The Role of the Laboratory in Evaluation of Kidney Function

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Evaluation of kidney function by physical examination alone is imprecise and limited. Quantitative, reproducible assessment of kidney function requires laboratory measurements of substances in plasma and urine, followed by reliable interpretation. Thus, glomerular filtration, urine protein excretion, water metabolism, and electrolyte disturbances may be quantified. These data are very useful in the single and serial assessment of patients with kidney disease and in evaluation of the effects of treatment.

This review is devoted to a consideration of the role of the clinical laboratory in the evaluation and care of patients with kidney disease as well as the evaluation of kidney function that is a necessary component of the initial assessment of all patients. Kidney function declines as patients age. Many drugs are dependent on urinary excretion for the termination of their effects, and adjustments in drug doses or dosing intervals may be required as kidney function diminishes (1). Many, if not most, patients with significant kidney disease have no symptoms, and patients with kidney disease almost never have symptoms or signs of kidney disease that permit even a gross quantitative assessment of the degree of impairment of kidney function. Thus, physicians are continually dependent on the clinical laboratory for measurements that permit the physiological and pathophysiological evaluation of kidney function.

Glomerular filtration is the initial event in the formation of urine. Proteinuria, most often reflecting loss of the normal glomerular impermeability to filtration of plasma proteins, is an early sign of kidney disease. Impairment of the normal capacities of various segments of the renal tubules to reabsorb water and electrolytes to effectively maintain the volume and composition of body fluids within normal limits may also be key manifestations of kidney dysfunction. Accordingly, the following sections are devoted to a consideration of laboratory measurements in the assessment of glomerular filtration rate, of proteinuria, and of the role of the kidney to maintain normal serum osmolality and electrolyte concentrations by the appropriate excretion of water and ions.

We will not discuss other important laboratory methods in the evaluation of urinary tract disease, including (a) examination of the urine sediment to detect dysmorphic erythrocytes (2), erythrocyte and hemoglobin casts in the diagnosis of glomerulonephritis or benign familial hematuria (3), and examination of the urine sediment for leukocytes and bacteria; (b) urine cultures in the evaluation of urinary infection; (c) cytological examination of the urine sediment for neoplastic cells; (d) use of radioisotope imaging in the evaluation of renal blood flow; nor (e) ultrasonography and other radiographic techniques with contrast agents to evaluate obstruction to urine flow and the anatomy of the urinary tract.

24-Hour Urine Collections

Measurement of 24-h urinary excretion rates of a wide range of substances is essential in the evaluation and follow-up care of many patients with kidney diseases. The laboratory can assist in this effort by providing physicians and their patients with proper containers and appropriate preservatives, if required, and clear and simple instructions for 24-h urine collections. Patients should be instructed to begin 24-h urine collections at a fixed time by voiding into the toilet and then saving all of the urine they pass thereafter, including urine collected at exactly the same time 24 h later. Patients should be reminded to void and collect their urine before defecation because of the frequent occurrence of inadvertent voiding during defecation. The laboratory can also assist in determining whether a 24-h urine collection is complete for an individual patient by always measuring the creatinine concentration as well as the volume of the urine and calculating the 24-h creatinine content of the specimen. The laboratory should request that patients submitting 24-h urine samples provide their weight, sex, and age, in addition to their name for identification of the specimen. Creatinine excretion increases primarily with weight (muscle mass), is lower among women, and decreases with age (4):

Men: 0.17–0.23 mmol (19–26 mg) of creatinine per kg of body weight daily
Women: 0.12–0.19 mmol (14–21 mg)/kg body wt. daily

Thus, one can compare a measured creatinine content (excretion rate) of a 24-h urine sample with a predicted value for an individual patient, thereby detecting 24-h collections that are either incomplete or more than complete. Incomplete collections occur most often because patients forget they are to collect all of their urine during the 24-h period. More-than-complete collections appear to occur most often because patients misunderstand the instructions and include the urine voided at the starting-time of the collection. Additional clinical data may be required to assess the completeness of 24-h
urine collections because, even when 24-h urine samples are accurately collected, creatinine excretion rates will be relatively low in relation to body weight, sex, and age among markedly obese patients and among patients with muscle-wasting due to malnutrition, intrinsic muscle diseases, or neurological diseases that produce extensive muscle denervation.

