Urea and creatinine concentration, the urea:creatinine ratio

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Summary

This second of two articles on understanding the clinical value of measuring urea concentration explores the clinical value of simultaneous measurement of urea and creatinine and calculating the urea:creatinine ratio. The article discusses the causes of increased and decreased ratio as well as the clinical application of the ratio.

This is the second of two articles that together aim to explore current understanding of the clinical value of measuring serum/plasma urea concentration.

The main focus of the first article [1] was physiological topics, such as urea production and renal processing of urea. The causes of increased and reduced plasma/serum urea concentration were also discussed. The main focus of this second article is the clinical value of simultaneous measurement of urea and creatinine and calculation of the urea: creatinine ratio.

The causes of increased and decreased ratio will be outlined and clinical application of the ratio will be discussed. The article begins with a short discussion of the comparative merits of urea and creatinine measurement for assessment of renal function; this discussion is helpful for an understanding of the potential clinical value of calculating the ratio.

Creatinine and urea blood levels reflect glomerular filtration rate (GFR)

The rationale for the use of creatinine or urea measurement to assess renal function is that plasma/serum levels of both reflect glomerular filtration rate (GFR), the parameter that defines

kidney function for the clinician. Irrespective of its cause, kidney disease is associated with decrease in GFR, and the severity of kidney disease correlates closely but inversely with GFR. A normal GFR (~125 mL/min) is presumptive evidence of healthy, functioning kidneys. As GFR (i.e. kidney function) declines, urinary excretion of urea and creatinine also declines and blood concentration of both increases.

For the blood concentration of an endogenously produced substance to most accurately reflect GFR in health and disease, that substance must have the following properties:

- It must be excreted only by the kidneys
- It must be freely filtered from blood at the glomerulus
- It must be neither reabsorbed from the filtrate to blood nor secreted from blood to the filtrate by renal tubule cells (i.e. all that is filtered at the glomerulus appears in urine, and all that is in urine is due to glomerular filtration)
- Blood concentration of the substance must be unaffected by diet and/or change in the rate of endogenous production (i.e. it is only affected by change in GFR)

Both plasma urea and plasma creatinine concentration are imperfect indices of GFR; neither analyse entirely fulfils the above criteria (see Table I below) and both lack sensitivity to detect minimal change in GFR.

Typically, GFR must be reduced by ~50 % before plasma urea or creatinine concentration rise above the upper limits of their respective reference range [2]. By comparison with urea, however, creatinine more closely fulfils the above criteria and for this reason is the preferred test for assessment of kidney function [3], [4].

Increased plasma creatinine is almost invariably a consequence of reduced GFR and therefore has a renal cause. Although reduced GFR (i.e. renal disease) is also associated with increased plasma urea concentration, there are other non-renal conditions that can give rise to increased plasma urea [1]. Interpretation of increased plasma urea is thus often aided by simultaneous measurement of creatinine and calculation of the urea: creatinine ratio in order to establish a renal or non-renal cause.

The distinction between BUN: creatinine ratio (BCR) and urea: creatinine ratio (UCR)

In the US and a few other countries, urea concentration is expressed as the nitrogen content of urea (MW 28) and reported as blood urea nitrogen (BUN) in non-SI units (mg/dL). In all other parts of the world, urea results are expressed as the whole urea molecule (MW 60) and reported as urea in SI units (mmol/L). These two different ways of reporting urea results give rise to two quite different values for the ratio.

The non-SI ratio (BCR) is BUN (mg/dL) / plasma creatinine (mg/dL). The reference range is around 8-15 [5] and the most commonly used cut-off value to define increased BCR is 20.

The SI ratio (UCR) is plasma urea (mmol/L) / (plasma creatinine (µmol/L) divided by 1000). The factor of 1000 is needed to convert creatinine result from µmol/L to mmol/L, the urea unit of measurement. The UCR reference range is much higher than that for BCR (of the order 40-100) because of the difference between urea and urea nitrogen, and is less clearly defined than that for BCR, possibly because the ratio is less often used.

A solution to this interpretative problem is to convert SI results for urea and creatinine to non-SI results before calculating the ratio. This allows calculation of the more commonly used and better referenced BCR.

