Chapter 1

The assessment of kidney function

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Case report

A 36-year-old woman was admitted to the medical ward for left Herpes Zoster ophthalmicus. She had developed breast cancer one year before, and had been treated by surgery, radiotherapy, and chemotherapy. The last treatment was three months before the current admission.

Her physical exam showed the ocular Herpes Zoster and the right mastectomy. She was thin. Her weight was 43 kg, and her height was 163 cm. Her blood pressure was 110/60 mmHg.

The serum chemistries showed a serum creatinine of 100 μmol/L (1.1 mg/dL) by the enzymatic IDMS traceable creatinine measurement. The estimated glomerular filtration rate (eGFR) reported by the hospital laboratory, according to the MDRD equation, was 56 mL/min/1.73 m². The blood urea was 8 mmol/L (BUN = 22 mg/dL). Acyclovir was given intravenously at the dose of 10 mg/kg three times a day for seven days, the usual dose for immunosuppressed subjects because she had been recently treated by chemotherapy.

After three days, she became confused and had hallucinations. There was an increase in serum creatinine and urea levels, to 115 μmol/L and 12.5 mmol/L, respectively. The urinalysis was unremarkable.

Encephalitis was ruled out. The antiviral treatment was temporarily stopped because acyclovir toxicity was felt to be the cause of the confused mental state.

The renal function returned to the initial value 36 hours after stopping acyclovir. It was started again orally at the dose of 800 mg twice daily for the next three days.

A 24-hour urine collection had only 450 mg of creatinine. The creatinine clearance was 28 mL/min, when the serum creatinine was 1.1 mg/dL. The urea clearance was also decreased, being 20 mL/min.

By using the Cockcroft formula, for the same serum creatinine, the creatinine clearance was 48 mL/min. By the Wright formula, the eGFR was 56 mL/min.

All these different values are summarized in Table 1.1.

This case shows the difficulty of accurately determining the GFR in patients with low body weight. This patient had low body weight and low muscle mass, as shown by the low total amount of creatinine in her 24-hour urine collection. This accounts for her low serum creatinine. Her GFR could also be estimated as the average of the creatinine and urea clearances, being 24 mL/min, instead of 56 as reported on the automatic lab report.

This patient’s actual GFR was probably closest to the value given by the 24-hour urine studies, and not by any formula. That is also based on her adverse response to the acyclovir.
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Introduction

This case illustrates the use of the serum creatinine and the equations dependent on its value to estimate the glomerular filtration rate (GFR). It shows clearly the difficulty in the assessment and management of reduced kidney function in subjects with cancer. In them, as in this patient, a low body and muscle mass will reduce the creatinine production, and what appears to be a normal serum creatinine will instead indicate a reduced GFR. The formula-based estimates of GFR appear in this case to have been overestimates, whereas the 24-hour urine studies indicated a GFR of about 25 mL/min. That latter value is consistent with her adverse response to the intravenous acyclovir.

The level, or amount, of kidney function is often conflated with the GFR, or even more commonly, with the level of the serum creatinine. While this approximation is useful for day-to-day management, it has some inaccuracies and it ignores some of the other aspects of kidney function, including proteinuria and the differentiation of tubular from glomerular injury. This chapter will discuss the assessment of kidney function by history and physical exam, urinalysis, testing the GFR, assessment of proteinuria and testing the renal tubular function.

History and physical exam

Past and family history may indicate a predisposition to kidney disease, for instance from diabetes or polycystic kidney disease, but these do not indicate the level of kidney function.

Table 1.1 Glomerular filtration rate (GFR) according to the method used, and for a serum creatinine of 1.1 mg/dL

<table>
<thead>
<tr>
<th>Method for GFR</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD formula</td>
<td>56 mL/min/1.73m²</td>
</tr>
<tr>
<td>Cockcroft-Gault formula</td>
<td>48 mL/min</td>
</tr>
<tr>
<td>Wright formula</td>
<td>56 mL/min</td>
</tr>
<tr>
<td>24-hour urine creatinine clearance</td>
<td>28 mL/min</td>
</tr>
</tbody>
</table>

