

Natural history of elevated creatinine levels

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ABSTRACT

OBJECTIVE To investigate what happens to the serum creatinine (SC) levels of people with initial mild elevations in SC; whether a stable, non-progressive elevation in SC level is the most common scenario; how common a progressive increase in SC is among primary care patients; and how often primary care patients with substantial elevations in SC ($>300 \mu\text{mol/L}$) progress to end-stage renal disease.

DESIGN Retrospective analysis of laboratory data and chart review.

SETTING Queen's University Family Medicine Centre in Kingston, Ont.

PARTICIPANTS All patients who had SC levels measured at a nearby hospital laboratory between January 1994 and December 1998.

MAIN OUTCOME MEASURES Recently recorded height and weight measurements, latest SC measurements (if available), whether patients had been referred to nephrologists, comorbidity, medications being taken, whether patients were currently undergoing dialysis or had received a renal transplant, and whether patients had died.

RESULTS In the 1434 charts of eligible patients, 64 (4.5%) had elevated initial SC levels ($>130 \mu\text{mol/L}$) recorded, and 57 of these contained follow-up SC levels also. Among these 57 patients, 32 (56%) saw their SC levels return to normal, including 50% of those whose initial levels had been $>300 \mu\text{mol/L}$. Only 7 patients (12%) with elevated SC levels progressed to higher levels during the follow-up period. Average age in the study group was 63 years; those with initial elevated SC levels were older than the average (70 years).

CONCLUSION More than half of those with initially elevated SC levels ($>130 \mu\text{mol/L}$) saw their levels return to normal, including patients whose initial levels had been $>300 \mu\text{mol/L}$. It seems that a single elevated SC measurement does not predict ongoing decline in renal function.

EDITOR'S KEY POINTS

- The 1999 guidelines from the Canadian Society of Nephrology suggest that family doctors investigate fully and possibly refer all patients found to have elevated serum creatinine (SC) levels. This recommendation is not based on good evidence from primary care settings.
- In this study of family practice patients in Kingston, Ont, only 4.5% were found to have elevated SC levels (defined here as $>130 \mu\text{mol/L}$) initially, and of those, almost 60% saw their levels return to normal, 25% saw their levels remain the same, and only 12% progressed to more serious disease.
- It appears that family doctors can expect that most of their patients with elevated SC levels will not progress to more serious disease and that they can follow up these patients without referral to nephrologists until deterioration is observed.

This article has been peer reviewed.
Full text available in English at www.cfpc.ca/cfp
Can Fam Physician 2006;52:1264-1265, e.1-5.

The rising incidence of chronic kidney disease (CKD) is a growing problem in Canada and around the world.¹ Patients with CKD can experience substantially reduced quality of life, since CKD can lead to anemia, acidosis, bone disease, and electrolyte disturbances, as well as ultimately to end-stage renal disease.

End-stage renal disease has a mortality rate of approximately 20% annually, despite advances in renal replacement therapy.² Researchers estimate that the prevalence of end-stage renal disease is rising at a rate of 6% to 10% annually in Canada.^{3,4} Because renal replacement therapy is a costly treatment, this increase poses a challenge to the health care system.

Late referral of and failure to refer patients to nephrologists is thought to be a serious problem in Canada and other countries, as family doctors have varying thresholds for referral.^{5,6} In studies of patients referred to nephrologists, late referral has been associated with increased morbidity, earlier mortality, longer and more frequent hospital stays, and higher overall costs.⁷⁻¹¹

Guidelines were developed in 1999 by the Canadian Society of Nephrology, working with the College of Family Physicians of Canada, on management and referral of patients with elevated SC levels. Serum creatinine levels are the most widely used (if imperfect) marker of kidney function.⁶ These guidelines made several key recommendations that seemed reasonable but that were not based on evidence from studies that looked at the natural history of elevated SC levels in primary care, since such studies were not available.¹² These recommendations stated:

