptive and comparative analyses were undertaken. The rates of events are presented as the number of events per 100 patient-years, based on the ratio of the number of events observed to the total number of patient-years of exposure up to the terminating event or censor. For patients without events, the date of censor was that of the last contact with the patient. For patients who experienced multiple events, survival analysis was restricted to the first event. For patients who subsequently died, classification of the terminating event could differ from that of the previous nonfatal event. Survival curves were estimated using the Kaplan-Meier product-limit method44 and compared using the Mantel-Haenszel (logistic-rank) test.25 The effect of prognostic factors on survival was evaluated using the stepwise Cox semiparametric regression model.18 The assumption of linearity for the Cox model was tested through visual inspection, and no violation of proportional hazards was found. We tested the variables of age, sex, serum cholesterol level, serum creatinine level, proteinuria, left ventricular hypertrophy on the electrocardiogram, smoking habits, body mass index (calculated as weight in kilograms divided by the square of height in meters), office and 24-hour mean BP and pulse pressures, diabetes, and antihypertensive drug treatment at the follow-up contact. We also divided patients by sex-specific quartiles of serum creatinine distribution. The partition values were 83, 92, and 103 µmol/L (0.94, 1.04, and 1.17 mg/dL) in men and 70, 76, and 84 µmol/L (0.79, 0.86, and 0.95 mg/dL) in women. A statistical software package (SPSS release 8.0; SPSS Inc, Chicago, Ill) was used to perform the analyses. Differences were considered statistically significant at P<.05.

A significant risk gradient for adverse events was evident across the quartiles of creatinine distribution. In a multivariate analysis, the excess risk compared with the first quartile was significant for the fourth quartile (creatinine level, ≥103 µmol/L [≥1.17 mg/dL]) in men and ≥84 µmol/L [≥0.95 mg/dL]) in women; relative risk, 1.61; 95% CI, 1.02-2.54; P =.047) and bordered significance for the third (relative risk, 1.56; 95% CI, 0.95-2.55; P =.08) and second (relative risk, 1.55; 95% CI, 0.95-2.51; P =.08) quartiles.

The rate of all-cause deaths was 0.66, 0.76, 0.73, and 1.71 per 100 patient-years in the first, second, third, and fourth quartiles of serum creatinine distribution, respectively (P =.01 by log-rank test). However, in a multivariate Cox regression analysis, only age, diabetes, male sex, and 24-hour pulse pressure were independent predictors of all-cause deaths (P<.05 for all), and the prognostic impact of serum creatinine concentration was no longer significant (P =.24).

COMMENT

Results of the present study show a strong relation between serum creatinine level and subsequent cardiovascular morbidity in patients with initially untreated and uncomplicated essential hypertension and normal baseline creatinine values. The relation was statistically significant and persisted after correction for the effect of several traditional risk factors, including age, sex, diabetes, cigarette smoking, left ventricular hypertrophy, serum cholesterol level, and office and 24-hour ambulatory BP values. For every 20-µmol/L (0.23-mg/dL) increase in creatinine concentration, there was a 30% increase in the observed age- and risk factor–adjusted risk of fatal or nonfatal cardiovascular end points.

PREVIOUS STUDIES

Among participants in the Hypertension Detection and Follow-up Program,18 a frankly elevated serum creatinine level (>150 µmol/L [>1.7 mg/dL]) was an uncommon finding, being present in 2.8% of the population, but represented a strong independent risk factor for mortality. In that study,15 despite a gradual increase in the crude mortality rate for baseline creatinine levels greater than 106 µmol/L (>1.2 mg/dL), the independent prognostic value of mildly elevated serum creatinine values was not assessed. In a case-control study27 of patients with treated hypertension, the all-cause mortality rate was lower in those with normal (<124 µmol/L [<1.4 mg/dL]) in men and <106 µmol/L [<1.2 mg/dL] in women) than elevated (>178 µmol/L [>2.0 mg/dL]) creatinine levels, but no significant difference was found compared with patients with intermediate values. In a recent overview28 of the placebo-treated control groups of 8 antihy-
pertensive intervention trials, a reduction by 30 mL/min in glomerular filtration rate, as determined using the Cockcroft formula, was associated with a significant and independent 27% increase in cardiovascular deaths during average follow-up of 5 years, but no data were reported on the prognostic significance of glomerular filtration rate in patients who did not have overt renal failure. In a different clinical setting, patients with asymptomatic or symptomatic left ventricular dysfunction from the Studies of Left Ventricular Dysfunction trials whose creatinine clearance was less than 1.00 mL/s (<60 mL/min) exhibited an increased risk for all-cause death, largely explained by an increase in pump-failure death. Taken together, available data could not provide a definite answer to the question regarding the prognostic impact of serum creatinine level in most patients with essential hypertension and normal or minimally elevated creatinine values.

