Reduction in Estimated Glomerular Filtration Rate in Patients with Elevated Blood Urea Nitrogen but Normal for any Other Markers of Kidney Damage

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Abstract

Background: It is unclear whether patients who present with elevated blood urea nitrogen (BUN), but are normal for other markers of kidney damage, are prone to develop chronic kidney disease (CKD). This study therefore investigated estimated glomerular filtration rate (eGFR), a marker of CKD, in these patients.

Methods: Patients with elevated BUN but normal for other markers of kidney damage who were followed-up for ≥48 months in our outpatient clinics were retrospectively evaluated. BUN, eGFR, and serum creatinine concentrations in the patient group were compared with findings in an age- and sex-matched control group.

Results: At baseline, BUN concentration was significantly higher in the patient than that in the control group (8.30 ± 1.10 vs 5.05 ± 0.91 mmol/L; $p <0.01$), but eGFR (111.94 ± 18.62 vs 111.25 ± 14.63 ml/min/1.73m^2) and serum creatinine concentrations (87.23 ± 8.59 vs 72.39 ± 10.06 µmol/L) were similar. At 1 year, however, eGFR in the patient group was significantly lower than in the control group (95.39 ± 18.52 vs 108.17 ± 16.99 ml/min/1.73m^2; $p < 0.01$), and was significantly lower than in the patient group at baseline (95.39 ± 18.52 vs 111.94 ± 18.62 ml/min/ 1.73 m^2, $p < 0.01$), with these differences becoming more pronounced over time.

Conclusions: Patients with elevated BUN but normal for other markers of kidney damage show significantly lower eGFR over time than matched controls.

Introduction

Glomerular filtration rate (GFR), serum creatinine and blood urea nitrogen (BUN) are the markers most frequently used to evaluate renal function. Although GFR is generally the most accurate, it is also difficult to determine in clinical practice. Empirical formulas, such as the Modification of Diet in Renal Disease (MDRD) formula, based primarily on creatinine and BUN concentrations, are used to estimate GFR in patients. Both serum creatinine and BUN can be completely filtered by the kidney, but BUN is actively reabsorbed. This reabsorption is related to the reabsorption of water and is therefore increased by hypovolemia or other causes of decreased renal perfusion pressure. In addition, protein intake, catabolism, and gastrointestinal bleeding can all influence BUN level, making BUN a less accurate marker of renal function than serum creatinine concentration.

Some patients who present with elevated BUN, however, are normal for other markers of kidney damage. It is still unclear whether these patients have kidney damage or are prone to develop chronic kidney disease (CKD). Elevated BUN has been associated with higher mortality rates in critically ill patients [1] and in patients with decompensated heart failure [2], independent of serum creatinine concentration [3]. Moreover, findings in our clinical practice have shown that patients with elevated BUN alone are prone to develop CKD. To determine whether these patients also show decreases in eGFR, we retrospectively evaluated long-term findings in patients with elevated BUN alone and compared them with a control group.

Methods:

Study design: Eligible patients who visited the clinic in our hospital from January 1, 2007, to December 31, 2008, were retrospectively screened using the Laboratory Information System (LIS). Patients with elevated BUN were deemed eligible if they were aged 18-70 years; had elevated BUN with no abnormalities in other markers of kidney damage at the first visit during the screening period; and agreed to undergo renal function testing at least once a year for 4 consecutive years.

The control group consisted of an equal number of age- and sex-matched patients with asymptomatic hematuria, with a normal eGFR. All control patients were aged 18–70 years; presented with asymptomatic hematuria at the first visit during the screen period; and agreed to undergo renal function testing at least once a year for 4 consecutive years.

Data collection: At baseline, age, gender; and concentrations of urinary protein, BUN, serum creatinine and albumin were collected from the LIS. The latter four items were recorded once a year, with a window period of 28 days. eGFR was calculated using the MDRD equation as:

$$GFR = 170 \times (Cr)^{-0.99} \times Age^{-0.176} \times BUN^{-0.170} \times Alb^{0.318} \times 0.762 \text{ (if female) [4]}.$$

Statistical analysis: All data were expressed as mean ± standard deviation (SD). eGFR, BUN, and serum creatinine at various time points were compared in the two groups by Analysis of Variance of Repeated Measures. Pearson's chi-Square test was used to compare the number of patients with proteinuria in the two groups. Differences were considered statistically significant when the p value was <0.05.

