Prevalence and Correlates of Elevated Serum Creatinine Levels

The Framingham Heart Study

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Background: Elevated serum creatinine (SCr) levels are a predictor of end-stage renal disease, but little is known about the prevalence of elevated SCr levels and their correlates in the community.

Methods: In this cross-sectional, community-based sample, SCr levels were measured in 6233 adults (mean age, 54 years; 54% women) who composed the “broad sample” of this investigation. A subset, consisting of 3241 individuals who were free of known renal disease, cardiovascular disease, hypertension, and diabetes, constituted the healthy reference sample. In this latter sample, sex-specific 95th percentiles for SCr levels (men, 136 µmol/L [1.5 mg/dL]; women, 120 µmol/L [1.4 mg/dL]) were labeled cutpoints. These cutpoints were applied to the broad sample in a logistic regression model to identify prevalence and correlates of elevated SCr levels.

Results: The prevalence of elevated SCr levels was 8.9% in men and 8.0% in women. Logistic regression in men identified age, treatment for hypertension (odds ratio [OR], 1.75; 95% confidence interval [CI], 1.27-2.42), and body mass index (OR, 1.08; 95% CI, 1.01-1.15) as correlates of elevated SCr levels. Additionally, men with diabetes who were receiving antihypertensive medication were more likely to have raised SCr values (OR, 2.94; 95% CI, 1.60-5.39). In women, age, use of cardiac medications (OR, 1.58; 95% CI, 1.10-2.96), and treatment for hypertension (OR, 1.42; 95% CI, 1.07-1.87) were associated with elevated SCr levels.

Conclusions: Elevated SCr levels are common in the community and are strongly associated with older age, treatment for hypertension, and diabetes. Longitudinal studies are warranted to determine the clinical outcomes of individuals with elevated levels of SCr and to examine factors related to the progression of renal disease in the community.

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SUBJECTS AND METHODS

STUDY SAMPLE

The selection criteria and study design of the Framingham Heart Study and the Framingham Offspring Study have been detailed previously.11,12 Original subjects of the Framingham Heart Study who participated in the 15th biennial examination (1977-1979; N = 2632) and adult participants in the second examination of the Framingham Offspring Study (1979-1983; N = 3853) constituted the study sample for this investigation. Blood samples for determination of SCr levels were obtained in 6233 individuals (96%). These 6233 participants constituted the broad sample; a healthy subgroup of 3241 individuals who were not taking cardiac or antihypertensive medications and who were free of known renal disease, hypertension, cardiovascular disease, or diabetes mellitus made up the reference sample.

BASELINE MEASUREMENTS AND DEFINITIONS

A medical history and physical examination were obtained on each subject at every clinic visit. Systolic and diastolic blood pressure measurements were obtained twice in the left arm of seated subjects by the examining physician using a mercury column sphygmomanometer positioned near eye level. The average of the 2 readings was used for each blood pressure variable. Height and weight were measured at each examination; body mass index (BMI) was computed as the weight in kilograms divided by the square of the height in meters. Serum creatinine values were determined by either the autoanalyzer technique13,14 or the creatinine imodohydrolase assay.15

The diagnosis of prevalent cardiovascular disease included coronary heart disease, congestive heart failure, intermittent claudication, stroke, and transient ischemic attack. Coronary heart disease included myocardial infarction, coronary insufficiency, and angina pectoris. The Framingham definitions of cardiovascular disease and related events have been described elsewhere.16 The diagnosis of hypertension was based on the following criteria of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure:17: blood pressure greater than or equal to 140 mm Hg systolic, greater than or equal to 90 mm Hg diastolic, or current antihypertensive drug treatment. Diabetes was defined on the basis of a nonfasting blood glucose level of greater than or equal to 11.1 mmol/L (200 mg/dL), a fasting blood glucose level of greater than or equal to 7.8 mmol/L (141 mg/L), or the use of insulin or an oral hypoglycemic agent. Use of cardiac medications was coded and included digoxin, nitrates, antiarrhythmics, and diuretics (for congestive heart failure). At each examination, the presence of previous renal disease was determined by the interviewing physician or by review of the participant’s medical history and records.

