Misapplications of Commonly Used Kidney Equations: Renal Physiology in Practice

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Equations for estimating GFR, quantifying urinary protein excretion, and assessing renal sodium handling are widely used in routine nephrology and general medical and surgical practice. If these equations are applied in circumstances inconsistent with the clinical situations for or extrapolated beyond the limits in which they were validated, clinicians can come to erroneous conclusions, which could be detrimental for patient care. This review uses clinical vignettes to demonstrate some of the common pitfalls that clinicians may encounter in the use of these equations and considers the physiologic principles underlying their use. Equations for assessing aspects of renal function should only be used in specific clinical situations, if the underlying assumptions regarding their calculations and values are satisfied.

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As physicians, we use equations to quantify physiologic and pathologic processes, such as measurement of renal function, estimation of proteinuria, and assessment of sodium handling, which are difficult to measure directly. Often, we do so without regard to the situation in which these formulas were initially derived and validated. By ignoring these important limitations, we may arrive at erroneous conclusions, risking compromise of the medical care we deliver to our patients. We use four case presentations to discuss common clinical settings in which the use and results of these equations may prove invalid.

Vignette 1–Use and Limitations of MDRD Formula

TN is a 46-yr-old, 95-kg African American man who presents for routine pre-employment physical examination. His past medical history is unremarkable, and he takes no medications. He denies use of tobacco, alcohol, and illicit drugs. He runs 5 d/wk and lifts weights at the local gym 3 d/wk. There is no personal or family history of kidney disease. Blood pressure (BP) is 112/74 mmHg, and there is no edema. The rest of the physical examination is unremarkable. His serum creatinine concentration (SCr) is 1.7 mg/dl, and estimated GFR (eGFR) is 56 ml/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD) equation. Urinalysis dipstick is negative for blood and protein, specific gravity is 1.017, and pH is 5.5. Microscopic analysis and renal ultrasound are normal.

Measurement of renal function, as GFR, is essential for patient care. Detection of diminution in GFR allows clinicians to identify and diagnose kidney disease, adjust medication dosages to prevent toxicity, evaluate the effectiveness of therapy for progressive disease, and assess the need for renal replacement therapy. The gold standard for determining GFR is inulin clearance (1), which is impractical for use in the clinical setting. Timed urine collection for measurement of creatinine clearance (CrCl) approximates GFR but is cumbersome and subject to improper collection. There is a reciprocal relationship between GFR and SCr in the steady state (2). Creatinine undergoes tubular secretion, and therefore CrCl generally overestimates GFR (1). However, SCr is currently the most expedient way to assess renal function in clinical situations.

Various equations have been devised to estimate GFR using SCr, including the Schwartz and Cockcroft–Gault formulas (3–5). Using data from the MDRD study (6), Levey *et al.* proposed the modified MDRD formula to estimate GFR (7). The objective of the multicenter, controlled MDRD trial was to study the effect of dietary protein restriction and strict BP control on the progression of chronic kidney disease (CKD) (6). Using data from 1070 subjects as a training sample, Levey *et al.* used stepwise multiple regression analysis to identify a set of variables that accurately predicted GFR, which was measured using ^{125}I-iothalamate, and subsequently validated the final equation in 558 patients. In this study, SCr was the most powerful predictor of GFR, accounting for 80% of the variation in GFR. It is important to note that the study subjects were primarily older (mean age 50.6 ± 12.7 yr), Caucasian (88%), and male (60%) with CKD (mean GFR of 39.8 ± 21.2 ml/min/1.73m^2 and mean CrCl 48.6 ± 24.5 ml/min/1.73m^2) (6). In fact, CKD, with a SCr ≥1.2 mg/dl for women and SCr ≥1.4 mg/dl for men, was an inclusion criterion for the study (6). The subjects recruited for the MDRD study were divided into two groups on the basis of severity of renal dysfunction. For Study A, the moderate renal disease group, GFR ranged from 25 to 55 ml/min/1.73m^2 at baseline and declined by 3.8 ± 4.2 ml/min/1.73m^2 per year

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during the follow-up period, which averaged 2.3 yr. The GFR in Study B, the advanced renal disease group, was 13 to 24 ml/min/1.73m^2 at baseline and decreased by 4 ± 3.1 ml/min/1.73m^2 per year during follow-up. Healthy subjects without renal disease, pregnant women, patients with >10 g of urinary protein excretion per day, transplant recipients, those older than 70 yr of age, those with body weight <80% or >160% of standard body weight, and insulin-dependent diabetes mellitus were specifically excluded from the MDRD study (6).