In patients with low muscle mass due to cachexia or severe illness, a 24-hour urine collection may be better to calculate the creatinine clearance rather than estimating the GFR from a formula derived from the plasma creatinine concentration alone. One could also use a reference technique for GFR determination such as iohexol, EDTA, or iothalamate. The European Medicines Agency (EMEA) recommends these latter techniques for the evaluation of new medicines in subjects with reduced kidney function. The expense of these tests may be well worthwhile, because that expense may avoid the morbidity of medication toxicity.
Features of the history include the exposure to potential nephrotoxins in sufficient amounts and with an appropriate chronology. The use of radiocontrast, for example, may cause acute renal failure within days of its use, but renal failure several weeks after its use is not due to radiocontrast. Knowledge of cancers that may involve the urinary tract should be sought in the history, such as lymphomas, or treatments that may affect kidney function, such as cis-platinum.

The timing of the onset of edema is usually straightforward. But in the absence of this symptom, the onset of kidney disease may be insidious. The degree of edema is not a good marker of the degree of kidney function loss. A loss of urine concentrating ability, which can occur at a GFR of 60 mL/min or less, may result in nocturia.

Hypertension may occur because of kidney disease, but is often asymptomatic and thus not a reliable feature of the history. A documented new onset of hypertension may be useful in timing the onset of kidney disease. The degree of blood pressure elevation is not a good marker of the level of kidney function.

A patient may provide information on a change in urine output or its color, which may help in identifying the timing of kidney disease.

Symptoms of renal failure, such as decreased appetite, may be noticed when the GFR is less than 20 mL/min, but nausea or vomiting are a later manifestations of renal failure, occurring when the GFR is 10 mL/min or less.

The physical exam is non-specific until over half of the normal kidney function is lost. Anemia, for instance, occurs in direct relation to the serum creatinine, but this relationship is imprecise and other causes for anemia may exist in a cancer patient. Muscle cramps may occur when the kidney function is down to 25% of normal, sometimes in association with hypocalcemia. A yellow ‘dirty-yellow’ hue to the skin may be apparent in a subject with chronic renal failure whose kidney function is less than 10% of normal. Itching also occurs in severe chronic kidney failure, generally when the serum creatinine has reached 400 µmol/L or higher, and scratch marks can be seen on the skin. But itching is not a feature of acute renal failure. Another skin finding is the occurrence of blotchy subepidermal hemorrhages, generally on the dorsum of the forearms. This can occur when the GFR is less than 25% of normal, and is related to the reduction in the platelet function in subjects with renal impairment.

Abnormalities of tubular function may cause symptoms and signs but these are even less specific than those of renal failure. A renal tubular acidosis caused by amphotericin could cause weakness, either related to acidosis or the hypokalemia. Deep tendon reflexes could even be lost at severe degrees of hypokalemia,
i.e. less than 2 mmol/L. Similarly, hypophosphatemia could result in weakness, but its cause would only be apparent upon lab testing.

The assessment of a patient’s extracellular volume status, by evaluating changes in body weight or blood pressure (BP), may be important in establishing the cause of renal failure. For instance, an increase in pulse of greater than 30 beats/min and a drop in BP of more than 20 mmHg on changing from the lying down to the standing up position may indicate extracellular volume depletion, which can cause pre-renal azotemia. However, those changes of the pulse and BP do not tell us the level of kidney function. In addition, these signs are not always present in a subject with volume depletion (1). A patient with reduced kidney function may have signs of fluid overload such as hypertension, edema, increased of jugular venous pressure, a cardiac gallop, or pulmonary crackles. Here again, these features do not tell us what is the level of kidney function.

**Urinalysis**

For this purpose, 10 mL of freshly voided urine should be centrifuged at 2500 rpm for 5 min. The supernatant should be tested chemically and the sediment placed on a slide using a Pasteur pipette.

The use of analytical ‘dipsticks’ and the conventional light microscopy are the standard tools for urine analysis that are easily available and very informative. Table 1.2 shows some features of the urinalysis that are useful in diagnosis. Fig. 1.1 shows muddy brown casts, which are seen in the urine sediment of patients with acute tubular necrosis, caused by sepsis and hypotension. Fig. 1.2 shows multiple uric acid crystals in a urine sediment, as might be seen in acute hyperuricemic nephropathy that could complicate the treatment of a rapidly growing lymphoma.