ANALYSIS AND STATISTICAL METHODS

After age and BMI were adjusted for, a small fixed difference in SCr values was found between the laboratory used for the original Framingham Heart Study participants and the laboratory used for the Offspring participants. This difference, 5 µmol/L (0.06 mg/dL) in men and 3 µmol/L (0.03 mg/dL) in women, was subtracted from the SCr values of the Offspring subjects. All reported SCr values reflect this calibration.

In the healthy reference sample, sex-specific 95th percentiles for SCr were labeled cutpoints, which defined the upper limit of normal values. Forward stepwise multiple logistic regression18 was applied to the broad sample to identify variables associated with SCr values that were greater than the cutpoints. Candidate variables in the logistic regression were age, BMI (truncated at 27.8 kg/m² in men and 27.3 kg/m² in women, corresponding to values used to define obesity),19 systolic blood pressure, diastolic blood pressure, pulse pressure, total serum cholesterol level, treatment for hypertension (no vs yes), cardiovascular disease (no vs yes), use of cardiac medications (no vs yes), diabetes (no vs yes), and current smoking status (no vs yes). Proteinuria, protein intake, and physical activity were not assessed. Furthermore, age-dependent cutpoints were not formulated owing to uncertainty in distinguishing the physiologic from the pathologic effects of aging on renal function.

All significant explanatory variables in the sex-specific stepwise models were tested for interaction. Finally, goodness-of-fit statistics were generated. All analyses were performed using a commercially available software system20 (SUN Ultra Enterprise 2). A 2-sided P value of less than .05 was the criterion for statistical significance.

sample was similar. The mean SCr value was 107 µmol/L (1.2 mg/dL) in men and 92 µmol/L (1.0 mg/dL) in women in the broad sample, and 105 µmol/L (1.9 mg/dL) in men and 90 µmol/L (1.0 mg/dL) in women in the reference sample. By definition, the blood pressure of the subjects in the reference sample was lower. A slightly higher proportion of subjects in the reference sample were current smokers (men, 36% vs 30%; women, 34% vs 30%). Serum lipid values did not differ much between the 2 samples.

Figure 1 illustrates the mean SCr levels by age and sex in the reference sample. Among individuals younger than 80 years, decade-specific mean SCr values varied by less than 5% in men and 6% in women. Men exhibited an 11% to 21% higher mean SCr level than women across this same age range.

ELEVATED SCr LEVELS: PREVALENCE AND SUBJECT CHARACTERISTICS

The sex-specific 95th percentile cutpoints for SCr were 136 µmol/L (1.5 mg/dL) in men and 120 µmol/L (1.4 mg/dL) in women. In the broad sample, 8.9% of men and 8.0% of women had an SCr value greater than these cutpoints (Figure 2). In men, the prevalence of elevated SCr levels changed little with age from the third to seventh decades of life. An abrupt increase in prevalence with age was observed thereafter. In women,
the prevalence increased from approximately 2.5% in the 20- to 49-year-old age range to 23% in the ninth decade of life.

Table 2 details the clinical characteristics of subjects with elevated SCr levels. It also provides comparison data with the remainder of subjects in the broad sample. In subjects above the 95th percentile cutpoint, the mean SCr value was 154 µmol/L (1.7 mg/dL) (median, 141 µmol/L [1.6 mg/dL]; range, 136-861 µmol/L [1.5-9.7 mg/dL]) in men and 139 µmol/L (1.6 mg/dL) (median, 133 µmol/L [1.5 mg/dL]; range, 120-686 µmol/L [1.4-7.8 mg/dL]) in women. More than one third of these subjects were receiving treatment for hypertension; 10% had diabetes; and 1 in 5 had cardiovascular disease.

