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Tobacco, hypertension, and vascular disease: Risk factors for renal functional decline in an older population

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Tobacco, hypertension, and vascular disease: Risk factors for renal functional decline in an older population.

Background. A decline in renal function with age has been noted in some but not all individuals. The purpose of this study was to identify risk factors associated with a clinically significant increase in serum creatinine (of at least 0.3 mg/dL) in an older nondiabetic population.

Methods. A retrospective case-control study was performed analyzing data obtained from 4142 nondiabetic participants of the Cardiovascular Health Study Cohort, all at least 65 years of age, who had two measurements of serum creatinine performed at least three years apart. Cases were identified as participants who developed an increase in serum creatinine of at least 0.3 mg/dL, with controls including participants who did not sustain such an increase.

Results. There was an increase in the serum creatinine of at least 0.3 mg/dL in 2.8% of the population. In a multivariate "best-fit" model adjusted for gender, weight, black race, baseline serum creatinine, and age, the following factors were associated with an increase in serum creatinine: number of cigarettes smoked per day, systolic blood pressure, and maximum internal carotid artery intimal thickness.

Conclusions. These data suggest that three very preventable or treatable conditions—hypertension, smoking, and prevalent vascular disease, which are associated with large and small vessel disease—are highly associated with clinically important changes in renal function in an older population.

Patients greater than 60 years of age form the most rapidly growing segment of the end-stage renal disease (ESRD) population [1]. The cause of ESRD in over 25% of patients is unknown [2]. Understanding factors associated with renal functional decline in older adults is therefore an important public health issue. With aging, the decline in renal function is not uniform, but varies for each individual. Lindeman, Tobin, and Shock studied longitudinal renal function in 446 individuals aged 22 to 96 years who had at least five creatinine clearance determinations performed at 12- to 18-month intervals in the Baltimore Longitudinal Study of Aging [3]. In this study, there was no change in renal function for up to 30% of the individuals, while 73 of 446 (16%) participants sustained a statistically significant decline in function. The decline in renal function with aging has serious repercussions. Decreased renal function with age may make older patients more vulnerable to such renal disorders as glomerulonephritis [4] and aminoglycoside nephrotoxicity [5] and may predispose them to the development of ESRD.

While studies such as the Baltimore Longitudinal Study of Aging have focused on changes that occur in the aging of a relatively healthy population, the purpose of the current investigation was to look at clinically significant declines in renal function in a population-based sample of older adults. We hypothesized that three factors (hypertension, atherosclerosis, and smoking) known to affect the renal vasculature and microvasculature would be associated with a large proportion of the clinically significant renal functional deterioration.

Hypertension has long been associated with changes in renal structure and function [6]. It has been associated with both renal artery stenosis [7] and microvascular changes in the renal circulation [8]. In the same way, both tobacco usage and extrarenal prevalent vascular disease have been associated with renal artery stenosis [9, 10] and changes in the renal microvasculature [11, 12]. Smoking has recently become of greater interest in terms of its potential effect on renal function [13].

The purpose of this study was to evaluate clinically significant changes in serum creatinine in a population that had two assessments of serum creatinine performed at least three years apart. An increase in serum creatinine of at least 0.3 mg/dL was considered clinically important, as such changes virtually always represent true declines

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in renal function, whereas changes of 0.1 and 0.2 mg/dL are quite common and frequently represent differences that are due to individual variability in daily serum creatinine values [14, 15].

METHODS

The Cardiovascular Health Study is a population-based cohort study of coronary artery disease and stroke in individuals greater than 65 years of age. The original study design called for enrollment of 1250 participants in each of four communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Allegheny County, PA, USA. Each community sample was obtained through random sampling of Medicare eligibility lists of the Health Care Financing Administration. Those eligible to participate included all persons living in each individual household sampled who were at least 65 years of age, were noninstitutionalized, were expected to be in the area for the three-year follow-up, were able to give informed consent, and did not require a proxy respondent at baseline. Individuals who were wheelchair-bound or receiving hospice treatment, radiation therapy, or chemotherapy for cancer were not included. Seventy percent of the cohort (3654 individuals) were selected from 11,955 letters mailed to individuals identified from eligibility lists, and 30% were recruited from eligible members in the sampled households. The enrolled participants in the original CHS cohort were younger, more highly educated, and more likely to be married than the baseline population [16, 17]. In 1992, 687 additional black participants were recruited from Forsyth County, NC, Sacramento, CA, and Pittsburgh, PA, by similar methods as the original cohort recruitment.