All patients with newly discovered renal insufficiency (as evidenced by serum creatinine elevated to a level above the upper limit of the normal range in that laboratory, adjusted for age and height in children) must undergo investigations to determine the potential reversibility of disease, to evaluate the prognosis and to optimize planning of care.⁶

Because the upper limit in many laboratories is around 120 $\mu\text{mol/L}$, we could conclude that even patients with SC levels of 130 $\mu\text{mol/L}$ should undergo the recommended investigations, including a battery of blood tests, 24-hour urine collection, and ultrasonography. The recommendations also stated that "a kidney biopsy is *often* required." We could assume from this recommendation that a large proportion of people with SC levels above the upper limit of normal would go on to develop progressive kidney disease, but there is no evidence that this happens. A suggestion that the test should first be repeated to confirm the elevation and the

patient's medical situation reviewed was not made until after the recommendation for multiple investigations. One of the questions we set out to answer in our study was whether most of these elevations progress to more serious disease or whether levels just return to normal with no or very little intervention.

The guidelines also stated, "Patients with rapidly increasing serum creatinine (eg, a 20% increase over a matter of days, weeks, or months) must undergo investigations (usually including kidney biopsy) on an urgent basis and should be referred promptly to a nephrologist."⁶ We can hardly argue with this statement, but it does imply that an important feature of managing elevated SC levels is to get repeat measurements. That is probably the best take-home message for family physicians. Repeating the tests is also the only way to confirm that patients have stable, mild renal insufficiency. There is a recommendation for this situation as well:

Patients with known stable, mild renal insufficiency, documented by serial determination of creatinine level over a period of a few years (especially if dipstick testing shows no hematuria or proteinuria), may be followed carefully, with particular attention to serial monitoring of blood pressure, protein excretion rate and kidney function, without referral to a nephrologist.⁶

This situation is referred to by the authors of the guideline as a possible exception to the first recommendation that states that all patients with elevated SC levels should have a large battery of tests. In fact, most family physicians would recognize this "exception" as one of the most common scenarios they encounter. Since this is only anecdotal evidence, we set out in this study to determine whether their impression is correct. The question was whether a stable, non-progressive elevation in SC level was the most common scenario.

The final recommendation of importance to family physicians was, "All patients with an established, progressive increase in serum creatinine should be followed with a nephrologist."⁶ This would seem prudent, so we set out to answer 2 additional questions. How common in primary care is progressive increase in SC? And how often do primary care patients with very high SC levels (>300 $\mu\text{mol/L}$) progress to end-stage renal disease?

METHODS

We reviewed the charts of all patients at the Queen's University Family Medicine Centre, a multi-practitioner primary care practice in Kingston, Ont, who had had their SC levels measured at a nearby hospital laboratory between January 1994 and December 1998. Data on all measurements done on these patients during that period were collected retrospectively from the laboratory

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in 1999. Data from their charts were collected retrospectively between June 2003 and June 2004. Patients were excluded from the study if they were younger than 18 years at the time of first SC measurement, if they were patients from another practice referred to the Centre solely for prenatal and obstetric care, or if their charts could not be located. We should note specifically that patients with known renal disease were not excluded.

Data obtained from laboratory records included age, sex, and dates and values of SC measurements. Data obtained from chart reviews included height; weight; latest SC measurement in the chart (if available); whether patients had been referred to nephrologists; whether patients had a diagnosis of ischemic heart disease, hypertension, diabetes, or renal disease, specifically CKD; whether patients were currently taking diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, or beta-blockers; whether patients were currently undergoing dialysis or had received a renal transplant; and whether patients had died.

A "normal" cutoff value of 130 $\mu\text{mol/L}$ was established for both men and women because this was the highest of the upper limits of the laboratory's normal ranges. Creatinine clearance was used to estimate the glomerular filtration rate (GFR) and was calculated using the Cockcroft-Gault equation.¹³ The cutoff value established for SC clearance was <60 mL/min, corresponding to a moderately decreased GFR that would require evaluation and treatment of complications, according to recently released American National Kidney Foundation guidelines.¹

For patients with no height or weight recorded in their charts, sex-specific mean values were imputed. For weight, 106 cases (7.4%) were imputed (male average was 86.0 kg; female average was 71.8 kg). For height, 440 cases (30.7%) were imputed (male average was 1.74 m; female average was 1.61 m).