Some examples of the utility of 24-h urine collections include:

- assessment of dietary Na intake. Urinary Na excretion in the acute steady-state accurately reflects the diet because urinary Na represents nearly all excreted Na; normally formed feces contain <3 mmol of Na per day and skin losses of Na average about 10 mmol/day in the absence of visible sweating.
- assessment of dietary protein intake. Urinary urea-nitrogen represents 85% or more of the nitrogen derived from protein catabolism. The urinary excretion of other nitrogen-containing compounds is relatively small (ammonium, creatinine, uric acid, amino acids), fecal nitrogen excretion is only about 1 g/day, and an approximately equivalent amount of nitrogen is lost by desquamated skin and the growth of hair and nails.
- evaluation of patients with nephrolithiasis for hypercalcuria, hyperoxaluria, hypocitraturia, hyperuricosuria, cystinuria, etc.

Glomerular Filtration Rate

The glomerular filtration rate (GFR) is estimated by the clearance method. That technique measures the theoretical volume of plasma that must be completely "cleared" of a substance, excreted only by glomerular filtration, per unit time, at the prevailing plasma (P) concentration of the substance that would account for the quantity of the substance excreted in the urine (U) during the same time. The substance must be freely filtered across the glomeruli and must be neither reabsorbed nor secreted by the tubules. The fructose poly-saccharide inulin, [125I]iothalamate, and 99mTc-labeled diethylenetriaminepentaacetic acid meet these requirements and are often used in research studies.

Consider, for example, the clearance of inulin:

\[ C_{\text{inulin}} \text{ (GFR), mL/min} = \frac{U_{\text{inulin}}, \text{ g/L} \cdot \text{volume of urine excreted, mL/min}}{P_{\text{inulin}}, \text{ g/L}} \]

Such measurements require continuous intravenous infusions or injections to sustain stable blood concentrations and three or four accurately timed short urine collections during water diuresis. The complexity and expense of such measurements make them impractical for the initial and serial evaluation of most patients.

Creatinine is an end product of muscle creatine metabolism and is added to body fluids at a rate that is constant for the individual in proportion to muscle mass. This creatinine is mainly disposed of by urinary excretion. Moreover, creatinine excreted into the urine is largely filtered and is thus an approximate marker of glomerular filtration, as is inulin. In health, only 10% to 20% of creatinine excreted into the urine is secreted by the tubules (C_{\text{creatinine}}/C_{\text{inulin}} = 1.1 to 1.2).

As illustrated in Figure 1, a review of early publications demonstrates that simultaneously measured creatinine clearances, usually during water diuresis, were closely correlated to simultaneous measurements of GFR, as estimated by the clearance of infused inulin. GFR ranged from 160 mL/min in normal subjects to 3 mL/min in patients with far-advanced kidney disease (5-9).

In a more recent study, in which GFR was measured with inulin or [125I]iothalamate and C_{\text{creatinine}} was measured simultaneously (10), C_{\text{creatinine}} was closely correlated to GFR (r = 0.90) as GFR ranged from 16 to 175 mL/min (Figure 2). Much more commonly, however, creatinine clearance is estimated from measurements of the creatinine concentration and the volume of a 24-h urine collection, together with measurement of the creatinine concentration in plasma or serum. This technique requires that patients make precisely timed and complete 24-h urine collections. Because this effort is difficult and often improperly performed, the quantity of creatinine present in the urine collection frequently fails to meet or exceed accepted standards.

Using accurate 24-h urine collections and measurements of serum creatinine concentrations in a large number of subjects, Cockcroft and Gault (11) developed a widely used and exceedingly effective relationship to estimate creatinine clearance from only the measurement of creatinine concentration in plasma or serum, and also taking into account age, weight, and sex:

\[ \text{Men: } C_{\text{creatinine}}, \text{ mL/min} = \frac{(140 - \text{age, yrs}) \cdot (\text{wt, kg})}{7.2(P_{\text{creatinine}}, \text{ mg/L})} \]