The baseline examination consisted of a home interview and a clinic examination. During the home visit, study interviewers asked to see all prescription medications that the participants had taken in the previous two weeks and asked for the frequency of usage. Activities of daily living and independent activities of daily living were assessed by self-report. Participants were considered to have a definite history of hypertension if they reported a history of hypertension and use of antihypertensive medications. Participants reporting a history of myocardial infarction, stroke, or peripheral vascular disease confirmed by their medical record were considered to have these conditions. Participants were considered to be diabetic if they reported a history of diabetes mellitus and were taking insulin or oral hypoglycemic medications. Participants were asked to fast 12 hours before coming to their clinic appointment; all examinations were scheduled in the morning. Blood pressure was measured in the right arm of seated participants after a five-minute rest using an appropriately sized cuff and a Hawksley random zero sphygmomanometer, model 7076 (Hawksley and Sons Limited, Sussex, UK). The average of the two measurements of the first and fifth Korotkoff sounds was used to determine systolic and diastolic blood pressures. Venipuncture was performed early in the clinic visit. Multiple aliquots of plasma or serum were prepared and frozen at −70°C and were shipped weekly on dry ice to the Central Blood Analysis Laboratory, where analyses were performed on the Kodak Ektachem 700 Analyzer (Eastman Kodak Corp., Rochester, NY, USA). Duplex ultrasonography of the carotid arteries was performed with a Toshiba SSA-270 A (Toshiba American Medical Systems, Tustin, CA, USA). B-mode imaging was performed to detect thickening of the arterial wall, disruption of normal wall interfaces, and development of focal plaques bilaterally. M-mode, two-dimensional, and Doppler echocardiographic examinations were performed with the Toshiba SSH-160A (Toshiba Medical Systems, Tustin, CA, USA), equipped with 2.5 and 3.75 MHz transducers. For the original cohort, at the three year follow-up, the participant history, physical examination, and laboratory determinations were repeated. For the added black cohort, these studies were conducted at four years of follow-up instead of three years of follow-up.

The following variables pertinent to these analyses were obtained: age, race, gender, weight, serum albumin, cholesterol, and creatinine. Information regarding medication usage was obtained at each annual examination, with analyses based on medication usage at baseline. Medications evaluated included angiotensin-converting enzyme inhibitors, diuretics, calcium channel blockers, cholesterol-lowering medications, and nonsteroidal anti-inflammatory medications. Prevalent cardiovascular disease was defined as present if participants had a confirmed history of myocardial infarction, stroke, or peripheral vascular disease at baseline. Subclinical atherosclerosis was assessed using the average intima-media wall thickness in the common carotid artery or the average maximum intima-media wall thickness in the internal carotid artery from the baseline ultrasound examination. Pack years of tobacco usage were calculated at baseline. Current smoking (cigarettes per day) was determined from the data derived at follow-up visits by asking the participant the average number of cigarettes smoked per day for the prior 30 days.

Statistical analysis

Analyses were performed for all individuals who had measurements of serum creatinine performed at both the baseline and follow-up examinations. Given the association of diabetes mellitus with diabetic nephropathy, participants with diabetes mellitus were excluded from the analysis. Differences between baseline and follow-up serum creatinine levels were determined. A logistic regression analysis was performed comparing individuals who sustained an increase in serum creatinine of at least

0.3 mg/dL with those who did not. Logistic regression analysis techniques were performed using SAS statistical software (Cary, NC, USA). The association between the previously described clinical parameters and an increase in creatinine were investigated in multivariate models. The variables significantly associated with large changes in serum creatinine were determined using a stepwise logistic procedure. Given the known associations between creatinine production, gender, race, age, and weight [18], these variables were forced into all models. In addition, since the change in serum creatinine is dependent on the baseline serum creatinine, the baseline serum creatinine was also included in all models. Variables were then entered into the model and removed if they did not reach a statistical significance level of $P < 0.05$.

To further explore the effect of cigarette smoking in different groups, a stratified analysis was carried out, first stratifying for race and then stratifying for gender.

Dose response analyses of current cigarette use were performed by comparing participants categorized by the average number of cigarettes smoked per day. The test of linear trend across these groups was performed by comparing the log likelihoods of a logistic model with a linear term reflecting group (coded 0 through 3) against a logistic model with three indicator variables reflecting cigarette use group.