If we estimate a prevalence of elevated SC of 5%, we would need a sample size of 200 patients to reflect with 95% confidence (19 times out of 20) the prevalence of elevated SC among patients similar to those in our study (patients of family doctors who had SC measured for any reason). Because our sample included 1434 patients, we had sufficient power to be certain of the validity of our results.

The study received ethics approval from the Queen's University Research Ethics Board.

RESULTS

Of an initial 1792 records, 157 (8.8%) were excluded because they were repeat records, records of patients younger than 18 years at the time of first recorded SC measurement, or obstetric patients. Among the remaining 1635 records, 201 (12.3%) charts could not be located. (These were mostly patients of one family doctor who

left the Centre taking many of her patients and their charts with her.) Patients whose charts were missing were slightly younger (57.0 years vs 62.8 years, $P=.00$) and were more likely to be women (77.1% vs 64.5%, $P=.00$). Mean first SC measurements did not differ significantly between these groups of patients (84.1 $\mu\text{mol/L}$ vs 83.7 $\mu\text{mol/L}$, $P=.89$), nor did the proportion of patients with a first SC level >130 $\mu\text{mol/L}$ (3.0% vs 4.3%, $P=.45$). Therefore, patients with missing charts were excluded, and 1434 patients were included in the study.

Sixty-two patients (4.3%) had initial SC measurements >130 $\mu\text{mol/L}$ recorded in their charts. For 57 of these patients, subsequent SC measurements had been recorded also.

Demographics

Patient characteristics are shown in **Table 1**. Patients with a first SC measurement >130 $\mu\text{mol/L}$ were significantly older than those with a first SC measurement <130 $\mu\text{mol/L}$ (69.7 years vs 62.5 years, $P<.01$). Sex distribution and body mass index were not significantly different between the 2 groups. Of all factors considered, only a diagnosis of hypertension and use of beta-blockers were not significantly higher in patients with a first SC measurement >130 $\mu\text{mol/L}$ (**Table 2**).

Outcomes

Outcomes of patients with elevated first SC measurements are shown in **Tables 3** and **4**. In **Table 3**, initial SC measurements were compared with the latest SC measurements available. This was either a recent value abstracted from patients' charts (65.8% of study patients) or, if this value was not available, the last SC value in the database, provided it was not the initial value (19.3% of study patients). Since 214 patients (14.9%) did not have subsequent SC measurements available for comparison, the numbers in **Tables 2** and **3** are based on 1219 patients. Mean follow-up time (defined as the time between first and last SC measurement) was 4.5 years with a standard deviation of 2.3 years.

To present a clearer clinical picture, SC levels were separated into somewhat arbitrary categories: ≤ 130 $\mu\text{mol/L}$ indicating a return to "normal" values, 131 to 200 $\mu\text{mol/L}$ indicating a mild degree of renal insufficiency, 201 to 300 $\mu\text{mol/L}$ indicating moderate renal insufficiency, and >300 $\mu\text{mol/L}$ indicating more severe renal insufficiency.

Of the 57 patients with elevated SC levels who had repeat measurements recorded in their charts, 32 (56.1%) had their SC levels return to normal over time, 6 (10.5%) saw their SC levels improve but remain above normal, and 12 (21.1%) remained stable. In fact, only 7 patients (12.3%) progressed to worsening SC levels. Interestingly, the same comparison over a shorter period (comparing first to last SC value recorded in the database (therefore

Table 1. Patient characteristics at the time of follow-up chart review

CHARACTERISTIC	STUDY POPULATION	FIRST SERUM CREATININE MEASUREMENT		P VALUE
		≤130 µMOL/L "NORMAL"	>130 µMOL/L "ELEVATED"	
Number of patients	1434	1372	62	NA
Age as of June 30, 2004 (y)	62.8	62.5	69.7	<.01
Sex (% female)	64.5	65	53.2	.08
Body mass index (kg/m ²)	28.1	28.1	27.7	.64

NA—not applicable.