Subsequent studies have indicated that the MDRD formula underestimates GFR in subjects without renal disease. Verhave *et al.* studied 850 patients with SCr <1.5 mg/dl and compared eGFR calculated using the MDRD equation to GFR measured by a continuous infusion of technetium 99m-diethylene triaminopentaacetic acid (8). The MDRD equation significantly underestimated GFR by approximately 10% (8). Rule and colleagues attempted to validate the MDRD formula by comparing GFR estimated using the MDRD formula with iothalamate clearance (9). They confirmed the validity of the MDRD equation in 320 patients with evidence of CKD, such as proteinuria, abnormal urinary sediment, or elevated SCr. In this cohort, the MDRD formula performed reasonably well, underestimating GFR by 6.2 ± 1.6%. However, in 580 healthy subjects who had iothalamate clearance as part of a kidney donor evaluation, the MDRD underestimated GFR by approximately 30%. They discovered a calibration bias in the measurement of SCr in the MDRD laboratory, but adjustment of the SCr for this bias did not improve the accuracy of the MDRD equation in healthy subjects. They postulated that the MDRD equation is a poor predictor of GFR in healthy individuals without kidney disease because fluctuations in SCr are more dependent upon dietary protein intake and muscle mass than they are in CKD patients, who are often chronically ill with muscle atrophy and may be on protein-restricted diets. In such individuals, SCr may more likely reflect GFR. The MDRD study excluded patients with weight greatly exceeding their ideal weight. Thus, because the MDRD equation does not accurately estimate GFR in healthy subjects, use of the MDRD equation should be limited to patients with CKD, consistent with the population in which the formula was validated (9).

It is not surprising that the MDRD equation has limitations because it is based on SCr. An ideal marker of GFR would be freely filtered but not reabsorbed, secreted, or metabolized by the tubules. Because creatinine undergoes tubular secretion, it is not an ideal GFR marker (1). In addition, other factors can affect circulating creatinine levels and daily creatinine production. First, creatinine is released by muscle cells, so creatinine production and delivery to the extracellular fluid is dependent on the patient's muscle mass (1,2). Estimating equations therefore may be imprecise in patients with chronic illness or HIV infection (10). Similarly, estimating equations may not be accurate in patients with ascites, congestive heart failure, or nephrotic syndrome because of abnormalities in muscle mass, volume of distribution, or renal hemodynamics (11–13). Race and gender are important determinants of muscle mass. At a given GFR, SCr is higher in blacks compared with Caucasians and in men compared with women (7,14). Although variations by gender and black/nonblack race are accounted for in the MDRD formula, it does not estimate values for other races/ethnicities. For example, several studies have shown that the MDRD and Cockcroft–Gault equations overestimate GFR in Asians, and it is proposed that this may be related to different muscle mass in patients of Asian ethnicity (15–17). Elderly or malnourished patients, who are expected to have a decline in muscle mass, may have significant renal dysfunction even when the SCr is within the normal range (1,2,8). Patients over 70 yr of age were excluded from the MDRD study. Conversely, obesity may be associated with hyperfiltration, and in such patients, use of weight can overestimate muscle mass (18). In addition, certain drugs such as trimethoprim and cimetidine interfere with tubular secretion of creatinine and can increase SCr without changing GFR (1). Finally, consideration should be given to body size. A fundamental advance in GFR measurement has been normalization for body size or surface area. It is intuitive that larger individuals require higher GFR to clear metabolic wastes, compared with smaller individuals. To take the extreme example, a mouse requires a much lower GFR than an elephant (19). Dietary intake varies with mass as well. Studies across mammalian species indicate that GFR tends to be proportional to metabolic rate, a parameter that is impractical to measure clinically (19). The MDRD formula reports eGFR normalized to 1.73 m^2 body surface area (BSA) and therefore, unlike the Cockroft–Gault formula, its estimation does not require knowledge of body mass. However, some have suggested BSA is not the most appropriate index and that normalization for extracellular fluid volume (which, like BSA, can be estimated from height and weight) may be superior (20). However, normalization for BSA has gained widespread acceptance. Because many factors affect the level of SCr, equations that use SCr to estimate GFR should be used with care in the populations in which they were validated.