Given the low prevalence of an 0.3 mg/dL increase in serum creatinine, it is assumed that the relative risk closely approximates the odds ratio in this study.

After review of the previously mentioned information, several analyses were performed. First, a linear model was created with change in inverse serum creatinine as a continuous outcome variable. Gender, weight, age, and race were again forced into the model. Another logistic regression model was created with an attempt to model percentage change in renal function as the outcome variable. Percentage change in renal function was denoted as the percentage change in reciprocal serum creatinine between the two measurements of serum creatinine. For the logistic regression model, a change of −24% was used as a cutoff, with patients who sustained a change in renal function of this magnitude representing 5% of the CHS population.

RESULTS

There were 5888 participants, of whom 502 diabetics were excluded from these analyses. Of the nondiabetic participants at the time of follow-up, 352 (6.5%) individuals had died; 717 (13.3%) did not have a clinic visit, and 175 (3.2%) had clinic visits, but no laboratory measurements of serum creatinine were obtained at either or both visits. There remained 4142 (76.9% of the original nondiabetic cohort) who were included in these analyses of change in serum creatinine. Table 1 shows the characteristics of the cohort by gender. There were 497 (12%) black participants in the nondiabetic cohort. Figure 1 shows the baseline serum creatinine values for men and women. The mean serum creatinine level was 1.2 mg/dL in men and 0.92 mg/dL in women. Figure 2 is a histogram showing changes in serum creatinine from baseline. There was an increase in serum creatinine of at least 0.3 mg/dL in 2.8% of these participants.

Table 1. Characteristics of the non-diabetic cohort by gender

Characteristic	Men	Women
Race (% White)	95.6	95.0
Race (% Black)	3.8	4.5
Age (y)	73.4 ± 5.8	72.4 ± 5.4
Weight (lbs.)	173 ± 26	146 ± 30
Use of antihypertensive (%)	41.3	43.5
Smoking status		
Never	32.0	56.7
Past	57.7	30.5
Current	10.3	12.8
Cigarettes smoked per day at year 5	1.04 ± 4.7	1.29 ± 4.7
Pack years of tobacco usage	26 ± 31	12 ± 21
History of hypertension %	41.3	45.2
Atherosclerosis %	19.5	8.2
Baseline serum creatinine *mg/dL*	1.2 ± 0.26	0.92 ± 0.22
Serum cholesterol *mg/dL*	199.4 ± 35.4	221.4 ± 37.8
HDL cholesterol *mg/dL*	48.0 ± 12.6	60.0 ± 15.8
LDL cholesterol *mg/dL*	124.9 ± 33.0	134.5 ± 36.1
Systolic blood pressure *mm Hg*	135 ± 21	136 ± 22
Diastolic blood pressure *mm Hg*	72 ± 11	69 ± 11

Continuous variables represented by the mean ± the standard deviation. Discrete variables are represented by percentage of cohort with condition.

Table 2 shows the results of logistic regression analysis for factors associated with changes in serum creatinine after adjustment for age, gender, and weight. Race, tobacco usage, prevalent cardiovascular disease, average maximum intima-media wall thickness in the internal carotid artery from the baseline ultrasound examination, and systolic and diastolic blood pressure were all associated with an increase in the serum creatinine of 0.3 mg/dL or more. Of note, nonsteroidal anti-inflammatory medication usage, activities of daily living, independent activities of daily living, left ventricular ejection fraction, serum total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were not significantly associated with changes in creatinine.

Table 3 shows a multivariate "best-fit" model into which weight, gender, age, black race, and baseline serum creatinine have been forced. As can be seen, systolic blood pressure, average maximum intima-media wall thickness in the internal carotid artery from the baseline ultrasound examination, and tobacco usage were all strong predictors of an increase in serum creatinine. There was a significant growing risk of creatinine increase with increases in the number of cigarettes smoked.