![Fig. 1. Creatinine clearances in relation to inulin clearance in health and kidney disease. Adapted from data in refs. 5-9](image-url)
Creatinine clearance rates based on the Cockcroft and Gault formulas have now also been compared with formal measurements of GFR obtained with inulin or [131I]iothalamate (Figure 3) (10). The correlation is very good \( r = 0.84 \) for GFR values from 16 to 175 mL/min, the range of greatest clinical interest. These considerations indicate that clinical laboratories can readily provide clinicians with close estimates of GFR based only on measurement of the plasma creatinine concentration, together with knowledge of the patient's age, body weight, and sex. A note of caution is, however, necessary with respect to the use of the Cockcroft and Gault formulas. When body weight or muscle mass in relation to total body weight deviates markedly from normal, as among patients with marked muscle wasting due to malnutrition, intrinsic muscle disease, or muscle denervation (spinal cord injury or severe neuropathies), creatinine production will be greatly reduced. Similarly, among markedly obese patients, creatinine production will also be low relative to total body weight. In any of these circumstances, one must measure the actual creatinine clearance, generally by using several measurements of 24-h urinary creatinine excretion and several measurements of creatinine concentration in plasma or serum (12).

The Cockcroft and Gault formulas may be used to monitor the evolution of GFR with time. Should a subject's weight not be recorded, the plasma creatinine alone will still be of use because the reciprocal of the plasma creatinine is linearly related to the GFR. This quotient may be multiplied by 100 to obtain a number similar to and directly correlated with the GFR in mL/min. A graph of 100/plasma creatinine vs time will show the temporal evolution of GFR (Figure 4). Thus, if the plasma creatinine concentration increases from a normal value of 10 mg/L to 20 mg/L, ~50% of GFR has been lost; when the plasma concentration reaches 40 mg/L, ~75% of GFR has been lost. Such a graph may allow evaluation of efficacy of therapy—the slope will be changed—or may predict when renal replacement therapy (dialysis) may be required (13, 14). The utility of such a graph will be enhanced if extended over the longest time available. When, in the follow-up of a patient with established kidney disease, the slope of creatinine clearance or of 100/plasma creatinine vs time becomes more negative, physicians should be urged to search for additional complications of kidney disease such as obstruction, renal artery stenosis (15), or superimposed glomerulonephritis (16).

Proteinuria

Proteinuria is a hallmark of kidney disease. Thus, detection of proteinuria is necessary for the recognition of most kidney diseases. In addition, quantification of proteinuria may be useful in categorizing kidney disease and in monitoring treatment. In health, the fixed negative charges on the normal components of the glomerular capillary wall (endothelial cell, basement membrane, and epithelial cell) create an effective bar-
rrier to the filtration of plasma proteins. Small amounts of protein that may be filtered, particularly β-globulins, can be reabsorbed by proximal tubule cells (17). In addition, various cells along the nephron may secrete proteins into the tubular fluid, e.g., nephrocalcin secreted by proximal tubule cells (18) and Tamm–Horsfall mucoprotein secreted by cells of the thick ascending loop of Henle (19). Thus, normal urine contains a mixture of proteins, approximately two-thirds of which have the electrophoretic mobility of globulins and the remainder that of albumin, the latter representing the small quantity of filtered albumin that has escaped reabsorption.

Abnormally increased quantities of protein may appear in the urine as a consequence of three major mechanisms. Most commonly, proteinuria is the result of glomerular disease. The normal permeability barrier of the glomerulus is impaired, and increased quantities of plasma proteins are filtered and excreted. Less commonly, proteins of relatively low molecular mass, to which even the normal glomerulus is relatively permeable, may appear in the plasma, undergo glomerular filtration, and be excreted. Examples include the excretion of immunoglobulin light chains (Bence Jones proteins) in the urine of some patients with multiple myeloma, the transient excretion of myoglobin in patients with extensive rhabdomyolysis, and the excretion of hemoglobin in rare cases of patients suffering transfusion reactions and intravascular hemolysis. Finally, impaired renal tubular reabsorption of the small quantities of protein that are filtered may occur in patients with tubulointerstitial kidney diseases. These qualitative changes in the types of proteins excreted into the urine can be detected by electrophoresis (20).