Results:

The two groups were well matched in gender and age (Table 1).

eGFR: At baseline, eGFR was similar in the elevated BUN and control groups (Table 2). Beginning at 1 year, eGFR was significantly lower in the elevated BUN group than in the control group (p < 0.01). eGFR in the elevated BUN group showed a gradual decline over time, with mean eGFR after 1–4 years being significantly lower (P < 0.01 each) than at baseline. In the control group, however, eGFR remained relatively unchanged over time.

BUN: At baseline, BUN was significantly higher in the elevated BUN than in the control group. BUN in the former group gradually increased over time, with findings at 1–4 years being significantly higher than at baseline (P < 0.01 each). In contrast, BUN remained constant over time in the control group.

Serum creatinine: At baseline, serum creatinine concentration was similar in the two groups. Over time, however, serum creatinine increased in the elevated BUN group, being significant higher after 1–4 years than

Table 1. Demographic characteristics

Group	Number of patients (n)	Gender (males/female) (n)	Age (years)
Elevated BUN group	75	44/31	58.6±10.6
Control group	75	40/35	55.0±10.8

Table 2. eGFR, BUN, and serum creatinine concentrations and number of patients positive for urinary protein at baseline and at 1-4 years in the elevated BUN and control groups.

Group		Baseline	1-year	2-year	3-year	4-year
eGFR (ml/min/1.73m^2)	Elevated BUN group	111.94±18.62	95.39±18.52	78.43±23.12*	64.88±24.72*	53.23±27.00*
	Control group	111.25±14.63	108.17±16.99	104.52±15.68	102.14±16.26	102.72±15.30
BUN (mmol/L)	Elevated BUN group	8.30±1.10*	9.91±2.32*	11.33±3.19*	13.16±4.22*	14.56±3.57*
	Control group	5.05±0.91	5.35±1.29	5.41±1.44	5.58±1.38	5.56±1.73
Serum creatine (μmol/L)	Elevated BUN group	87.23±8.59	105.64±18.07*	119.20±9.30*	135.38±7.48*	156.01±7.24*
	Control group	72.39±10.06	75.12±9.55	78.24±12.86	81.56±14.82	82.89±16.32
Number of patients with proteinuria N (%)	Elevated BUN group	0(0)	17(22.67)*	35(46.67)*	54(72.00)*	67(89.33)*
	Control group	0(0)	5(6.67)	12(16.00)	34(45.33)	47(62.67)

* p < 0.01, compared with the control group at the same time point.

at baseline, as well as being significantly higher than in the control group (P < 0.01 each).

Proteinuria: At baseline, none of the patients in either group had proteinuria. After 1–4 years, the number of patients with proteinuria was significantly higher in the elevated BUN than in the control group.

Discussion

BUN is generally considered a less accurate marker of renal function than serum creatinine. Patients with elevated BUN but normal for other markers of kidney damage, including serum creatinine, have frequently been considered normal. This study showed, however, that these patients were prone to develop CKD, as shown by their progressive reductions in eGFR.

Serum creatinine levels, which are used to calculate eGFR, are prone to misinterpretation due to several shortcomings. First, the production of creatinine is not constant; rather, it depends on muscle mass and food habits, especially the consumption of meat. Second, tubular secretion of creatinine is most pronounced when renal function is compromised. Thus, overestimation of creatinine clearance due to tubular secretion of creatinine and urine collection errors can render estimates of GFR unreliable. Moreover, even if these patients' actual GFR were normal, as defined by the K/DOQI [4], the presence of other markers of kidney disease may indicate that these patients have CKD.

To estimate GFR more accurately, large studies have generated empirical formulas based on serum creatinine and BUN concentrations [5]. One of the most common formulas is the MDRD formula. However, the MDRD formula has been found to overestimate real GFR at lower levels of true GFR and to underestimate real

GFR at higher levels of true GFR [6]. Furthermore, the MDRD formula was derived from patients with CKD, thus overestimating GFR in individuals with normal or nearly normal true GFR. Thus, due to the shortcomings of eGFR and serum creatinine, patients who present with elevated BUN but normal eGFR and normal serum creatinine may have mild kidney damage.

In conclusion, this study suggested that elevated BUN in the presence of normal levels of other markers of kidney damage may suggest that these patients have mild kidney damage or may be a prelude to CKD. The renal function of these patients should be monitored regularly to prevent its further deterioration.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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