For example:

Patient A has: plasma urea 5.0 mmol/L
plasma creatinine 75 µmol/L

The UCR for this patient is 5.0 / (75/1000) = 66

To calculate BCR for this patient we must first convert urea mmol/L to BUN mg/dL and creatinine µmol/L to creatinine mg/dL.

To convert urea mmol/L to BUN mg/dL – divide by 0.357.

To convert creatinine µmol/L to creatinine mg/dL – divide by 88.4.

So for Patient A: BUN is 5.0 / 0.357 = 14 mg/dL
Creatinine is 75 / 88.4 = 0.85 mg/dL

Criteria of a substance for its plasma concentration to most accurately reflect GFR	Urea	Creatinine
Excreted only by the kidneys	Not entirely – a small amount (<10%) is excreted via nonrenal route in sweat and feces.	Yes, the kidneys are normally the only route of excretion. (Some creatinine may be excreted via non-renal route in patients with most advanced renal disease).
Freely filtered at glomerulus	Yes	Yes
Not reabsorbed or secreted by renal tubule cells	A variable quantity of urea reabsorbed from filtrate, dependent on state of hydration, renal blood flow, etc. Urea is also secreted by renal tubules. Only 40-50% of filtered urea appears in urine.	Creatinine is not reabsorbed. Virtually all filtered creatinine appears in urine. However, a small amount is secreted by proximal tubules.
Concentration in blood unaffected by factors other than GFR, i.e. must be unaffected by diet and produced at a constant rate	A number of non-renal factors materially affect urea production/concentration including: • state of hydration • amount of dietary protein • liver disease • GI bleed • pregnancy • ageing	Creatinine production and therefore plasma creatinine concentration is constant so long as muscle mass remains unchanged. Plasma levels are ethnically and gender dependent, and are transiently increased by eating cooked meat.

TABLE I: Comparison of urea and creatinine as markers of GFR

Plasma urea increased/Plasma creatinine normal

• Dehydration
• Heart failure (without renal involvement)
• Gastrointestinal bleed
• High-protein diet
• Catabolic state due to: - trauma
                                      - severe infection
                                      - starvation
                                      - corticosteroid drugs

Plasma urea normal/Plasma creatinine reduced
• Decreased muscle mass
Plasma urea disproportionately higher than increased plasma creatinine AKI caused by prerenal mechanisms: • shock • hypovolemia due to blood loss, vomiting, etc. • hypoperfusion due to: - cardiorenal syndrome, heart failure   - severe hypotension

TABLE II: Causes of increased BCR/UCR

And BCR is 14 / 0.85 = 16

All numerical values for the urea: creatinine ratio in this article will be BCR, not UCR values unless specifically stated.

Increased BCR/UCR can present, theoretically at least, in one of three ways:

- Increased plasma urea and normal plasma creatinine
- Normal plasma urea and decreased plasma creatinine
- Increase in plasma urea disproportionately greater than increased creatinine

The principal causes of increased BCR/UCR are listed in Table II below under these three headings.

Decreased BCR/UCR [6] is less common and usually of less clinical significance. It is a feature of very rare inherited disorders of the urea cycle, and advanced liver disease. Both are typically associated with reduced plasma urea but normal plasma creatinine. Spuriously raised plasma creatinine (due to substances that interfere with creatinine estimation) can cause decreased BCR/UCR.

Clinical application of BCR/UCR 1. Gastrointestinal (GI) bleed

Gastrointestinal bleeding represents a non-renal cause of increased plasma urea. In the absence of concomitant renal insufficiency those with a GI bleed have a normal plasma creatinine and thus a raised BCR/UCR.

Two mechanisms have been proposed to explain the increased urea and consequent increased BCR/UCR associated with GI bleed. The first of these

assumes increased urea production consequent on digestion of blood and increased absorption of derived amino acids; blood in the gut is effectively a "high-protein meal".

The second mechanism relates to the hypovolemia and reduced renal perfusion associated with any significant blood loss. Part of the adaptive response to hypovolemia and reduced renal perfusion involves increased renal reabsorption of urea and consequent reduced urea excretion with increased plasma urea concentration. Since GFR is unaffected (initially at least) by this so-called prerenal azotemia, plasma creatinine remains within normal limits.