A ‘benign’ urinalysis (i.e. one without proteinuria or formed elements in the sediment) can also be informative inasmuch as it may suggest causes of renal failure outside the kidneys, such as urinary tract obstruction or pre-renal azotemia.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Site of injury</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria, 2+ or more</td>
<td>Glomerulus</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Red cell cast</td>
<td>Glomerulus</td>
<td>Crescentic glomerulonephritis</td>
</tr>
<tr>
<td>Urine pH &gt; 6.5</td>
<td>Tubule</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Muddy brown casts</td>
<td>Tubule</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td>Uric acid crystals</td>
<td>Tubule</td>
<td>Hyperuricemic nephropathy</td>
</tr>
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</table>
Proteinuria

In health, urine contains little or no protein. An injury to the glomeruli or the tubules could result in proteinuria. The albumin contained in the serum, normally at 40 g/L concentration, traverses the glomerular filtration barrier in only scant amounts. Thus, the glomerular filtrate contains albumin, but only at a concentration of 3.5 mg/L (2). The majority of this filtered albumin is

![Fig. 1.1](image1) A photomicrograph of muddy-brown casts seen in an unstained urine sediment. These are typical of acute tubular necrosis, as might be seen after use of radiocontrast dye or in a hypotensive septic patient.

![Fig. 1.2](image2) Photomicrograph of uric acid crystals seen in an unstained urine sediment. The typical rhomboid shape is apparent. Such abundant uric acid crystals might be seen after cell lysis, as might occur subsequent to chemotherapy for Burkitt lymphoma.
reabsorbed by the tubules, by a receptor-dependent endocytosis, and normal urine contains no more than 30 mg of albumin per day, and no more than 100 mg of protein per day. That amount is below the detection limit of the standard dipstick test for proteinuria, and will also not be detected by the sulfosalicylic acid test. Microalbuminuria, which is urinary albumin between 30 and 300 mg per day, is important in the management of subjects with diabetes and nascent diabetic nephropathy, but has little importance in cancer patients.

With a normal GFR of 120 mL/min (2 mL/s or ∼150 L/day), there are thus about 500 mg of albumin in the daily total glomerular ultrafiltrate. Urinary albumin in quantities greater than this suggests glomerular injury. Alterations in the charge and the pore-size characteristics of the glomeruli may permit greater amounts of serum protein to traverse the glomeruli, including albumin as well as globulins. But globulins, specifically light chains, may reach the urinary space without the requirement for a change in the glomerular filtration barrier. An analysis of urinary protein by use of electrophoresis will differentiate these circumstances (Fig. 1.3). Albuminuria greater than 3 g per day may result from the nephrotic syndrome, whereas light chain proteinuria indicates a paraproteinemia. These are discussed in Chapters 2 and 5, respectively.

The quantification of proteinuria has historically been made by urinalysis followed by 24-hour urine collections. The use of a single, ‘spot’ urine specimen to assess proteinuria is well established as a reliable way to quantify urine protein (3). This test yields a ratio that is closely correlated to the 24-hour urine protein. A urine protein-to-creatinine ratio of less than 0.1 is normal, i.e. shows no excess urinary protein, while a ratio of 2 g/g suggests nephrotic range proteinuria, i.e. greater than 3 g of urinary protein excreted per day.

Glomerular filtration rate

Clinical use of the serum creatinine concentration for assessment of the kidney function is over 75 years old (4). Its elevation beyond 3 mg/dL (−250 μmol/L) was an acknowledged correlate of uremia. By 1954, the elevation of the serum creatinine to 2 mg/dL (180 μmol/L) or more was deemed abnormal (5). Since creatinine is freely filtered by the glomeruli, and because its tubular secretion is quantitatively a lot less than its filtration, its clearance from the body approximates the actual GFR (Fig. 1.4). It varies inversely with GFR. Twelve- or 24-hour urine collections are used for the calculation of the creatinine clearance, in mL/min, using the clearance formula, clearance = U × V/S. In this equation, U is the urinary creatinine, V is the urinary volume per minute, and S is the serum creatinine. Mass units or Système international (SI) units can be
used, as long as they are the same in the numerator and denominator. A timed urine collection begins at a specified time, at which the voided urine is discarded. All of the subsequent voided urine is collected, up to and including the ending time of the collection. A simultaneous blood sample is taken for serum creatinine. The amount of creatinine excreted is directly proportional to muscle mass because creatinine is a non-enzymatic breakdown product of the muscle creatine. The amount of creatinine excreted in 24 h provides an indication of the completeness of the urine collection, it being 15–20 mg/kg body weight in women and 20–25 mg/kg in men. These normal values might be less in a cancer patient who has lost muscle mass. Such a patient might have a lower than expected serum creatinine level, yet have a normal, or even reduced