LOGISTIC REGRESSION ANALYSIS

When cutpoints generated from the healthy reference group were applied to the broad sample, forward stepwise multiple logistic regression identified several variables that were significantly associated with elevated SCr levels (Table 3). In men, age² (OR, 1.10 for [(age – 55)/10]²; 95% confidence interval [CI], 1.04-1.15), treatment for hypertension (OR, 1.75; 95% CI, 1.27-2.42), and
BMI (OR, 1.08; 95% CI, 1.01-1.15) were significantly associated with elevated SCr levels. Additionally, diabetic men who were receiving antihypertensive medication were more likely to have SCr values greater than the cutpoint (OR, 2.94; 95% CI, 1.60-5.39). In women, age (OR, 1.66 for [age − 55]/10; 95% CI, 1.50-1.84), the use of cardiac medications (OR, 1.58; 95% CI 1.10-2.96), and treatment for hypertension (OR, 1.42; 95% CI 1.07-1.87) were identified as significant predictors of elevated SCr levels. The final sex-specific models generated acceptable goodness-of-fit statistics (men, $P = .48$; women, $P = .42$).

From the healthy reference sample, we also generated cutpoints using the sex-specific upper 10th percentile (127 µmol/L [1.4 mg/dL] in men and 112 µmol/L [1.3 mg/dL] in women). These cutpoints were applied to the broad sample, in which the prevalence of SCr values exceeding the 90th percentile was 12.0% in men and 13.6% in women. Using forward multiple logistic regression, similar variables were found associated with elevated SCr levels: in men, age, treatment for hypertension, BMI, and diabetes; in women, age, prevalent cardiovascular disease, treatment for hypertension, and smoking.

### Table 2. Clinical Characteristics of Subjects in the Broad Sample Less Than and Greater Than the 95th Percentile Cutpoints for Serum Creatinine Values*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men Less Than Cutpoint (n = 2592)</th>
<th>Men Greater Than Cutpoint (n = 252)</th>
<th>Women Less Than Cutpoint (n = 3118)</th>
<th>Women Greater Than Cutpoint (n = 271)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.1 ± 14.5</td>
<td>55.0 ± 16.0</td>
<td>54.2 ± 15.2</td>
<td>66.4 ± 13.3</td>
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<tr>
<td>Weight, kg</td>
<td>80.5 ± 12.3</td>
<td>80.9 ± 12.7</td>
<td>64.1 ± 12.6</td>
<td>63.9 ± 12.7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6 ± 3.6</td>
<td>27.1 ± 3.7</td>
<td>25.2 ± 4.8</td>
<td>25.7 ± 4.8</td>
</tr>
<tr>
<td>Serum creatinine, µmol/L (mg/dL)</td>
<td>102 ± 18 (1.2 ± 0.2)</td>
<td>154 ± 59 (1.7 ± 0.7)</td>
<td>88 ± 17 (1.0 ± 0.2)</td>
<td>139 ± 37 (1.6 ± 0.4)</td>
</tr>
<tr>
<td>Estimated creatinine clearance, ml/min</td>
<td>87.8 ± 28.5</td>
<td>58.5 ± 19.3</td>
<td>68.4 ± 25.3</td>
<td>36.5 ± 11.2</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/L (mg/dL)</td>
<td>5.42 ± 0.98 (209.3 ± 37.9)</td>
<td>5.47 ± 1.06 (211.7 ± 40.8)</td>
<td>5.60 ± 1.15 (216.7 ± 44.5)</td>
<td>6.08 ± 1.19 (235.0 ± 46.0)</td>
</tr>
<tr>
<td>High-density lipoprotein, mmol/L (mg/dL)</td>
<td>1.12 ± 0.31 (43.5 ± 12.1)</td>
<td>1.06 ± 0.30 (41.0 ± 11.6)</td>
<td>1.39 ± 0.37 (53.8 ± 14.4)</td>
<td>1.34 ± 0.38 (51.9 ± 14.8)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L (mg/dL)</td>
<td>1.69 ± 0.94 (150.0 ± 82.9)</td>
<td>2.04 ± 1.10 (180.7 ± 97.0)</td>
<td>1.24 ± 0.67 (109.7 ± 59.5)</td>
<td>1.43 ± 0.82 (126.6 ± 72.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129.7 ± 17.0</td>
<td>131.4 ± 18.7</td>
<td>125.8 ± 19.8</td>
<td>135.2 ± 21.6</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79.5 ± 9.8</td>
<td>80.1 ± 11.3</td>
<td>75.2 ± 9.4</td>
<td>75.0 ± 11.0</td>
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<tr>
<td>Antihypertensive medications, %</td>
<td>16.8</td>
<td>29.8</td>
<td>20.4</td>
<td>40.2</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>5.8</td>
<td>10.7</td>
<td>3.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>13.9</td>
<td>18.7</td>
<td>9.3</td>
<td>20.3</td>
</tr>
<tr>
<td>Coronary disease, %</td>
<td>10.0</td>
<td>14.3</td>
<td>6.0</td>
<td>16.2</td>
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<tr>
<td>Congestive heart failure, %</td>
<td>0.8</td>
<td>2.4</td>
<td>1.5</td>
<td>2.6</td>
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<tr>
<td>Intermittent claudication, %</td>
<td>3.4</td>
<td>3.2</td>
<td>2.2</td>
<td>4.4</td>
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<tr>
<td>Cardiac medications, %</td>
<td>7.3</td>
<td>12.3</td>
<td>7.0</td>
<td>18.1</td>
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<tr>
<td>Current smoker, %</td>
<td>30.9</td>
<td>25.4</td>
<td>31.2</td>
<td>19.3</td>
</tr>
</tbody>
</table>