Quantification of urinary protein excretion is also helpful in the evaluation and follow-up of patients with kidney disease. In healthy adults, urinary protein excretion averages about 40 mg/day (21) and the upper limit of normal is about 150 mg/day (20). Urinary protein excretion rates of more than 3 or 4 g/day provide unequivocal evidence of glomerular disease and define the nephrotic syndrome. Intermediate rates of abnormal protein excretion, between 150 mg/day and 3 to 4 g/day, may be seen in patients with kidney diseases of any type. These estimates require simultaneous measurements of daily urinary protein excretion and urinary creatinine excretion to ensure completeness of urine collections. However, it is inconvenient and difficult to collect accurate and complete 24-hr urine samples. Moreover, measuring urine volume is a time-consuming laboratory task. Several studies now suggest that the urinary protein/creatinine concentration ratio in random (untimed) urine samples accurately reflects 24-hr urine protein excretion (21, 22). As shown in Figure 5, for healthy subjects with urinary protein excretion rates of <150 mg/day, the ratio of protein to creatinine in either 24-hr urine specimens or untimed urine samples from the same patients were always <100 mg of protein per gram of creatinine. As illustrated in Figure 6, there is an excellent correlation between the protein/creatinine concentration ratios in untimed urine samples and in 24-hr urine samples among healthy subjects, patients with kidney disease of all types, and patients with kidney transplants. Protein/creatinine concentration ratios >2000 mg/g are comparable with daily urinary protein excretion rates of >3 to 4 g/day. Such "nephrotic range" proteinuria is strong evidence for glomerular disease (20, 21).

**Water and Electrolytes**

In health, plasma concentrations of electrolytes are maintained within narrow ranges. The mean values and ranges in health (mean ± 2 SD) are shown in Table 1. Because rates of glomerular filtration in health range from about 120 to 220 L/day (83–153 mL/min; 1.4–2.5
Table 1. Concentrations of Some Plasma Constituents
In Healthy Adults

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolality, mOsm/kg</td>
<td>283.0</td>
<td>271–293</td>
</tr>
<tr>
<td>Water loaded</td>
<td>292.0</td>
<td>280–307</td>
</tr>
<tr>
<td>Na, mmol/L</td>
<td>140.0</td>
<td>135–145</td>
</tr>
<tr>
<td>K, mmol/L</td>
<td>4.2</td>
<td>3.5–4.8</td>
</tr>
<tr>
<td>Cl, mmol/L</td>
<td>100.0</td>
<td>95–105</td>
</tr>
<tr>
<td>HCO3, mmol/L</td>
<td>27.0</td>
<td>23–31</td>
</tr>
<tr>
<td>Ca, mmol/L</td>
<td>2.42</td>
<td>2.25–2.60</td>
</tr>
<tr>
<td>PO4, mmol/L</td>
<td>1.20</td>
<td>0.85–1.55</td>
</tr>
<tr>
<td>Mg, mmol/L</td>
<td>0.9</td>
<td>0.75–1.05</td>
</tr>
</tbody>
</table>

mL/s) and all electrolytes are almost completely filterable, it is evident that precise moment-to-moment adjustments in tubular reabsorption of ions and water are crucial to the maintenance of normal plasma electrolyte concentrations and the volumes of body fluids.

Plasma electrolyte concentrations lower than normal may reflect: (a) reduced dietary intake, (b) shifts into intracellular fluid or extrarenal losses in the presence of a normal maximal renal conservation of the ion, or (c) renal wasting of the ion. Thus, assessment of urinary ion excretion rates relative to plasma ion concentrations provides exceedingly useful initial data for identifying the mechanisms for reduced concentrations of plasma ions. By contrast, plasma ion concentrations that are higher than normal may reflect (a) sudden and rapid additions of the ion to body fluids, usually as the result of intravenous administration; (b) enhancement of normal tubular reabsorption of the ion when the entry rate of the ion into body fluids from the diet (gut) and body tissues is normal; (c) marked reductions in GFR; or (d) impaired tubular secretion of the ion.

Several approaches to the quantitative assessment of electrolyte excretion have been used:

• The urinary concentration of an ion may permit evaluation of renal ion conservation or wasting. This measurement alone is not often of discriminatory value because the urinary concentration of a given ion will be determined not only by the excretion rate of the ion itself but also by the simultaneous rate of water excretion, which can vary in health from <0.3 mL/min during antidiuresis to >10 mL/min during maximum water diuresis.

• The concentration of an ion in the urine (U) relative to the concentration in plasma (P) is assessed by the U/P concentration ratio. Such measurements have the same disadvantage as that of the urinary ion concentration alone.