Fig. 1.3 These show serum and urine immunoelectrophoretic patterns. Fig. 1.3a shows the serum and urine immunoelectrophoretic pattern in a subject with an IgG kappa paraproteinuria. The right panel shows the dense band of the monoclonal IgG paraprotein in the serum. The left panel shows the corresponding dense band of the free monoclonal kappa chains in the urine. Fig. 1.3b shows the urine immunoelectrophoresis in a subject with non-selective proteinuria. Albumin and globulin are present and there is no monoclonal band. These images were provided by Dr. Carl Becker, Medical College of Wisconsin, Milwaukee, Wisconsin, USA.
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GFR. This is shown by the case for this chapter, in which the 24-hour urine creatinine was only 10 mg/kg, a value which shows a low creatinine production. Her initial serum creatinine was near the normal range for the hospital laboratory but her GFR was very much reduced.

The studies of Rehberg (6) established the correlation of creatinine clearance to the glomerular filtration rate (GFR). Further studies confirmed the close correlation of creatinine clearance to the GFR, the latter being measured by inulin clearance (7) (Fig. 1.5). This correlation of creatinine clearance to the GFR depends on a steady state of creatinine production, its complete glomerular filtration, and a lack of significant tubular secretion of creatinine. Inulin clearance is a reliable, albeit a cumbersome method for the calculation of the GFR, because inulin, a 5000 dalton polysaccharide, is filtered at the glomeruli, but not reabsorbed or secreted by the tubules. No matter what the substance used, clearance calculations cannot be relied on when subjects are not in a steady state, as might occur with rapidly changing renal function. Abrupt increases in creatinine production, as in rhabdomyolysis, could cause the serum creatinine to rise before the kidneys were damaged by the myoglobinuria, which would invalidate the measured clearance. Certain drugs, including trimethoprim and cimetidine, block creatinine secretion, thus raising the serum creatinine level by about 20 to 25% without affecting the glomerular creatinine clearance.

Fig. 1.4 A schematic representation of the clearance concept. For a substance that is filtered but not re-absorbed or secreted, the quantity filtered (Qf) will equal the quantity excreted (Qe). The serum concentration of that substance [S] times the glomerular filtration rate (GFR) will equal Qf. The quantity excreted will equal the urinary concentration of the substance [U] times the urinary volume (V). Thus, GFR = ([U] x V) / [S].

\[ Q_f = [S] \times GFR \]

\[ Q_e = [U] \times V \]

\[ [S] \times GFR = [U] \times V \]

\[ GFR = ([U] \times V) / [S] \]
A good correlation exists between the GFR and the average of the creatinine and urea clearances (8). The urea clearance is normally less than the GFR, because of the tubular reabsorption of urea. The creatinine clearance is a bit higher than the GFR, because of tubular secretion of creatinine. The calculation of the urea clearance uses the familiar $U \times V/S$ formula, where $U$ is the urinary concentration of urea nitrogen, $V$ is the urinary volume per minute, and $S$ is the blood urea nitrogen (BUN). Mass units or Système international (SI) units can be used, as long as they are the same in the numerator and denominator.

Of more immediate use is the correlation of serum creatinine to creatinine clearance. This inverse relationship is predictable based on the clearance equation, but like all inverse relationships, it is not intuitive for easy clinical use. When the serum creatinine rises from 1–2 mg/dL, one has lost 50% of the normal GFR, which is more than the loss of function than when the serum creatinine rises from 2–10 mg/dL.