To further explore the relationship between smoking and the risk of renal functional decline, participants were

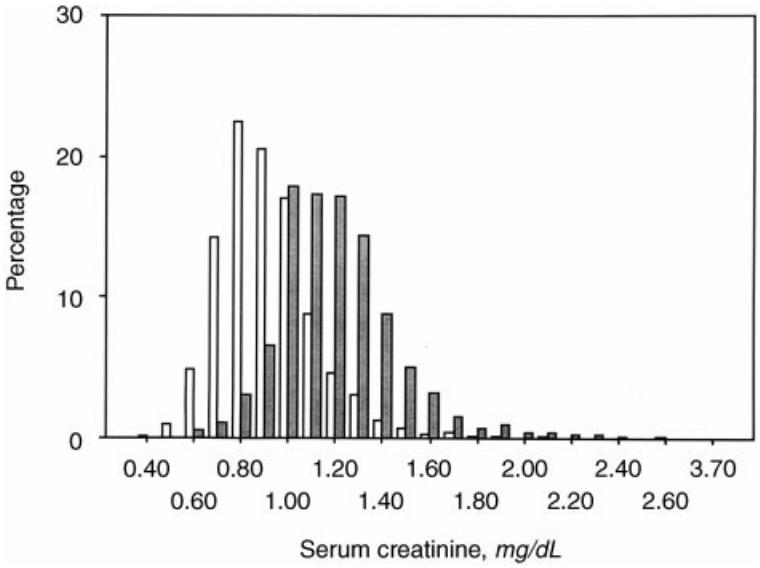

Fig. 1. Baseline serum creatinine by gender. Symbols are: (□) females; (▩) males.

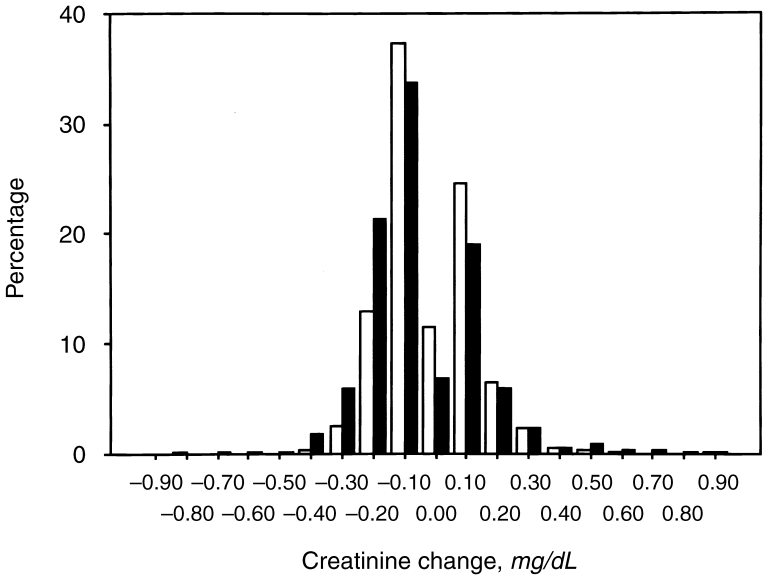

Fig. 2. Changes in serum creatinine by gender. Symbols are: (□) females; (■) males.

divided into groups according to current smoking status. Figure 3 shows the odds ratio of a creatinine increase for participants grouped according to smoking habits. With an increase in tobacco usage, there was an increased risk of serum creatinine rise, up to 20 cigarettes per day. The hypothesis of a linear trend for cigarette use, indicating a dose response, was not rejected in the logistic model. While increasing cigarette consumption was associated with an increased odds ratio of serum creatinine increase, it is important to note that only 2.8% of the population experienced an increase in serum creatinine, and only 8.8% of men and 9.8% of women in the study were current smokers, resulting in an increase in serum creatinine of 0.3 mg/dL in only 14 smokers.

Given differences in follow-up, the analysis was next stratified by race. For the black participants, after adjustment for age, weight, gender, and baseline serum creatinine, no other variable was significantly associated with a large change in serum creatinine. However, the power was significantly decreased, as there were only 37 blacks experiencing a large serum creatinine change. The stratified model for white participants was very similar to the overall model in Table 3. The analysis was then stratified by gender. For female participants, only systolic blood pressure was associated with a large creatinine change [1.02 (1.10 to 1.37) increased the odds ratio for each 10 mm Hg increase in systolic blood pressure]. For male participants, the model was again similar to the model

Table 2. Logistic regression models on large change in serum creatinine (≥0.3 mg/dL) for each individual characteristic after adjusting for age, weight, and gender