• The rate of urinary excretion of an ion relative to the GFR can be estimated as follows:

\[
U_{ion} \cdot \frac{V}{GFR}, \text{mmol/L} = \frac{U_{ion}, \text{mmol/L} \cdot \text{vol urine, L/time}}{GFR, \text{L/mol}}
\]

Because \(GFR = \frac{U_{creatinine}, \text{mmol/L} \cdot \text{vol urine, L/time}}{U_{creatinine}, \text{mmol/L}}\), the above equation simplifies to

\[
U_{ion} \cdot \frac{V}{GFR}, \text{mmol/L} = \frac{U_{creatinine}, \text{mmol/L} \cdot \text{Pcreatinine, mmol/L}}{U_{creatinine}, \text{mmol/L}}
\]

Such an assessment requires only a random urine specimen, not a timed one. When such urine measurements are assessed in relation to simultaneously measured plasma ion concentrations, together with knowledge of the expected ranges in health, one can evaluate the appropriateness of renal ion conservation when concentrations of plasma ions are low or the appropriateness of renal excretion rates when concentrations of plasma ions are higher than normal.

• The urinary excretion rate of an ion relative to the GFR of the ion can be assessed as a fraction or as a percentage. In formal terms,

\[
\text{Fractional excretion of ion} = \frac{(\text{excreted/filtered ion})}{\text{GFR, L/time} \cdot \text{P}_{ion}, \text{mmol/L}}
\]

or

\[
\text{E/F}_{ion} = \frac{U_{ion}, \text{mmol/L} \cdot \text{P}_{creatinine, mmol/L}}{U_{creatinine, \text{mmol/L} \cdot \text{P}_{ion}, \text{mmol/L}}}
\]

The latter, expressed as a percentage, is written as \%E/F_{ion}. The utility of these equations will be illustrated subsequently.

Water

In health, plasma osmolality (Posm) ranges from 270 to 300 mOsm/kg. Because water excretion may vary from <0.3 to >10 mL/min, and because deviation from normal body osmolality may significantly affect cellular function (23), precise, rapid, and multiple regulation of osmolality and water excretion is necessary. Increases in Posm are antagonized by antidiuretic hormone (arginine vasopressin; AVP) and renal water conservation as well as by thirst (with consequent water intake), whereas decreases in Posm are antagonized by inhibition of antidiuretic hormone secretion, a water diuresis, and inhibition of thirst.

The main determinant of effective osmolality (tonicity) of the extracellular fluid (ECF) is Na and its attendant anions. Thus, normal ECF tonicity may be readily approximated as \(2 \times \text{plasma [Na+], mmol/L}\). The determinants of intracellular fluid (ICF) tonicity are not known with certainty, but because cells are permeant to water, losses of water or addition of impermeant solutes to one compartment or the other will be counteracted by water flow to equalize ICF and ECF tonicity. Permeant solutes such as urea do not, however, materially contribute to osmotic water movements. All solutes will be accounted for in measurements of osmolality, customarily made by the freezing-point-depression method, because that method accounts for all osmotically active particles and does not reflect their capacity to readily
permeate cells in vivo. Thus, measured hyperosmolality may not imply hypertonicity. Plasma tonicity (effective osmolality) may be estimated by the following equation:

\[
\text{tonicity (mOsm/kg plasma water)} = 2 \times [\text{Na}^+] \text{ mmol/L} + ([\text{glucose}], \text{mg/L/180})
\]

\[
= 2 \times [\text{Na}^+] \text{ mmol/L} + [\text{glucose}], \text{mmol/L}
\]

Measured Posm may differ significantly from tonicity when large amounts of permeant solutes, e.g., urea or ethanol, are present. Most commonly, however, the plasma Na\(^+\) concentration provides the most rapid estimate of body tonicity. Increases in plasma Na\(^+\) >145 mmol/L almost invariably indicate hypertonicity, although plasma Na\(^+\) <135 mmol/L may not always indicate hypotonicity. As suggested by the preceding equation, hyperglycemia may contribute to hypertonicity even when the measured plasma Na is below normal; further confusion may arise with extreme hyperlipidemia. Moreover, hyperlipidemia is more likely in patients with marked hyperglycemia. These lipids can interfere with flame photometric measurements of plasma Na\(^+\) because they occupy a disproportionate volume of test plasma (24).

