Serum Creatinine as an Independent Predictor of Coronary Heart Disease Mortality in Normotensive Survivors of Myocardial Infarction

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Background. Serum creatinine has been reported in previous studies to be a prognostic indicator for overall mortality, in particular in a hypertensive population.

Methods. The Program on the Surgical Control of the Hyperlipidemias (POSCH) was a randomized, controlled clinical trial. All patients had survived a single myocardial infarction, were normotensive, were not obese, were not having heart failure, and were free of diabetes mellitus and renal disease at entry into the study. POSCH had followed its control group patients (N = 417) for a minimum of 7.0 years. In this group, a prospective post hoc analysis of the relationship of baseline serum creatinine with subsequent overall and atherosclerotic coronary heart disease mortality was performed.

Results. The baseline serum creatinine values in the control group patients ranged from 0.7 to 1.9 mg/dL (60 to 170 μmol/L), and were found to be independent predictors ($P < .01$) of both overall mortality and atherosclerotic coronary heart disease mortality. Each 0.1 mg/dL (9 μmol/L) increment in the baseline serum creatinine increased the relative risk for subsequent overall mortality by 36% and the relative risk for subsequent atherosclerotic coronary heart disease mortality by 47%.

Conclusions. These results demonstrate that a serum creatinine value, obtained in normotensive, nonobese, normoglycemic survivors of a myocardial infarction without preexistent renal disease or heart failure, provides independent prognostic information regarding subsequent overall and atherosclerotic coronary heart disease mortality.

Key words. Creatinine; atherosclerosis; hyperlipidemia.
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The importance of the serum creatinine level as a prognostic indicator for subsequent overall mortality has been reported by two studies. The Hypertension Detection and Follow-up Program (HDFP),[1,2] with 10,940 hypertensive subjects followed for at least 8 years, found that persons with serum creatinine levels of 1.7 mg/dL (150 μmol/L) or greater had an 8-year overall mortality rate three times greater than those with a serum creatinine level below 1.7 mg/dL (150 μmol/L). The Beta-blocker Heart Attack Trial (BHAT),[3] following 3837 postmyocardial infarction patients for an average of 25 months, also found an independent association between a high normal serum creatinine level greater than 1.0 mg/dL (90 μmol/L) and subsequent overall mortality. No clear explanation for the independent association of serum creatinine with subsequent mortality has been presented.

This prospective post hoc analysis examines the re-

**POSCH denotes Program on the Surgical Control of Hyperlipidemias. For a list of group members, see Acknowledgments.*

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lationship between serum creatinine and subsequent overall and atherosclerotic coronary heart disease (ACHD) mortality in the control group patients enrolled in the Program on the Surgical Control of the Hyperlipidemias (POSCH). In addition, relationships of serum creatinine with other baseline characteristics and changes in serum creatinine over time are assessed in order to define further the prognostic value of serum creatinine as a predictor of subsequent overall and ACHD mortality.

Methods

Trial Design

POSCH was a randomized, controlled clinical trial designed to assess whether the lipid modification induced by partial ileal bypass surgery would have a beneficial effect on subsequent overall mortality, atherosclerotic mortality and morbidity, and changes on sequential coronary arteriograms in hypercholesterolemic survivors of a single myocardial infarction (MI). Between 1975 and 1983, 838 patients were randomized into the trial, with 417 patients assigned to receive instruction in the American Heart Association Phase 2 diet (control group) and 421 patients assigned to receive similar dietary instruction plus a partial ileal bypass (surgery group). All patients were between 30 and 64 years of age, were male or female, had survived a single MI as documented by an electrocardiogram (ECG) and enzyme levels, and had a total plasma cholesterol level of at least 220 mg/dL (5.70 mmol/L) or a low-density lipoprotein (LDL) cholesterol concentration of at least 140 mg/dL (3.60 mmol/L), if the total plasma cholesterol was from 200 to 219 mg/dL (5.20 to 5.65 mmol/L).

Patients with moderate or severe hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥105 mm Hg) or obesity (40% above ideal weight) were excluded. Patients taking antihypertensive medications were required to discontinue the medication for at least 3 weeks before the blood pressure determinations. Patients with heart failure were excluded. Patients taking digitalis or diuretics were required to discontinue their medications for at least 4 weeks before being examined for heart failure.