Measurement of plasma urea and calculation of BCR/UCR has proven clinically useful in localizing the site of GI bleeding. Specifically, it helps in distinguishing between an upper and lower gastrointestinal bleed. The anatomical site that is used to define the border between upper and lower gastrointestinal tract is the junction of the duodenum and jejunum, where the ligament of Treitz is attached.

A number of studies [7], [8], [9], [10], [11], [12] have demonstrated that BCR/UCR is significantly higher among patients with an upper GI bleed than it is among those with a lower GI bleed. The most widely recommended BCR cut-off value to distinguish upper and lower GI bleed is 30 [13]. (The equivalent value for UCR is of course higher, 90-100) [7], [9].

A BCR value greater than 30 identifies upper GI bleed with a specificity around 95-99% and sensitivity around 50% [13].

It is thus rare indeed for bleeding at a site below the duodenal-jejunum junction to be associated with BCR >30.

The supposed reason for lower BCR/UCR among patients with lower GI bleed is that the offending blood would, more often than not, be below the site in the small intestine where most amino acid absorption occurs; the "high-protein meal" mechanism of increased urea production cannot then operate.

Quite apart from its role in localizing the site of a GI bleed, urea measurement has a role in determining the severity of bleeding. In 1980 Pumphrey and Beck [14] demonstrated a positive correlation between estimated blood loss and plasma urea concentration among 57 patients with upper gastrointestinal hemorrhage.

Confirmation that plasma urea concentration is a potential marker of substantial blood loss among patients with upper GI bleed led to inclusion of plasma urea concentration in the now well-validated Glasgow-Blatchford scoring system [15], [16], [17].

This simple scoring system based on patient pulse, blood pressure, plasma urea and hemoglobin concentration is used to initially assess patients with upper GI bleed in order to identify those at high risk (in need of urgent transfusion/endoscopy) and those at low risk (who can be safely discharged without further investigation/treatment).

Clinical application of BCR/UCR 2. Acute kidney injury (AKI)

Chronic kidney disease (CKD) is defined by reduction in GFR, which in turn is associated with increased plasma creatinine and urea concentrations. As CKD progresses, plasma levels of both rise in tandem, so that BCR/UCR usually remains within normal limits in CKD. Although reduced GFR is also a defining feature of acute kidney injury (AKI), plasma creatinine and urea levels do not necessarily rise in tandem and the BCR/UCR is sometimes increased.

This has allowed a role for calculation of BCR/UCR in the early assessment of patients suffering AKI. To understand this application of the BCR/UCR, it is necessary to briefly consider the causes of AKI.

The causes of AKI are categorized under three headings: prerenal (reduced renal perfusion, often because of hypovolemia), intrinsic renal (damage to the kidney itself – glomerular or tubular), postrenal (obstruction of urine flow) [18].

Prerenal causes (hypovolemia due to severe vomiting, blood loss, osmotic diuresis, etc. or reduced renal blood flow due to, for example, cardiorenal syndrome associated with heart failure, sepsis) account for 70% of AKI cases. Whatever the precise cause, prerenal AKI exists despite a presumed normally functioning kidney.

It is the hemodynamic instability that accounts for reduced GFR in prerenal AKI. Part of the response to the hemodynamic instability that underlies prerenal AKI is increased renal reabsorption of urea [19] and this contributes to the rising plasma urea consequent on reduced GFR. Since creatinine is not reabsorbed, but is increased only as a result of reduced GFR, plasma urea concentration tends to rise out of proportion to the rise in plasma creatinine concentration in patients with prerenal AKI, and this results in increased BCR/UCR.

This has allowed a long-established role for BCR/UCR in helping to distinguish AKI caused by prerenal mechanisms (associated with BCR >20) from AKI due to intrinsic renal or postrenal mechanisms (associated with BCR <20) [[2], [5], [20].

The distinction is important because prerenal AKI is often easily reversible with early fluid resuscitation and is associated with lower mortality than either intrinsic or postrenal AKI. An increased BCR (>20) has thus been thought to be a good prognostic indicator in patients with AKI.