In health, changes in body tonicity result in changes in urinary osmolality (Uosm) that tend to preserve homeostasis. This relationship is shown in Figure 7 for a wide range of plasma osmolalities in normal subjects. Points to the left of the band suggest overconcentration of the urine, such as might occur in syndromes of nonosmotic stimulation (excess) of antidiuretic hormone secretion (so-called SIADH), and could result from medication (e.g., carbamazepine or chlorpropamide), from pain and vomiting, or because of unregulated tumoral antidiuretic hormone secretion (as in oat cell lung cancer). Conversely, points to the right of the band suggest inadequate urinary concentration, such as might occur in syndromes of antidiuretic hormone deficiency (neurogenic diabetes insipidus) or impaired antidiuretic hormone action (nephrogenic diabetes insipidus). Polydipsia alone should not alter the Posm–Uosm relationship; Posm tends to drop with copious water intake and the urine will be correspondingly dilute. In contrast, altered set points of AVP secretion (as in pregnancy) tend to shift the curve to the left (25).

In healthy adults, Uosm can range from 50 mOsm/kg during maximum water diuresis and AVP suppression to 1200 mOsm/kg when AVP stimulates maximum renal water conservation (Figure 7). Uosm may be estimated rapidly by measuring the relative density (d; specific gravity) of urine in the absence of abnormal urinary solutes (e.g., glucose, mannitol, radiocontrast agents). The relative density of water is 1.000 (by definition), and that of urine may range from 1.002 to 1.035. Multiplying the last two digits (thousandths) of the relative density measure of a urine by 30 provides an estimate of the Uosm. Urinary dilution depends on adequate removal of solutes from tubular fluid and absence of water reabsorption at the position of the distal nephron, a process dependent on appropriate suppression of AVP. If AVP is detectable in plasma when the urine is dilute, tubular insensitivity to AVP may be inferred. Urinary concentration, on the other hand, depends not only on adequate release and action of AVP, but also on the presence of a solute gradient from the renal cortical to medullary level that acts to remove water from the collecting ducts. Medulary damage from sickle-cell anemia, or any other disorder that impairs the medullary gradient, reduces urinary concentrating ability.

Posm is a direct stimulus for AVP secretion. The threshold for AVP release is ~280 mOsm/kg (26), a figure that corresponds rationally to a plasma Na of 140 mmol/L (Figure 8). Minor interindividual threshold variations may occur, and a 10 mOsm/kg threshold decrement occurs during pregnancy (25). Thus, if Posm is >280 mOsm/kg, or plasma Na is >140 mmol/L, AVP should be measurable and its plasma concentration should increase linearly to ~10 ng/L at Posm = 300 mOsm/kg. AVP is released within minutes in response to increases in Posm, and acts equally quickly to enhance renal cortical and medullary water conservation. Restoration of "eutonicity" rapidly closes the feedback loop because the plasma half-life of AVP is only 10 to 25 min (27).

Fig. 7. Relationship between Uosm and Posm in healthy subjects: thirsting (III); during maximum water diuresis (O); and during intermediate state of hydration (A), neither thirsting nor water-loaded.

Fig. 8. Relationship between plasma concentration of AVP and Posm
The approximate threshold for thirst is indicated at 280 mOsm/L. Adapted from ref. 26, by copyright permission of The American Society of Clinical Investigation.
Thirst, the sensation of need for water, derives mainly from increases in body tonicity to >290 mOsm/kg. This threshold may be decreased by volume depletion of ECF, and if more than one-fifth of total blood volume is lost, thirst may occur independently of changes in body tonicity. Although not readily quantifiable, thirst tends to become more severe with greater degrees of hypertonicity or hypovolemia, and occurs only after AVP release at Postr ≥290 mOsm/kg (Figure 8). This osmolality corresponds to an AVP concentration of ~5 ng/L, at which Uosm should reach 1000 to 1200 mOsm/kg (Figure 9). Viewed teleologically, it is appropriate that the sensation of thirst should arise only when the finer mechanisms of water regulation have reached their limit.

One may make an initial evaluation of water metabolism from knowledge of a subject’s weight, plasma Na, and Uosm. For greater precision, one may measure the concentration of plasma AVP, but the presence or absence of AVP can usually be deduced when existing kidney function is normal as measured by Uosm; Uosm is high when AVP is present, low when it is not. Thirst is a clinical datum, not readily quantified in the laboratory. Measuring urine volume will identify subjects with polyuria, defined as urine output of >3 L/day.