The correlation of serum (or plasma) creatinine to the GFR is imperfect. Recent studies show that this correlation is particularly imprecise in the GFR range of 60–20 mL/min (Fig. 1.6). Some authors state that the serum creatinine level might be 1.5 mg/dL for a GFR of 60 mL/min and also be at this level for a GFR of 40 mL/min. In practice, this imprecision is an inter-subject rather than an intra-subject problem. Thus, if the serum creatinine is 1.5 mg/dL at a GFR of 60 mL/min, a further decline in the GFR to 40 mL/min is
accompanied by an increase in the serum creatinine level, perhaps to 2 mg/dL. Thus, serial monitoring of the serum creatinine or the derivative values, such as the 100/serum creatinine quotient, remain valid in clinical patient care such as in a cancer patient treated repetitively with potential nephrotoxins such as cis-platinum, ifosfamide, or amphotericin.

There are potential problems with the method of testing for creatinine. Ketones could cause a modest increase in the creatinine level as tested by the picric acid assay, the so-called Jaffé reaction. There is also an enzymatic assay for creatinine, with creatininase, creatinase, sarcosine oxidase, and an imine dye colorimetric endpoint (Roche®). The enzymatic assays for serum creatinine using the Ektachem analyzer may be falsely elevated in the presence of flucytosine (9). There has been much recent discussion of the method for creatinine measurement. The ‘gold standard’ is the isotope dilution mass spectrometry method (IDMS). Other methods can be calibrated or adjusted to yield values consistent with this method. The method of testing the serum

Fig. 1.6 This shows the imprecise relationship between the serum (plasma) creatinine and the simultaneously measured inulin clearance. These cross-sectional data show that at an inulin clearance of 60 mL/min, for instance, the serum creatinine could be in the normal range, at 1 mg/dL, or it could be above that, at 1.5 mg/dL. But, importantly, this cross-sectional variability does not mean that the serum creatinine will remain deceptively stable in a subject whose kidney function declines. Thus, serial measurements of the simple serum creatinine level retain their utility in an individual. From Ovadia Shemesh, Helen Golbetz, Joseph P Kriss and Bryan D Myers (1985). Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney International*, **28**:830-8. Reprinted by permission from Macmillan Publishers Ltd.
creatinine affects the form of the MDRD equation. Even with use of the most precise method, some analytical and biological variability remains, such that formula-based measurements of the GFR may yield values that differ by 10–15 mL/min from the true value (10). In the case at the beginning of this chapter, there was a much greater difference between the formula-based estimate of the GFR and the measured kidney function because of the cancer-related loss of muscle mass.

Because the serum level of creatinine depends on its constant release from the creatine in the muscle, and because children have a lesser muscle mass compared to adults, the expected normal serum creatinine ranges are lower in children as compared to adults. These are shown in Fig. 1.7.

Conversion of the serum creatinine to its reciprocal, 1/serum creatinine, converts a non-linear indicator of the GFR to a linear one. Multiplication of 1/serum creatinine times 100 yields a number that approximates the GFR in absolute numbers, when the serum creatinine is expressed in mg/dL. This is valid for adults, but not for children, because their lesser absolute value of serum creatinine does not correspond to a higher-than-adult GFR. When the serum creatinine is expressed in μmol/L, one can create a similar quotient, as 1000/serum creatinine. One can graph the 100/serum creatinine quotient vs. time to gauge the pace of decline of kidney function, to test whether an intervention has changed the course of renal failure, or to predict the occurrence and timing of an end-stage renal disease, i.e. terminal renal failure. Fig. 1.8 shows the progressive loss of kidney function as 100/s creatinine vs. time in a patient who was treated with cis-platinum and ifosfamide, a combination that can be particularly nephrotoxic.

The correlation of the level of function with symptoms and signs is a useful concept. It is unlikely, for instance, that a patient with a serum creatinine of

![Graph](image-url)

**Fig. 1.7** This shows the usual range for the serum or plasma creatinine levels in mg/dL, depending on age, in children. A progressive increase is seen in the value corresponding to normal kidney function, which is the consequence of increasing muscle mass with age (multiply values by 88 for S.I. units).
1.5 mg/dL would be anemic because of an impaired kidney function. So, too, would it be very unlikely for a patient with a serum creatinine of 1.5 mg/dL to have itching related to an impaired kidney function. Fig. 1.9 shows the approximate correspondence of symptoms and signs to the serum creatinine level and to the approximate corresponding GFR. These levels and their correlations are valid for adults.