Patients on antiarrhythmia medication were excluded from the study unless they could discontinue their medication for at least 2 weeks before being examined for dysrhythmias and conduction defects. In addition, patients with a history of chronic renal disease or with known renal insufficiency (serum creatinine level >2.8 mg/dL [250 μmol/L]) and diabetes (glucose tolerance test: total of the fasting level plus the post-glucose load levels at 1, 2, and 3 hours ≥600 mg/dL [33.3 mmol/L]) were ineligible for the trial. The POSCH design and patient selection criteria,[4] baseline characteristics,[5] and clinical results[6] have been published. For this analysis of the relationship between baseline serum creatinine and subsequent overall and ACHD mortality, only mortality data from the first 7 years of follow-up in the control group patients are employed. This cut-off interval was chosen because all patients had a minimum of 7 years of follow-up.

Serum Creatinine Determinations

Serum creatinine levels were determined at baseline and at annual in-clinic follow-up visits over 5 years. Baseline determinations were made within 6 months before randomization into POSCH. Baseline serum creatinine values greater than 2.8 mg/dL (250 μmol/L) were used to exclude patients with renal insufficiency from POSCH. Patients with values from 2.1 to 2.8 mg/dL (190 to 250 μmol/L) were required to have a normal intravenous pyelogram for inclusion. One control group patient with clinically normal renal function had a missing baseline serum creatinine value and is not included in this report, leaving 416 control group patients with baseline serum creatinine levels available for analysis.

Initially, two of the four POSCH centers determined serum creatinine levels in their local hospital laboratories. As of July 1981, all clinics used the same central laboratory for serum creatinine determinations (SmithKline Bio-Science, Van Nuys, CA 91405). The serum creatinine values were reported in mg/dL to the nearest 0.1 mg.

Mortality Analysis

For this analysis, complete mortality data from the first 7 years of follow-up are used. Each death has been assigned a specific cause by the POSCH Mortality Review Committee. The committee determined whether or not each death was caused by ACHD. If it was determined to be an ACHD death, then it was assessed further for the presence of myocardial infarction, electrical death, or pump failure. The detailed criteria for death classification have been previously described.[4] In determining the cause of death, members of this committee were unaware of the patient's baseline serum creatinine value. The vital status of all patients was known as of July 20, 1990.

Statistical Methods

Spearman's rank correlation[7] was used to assess the relationships between baseline serum creatinine and other

Table 1. Distribution of Baseline Serum Creatinine Levels in POSCH Control Group (N = 416)

Serum Creatinine Level (mg/dL)	Percent of Subjects
0.7	0.7
0.8	4.1
0.9	12.0
1.0	19.7
1.1	22.1
1.2	21.2
1.3	13.7
1.4	3.1
1.5	2.6
1.6	0.2
1.7	0.2
1.8	0.0
1.9	0.2

Mean creatinine level 1.11 (±0.17).

baseline patient characteristics. An unpaired Student's *t* test or a one-way analysis of variance (ANOVA) F test was used to compare serum creatinine levels between subgroups. Changes in serum creatinine values from baseline were assessed with a paired Student's *t* test. The relationships between overall and ACHD mortality and quintiles of serum creatinine levels were assessed using a chi-square test for a linear trend.[8] The quintiles were formed by finding the five groups most similar in size. The relationships between overall and ACHD mortality and serum creatinine values, alone and adjusted for other baseline patient characteristics, were examined using proportional hazards regression analysis with a score statistic used to assess the models.[9] All patients were counted up to time of death regardless of intervening events such as myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty. All *P* values given are two-sided and were considered statistically significant if less than .05. Given the number of comparisons, caution should be exercised when interpreting *P* values between .05 and .01.

Results

The distribution of the baseline serum creatinine levels is presented in Table 1. Values ranged from 0.7 to 1.9 mg/dL (60 to 170 μmol/L), with only 6.5% of the patients having serum creatinine levels of 1.4 mg/dL (120 μmol/L) or greater.

Selected baseline characteristics of the 416 control group patients included in this analysis are presented in Table 2. In addition to the mean, standard deviation, and minimum and maximum values, the correlation of each variable with the baseline serum creatinine level is given. Age, Quetelet index, fasting glucose, serum uric acid, and diastolic blood pressure were found to have significant positive correlations ($P < .05$) with the baseline serum creatinine level. Cigarette smoking history as measured in pack years,* total plasma cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and resting heart rate were found to have significant negative correlations ($P < .05$) with the baseline serum creatinine level.