Body water (in liters) ranges from 50% to 60% of body weight (in kilograms). When body water is normal for a given individual, Postr is also in the normal range, as reflected by a plasma Na in the physiological range (135–145 mmol/L). A relative or absolute water deficit results in hypertonicity, with an increase of the plasma Na concentration. The increment in plasma Na concentration may be used to calculate the water deficit. For a plasma Na of 150 mmol/L in a 70-kg man, the calculation will be as follows:

\[
\text{Total body water (TBW), } L = 0.6 \times 70 = 42 \text{ L}
\]

\[
\frac{\text{Current plasma Na}}{\text{Normal plasma Na}} = \text{hypertonicity ratio}
\]

Hypertonicity ratio \( \times \) TBW = body water (TBW) at which plasma Na would return to normal

\[
\text{TBW} - \text{TBW}_0 = \text{water deficit}
\]

Thus, \([(150/140) \times 42] - (42) = 3 \text{ L}

By analogy, subnormal plasma Na concentrations (e.g., 120 mmol/L) not only may indicate hypotonicity, but also should allow calculation of water excess.

\[
\frac{\text{Current plasma Na}}{\text{Normal plasma Na}} = \text{hypotonicity ratio}
\]

Hypertonicity ratio \( \times \) TBW = body water (TBW) at which plasma Na would return to normal

\[
\text{TBW} - \text{TBW}_0 = \text{water excess}
\]

Thus, (42) - [(120/140) \times 42] = 6 \text{ L}

This latter example does not imply that subnormal plasma Na concentrations ought to be rapidly corrected. Indeed, partial correction of symptomatic hyponatremia is often sufficient. Rapid correction (>12 mmol/L per day) may predispose patients to syndromes of demyelination of the central nervous system (28).

Pure syndromes of AVP excess ("SIADH") are recognized by their attendant plasma hypertonicity with hyponatremia and (inappropriate) urinary concentration. Even a Uosm of 200 mOsm/L may be excessive when the plasma Na is, e.g., 125 mmol/L. The plasma uric acid may be low (29), and AVP concentrations, if measured, will not only be detectable but may be quite high. Typically, plasma potassium will be normal in these syndromes, but may be low when hyponatremia is the result of diuretics or vomiting (30).

It may be more difficult to sort out the cause of polyuria. The absence of a solute diuresis (e.g., glucose, mannitol, radiocontrast) implies a water diuresis. Uosm in the latter case will be <150 mOsm/kg, corresponding to \( d \leq 1.005. \) The major causes of a water diuresis are polydipsia, neurogenic (or central) diabetes insipidus, and nephrogenic diabetes insipidus, and these disorders may be differentiated by evaluation of the response to dehydration and to administered AVP (31, 32).

Sodium

In health, the daily urinary Na content is largely determined by dietary Na, because <10 mmol Na is lost in stool and sweat daily. Thus, an accurate 24-h urine collection reflects Na intake. Current diets in the U.S. provide 8–16 g of NaCl per day (i.e., 140–280 mmol). Diets containing <100 mmol of Na per day may be useful in the management of edematous states and the care of patients with kidney disease. Dietary compliance may be monitored by measurement of 24-h urinary Na excretion.

Because Na represents the "ionic skeleton" of the ECF, Na balance is ultimately reflected in the fluid volume status of a subject. Without appropriate regula-
tory mechanisms, Na excess results in expansion of ECF volume, with development of edema, circulatory congestion, and, sometimes, hypertension. Conversely, Na depletion results in ECF deficit and lower blood pressure. One may assess the adequacy of body stores of Na and ECF volume principally by examining the patient and measuring weight, blood pressure, and heart rate. No biochemical measurement allows precise assessment of the adequacy of ECF volume. Nevertheless, measurement of the fractional or percent urinary excretion of filtered Na (%E/FNa) may be very helpful in assessing the adequacy of renal Na conservation when ECF-volume depletion is thought to be present.

Urinary Na derives from the glomerular filtrate, which, if we disregard the minor contribution of the Donnan effect, is equivalent to plasma water and its constituent solutes. At a normal GFR of 150 L/day, the total daily tubular Na load is ~21 000 mmol. Tubular reabsorption, first proximally and then in the distal nephron, acts to limit Na excretion, processes finely regulated by intrarenal physical forces, renal nerves, and local and systemic hormonal mechanisms (33).