PRESENT STUDY

To our knowledge, this is the first report of an association between serum creatinine concentration and subsequent cardiovascular morbidity in a large, untreated hypertensive population with normal creatinine values and without cardiovascular disease at baseline evaluation. The association was maintained after adjustment for mean BP and pulse pressure, which seems to be the strongest predictor of adverse prognosis in hypertension. Also, besides serum creatinine level, another simple indicator of kidney damage and a valuable prognostic marker in hypertension is proteinuria. In our study, however, the proportion of patients with dipstick-detectable proteinuria was only 7%, and the independent prognostic value of creatinine concentration was confirmed also when the analysis was restricted to patients free of proteinuria. Thus, a high-normal creatinine level seemed to be a more sensitive marker of kidney damage than proteinuria and a more valuable tool for risk stratification in patients with uncomplicated hypertension. There is also initial evidence that microalbuminuria can be associated with a greater risk for cardiovascular complications in hypertension; determination of microalbuminuria was not available routinely in the PIUMA Study.

Our study does not allow us to draw firm conclusions about the potential mechanisms underlying the association between serum creatinine level and cardiovascular morbidity.
An increased risk for cardiovascular events was detectable for creatinine values of 103 µmol/L or greater (≥1.17 mg/dL) in men and 84 µmol/L or greater (≥0.95 mg/dL) in women. These findings have important implications for clinical practice. The Joint National Committee V1 guidelines recommend serum creatinine determination in all patients with hypertension, but only a frankly elevated creatinine level and the presence of proteinuria are considered relevant findings for the assessment of cardiovascular risk in a given hypertensive patient, despite being relatively uncommon in uncomplicated hypertension.13 Our study adds to the current literature by showing that a high-normal serum creatinine level in an untreated patient with hypertension should be regarded not only as a risk factor for renal failure but as an important sign of target organ damage and as a simple and valuable tool for cardiovascular risk stratification.

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STUDY LIMITATIONS

The large number of cardiovascular events in the present study allowed adjustment for the confounding effects of several risk markers. However, the number of fatal events was smaller, and this might have precluded the observation of an independent association between creatinine concentration and the all-cause mortality rate. Our findings have been obtained in initially untreated white patients, so results might not be extended to different racial groups or to patients receiving antihypertensive drug treatment at the time of the qualifying serum creatinine determination. Finally, serum creatinine levels are affected by a variety of conditions not associated with glomerular filtration rate, including muscle mass, vigorous exercise, ingestion of cooked meat, and treatment with some drugs.8 Creatinine clearance is a more accurate measure of renal function than is serum creatinine level but requires a 24-hour urine collection, which is impractical in large studies.

CLINICAL IMPLICATIONS

Our findings show a powerful and independent relation between baseline serum creatinine concentration and cardiovascular risk in initially untreated men and women with essential hypertension free of overt cardiovascular disease and with creatinine values below commonly accepted upper limits of normal (<136 µmol/L [<1.5 mg/dL]) in men and <120 µmol/L [<1.4 mg/dL] in women).20 An increased risk for cardiovascular events was detectable for creatinine values of 103 µmol/L or greater (≥1.17 mg/dL) in men and 84 µmol/L or greater (≥0.95 mg/dL) in women. These findings have important implications for clinical practice. The Joint National Committee V1 guidelines recommend serum creatinine determination in all patients with hypertension, but only a frankly elevated creatinine level and the presence of proteinuria are considered relevant findings for the assessment of cardiovascular risk in a given hypertensive patient, despite being relatively uncommon in uncomplicated hypertension.13 Our study adds to the current literature by showing that a high-normal serum creatinine level in an untreated patient with hypertension should be regarded not only as a risk factor for renal failure but as an important sign of target organ damage and as a simple and valuable tool for cardiovascular risk stratification.

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