In the 95-kg patient described in Vignette 1, a 24-h urine collection showed a creatinine excretion of 2200 mg/24 h, with a urinary protein excretion of 95 mg/24 h. Calculated CrCl was 91 ml/min. Because this patient does not have CKD, the use of the MDRD formula is not appropriate.

Vignette 2–Estimating GFR in Pregnancy

LS is a 29-yr-old Caucasian woman who presents for her first prenatal visit with an obstetrician. She is approximately 12 wk pregnant on the basis of her last menstrual period. The BP was 95/60 mmHg, abdominal exam was consistent with 12-wk gravid uterus, and there was no peripheral edema. Routine laboratories showed that her SCr was 0.8 mg/dl. The resident calculated her eGFR as 90 ml/min/1.73m^2 using the MDRD formula.

Many physiologic changes occur in the kidney during pregnancy. GFR increases by 40 to 65% as a result of an even larger increase in renal blood flow (21). This increase occurs by the early second trimester and is maintained until the middle of the third trimester when renal blood flow begins to decline toward prepregnancy levels. In addition, plasma volume expands by 30 to 50%, resulting in hemodilution. As a result of both of these

changes, SCr levels fall by an average of 0.4 mg/dl in pregnancy compared with prepregnancy levels (22).

Women with moderate to severe decrements in GFR are at increased risk for premature labor, preeclampsia, intrauterine growth restriction, neonatal death, and other maternal and fetal complications (23–25). Thus, it is important to accurately assess renal function in this patient population so that appropriate monitoring is undertaken. Recently, two prospective studies have reported, for the first time, on the accuracy of GFR-estimating formulas in pregnant women. Smith *et al.* compared eGFR calculated using the MDRD formula with inulin clearance in 24 healthy women, both during and after pregnancy (26). They found that GFR estimated by the MDRD formula closely approximated inulin clearance in the postpartum period (bias 11.9 ml/min). However, during pregnancy, the MDRD formula underestimated true GFR on the basis of inulin clearance by more than 40 ml/min. It is important to note that the results of the inulin clearances in this study were reported in milliliters per minute, without correction for BSA, which may account for some of the discrepancy between the inulin clearance and the MDRD eGFR.

Alper and colleagues studied GFR estimation in a cohort of 209 pregnant women with preeclampsia (27). Similarly to Smith *et al.*, they found the MDRD formula underestimated GFR as compared with CrCl, although the degree of bias was less (12 to 20 ml/min). Again, eGFR (ml/min/1.73 m^2) was compared directly to CrCl (ml/min), potentially accounting for some of the discrepancy. It is also important to note that, in both studies, the mean GFR of study subjects was well over 60 ml/min, a GFR range in which the MDRD formula is known to be biased in the nonpregnant population. There are currently no published data on the accuracy of the MDRD formula in pregnant subjects with GFR <60 ml/min. Given these issues, 24-h urine collection for CrCl remains the gold standard for GFR estimation in pregnancy.

Although a SCr of 0.8 mg/dl as described in the Vignette is within the normal range for nonpregnant women, it may reflect diminished renal function in the setting of pregnancy. A 24-h urine collection for determination of CrCl should be performed whenever renal insufficiency is suspected in a pregnant patient.