Parameter	Reference group	Risk group	Odds ratio (95% confidence interval)	*P* value
Gender[a]	Female	Male	1.4 (0.92–2.1)	0.12
Weight[b]		↑ by 10 lb.	1.06 (0.99–1.13)	0.11
Age[c]		↑ by 5 y	1.52 (1.30–1.77)	0.0001
Black race	Nonblack	Black	0.64 (0.20–2.1)	0.45
Antihypertensive usage	Non-user	User	1.7 (1.1–2.4)	0.008
NSAID usage	Non-user	User	1.1 (0.64–1.96)	0.69
Ever smoker at baseline	No	Yes	1.2 (0.81–1.8)	0.36
Current smoker (at baseline)	No	Yes	2.1 (1.3–3.6)	0.0053
Number of cigarettes smoked per day at year 5		↑ of 5 per day	1.25 (1.09–1.44)	0.0017
History of hypertension	No	Yes	2.10 (1.4–3.1)	0.0001
Atherosclerosis	Absent	Present	2.43 (1.6–3.8)	0.0001
Systolic blood pressure		↑ of 10 mm Hg	1.16 (1.07–1.26)	0.0003
Diastolic blood pressure		↑ of 10 mm Hg	1.13 (0.96–1.34)	0.14
Mean arterial pressure		↑ of 10 mm Hg	1.23 (1.06–1.41)	0.005
Serum creatinine		↑ of 1 mg/dL	2.9 (1.3–4.2)	0.007
Serum albumin		↑ by 1 g/dL	0.52 (0.27–0.99)	0.05
Serum cholesterol		↑ of 1 mg/dL	1.00 (1.0–1.0)	0.74
LDL cholesterol		↑ of 1 mg/dL	1.00 (1.0–1.0)	0.84
HDL cholesterol		↑ of 1 mg/dL	0.99 (0.99–1.0)	0.047
Common carotid thickness		↑ by 10 mm	1.10 (1.01–1.19)	0.025
Internal carotid thickness		↑ by 10 mm	1.05 (1.01–1.08)	0.005

[a]Adjusted for weight and age
[b]Adjusted for gender and age
[c]Adjusted for gender and weight

Table 3. "Best fit" logistic regression model for changes in serum creatinine ≥0.3 mg/dL with gender, age, weight, and baseline serum creatinine included in the model

Parameter	Reference group	Risk group	Odds ratio (95% confidence interval)	*P* value
Gender	Male	Female	0.87 (0.56–1.35)	0.53
Weight		↑ by 10 lb.	1.12 (1.05–1.20)	0.0005
Age		↑ by 5 y	1.66 (1.40–1.97)	0.0001
Baseline serum creatinine		↑ by 1 mg/dL	1.12 (1.06–1.19)	0.0001
Carotid intimal thickness		↑ by 0.1 mm	1.52 (1.01–1.08)	0.011
Systolic blood pressure		↑ of 10 mm Hg	1.16 (1.07–1.26)	0.0003
Number of cigarettes smoked		↑ by 5 cigarettes/day	1.31 (1.12–1.52)	0.0011

in Table 3, with black race, baseline serum creatinine, atherosclerosis, and tobacco usage associated with an increase in serum creatinine.

In the multivariate best-fit model, which was created using change in inverse serum creatinine as a continuous outcome variable, male gender ($P < 0.0002$), black race ($P < 0.0001$), declining serum albumin ($P < 0.0001$), and increasing systolic blood pressure ($P < 0.0001$) were the only variables associated with increasing serum creatinine.

In the model looking at the percentage of change in renal function, the following variables were predictive of a greater than 24% decline in inverse serum creatinine: male versus female gender, 3.40 (2.30–4.97); black versus white race, 2.49 (1.78 to 3.49); nonsteroidal usage, 1.50 (1.04 to 2.16); increase in systolic blood pressure by 10 mm Hg, 1.01 (1.00 to 1.02); and decrease in serum albumin by 10 g/L, 2.78 (1.70 to 4.76).

DISCUSSION

In the present study, an increase in serum creatinine was associated with several important characteristics. Systolic blood pressure was found to be a better predictor of renal decline than diastolic blood pressure or mean arterial pressure, as has been noted by others [19, 20]. Changes in renal function resulting from hypertension could be related to either large or small vessel disease. Hypertension has been associated with renal artery stenosis [7], and hypertension has also been found in pathologic investigations to be associated with renal arteriolar intimal proliferation and medial hypertrophy [21]. The use of antihypertensive agents did not have a significant impact on changes in serum creatinine, which is an issue more fully addressed in another publication [22].