*Cutpoints generated from the reference sample: for men, $\geq 136$ µmol/L ($\geq 1.5$ mg/dL); for women, $\leq 120$ µmol/L ($\leq 1.4$ mg/dL). Values other than percentages are mean ± SD.

†Calculated using Cockcroft-Gault formula.‡

‡Not available on 292 original cohort participants.
From a healthcare planning perspective, it is imperative that we learn more about the prevalence and correlates of impaired renal function in the community, since the prevalence of ESRD in developed countries continues to rise. Several investigators have attempted to quantify this problem, but have had difficulties with referral bias or have limited their study to the immediate predialysis population. To our knowledge, this study is the first to address these issues in a large community sample, with inherently minimal bias. We found that 8.9% of men and 8.0% of women had elevated SCr values.

The comorbidity in individuals with raised SCr levels was striking. Nearly 20% of this cohort had preexisting cardiovascular disease; more than 1 in 3 persons were receiving treatment for hypertension; 10% were diabetic; and there was a tendency toward higher total serum cholesterol levels and higher triglyceride levels.

By far, age had the strongest impact on SCr levels. We looked for this effect in 2 ways. First, analysis in the reference sample revealed little change in mean SCr values up to the ninth decade of life (Figure 1); however, the small number of individuals older than 80 years limited the precision of the mean SCr estimates, and thereby limited our ability to draw conclusions about creatinine trends in this oldest age group. Second, the impact of age on the prevalence of elevated SCr levels was assessed (Figure 2). Here, the effect of age was more dramatic. This age effect was statistically confirmed in the regression analyses, in which age terms were significant in both men and women. In men, there was a quadratic relationship between age and elevated SCr levels: odds of hypercreatininemia increased geometrically as age differed from 55 years; the rate of increase was (1.095)x, where x = (age − 55)/10. For example, the increase in age from 60 to 70 years was associated with a 21% increase in the odds of hypercreatininemia being present. The failure of the risk of hypercreatininemia to increase with age in men aged 30 to 55 years may reflect the relative contribution of an age-related decline in muscle mass. In women, the relationship of age with elevated SCr levels was linear. For every 10-year increase in age, the odds of having an elevated SCr level was increased by 66%. The association of age with SCr levels in this study is in keeping with prior reports demonstrating an age-related decline in creatinine clearance. Aging results in a loss of renal mass, in an increase in sclerotic glomeruli, and thus in impaired filtration. Pharmacological treatment for high blood pressure was associated with elevated SCr levels in men and women. No other blood pressure variable was associated with elevated SCr levels once hypertension treatment was entered. Hypertension treatment is likely a marker for individuals with the most severe hypertension and for those most likely to have target organ damage, including renal impairment. It is also possible that the antihypertensive medication played a causal role in these findings. Diuretics can lead to reduced glomerular filtration, which is typically reversible. Antihypertensive drugs may also render the kidney more vulnerable to noxious stimuli, such as the combination of a diuretic and a nonsteroidal anti-inflammatory drug. In this analysis, we did not examine the type of antihypertensive drug prescribed, and we did not investigate whether the subjects used anti-inflammatory medications. Angiotensin-converting enzyme inhibitors were not commonly used during the time period involved in this study.