Vignette 3–Equations in Acute Kidney Injury

JB is a 35-yr old Asian man with neurogenic bladder who presented to the emergency room with a 3-d history of decreased urine output. He frequently has urinary tract infections and recently completed a course of therapy with ciprofloxacin. At admission, his SCr was 7.1 mg/dl, increased from a previously stable SCr of 0.9 mg/dl. During the hospitalization, his SCr rose on a daily basis, peaking at 13.1 mg/dl, at which time his eGFR based on the MDRD formula was 6 ml/min/1.73m^2 and his urine protein:creatinine ratio was reported by the medical student to be 4.5. The BP was 135/87 mmHg, he had no peripheral edema, and his serum albumin concentration was 4 g/dl. Microscopic examination of urine sediment showed many white blood cell clumps, and the patient had eosinophilia and eosinophiluria. These findings were consistent with acute interstitial nephritis, but the student focused her differential diagnosis on the causes of acute renal failure in the setting of nephrotic syndrome.

Formulas that use the SCr to estimate GFR, such as the MDRD (7) and Cockroft–Gault (3) equations, were derived in subjects with chronic, not acute, kidney disease. Furthermore, the theoretical underpinnings of using a single serum creatinine measurement to estimate GFR rely on the assumption that a patient is in steady state with regard to creatinine production and excretion—an assumption that does not hold for patients with acute kidney injury (AKI). The SCr represents the balance between creatinine production and excretion, distributed in a perhaps dynamically changing volume. As an example, a 70-kg man would be expected to have a daily creatinine production of 18 to 25 mg/kg (28). If this patient developed AKI with reduction in GFR to zero, assuming that the creatinine produced is completely distributed in a space approximately equal to 50 to 60% of weight, or the approximate volume of the total body water (about 35 to 42 L in this patient) (29), his SCr would be expected to rise by up to 3.3 to 4.0 mg/dl per day. In practice, observed increases are less, because creatinine production may be diminished in critically ill patients, and renal function does not usually decrease to zero in patients with AKI. Changes in SCr lag behind changes in GFR in the setting of AKI. The improvement in GFR often precedes the decline in SCr by days (30). Mathematical models have been proposed to predict GFR on the basis of changes in SCr during AKI, but are not practical for clinical applications (30). Nevertheless, in the situation described in the vignette, the SCr at any given point in time does not reflect the GFR as it would for a patient with stable, but impaired, renal function. Thus, the MDRD and other formulas based on SCr should not be used to estimate GFR in the setting of AKI when SCr is fluctuating.

Proteinuria is usually a sign of renal injury, and persistent proteinuria may be a sign of ongoing renal damage. Abnormal albuminuria is a reflection of glomerular basement membrane permeability dysfunction or ineffective tubular reabsorption (31,32). Urine dipsticks are commonly used to screen for proteinuria, but the sensitivity and specificity of this test vary widely so confirmation is needed (33). Urinary protein excretion may be influenced by a variety of factors, such as diet, activity level, and fever, and urinary protein concentrations may vary significantly during the day and from day to day because of changes in water intake and rate of diuresis, making random urinary protein concentrations less useful. The gold standard for quantification of proteinuria is the 24-h urine collection, but timed urine collections are cumbersome and may be difficult to obtain accurately.

Use of the urine protein:creatinine ratio has become well accepted (34,35) and the urinary albumin:creatinine ratio is now recommended by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for detection and monitoring of proteinuria in patients with CKD (36). The urinary protein:creatinine ratio is useful because it provides a point estimate of proteinuria relative to creatinine excretion, which is typically constant. In contrast to the urinary protein concentration, the protein:creatinine ratio

controls for the extent of renal tubular fluid reabsorption. The spot urinary protein:creatinine ratio correlates well with 24-h urine protein excretion in the steady state (34), particularly if first morning urine samples are used, and is much more convenient to obtain. The urinary protein:creatinine ratio is an extremely powerful tool with empiric data to support its use in diverse clinical circumstances (37,38). Sensitivities and specificities for the ratio have ranged from 69 to 96% and 41 to 97%, respectively, whereas positive predictive and negative predictive values have ranged between 46 and 95% and 45 and 98%, respectively (37). It appears the urine protein:creatinine ratio has been used preferentially in clinical trials (37).

Clinically, nephrologists often use a rule of thumb that the urine protein:creatinine ratio—a unitless number—approximates the 24-h protein excretion in grams. This approximation is based on the assumption that the 24-h urine creatinine excretion is approximately 1000 mg, as the following derivation shows:

$$24hUPro(mg/d) = UPro(mg/dl) \times V(dl/d), \quad (1)$$

where *UPro* is the urine protein concentration and *V* is the urine volume.