The distributions of various baseline categorical variables and the average creatinine level for each subgroup are summarized in Table 3. Women were found to

**Pack years is a reference measurement calculated by multiplying the number of years a patient smoked by the average number of cigarettes smoked per day.*

Table 2. Baseline Characteristics of POSCH Control Group and Correlations with Baseline Serum Creatinine (N = 416)

Patient Variables	Mean	SD	Minimum	Maximum	*r*
Age (y)	50.62	7.66	31	64	.134*
Time between MI and randomization (y)	2.24	1.24	.44	5.00	.079
Quetelet index (gm/cm^2)	2.71	.31	1.92	3.34	.160†
Cigarette smoking history (pack years)	31.52	26.73	0	140	−.112‡
Fasting glucose (mg/dL)	97.11	9.73	66	132	.098‡
Glucose tolerance test (mg/dL)§	426.91	66.17	268	586	.048
Serum uric acid (mg/dL)	6.48	1.29	2.4	12.2	.231†
Total plasma cholesterol (mg/dL)	250.47	35.14	200	455	−.139*
HDL cholesterol (mg/dL)	40.57	9.72	22	90	−.119*
LDL cholesterol (mg/dL)	178.56	36.63	55	390	−.092‡
VLDL cholesterol (mg/dL)	30.86	23.01	6	242	.062
Systolic blood pressure (mm Hg)	121.50	13.99	90	170	.069
Diastolic blood pressure (mm Hg)	78.92	9.24	56	102	.100‡
Heart rate (beats/min)	68.94	10.16	44	100	−.127*
Ejection fraction (%) (n = 398)	56.01	12.22	16	86	−.018

*P < .01.
†P < .001.
‡P < .05.
§*Sum of fasting, 1-hour, 2-hour, and 3-hour glucose determinations.*
MI denotes myocardial infarction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low density lipoprotein.

Table 3. Baseline Characteristics for Categorical Variables and Subgroup Levels of Serum Creatinine (N = 416)

Categorical Variables	Serum Creatinine, mg/dL Percent	Mean (SD)
Sex		
Male	92.3	1.13 (±0.16)
Female*	7.7	.92 (±0.13)
Type of MI		
Q-wave	81.2	1.12 (±0.17)
Non-Q-wave	18.8	1.11 (±0.19)
History of angina		
Yes	45.4	1.11 (±0.17)
No	54.6	1.12 (±0.17)
Race/ethnicity		
White	98.1	1.11 (±0.17)
Other	1.9	1.10 (±0.21)
Urinary protein†		
Positive	2.4	1.10 (±0.22)
Negative	97.6	1.11 (±0.17)
Number of coronary arteries with >50% stenosis‡		
0	10.9	1.07 (±0.13)
1	43.0	1.11 (±0.17)
2	31.3	1.13 (±0.17)
3	14.8	1.12 (±0.18)

*P < .001.
†Percentages based on N = 415 because of missing data.
‡Percentages based on N = 412 because of missing data.
MI denotes myocardial infarction.

have a significantly lower ($P < .001$) average serum creatinine level than men. Although the baseline serum creatinine differences among the subgroups based on coronary artery disease severity (number of major vessels with a ≥50% lesion) were not significant ($P = .22$ by one-way ANOVA), patients with no lesion ≥50% in any of the three major coronary arteries tended to have lower serum creatinine values than patients with a large lesion (≥50%) in at least one major artery ($P = .09$).

Peripheral arteriography results were available for 214 of the 416 patients. The correlation between baseline serum creatinine and atherosclerotic peripheral vascular disease severity (number out of seven peripheral artery segments with ≥20% stenosis) was negative ($r = -.07$) but not statistically significant ($P = .11$).

The follow-up serum creatinine levels and changes from baseline for all patients are given in Table 4. Serum creatinine increased only slightly over 5 years, but at 2 through 5 years the changes reached statistical significance. The largest increase occurred between baseline and 5 years (.08 mg/dL [7 μmol/L]; $P < .001$). Among the 45 patients who died, the average follow-up changes, some of which were reductions from baseline, were not

Table 4. Follow-up Serum Creatinine Levels and Changes from Baseline

Years to Follow-up	Number of Patients	Mean Follow-up Levels, mg/dL (SD)	Changes from Baseline Level, mg/dL (SE)
1	400	1.12 (±0.28)	.006 (0.012)
2	382	1.14 (±0.28)	.031 (0.013)*
3	375	1.16 (±0.24)	.052 (0.011)†
4	362	1.18 (±0.25)	.075 (0.012)†
5	347	1.18 (±0.19)	.078 (0.009)†

*P < .05.
†P < .001.
SD denotes standard deviation; SE, standard error.

statistically significant. The largest average increase was .09 mg/dL (8 μmol/L) at 5 years.