There were 325 subjects with diabetes (178 men and 147 women) in the broad sample of our study. In men, logistic regression identified diabetes as an additional correlate of raised SCr levels; however, further analysis revealed an interaction with hypertension treatment whereby correlation with hypercreatininemia existed only in men with diabetes who were receiving treatment for hypertension. This finding is consistent with the present understanding of diabetic nephropathy. In both cross-sectional and longitudinal studies, diabetic renal disease has been linked to high blood pressure. This relationship likely reflects not only elevation of blood pressure in response to renal disease, but also the contribution of blood pressure to the progression and pathogenesis of diabetic nephropathy. In women, we did not find an association between diabetes and elevated SCr levels. This is difficult to explain without data on the duration of diabetes or glycemic control, variables strongly related to the development of small vessel disease.

Body mass index was also associated with elevated SCr levels in men, but not in women. It is generally understood that men have a greater percentage of muscle mass than women at any level of BMI. As creatinine is formed from muscle creatine, it is not surprising that BMI was associated with higher SCr values. It is plausible that a better measure of muscle mass, such as that obtained from bioimpedance or dual energy x-ray absorptiometry, would provide more significant correlations with SCr values.

In women, the use of cardiac medications was identified as an additional association with elevated SCr values. It is possible that the use of cardiac medications is a marker for generalized vascular disease, which in turn is associated with impaired renal function. Alternatively, the elevated SCr values may be attributable to drug treatment rather than to the disease it is being used to treat. Several limitations should be considered in the interpretation of this study’s results. First, the study sample was overwhelmingly white. The reported reference values and identified correlates of elevated SCr levels may not apply to nonwhite, non-European populations. Our overall prevalence rates may underestimate the prevalence of elevated SCr levels in African American or American Indian subjects, in whom prevalent ESRD rates are 3 to 4 times higher than those in white Americans. Such a discrepancy may also exist in the prevalence of milder forms of renal impairment. Furthermore, we may be overestimating the prevalence in white Americans. Our data represent a cohort of generally older individuals. Approximately 30% of our participants were 65 years of age or older. This contrasts with only 14% of the 1994 US white population. Accordingly, our decade-specific prevalence rates may be more useful than the composite rates for the entire sample. Second, SCr values were used as the marker for impaired renal function. Because of a reciprocal relationship between SCr values and glomerular filtration rate, a large change in the rate of glomerular filtration is required to increase SCr levels from the normal to the el-
evated range. Also, many conditions not associated directly with glomerular filtration can alter SCr levels, including muscle wasting, vigorous prolonged exercise, ingesting cooked meat, and therapy with certain cephalosporins, cimetidine, or trimethoprim.3,15 It is important to stress that an SCr value within the “normal” range does not necessarily imply a normal glomerular filtration rate. Ideally, an alternative more accurate measure of glomerular filtration should be used.

Third, we chose the 95th percentile for the cutpoint in the healthy reference sample. This was an arbitrary decision, as there are no scientifically based guidelines in the literature. As with most continuous biological variables, the cutpoint to divide normal from abnormal is often arbitrary, and frequently changes with time. Serum cholesterol and blood glucose levels are good examples.

Finally, this is a cross-sectional study. Such a study is useful for descriptive purposes, and to identify associations, but not to determine causation.

In conclusion, elevated SCr levels in the community are common and are strongly associated with age, hypertension treatment, and diabetes. Longitudinal studies are warranted to determine the clinical outcomes of individuals with elevated SCr levels and to examine factors related to the progression of renal disease in the community. We are currently analyzing longitudinal follow-up data on our study sample.

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