Similarly, 24-h creatinine excretion is calculated by:

$$24hUCr(mg/d) = UCr(mg/dl) \times V(dl/d) \quad (2)$$

Rearranging and substituting for *V* in equation 1 gives:

$$24hUPro(g/d) = \frac{\mathrm{U}Pro\ (mg/dl)}{UCr\ (mg/dl)} \times 24hUCr \quad (3)$$

If 24-h urinary creatinine excretion (*24hUCr*) is assumed to be 1 g/d, then the 24-h urinary protein excretion in grams per day is approximately equal to the unitless protein:creatinine ratio.

However, this assumption is inaccurate in at least two common clinical circumstances: extremes of muscle mass and AKI. Because creatinine production is proportional to muscle mass (approximately 18 to 25 mg/kg body wt/d for men and 16 to 22 mg/kg body wt/d for women) (28), 24-h creatinine excretion is often much higher than 1000 mg/d. In fact, it is in the range of 1400 mg per day for a 70-kg man. In such individuals, the urinary protein:creatinine ratio may grossly underestimate the 24-h protein excretion. The patient's muscle mass also should be taken into account when equating the urinary protein:creatinine ratio to 24-h protein excretion.

Second, in AKI, urinary creatinine excretion is dramatically but variably decreased until a new steady state is achieved (30). The urinary protein:creatinine ratio provides information on the urinary protein excretion relative to the urinary creatinine excretion. If the latter is extremely low because of AKI, the ratio will overestimate 24-h protein excretion. This may result in misclassification of patients with AKI as having nephrotic-range proteinuria, confounding the diagnostic process.

In addition, urinary protein excretion may diminish in patients with AKI. Hence, the urine protein:creatinine ratio should not be applied to subjects with AKI. Few data exist regarding changes in urinary protein excretion in patients with AKI, with or without pre-existing diabetic nephropathy or nephrotic syndrome. Backleak, or decrease in the filtered protein load, could contribute to a decrease in urinary protein excretion in patients with AKI (39). Velosa and colleagues attempted to decrease urinary protein excretion in patients with the nephrotic syndrome by decreasing GFR using nonsteroidal anti-inflammatory drugs (40). In the vignette presented, quantification of proteinuria using the urinary protein:creatinine ratio should be deferred until the episode of AKI has resolved and the patient is once again in steady state with regard to creatinine production and excretion.

Empirical studies have validated the urine protein:creatinine ratio for estimation of proteinuria in several clinical settings. Meta-analysis has confirmed that most studies showed strong correlation between urine protein:creatinine ratio and 24-h urinary protein excretion ($r > 0.9$ in most cases) despite differences in pathologic conditions studied (37). Xin *et al.* confirmed a strong correlation between results of 24-h urine collection and the urine protein:creatinine ratio ($r = 0.841$, $P < 0.001$) for patients with CrCl >10 ml/min (41). However, the correlation was nonsignificant when CrCl was <10 ml/min ($r = 0.002$, $P = 0.994$) (41).

Lane *et al.* demonstrated a logarithmic relationship between the urine protein:creatinine ratio and 24-h urinary protein excretion ($R^2 = 0.85$, $P < 0.0001$) (42). The urinary protein:creatinine ratio significantly underestimates the 24-h protein excretion at increasing levels of proteinuria, being particularly inaccurate when urinary protein excretion exceeds 1 g/d (33,42).

Therefore, the urine protein:creatinine ratio should be interpreted with caution in AKI, in severe CKD, and at very high levels of urinary protein excretion. Thus, the role of the urinary protein:creatinine ratio is two-fold. First, it may be used in place of the 24-h urine collection to confirm the presence or absence of clinically significant proteinuria in many patients. It allows for broad classification of patients' level of urinary protein excretion (*i.e.*, normal/none, low-grade, or nephrotic-range proteinuria), providing diagnostic information. Second, the urinary protein:creatinine ratio allows the clinician to conveniently follow trends in urinary protein excretion over time in individual patients in steady state as a way to assess progression of renal disease or response to therapy. When an accurate determination of protein excretion is required, the 24-h urine collection should be used.