Table 2. Patients' diagnosis and treatment noted on charts

TREATMENT AND DIAGNOSIS	STUDY POPULATION N (%)	FIRST SERUM CREATININE MEASUREMENT		P VALUE
		≤130 µMOL/L "NORMAL" N (%)	>130 µMOL/L "ELEVATED" N (%)	
Referred to nephrologists	57 (4.0)	47 (3.4)	10 (16.1)	0
Ischemic heart disease	293 (20.4)	268 (19.5)	25 (40.3)	0
Hypertension	669 (46.7)	633 (46.1)	36 (58.1)	.09
Diabetes	256 (17.9)	236 (17.2)	20 (32.3)	<.01
Taking diuretics	422 (29.4)	393 (28.6)	29 (46.8)	<.01
Taking angiotensin-converting enzyme inhibitors	426 (29.7)	398 (29.0)	28 (45.2)	.01
Taking calcium channel blockers	241 (16.8)	224 (16.3)	17 (27.4)	.04
Taking beta-blockers	222 (15.5)	209 (15.2)	13 (21.0)	.3
Diagnosed with chronic kidney disease	53 (3.7)	36 (2.6)	17 (27.4)	0
Receiving dialysis	0 (0.0)	0 (0.0)	0 (0.0)	NA
Had a renal transplant	3 (0.2)	1 (0.1)	2 (3.2)	<.01
Died between time of initial serum creatinine measurement and follow-up	141 (9.8)	126 (9.2)	15 (24.2)	0

NA—not applicable.

Table 3. Outcomes of patients with elevated serum creatinine levels

FIRST SERUM CREATININE MEASUREMENT (µMOL/L)	LAST SERUM CREATININE MEASUREMENT N (%)				TOTAL PATIENTS
	≤130 µMOL/L "NORMAL"	131-200 µMOL/L	201-300 µMOL/L	>300 µMOL/L	
≤130 "normal"	1117 (96.1)	35 (3.0)	8 (0.7)	2 (0.2)	1162
131-200	26 (57.8)	12 (26.7)	5 (11.1)	2 (4.4)	45
201-300	3 (50.0)	3 (50.0)	1 (16.7)	0 (0.0)	6
>300	3 (50.0)	2 (33.3)	1 (16.7)	0 (0.00)	6

Table 4. Outcomes of patients with elevated creatinine clearance

FIRST CREATININE CLEARANCE MEASUREMENT ML/MIN	LAST CREATININE CLEARANCE MEASUREMENT N (%)				TOTAL PATIENTS
	≥90 ML/MIN "NORMAL"	60-89 ML/MIN	30-59 ML/MIN	<30 ML/MIN	
≥90 "normal"	439 (79.7)	100 (18.1)	10 (1.8)	2 (0.4)	551
60-89	48 (12.5)	223 (57.9)	109 (28.3)	5 (1.3)	385
30-59	9 (3.5)	36 (14.1)	177 (69.4)	33 (12.9)	255
<30	3 (10.7)	3 (10.7)	7 (25.0)	15 (53.6)	28

limiting the time frame to a maximum of 4 years) shows a similar pattern, indicating that most patients' recovery occurs relatively quickly.

Table 4 shows the same outcomes using creatinine clearance values calculated from the recorded SC measurements. It is clear that using a cutoff creatinine clearance of <60 mL/min rather than an SC level of >130 $\mu\text{mol/L}$ draws many more patients into the category of CKD (283 vs 57). Patients in this category are less likely to see improvement in their clearance over time: 51 patients (18.0%) returned to a creatinine clearance of ≥ 60 mL/min; 7 patients (2.5%) saw improvement but remained at <60 mL/min; 177 patients (62.5%) remained stable between 30 and 60 mL/min; and 48 patients (17.0%) either worsened or remained at <30 mL/min.