Smoking was highly associated with an increase in serum creatinine. This increase was of special interest. While an association between renal deterioration in dia-

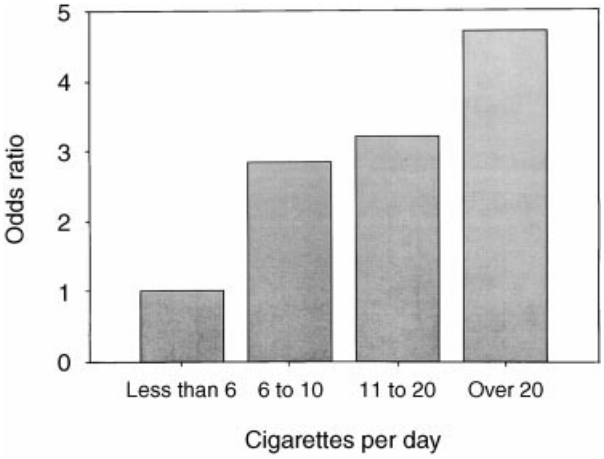

Fig. 3. Adjusted odds ratios of a serum creatinine increase of at least 0.3 mg/dL by tobacco usage.

betic nephropathy and smoking has been described [23], there is very little information regarding the renal effects of tobacco usage in the general population. Smoking has been noted to increase the risk of ESRD in individuals screened in the Multiple Risk Factors Intervention Trial [24]. In addition, smoking is an important predictor of renovascular disease [10], as well as pathologic changes in the renal microcirculation. In an autopsy study smoking was associated with increased intimal thickening in renal arterioles <555 μm in diameter [12]. In the current study, an increase in current cigarette consumption was associated with worsening renal function. The finding of an association between current cigarette use and an increase in serum creatinine suggests that even in older individuals, smoking cessation is of significant importance in preserving health.

When the analysis was stratified for race and then for gender, it was found that the association of tobacco usage with serum creatinine increase was seen in men but not women, and white race but not black race. This may be due to the fact that in our cohort cigarette smoking occurred at higher levels in men compared with women, and there were fewer events in African American patients, which may not have allowed enough statistical power.

Finally, average maximum intima-media wall thickness in the internal carotid artery from the baseline ultrasound examination was highly associated with serum creatinine change. These changes could be related to either large or small vessel disease. Common and internal carotid intima-media thickness correlated with serum creatinine change in models, which adjusted for age, gender, weight, and black race. Renal artery stenosis is extremely common in older individuals; its presence is associated with atherosclerosis occurring in other blood vessels [10]. In an autopsy study of patients without clinically overt renal disease, Kasiske et al found glomerulosclerosis to occur more commonly in patients with moderate-to-severe atherosclerosis than in those with mild atherosclerosis [25]. Independent associations between age, intrarenal vascular disease, and glomerulosclerosis were identified. Tracy et al found that renal arteriolar hyalinization correlated with raised lesions in the coronary arteries and aorta in an autopsy study of individuals aged 25 to 54 years [11].

As can be seen in Figure 1, there was some variation in baseline serum creatinine, including some participants likely having renal insufficiency. Figure 2 demonstrates that a decline in serum creatinine of 0.1 mg/dL was the most frequent change in serum creatinine. This decline likely represents a decrease in muscle mass and creatinine generation rather than "true" improvement in renal function. An increase in serum creatinine of at least 0.3 mg/dL occurred in approximately 3% of the population. This increase likely underestimates the number of participants who had important renal functional decline. Significant renal functional deterioration, when associated with muscle wasting from disease and aging, may result in a stable serum creatinine or only a mild increase. The occurrence of renal functional decline in at least 3% of the aging United States population places numerous individuals at risk for the development of future ESRD and mortality [26], and has broad public health implications.

There are many limitations to the use of serum creatinine as a marker for renal function. Serum creatinine is determined not only by glomerular filtration rate, but also tubular secretion and creatinine production [27]. With aging comes a decrease in muscle mass and a decrease in creatinine production [18], which results in variability in the relationship between serum creatinine and glomerular filtration rate. In addition, while small changes may reflect large differences in glomerular filtration rate, small changes may also represent this daily variation in serum creatinine. Changes in serum creatinine of 0.1 mg/dL were common in our study and frequently may have been the result of such variation. In a longitudinal study of urinary creatinine and creatinine clearances in normal subjects, there was a 14% within individual variability in serum creatinine [28], reflecting an absolute change in serum creatinine of approximately 0.1 to 0.2 mg/dL. Sterner, Wroblewski, and Rosen noted a 30% increase in serum creatinine levels associated with an increased protein intake [15]. For this reason, in our study, changes in serum creatinine of 0.3 mg/dL or greater were considered to be of clinical importance.