Vignette 4–FENa in CKD

NF is a 65-yr-old Caucasian woman with chronic interstitial renal disease who presented to the emergency room with weakness and a 3-d history of diarrhea. She has noted little change in urine output. BP and pulse were 108/88 mmHg and 98 beats/min supine, respectively, and 84/60 mmHg and 120 beats/min standing, respectively. The patient had dry mucous membranes, tenting of the skin, and no peripheral edema. Serum sodium was 157 mEq/L and her SCr was 3.4 mg/dl. Her baseline SCr in the electronic medical record was found to be 1.7 mg/dl. On admission, the urinalysis showed trace proteinuria, specific gravity 1.010, and a bland microscopic analysis. Urine output during the first 4 h of observation, before admission and institution of any therapy, was 500 ml. Urine sodium concentration was 50 mEq/L,

and urine creatinine concentration was 75 mg/dl. The medical student used urinary parameters to make a diagnosis of acute tubular necrosis (ATN).

The fractional excretion of sodium (FENa) is a fundamental parameter for nephrologists. The FENa is the proportion of the filtered sodium that is excreted in urine:

$$FENa = \frac{Na\ excreted}{Na\ filtered} = \frac{UNa \times V}{SNa \times GFR} \quad (4)$$

where *V* is urinary volume, *UNa* is urinary sodium concentration, and *SNa* is serum sodium concentration. Assuming the GFR is approximately equal to the CrCl:

$$GFR = \frac{UCr \times V}{SCr} \quad (5)$$

And substituting for *GFR* in equation 4, we have:

$$FENa = \frac{UNa\ (mg/dL) \times V}{SNa\ (mg/dL) \times \frac{UCr \times V}{SCr}} \quad (6)$$

Cancelling the urinary volume (*V*) and rearrangement yields the familiar equation:

$$FENa = \frac{UNa\ (mg/dL) \times SCr\ (mg/dL)}{UCr\ (mg/dL) \times SNa\ (mg/dL)} \quad (7)$$

The FENa can also be conceptualized as the ratio of the sodium clearance to the CrCl (42).

$$\frac{\frac{UNa \times V}{PNa}}{\frac{UCr \times V}{PCr}} \Rightarrow \frac{\frac{UNa}{PNa}}{\frac{UCr}{PCr}} \quad (8)$$

In this formulation, urinary volume (*V*) cancels out, resulting in a formula equivalent to that given in equation 7.

The typical range for the FENa varies based on dietary sodium intake and can be approximated by a simple thought experiment. The Institute of Medicine has set the recommended upper limit of daily sodium intake at 2.3 g (100 mEq) for adults (44); however, the typical American diet contains more than 3.5 g (150 mEq) of sodium per day (45). If the GFR is 125 ml/min (180 L/d), and the serum sodium concentration is 140 mEq/L, the daily filtered load of sodium is 25,200 mEq (the product of these factors) because sodium is completely filtered by the glomeruli. If a patient has normal renal function and is in steady state, without edema, sodium intake equals sodium excretion. Thus, a typical ratio of sodium excretion to the filtered load can be approximated at 150 mEq/25,200 mEq, or about 0.6%. The critical assumptions in this analysis are that the patient is in sodium balance, is not experiencing sodium retention, is not taking diuretics, and has normal renal function.

The FENa is typically measured in the setting of AKI to distinguish between prerenal azotemia and ATN (46,47). In a patient without kidney disease who is volume depleted, decreased renal perfusion stimulates physiologic mechanisms to increase sodium and water reabsorption, resulting in a decrease in urinary sodium excretion. Thus, a low value of the FENa suggests a prerenal etiology in a patient with oliguric AKI with pre-existing normal renal function. In such a case, a FENa >1% is always pathologic, suggesting the impairment of tubular ability to reabsorb sodium. The classic differentiation by urinary indices of prerenal azotemia from ATN rests on these assumptions (46,47).