Patients with SC levels >130 $\mu\text{mol/L}$ had an increased risk of dying during the study period, even after correcting for age (corrected odds ratio 2.3, 95% confidence interval 1.2 to 4.3)

DISCUSSION

We started with specific questions about what happens to patients with elevated SC levels over time. We found some answers.

What happens to the SC levels of people with initial mild elevations?

Among patients with initial SC levels between 130 and 200 $\mu\text{mol/L}$, 58% saw their levels return to normal (<130 $\mu\text{mol/L}$), 27% saw their levels remain the same, and 15% progressed. We can say that only 15% of patients with SC levels between 130 and 200 $\mu\text{mol/L}$ will have deteriorating renal function over an average of 4.5 years' follow-up.

Is a stable, non-progressive elevation in SC level the most common scenario?

Of the 57 people with initial SC levels >130 $\mu\text{mol/L}$, only 12 (21%) remained within the same category of elevation of their initial reading, 44 (77%) improved, and only 12% progressed. We can say that the most common scenario for patients with elevated SC levels is that they improve.

How common in primary care is progressive increase in SC levels?

It appears from our data that, in a primary care population, 12% of people with elevated SC levels will progress to more severe renal dysfunction.

How often do patients with large elevations in SC (>300 $\mu\text{mol/L}$) progress to end-stage renal disease in primary care?

Our numbers are very small for this group, so we cannot make much of it. All 6 patients whose initial SC

measurements were >300 $\mu\text{mol/L}$, however, saw a decrease in their SC levels over time rather than a progression. Analyzing the data using a calculated creatinine clearance rate to estimate GFR¹⁴⁻¹⁷ revealed a similar pattern, although with a lower proportion of patients returning to normal levels and a far higher number of patients identified as having poor renal function. Clearly, in this patient population, many more patients would be referred to nephrologists if the cutoff for referral was a GFR of <60 mL/min rather than an SC level of <130 $\mu\text{mol/L}$. It is not clear whether the additional patients identified by using the GFR would benefit from these referrals. A larger, population-based outcomes study is needed.

Predicting progression to serious disease

These data indicate that most patients with high SC levels recover in time, although some do progress to more serious kidney disease. It would help physicians if there were ways to identify patient factors that predict progression. We looked at certain diagnoses, such as ischemic heart disease, hypertension, and diabetes, as well as use of medications, such as diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, and beta-blockers, in an effort to identify associations with progression of renal disease. It was not always possible, however, to determine whether these conditions existed before or occurred after the initial elevated SC levels.

Limitations

Limitations of this study include retrospective data collection (charts do not always clearly convey the details of physicians' diagnoses and treatment plans) and the fact that there was high turnover in our patient population, which limited follow-up time. The study is also limited by the small number of patients who had elevated SC levels. Because this number was small, the study did not have enough power to clearly identify factors that might predict progression of kidney disease. Despite this, we think that the data presented on the natural history of elevated SC measurements are a valuable addition to the discussion of appropriate management of primary care patients.

This is the first study in Canada, or anywhere as far as we can determine, to look at the progression of elevated SC levels in primary care patients. Our study had a historical cohort design, which is by nature retrospective. A prospective cohort study needs to be conducted to confirm our findings.

Conclusion

Most primary care patients who have elevated SC levels appear to have their levels return to normal or improve over time. Only 12% of patients get worse. This new information should be considered in future guideline

recommendations for management of elevated SC levels. Primary care physicians need to consider each case individually when deciding about referral to nephrologists. Guidelines that make rigid recommendations for referral based on a single elevated SC level or calculated GFR might lead to over-referral and hence overuse of the health care system.

The Canadian Society of Nephrology will be publishing an update to the guidelines shortly. The data in this paper will be taken into consideration in this update. ❁

Contributors

Dr Marcotte and Dr Godwin contributed to concept and design of the study; data gathering, analysis, and interpretation; and preparing the article for submission.

Competing interests

None declared

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