Overall, this group of patients had a 1.8 mm Hg increase in systolic blood pressure ($P < .05$) and a nonsignificant increase of 0.7 mm Hg in diastolic blood pressure at 5 years. Among the patients who died, there were nonsignificant increases in systolic blood pressure at 2 years follow-up (2.5 mm Hg) and at 4 years follow-up (4.7 mm Hg) and nonsignificant decreases at 1 year follow-up (.03 mm Hg), at 3 years follow-up (1.6 mm Hg), and 5 years follow-up (2.6 mm Hg). At entry into the study there were 50 patients receiving medication for "hypertension." Either alone or in combination, there were 31 patients on thiazide diuretics, 1 patient on a vasodilator, 6 patients on centrally acting antiadrenergics, and 19 patients on beta-blockers. No patients were receiving angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, or other diuretics for "hypertension" at entry. Of those patients who survived 7 years and of those who died within 7 years, 12% and 13%, respectively, had been receiving medication for "hypertension" at baseline.

In 7 years of follow-up, there were 45 deaths, of which 32 were caused by ACHD. Among the ACHD deaths, 28 were determined to be electrical deaths; four of these were accompanied by an MI, and none was accompanied by pump failure. The remaining four ACHD deaths were determined to be caused by pump failure, and three of these were accompanied by an MI. Of the non-ACHD deaths, five were caused by cancer, two by complications of coronary artery bypass surgery, one by a cerebrovascular accident, one by pneumonia, one by an accident, one by suicide, one by homicide, and one by unknown cause.

In Table 5, the percentages of overall and ACHD mortality are presented in quintiles based on baseline serum creatinine levels. Overall and ACHD mortality increased significantly with higher baseline serum creatinine values ($P < .005$).

The relationship of serum creatinine with the rela-

Table 5. Seven-Year Overall and ACHD Mortality by Quintile of Baseline Serum Creatinine Level

Serum Creatinine Level (mg/dL)	No. of Patients	Overall Mortality, %	ACHD Mortality, %
≤0.9	70	7.1	1.4
1.0	82	4.9	4.9
1.1	92	7.6	6.5
1.2	88	14.8	12.5
≥1.3	84	19.1	11.9

Chi-square test for linear trend resulted in P = .002 *and* P = .003.
ACHD denotes atherosclerotic coronary heart disease.

tive risk of overall and ACHD mortality was estimated using proportional hazards regression analysis (Table 6). An increase of 0.1 mg/dL (9 μmol/L) in serum creatinine was associated with a 36% increase ($P < .001$) in the relative risk of overall mortality and a 47% increase ($P < .001$) in the relative risk of ACHD mortality, with P values for the score statistic both <.001. For increases in serum creatinine of 0.2 mg/dL (18 μmol/L), .3 mg/dL (27 μmol/L), and so on, the relative risk values in the table would be squared, cubed, and so on, respectively. The relative risk increases between adjacent quintiles were similar to the increases found with the actual serum creatinine values.

The effect of serum creatinine on the relative risk of overall and ACHD mortality remained significant ($P < .01$) after adjustment for the following baseline variables: age, Quetelet index, cigarette smoking, fasting blood glucose, serum uric acid, HDL cholesterol, LDL cholesterol, very low-density lipoprotein (VLDL) cholesterol, diastolic blood pressure, heart rate, time from MI to randomization, ejection fraction, number of significantly diseased coronary arteries, history of angina, and qualifying MI type. Sex was not included as a covariate because there were convergence problems as a result of there being no ACHD deaths among the women in the POSCH control group. Score statistics had P values <.01.

Table 6. Relative Risks of Actual and Adjacent Quintile Values for a 0.1 mg/dL Increase in Serum Creatinine on Overall and ACHD Mortality as Determined by Survival Analysis Using Proportional Hazards Regression

	Actual Values	Quintile Values
Death		
Alone	1.36*	1.43†
Adjusted	1.39†	1.42†
ACHD		
Alone	1.47*	1.52†
Adjusted	1.59*	1.54†

*P < .001.
†P < .01.
ACHD denotes atherosclerotic coronary heart disease.

Similar analyses using additional follow-up data beyond 7 years were also performed. The results were similar. Among the other variables included in the proportional hazards regression analysis, only two other variables had statistically significant relationships with overall mortality, pack years of cigarette smoking, and number of coronary arteries with ≥50% stenosis, and only the number of coronary arteries with ≥50% stenosis was significantly related to ACHD mortality. For overall mortality, an increase of 10 pack years was associated with a relative risk of 1.15, and an increase of one artery with ≥50% stenosis was associated with a relative risk of 1.53. For ACHD mortality, an increase of one artery with ≥50% stenosis was associated with a relative risk of 1.79. Thus, among this set of variables, in addition to serum creatinine, only two other independent predictors of subsequent mortality were found.