A number of formulas have been created to estimate the GFR without using a urine collection. The best known are the Cockcroft–Gault and the MDRD formulas in adults, and the Schwartz formula in children (11–13) (Table 1.3). The correlations of these formulas with the ‘gold-standard’ measurements of the GFR are very good. None of these formulas are valid in acute renal failure, however.

For the purposes of clinical follow-up, the simple serum creatinine or its reciprocal are important and useful indicators of the GFR. Formula-derived estimates of the GFR, such as the Cockcroft–Gault formula or the MDRD formula, are also useful. There are websites that permit the rapid calculation of the formula-based GFR estimates, such as www.hdcn.com. It is not established what is the best way to adjust drug doses for the actual GFR. In practice, the Cockcroft–Gault formula is often used to guide dose adjustments. The Food and Drug Administration (FDA) uses this formula to guide drug dosing. The Cockcroft–Gault formula is more immediately useful than the MDRD formula, because it can be quickly derived on a pocket calculator. Besides, there are over 30 years of experience with the Cockcroft–Gault formula and it is useful and accurate in cancer patients, for instance in the dose adjustment of carboplatin (14). The Wright formula has been developed for use in cancer patients (15). It is GFR = {[(6580 – (38*age)) * BSA * [1–(0.168*0 if male)]}/S

**Fig. 1.8** The evolution of kidney function in a recent case, as a function of time. This is graphed as 100/serum creatinine, latter in mg/dl, vs time. The steady decline of kidney function is shown, since the use of cisplatinum and ifosfamide. No other cause for chronic renal failure has been found in this case.
Glomerular filtration rate (GFR) is calculated using creatinine concentrations in plasma or serum, typically measured in μmol/L. This formula requires knowledge of the body surface area (BSA) and is thus not easy to use. Statistical analysis suggests that the MDRD formula may have a slight advantage over the Cockcroft–Gault formula for adjusting drug dosages according to the GFR, but this analysis did not use patient outcome data (16).

**Fig. 1.9** Scheme of the relationship between the level of kidney function and common signs and symptoms. Features that may be absent are in parentheses. Kidney function is shown as the serum, or plasma, creatinine, in mg/dL, and as the approximate corresponding glomerular filtration rate in mL/min (GFR). The downward directed arrows display the progressive nature of many kidney diseases.

Creatinine, in μmol/L. This formula requires knowledge of the body surface area (BSA) and is thus not easy to use. Statistical analysis suggests that the MDRD formula may have a slight advantage over the Cockcroft–Gault formula for adjusting drug dosages according to the GFR, but this analysis did not use patient outcome data (16).

**Table 1.3** Equations to estimate the glomerular filtration rate (GFR)

<table>
<thead>
<tr>
<th>Formula name</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault creatinine clearance</td>
<td>( \frac{[(140\text{-age})(\text{wt, kg})]}{72 \times \text{Scrat(mg/dl)}} \times 0.85 \text{ in women} )</td>
</tr>
<tr>
<td>MDRD GFR</td>
<td>( 175 \times (\text{Scrat(mg/dl)} ^{(-1.154)}) \times (\text{age, years}) ^{(-0.203)} \times 1.21 \text{ for blacks times 0.742 for women} )</td>
</tr>
<tr>
<td>Schwartz GFR/1.73 m^2</td>
<td>( \frac{\text{kL/serum creatinine(mg/dl)}, \text{ when L is body length in cm and}}{k \text{ is 0.7 in teenage boys and 0.55 in children and teenage girls}} )</td>
</tr>
</tbody>
</table>

Note: MDRD expressed for serum creatinine measurement made by or traceable to IDMS method.
The perceived shortcomings of the use of serum creatinine or the formula-dependent ways of estimating the GFR have prompted the study of alternative markers of the GFR. In recent years, cystatin C, a 13 kD endogenous protease inhibitor, has been studied as such a marker. There may indeed be a modest gain in sensitivity of detection for renal insufficiency when using cystatin C levels compared to those of creatinine (17–18). The elevation of serum cystatin C levels may begin at lesser degrees of reduction in the GFR than is the case for serum creatinine. But the measurement of cystatin C is four times as expensive as measuring serum (or plasma) creatinine. Thus, its greater sensitivity may not be cost beneficial. Finally, there are reports that the cystatin C levels may be increased in cancer patients in the presence of normal creatinine clearance (19). Thus, cystatin C measurements are not recommended for the assessment of kidney function in cancer patients.