Recent study [21], [22] challenges the validity of this traditional use of BCR/UCR. These studies suggest that a high BCR can be associated with poor prognosis and therefore not necessarily indicative of just prerenal AKI. The authors of one of these studies [22] caution that BCR/UCR should

not be used to distinguish prerenal AKI from other forms of AKI, at least in the critically ill. Credence for this view is provided by the observation that for critically ill patients with normal serum creatinine, plasma urea concentration is independently associated with mortality [23].

Clinical application of BCR/UCR 3. Heart failure

Heart and kidney function are closely related in health and disease. Pathologically this link is manifest as the cardiorenal syndrome [24]. Around 60% of heart failure (HF) patients have some degree of renal dysfunction that increases both morbidity and mortality due to heart failure [24].

Identification of HF patients at highest risk of death involves assessment of renal function, and a number of recent studies [25], [26], [27] suggest that calculation of patient BCR/UCR has important prognostic value.

This role is born of the observation that serum/plasma urea is a more powerful predictor of survival among heart failure victims with renal dysfunction than conventional renal function measures (plasma creatinine and estimated GFR) [28].

In summary, these studies suggest that for patients with heart failure, the higher the BCR/UCR, the greater is the risk of worsening renal dysfunction and death. BCR/UCR within normal limits is a favorable prognostic sign for these patients.

Clinical application of plasma urea measurement alone 1. Acute pancreatitis

Measurement of serum/plasma urea has value in the early (emergency room) assessment of patients with acute pancreatitis. Specifically it helps distinguish those whose acute pancreatitis is likely to run a relatively benign self-limiting course from the approximately 20% of patients who will develop severe acute pancreatitis, a rapidly

evolving life threatening condition that can result in overwhelming infection, sepsis and multiple organ failure.

These patients require immediate transfer to intensive care for optimal care and best chance of survival.

The notion that increased plasma/serum urea at admission and/or rising plasma/serum urea during the first 24 hours is a poor prognostic sign and indicative of severe acute pancreatitis has been appreciated for many years [29], [30]. A recent confirmatory study validated this clinical application of urea measurement [31]. The authors of this study retrieved plasma BUN (urea) results at admission and 24 hours later from 1043 patients with acute pancreatitis.

Highest mortality (15-20%) was evident in those with an elevated urea, >20 mg/dL (7.1 mmol/L) at admission without a decline of at least 5 mg/dL (1.7 mmol/L) during the 24 hours that followed. A decline of more than 5 mg/dL was found to reduce the risk of death substantially for those with an elevated urea at admission (mortality just 0-3.2%).

Lowest mortality (0-1%) was found in those with normal urea, <20 mg/dL (7.1 mmol/L) at admission and without an increase >2 mg/dL (0.7 mmol/L) at 24 hours. An increase of more than 2 mg/dL (0.7 mmol/L) during the 24 hours following admission was found to increase mortality (6-11%) for those with a normal urea at admission.

Clinical application of plasma urea measurement alone 2. Hemodialysis

Measurement of plasma/serum urea concentration has a long-established role in monitoring the adequacy/dose of intermittent hemodialisis, the life-preserving renal replacement therapy for patients with end-stage renal disease. Pre- and postdialysis plasma urea concentrations are used to calculate the urea reduction ratio (URR) thus:

URR = [1 – Postdialysis urea) / Predialysis urea] × 100

URR > 65% is widely regarded as indicating adequate dialysis [32].

An alternative parameter, Kt/V based on urea kinetic modeling is also used to determine adequacy/dose of intermittent hemodialysis. Calculation of Kt/V also requires input of pre- and postdialysis plasma urea concentrations.

K = total dialysis urea clearance (mL/min)
t = dialysis time (min)
V = total body water (L).
A Kt/V value >1.2 indicates adequate dialysis [32].

Summary

Serum/plasma urea is not recommended for routine assessment of renal function because it is a less specific marker of glomerular filtration rate (GFR) than plasma creatinine, the blood test of choice for assessing and monitoring renal function. Urea measurement does, however, have some clinical value, especially when measured in tandem with plasma creatinine.

Measurement of urea alone has proven value in assessment of patients with acute pancreatitis and monitoring effectiveness of hemodialysis.

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