Autopsies were performed on 11 of the 45 patients who died during the 7-year follow-up period. In one case, arteriolar nephrosclerosis was noted. The kidneys were reported as normal in seven cases. In three cases, however, only limited autopsies, which excluded examination of the kidneys, were performed. Three patients developed renal failure, but all were alive at 7 years.

Discussion

This analysis of the relationship between serum creatinine and subsequent overall and ACHD mortality in POSCH has demonstrated a significant independent association of serum creatinine with overall and ACHD mortality. Similar findings were reported by the HDFP; however, the POSCH control group was distinctly different from the HDFP population. POSCH patients were normotensive and had survived a single MI. The HDFP patients were hypertensive and were recruited from the general population.[1,2] In both studies, increased serum creatinine levels were independently related to increased overall mortality. In POSCH, increased serum creatinine levels were associated with increased ACHD mortality as well.

If higher serum creatinine values were simply an indicator of more generalized atherosclerosis, a strong positive relationship between serum creatinine and both coronary and peripheral atherosclerosis severity would be expected. The associations between serum creatinine and coronary and peripheral vascular disease severity were not statistically significant in POSCH, supporting the independence of the relationship of serum creatinine to overall and ACHD mortality. Also, after adjustment for the severity of baseline coronary artery disease and other baseline characteristics, serum creatinine remained a sta-

tistically significant independent predictor of subsequent overall and ACHD mortality. Although the autopsy data are limited, they too do not suggest that an elevated serum creatinine and significant nephrosclerosis were related in this population. However, the possibility of a subtle renal vascular or functional abnormality being related to serum creatinine cannot be excluded.

Proportional hazards regression analyses were initially performed with serum creatinine as the only baseline covariate. Significant increases in the relative risks of overall and ACHD mortality were observed with rising serum creatinine levels. Serum creatinine was found to be significantly correlated with several risk factors for ACHD (eg, age and serum uric acid), but after adjusting for these baseline covariates, the results remained statistically significant, indicating again that serum creatinine is an independent predictor of overall and ACHD mortality in this population.

Extreme values can have a substantial influence on regression analyses. Therefore, the proportional hazards regression analyses were repeated using quintile values. In these conservative proportional hazards regression analyses, the relative risks remained statistically significant, as were the results when a chi-square test for a linear trend was employed.

During the first 5 years of follow-up in POSCH, the serum creatinine levels rose only slightly but significantly, except in the patients who died, who exhibited no significant increase through 5 years of follow-up. Thus, there was a rise in serum creatinine values over time but no increase in the development of what is usually regarded to be clinically significant hypercreatinemia.

Many large-scale clinical trials have been conducted, eg, the Coronary Drug Project,[10] the Multiple Risk Factor Intervention Trial,[11] and the Lipid Research Clinics Coronary Primary Prevention Trial,[12] that have examined the relationship of risk factors and subsequent overall and ACHD mortality. Only the HDFP and the POSCH studies have reported a strong independent relationship between serum creatinine and overall mortality. The Beta-blocker Heart Attack Trial[3] observed a relationship between mortality and high normal baseline serum creatinine levels (those greater than 1.0 mg/dL [9.0 μmol/L]) that was statistically significant. The BHAT group only concluded, however, that renal function should be considered in interpreting their results. It is not known whether other major studies of atherosclerosis have examined serum creatinine as a risk factor for subsequent overall and ACHD mortality but found no correlation, or found a correlation but without a firm biological mechanism and did not publish their findings. The above studies, if and where a relationship between serum creatinine and mortality was observed, involved patients with hypertension or a myocardial infarction. It is possible that these disease processes lead to organ damage that is then reflected in the serum creatinine.

The serum creatinine level was measured at baseline, and an elevated baseline level related to a higher subsequent mortality. Could there be baseline variables, measured or unmeasured, that are correlated with serum creatinine and thus explain this relationship? Could a higher level of serum creatinine have been the result of some earlier biological or disease process that resulted in an increased mortality rate? Even though the relationship of elevated serum creatinine to increased risk of death persisted when adjustments for baseline variables known to be associated with mortality or correlated with serum creatinine were made, the answers to the preceding questions could be yes. If such explanations could be found, serum creatinine would not be an independent predictor of mortality. It would still be an easily measured marker, however, for whatever other factor is found.

The results reported in this analysis demonstrate that a serum creatinine level carries independent prognostic implications for subsequent overall and ACHD mortality in normotensive, nonobese, normoglycemic survivors of a single MI with normal renal function. We propose that critical attention should be directed in future studies, and possibly retrospectively and meta-analytically in prior studies, to the relationship of serum creatinine levels with subsequent overall and ACHD mortality.

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