**Tubular function**

The normal tubules, proximal and distal, act to reabsorb much of the glomerular filtrate, to achieve electrolyte and acid-base balance, and to adjust water excretion to maintain body tonicity. Abnormalities of the tubular function may be evident as changes in tubular excretion of normally reabsorbed substances, abnormalities of urine pH or acid excretion, or abnormalities of body tonicity.

Tests of β-2-microglobulin levels in blood or urine may be useful. This protein of 12 kD size, is freely filtered by the glomeruli, then almost completely reabsorbed by the proximal tubules (20). Its normal serum concentration is 1–2 mg/L, which may be raised in patients with multiple myeloma, without there being a change in kidney function. It is not surprising that this may occur because β-2-microglobulin is a component of the class I major HLA complex on the surface of all nucleated cells. The increased numbers of the malignant plasma cells would be directly responsible for higher blood levels of β-2-microglobulin. Increased urinary β-2-microglobulin, over its expected amount of less than 500 mg/24 h, may occur in a variety of disorders including aminoglycoside, cis-platinum, or radiocontrast nephrotoxicity, as well as, interstitial nephritis. This could occur because of the failure of tubular reabsorptive function.

The evaluation of the excretion of various cations and anions may be helpful in the evaluation and management of subjects with altered kidney function (3).

In health, 99% of the filtered sodium is reabsorbed by the tubules, such that the normal fractional excretion of sodium (FENa) is 0.01 or 1%, when expressed as a percentage. The FENa is the clearance of sodium divided by that
of creatinine, which may also be written as \[\frac{(UNa \times Screat)}{(Ucreat \times SNa)}\]. This number is multiplied times 100 to express it as a percentage. The FENa rises in chronic renal failure, such that the lesser nephron numbers can proportionally excrete more sodium, thus tending the body towards sodium balance. In the steady state, in chronic renal failure, the FENa, as a percentage, approximates the serum creatinine, in mg/dL.

The FENa also rises in acute renal failure, because the damaged tubular epithelium reabsorbs less of the filtered sodium. The FENa is below its expected value when there is under-perfusion of the kidneys, so-called pre-renal azotemia. This occurs because under-perfusion of the kidneys, as might occur in hemorrhage, is accompanied by activation of sodium-conserving mechanisms, including renal nerves and the renin-angiotensin system.

A significant adjunct to the calculation of the fractional excretion of sodium is the calculation of the fractional excretion of urea (21). Both creatinine and urea are filtered at the glomeruli, but urea is also reabsorbed in the distal nephron, in part to play a role in establishing a medullary concentrating gradient for the reabsorption of water. Thus, the normal urea clearance is only about 60 mL/min, in contrast to that of creatinine, which is 100 mL/min or more. The fractional excretion of urea is thus normally about 0.6, or 60%. It is calculated as \[\frac{(Urine \text{ urea nitrogen} \times Screat)}{(Ucreat \times BUN)}\], which is multiplied times 100 for its expression as a percentage. In states of hypotension or volume depletion, the reduction in urinary flow and the release of vasopressin cause enhanced urea reabsorption, thus reducing its fractional excretion. When the FEurea is 35% or lower, there is evidence of pre-renal azotemia. The calculation of the FEurea is useful if a patient is using diuretics, because diuretics will raise the FENa but they will not raise the FEurea.

Potassium is also freely filtered by the glomeruli, but in effect only 90% reabsorbed by the tubules. Thus in health, the FEK as a percentage is about 10%. The FEK rises in chronic renal failure, such that its value, in percent, approximates 10 times the serum creatinine in mg/dL. In a subject with hyperkalemia caused by kidney diseases or by drugs, such as ACE inhibitors or non-steroidal anti-inflammatory agents, the FEK would be lower than expected.

In the assessment of potassium excretion, the transtubular potassium gradient (TTKG) has been used. This is the potassium (K) clearance divided by the osmolar clearance, and gives an insight into the activity of the distal nephron, where K excretion takes place (22). There are, however, less data for the TTKG than there are for the FEK, and it is less easily understood.