When interpreting the FENa, it is also necessary to consider the level of renal function and whether the patient has pre-existing CKD to determine if sodium is being appropriately conserved. Patients with CKD typically maintain sodium balance until late stages of the disease (48). The increase in the fractional excretion of a given substance in patients with chronically decreased renal function in the steady state is predicated by the mathematics of the equation and is verified by clinical experience (48). Consider a patient with pre-existing CKD with a GFR of 45 L/d (one-quarter of normal) ingesting a typical sodium diet of 150 mEq/d, contrary to the suggestions of the nephrologist. Such a patient would be expected to have a usual FENa of about 2.4% [(150 mEq Na/d)/(45 L/d × 140 mEq/L Na)], if he or she were in sodium balance, approximately 4 times that of a person with normal renal function on a typical sodium intake. Similar findings have been demonstrated in animals with experimentally induced chronic decrements in GFR (49).

There are few data regarding the renal tubular reabsorptive responses in patients with CKD and volume depletion. In CKD patients who are abruptly salt-restricted, urinary sodium excretion transiently exceeds sodium intake until a new steady state characterized by diminished sodium excretion is established over time (50). Similar findings were noted in animals in experimental settings (49).

We can conservatively estimate NF would have an eGRF of 32 ml/min/1.73m^2 at her steady state with a SCr of 1.7 mg/dl, determined by the MDRD formula. This is not the case, given the patient's presentation. Given the caveats expressed in Vignette 3, we can assume that at presentation to the emergency room, with AKI superimposed upon CKD, the level of GFR is at most approximately half of baseline, or about 16 ml/min/1.73m^2. Using the reasoning described above for a CKD patient in sodium balance, her baseline FENa can be estimated at approximately 2.3% (150 mEq Na/d/46.1 L/d × 140 mEq/L Na). The clinical presentation, physical examination, and laboratory examination of the patient are consistent with volume depletion. Although abnormal urinary sodium and water losses may contribute to the development of prerenal azotemia in this patient with interstitial renal disease and tubular dysfunction, the measured FeNa of 1.45% represents some component of appropriate tubular reabsorption of sodium, given this patient's usual level of renal dysfunction. The findings are consistent with the patient presenting in a nonsteady state in transient sodium imbalance (50).

Exceptions to these generalizations should be noted. A low FENa can be present in patients with presumably normal pre-existing renal function with oliguric AKI with contrast nephropathy (51,52), rhabdomyolysis and hemoglobinuria (51,53), and urinary tract obstruction (47). In contrast, metabolic

alkalosis in patients with volume depletion and prerenal azotemia may be associated with a high FENa, because the excretion of relatively nonreabsorbable anions obligates inappropriate natriuresis (54). The use of diuretics can be associated with levels of FENa >1% in patients with prerenal azotemia (55). Evaluation of the fractional urea excretion may provide a more sensitive and specific marker of prerenal azotemia in such patients (55). Its use in patients with CKD, volume depletion, and AKI however, remains to be explored. In addition, because the patient in the vignette is not oliguric in the face of clinical signs of volume depletion, a consequence of her renal tubular disease, the assumptions outlined in the classic study of Miller *et al.* have not been met (47).

Summary

A classic article suggested evaluation of renal parameters is most useful in specific contexts, with cognizance of the indications for and limitations of the tests in well delineated clinical circumstances (54). For instance, the FENa is primarily useful in patients with AKI and oliguria, in the absence of metabolic alkalosis and excretion of nonreabsorbable anions. Although new parameters have come into clinical use, the guiding principles of nephrologic practice remain the same. Tools for assessing aspects of renal function are only useful when the underlying assumptions are met in a specific clinical situation. The GFR-estimating equations generated from the MDRD study have limitations and can be used with confidence, but only in populations in which they have been studied and validated. In particular, they cannot be used with confidence in patients with normal renal function, suggesting that some of the recent epidemiologic literature regarding associations of laboratory values with CKD may have flaws. The urine protein: creatinine ratio cannot be used with confidence in patients with AKI and unknown as well as nonsteady state urine creatinine excretion. In addition to well known caveats regarding the use of the FENa, consideration of the patient's baseline level of renal function is critical in establishing meaningful cutoffs for clinical decision making.

Disclosures

None.

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