Given that decreases in serum creatinine were unlikely to represent improved renal function, but rather weight loss or decreased protein intake, and given that most changes in serum creatinine were very small and could reflect daily variation in laboratory test results or creatinine production, a linear model with the change in serum creatinine analyzed as a continuous dependent variable

was considered to have significant shortcomings compared with a model specifically identifying participants with clinically significant increases in serum creatinine. A linear model would give equal weight to a decline in serum creatinine of 0.1 mg/dL (likely not to represent improved renal function) with an increase in serum creatinine of 0.1 mg/dL. Moreover, because of the predominant number of patients with a change in serum creatinine of less than 0.1 mg/dL, the development of the model would depend almost exclusively on very small changes in serum creatinine, which may be too small to identify true changes in renal function.

When a linear model with changes in inverse serum creatinine was created, systolic blood pressure, black race, and declining serum albumin were all significant. In addition, male gender was highly associated with worsening serum creatinine. This is likely because male patients would have more muscle mass and would be more likely to preserve muscle mass. Changes in serum creatinine in these patients would likely be more reflective of changes in renal function than changes in nutritional status. Female participants would be likely to have less muscle mass and more likely to have a decline in serum creatinine with stable renal function compared with males. Other variables that were significant with the logistic model were not significant in the linear model because of the many small changes in serum creatinine and the imprecision of this measurement.

In addition to analyzing the decline in renal function, the percentage decline in renal function was also evaluated. A greater than 24% decline in inverse serum creatinine was experienced by 5% of the Cardiovascular Health Study population. Factors associated with this included black race, systolic blood pressure, serum albumin, and nonsteroidal usage. In addition to change in serum creatinine, the percentage decline in renal function is dependent on renal reserve, baseline renal function, and the relationship between loss of renal function and baseline renal function.

A weakness of this study is that there was an interval follow-up of four years between serum creatinine measurements for most of the black participants in the cohort and only three years for the white participants. This allowed a longer time for black participants to develop progression of renal insufficiency. The increased risk of developing renal insufficiency in black participants in these analyses then could be due to the longer interval in follow-up or due to the fact that blacks are more likely to develop renal insufficiency. A number of investigations have previously shown that black individuals are at a markedly increased risk of development and progression of renal disease [29–31]. There was little variation in the multivariate models whether or not the black participants were included because of the smaller number of black participants in our cohort.

The finding of smoking, prevalent cardiovascular disease, and systolic hypertension as risk factors for increases in serum creatinine is noteworthy for several reasons. First, these findings point to atherosclerosis—likely both small and large vessel disease—being of marked importance in pathophysiologic changes in serum creatinine over time. When the etiology of ESRD is investigated, emphasis is usually placed on conditions such as glomerulonephritis or inherited cystic disease. This study highlights a growing belief that vascular disease is important in the development of renal failure and potentially ESRD. Large-vessel renal disease is becoming much easier to diagnose because of techniques such as renal duplex sonography [32] and magnetic resonance imaging [33]. However, small-vessel renal disease is extremely difficult to diagnose in the clinical setting and may be the cause of ESRD in some of the 25% of older patients who develop ESRD from presently unknown etiologies.

An alternate potential explanation for the rise in serum creatinine is that participants with prevalent cardiovascular disease, tobacco abuse, and systolic hypertension are in general more frail and are more likely to be exposed to insults such as hypotension or sepsis, which could lead to acute tubular necrosis. In the univariate model, individuals with a low serum albumin were also more likely to develop increases in serum creatinine. However, other markers of sickness, such as left ventricular ejection fraction or the ability to perform activities of daily living, were not associated with increases in creatinine in either models adjusting only for gender, age, and weight, or in the "best-fit" multivariate model.

It is important and significant that current smoking habits and elevated systolic blood pressure—two conditions amenable to treatment—were significant predictors of renal functional decline in individuals at least 65 years of age. These findings discourage the notion that years of hypertension and smoking have already resulted in damage in this age group, and therefore, their continued presence in the older population is unlikely to affect outcome. The results of this study indicate that cessation of smoking and reduction in systolic blood pressure in people over 65 could result in decreased risks of renal insufficiency in this older group.

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