Calcium excretion depends on its dietary intake, filtration of its diffusible fraction, the action of parathyroid hormone (PTH), and the sodium balance. In health, the total daily urinary calcium excretion should not exceed 4 mg/kg
in men and 3 mg/kg in women. The normal fractional excretion of calcium, is 0.02 and that calculation should use the diffusible, or the ionizable calcium, in the formula \[ \frac{UCa \times Scrat}{Ucreat \times SCa} \times 100. \] With moderate renal insufficiency, the FECa falls below 0.02 (or 2%, when expressed as a percentage) and does not rise above that level until the GFR is 10 mL/min or less (23). In hypercalcemia of malignancy, the FECa could be higher than normal because of a high filtered load, or, if mediated by PTH-related-peptide, could be lower (24). In a series of 31 subjects with solid cancers and hypercalcemia, 29 had low urinary calcium excretion, suggesting the role of a PTH-like substance in humoral hypercalcemia of malignancy (25).

The urinary excretion of phosphorus, as phosphate, is also dependent on its dietary intake, and also on parathyroid hormone. The fractional excretion of phosphorus is 15% in normal subjects, and rises in a linear fashion to over 50% in severe renal failure, with a GFR of 10 mL/min or less (23). Both the PTH and the PTH-related peptide will cause phosphaturia, i.e. elevation of the fractional excretion of phosphorus. In the rare syndrome of oncogenic osteomalacia, hyperphosphaturia, hypophosphatemia, and osteomalacia may occur in association with mesenchymal tumors and a humoral factor, now identified as the fibroblast growth factor 23 (26). This syndrome, and the tubular phosphate leak, should resolve on resection of the tumor. Hypophosphatemia, and a higher than normal fractional excretion of phosphate, was also reported as a side effect of imatinib therapy (27).

**Urinary acidification**

The excretion of the fixed acid of daily metabolism is achieved by tubular reclamation of filtered bicarbonate, by ammoniagenesis, and by excretion of titratable acid. The achievement of an acidic urine pH in itself is only a minor player in urinary acidification, given that the [H+] in urine is 100 micro-equivalents at a pH = 4. The urine ammonium excretion, NH4+, which is in milli-equivalents per liter, may be estimated by use of the urine anion gap, UNa + UK – UCl, which will have a greater negative value with greater amounts of urinary NH4+ (28). As a consequence of renal insufficiency per se, acidosis does not occur until the GFR is reduced to 25% of normal, i.e. less than 30 mL/min. That is because the renal tubular epithelium can increase ammoniagenesis fourfold. A greater than fourfold reduction in the renal tubular mass is thus required before there would be acidosis resulting from insufficient overall renal function. In a subject with acidosis, i.e. serum bicarbonate of 15 mmol/L or less, a urine pH greater than 6 would suggest a tubular acidification defect, as would a urine anion gap having a positive value.
Urinary concentrating ability

The maintenance of body tonicity, expressed as osmolarity, is ensured by the sensation of thirst and the regulation of water excretion. In health, urinary osmolarity may vary from 50 to 1000 mOsm/L, depending on the requirements for water excretion or water conservation by the kidneys. The urinary osmolarity can be measured by freezing point depression, or it can be estimated using the urinary specific gravity. The absolute value of the hundredths and the thousandths digit of the specific gravity may be multiplied 30 times as an estimate of a urinary osmolarity. For instance, a urinary specific gravity of 1.015 corresponds to an osmolarity of 450 mOsm/L.

Hyponatremia may occur as a manifestation of cancer (see Chapter 3). When that is mediated by an inappropriate and an unregulated secretion of vasopressin (anti-diuretic hormone), the urine osmolarity is inappropriately elevated, often higher than the osmolarity of the serum. It is not necessary to measure the vasopressin levels to make the diagnosis of the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). That is because most cases of hyponatremia depend on increased vasopressin levels. Their confirmation does not indicate the cause of the hyponatremia. The diagnosis of the SIADH, in particular, depends on the clinical exclusion of other causes of excess vasopressin. Mere extra-cellular volume depletion may cause a stimulation of vasopressin secretion and thereby cause water retention with subsequent hyponatremia. Such a problem may be identified by a urine sodium concentration of less than 30 mmol/L (29).

References