In health, the %E/FNa (commonly but imprecisely written as FENa) ranges between 0.5% and 1% and, as described previously, is estimated from measurements of creatinine and Na concentrations in an untimed urine specimen and a simultaneously collected blood sample. The %E/FNa provides an index of renal Na conservation. When dietary NaCl intake is reduced to 10 mmol/day, urinary Na excretion decreases to <10 mmol/day within three days, and %E/FNa thus decreases to ~0.05%. Significant blood loss or a decline in cardiac output, on the other hand, leads to activation of Na-receptive mechanisms within minutes (34). Extrarenal fluid losses, as with vomiting, diarrhea, sweating, or burns, also activate Na-receptive mechanisms. These, in turn, promote renal conservation of Na, a homeostatic defense to preserve ECF volume and thus perfusion to vital organs. A very low urinary Na concentration alone may reflect volume depletion. However, because urinary Na concentration depends on the rate of water excretion as well as the rate of Na excretion, the calculation of %E/FNa may be of greater precision in assessing the response of the kidney to volume depletion. Thus, the hypotensive subject would be expected to excrete urine with a low Na concentration, but, more significantly, one with a low %E/FNa. If this is not the case, and the %E/FNa is >1%, renal Na conservation has failed. This reasoning is the basis for the use of %E/FNa in the differential diagnosis of oliguric states (35).

A low %E/FNa (<1%) usually implies prerenal azotemia, i.e., an increase in plasma urea or creatinine concentrations from decreased renal perfusion alone, but Na excretion may also be low in patients with acute glomerulonephritis, in which intact tubules reabsorb relatively greater amounts of reduced filtrate. A higher %E/FNa (>1%) reflects tubular failure from any cause, e.g., acute tubular necrosis, urinary tract obstruction, or nephrotoxic injury (Figure 10).

Stable chronic renal insufficiency with unchanged Na intake is also accompanied by an increase in %E/FNa, reflecting higher Na excretion per nephron as total GFR declines (36, 37), an adaptive response that maintains Na balance. The %E/FNa may increase to 20% in severe chronic renal failure, when GFR is <5 mL/min (Figure 11). One might expect that deviations from expected %E/FNa at a given GFR imply changes in renal perfusion. Indeed, volume expansion in uremic subjects is accompanied by a further reduction in Na reabsorption, that is, by appropriate increase in Na excretion (36).

Potassium

In health, nearly all potassium entering the tubular fluid by glomerular filtration is reabsorbed. Thus, nearly all urinary K excretion reflects distal tubular secretion of K, a process stimulated by aldosterone and by the rate of K entry into the plasma from the diet and from cells (38). In response to dietary K deprivation in health, plasma K concentration decreases rapidly in proportion to the quantities of K lost because of ongoing normal colonic secretion of K into the feces, normally less than absolutely complete renal K conservation, and minor insensible sweating (39). At the other extreme, rapid oral administration of K salts in doses of 2.5

![Figure 10](image1.png)

**Figure 10.** The %E/FNa in patients with oliguric acute renal failure, nonoliguric acute renal failure, urinary tract obstruction, acute glomerulonephritis, or prerenal azotemia

Adapted with permission from ref. 35

![Figure 11](image2.png)

**Figure 11.** Relationship between the %E/FNa and GFR for patients with kidney disease of varying severity, eating diets providing 7.0 and 3.5 g of NaCl per day

Adapted from ref. 36, by copyright permission of The American Society for Clinical Investigation.
mmol/kg (175 mmol/70 kg) over about 30 min can lead to dangerously high plasma K (≥7 mmol/L) because such rates of K loading exceed the capacity of even the normal kidney to secrete K (40).

Among patients with hypokalemia, assessment of \( U_K \) V/GFR permits rapid clarification as to whether hypokalemia is the consequence of inadequate dietary K intake or extrarenal K losses (diarrhea) or of renal K wasting. Figure 12 illustrates the range of urine \( U_K \) V/GFR in relation to plasma K among normal subjects eating normal diets or diets providing <3 mmol of K per day (41, 42). When plasma K is <3.5 mmol/L, the lower limit of normal, \( U_K \) V/GFR is generally <0.15 mmol/L. Among patients with hypokalemia and greater rates of K excretion, one must consider the possibility of renal K wasting as a result of stimulation of distal tubular K secretion. Common causes include therapeutic administration or surreptitious use of diuretics, or the effects of excessive mineralocorticoid as in primary aldosteronism or Bartter's syndrome.

Hyperkalemia may result from excessively rapid intravenous K administration (even in the presence of normal kidney function), impaired renal K excretion, or both. The capacity of the distal renal tubule to secrete K may be impaired by mineralocorticoid deficiency, as in adrenal insufficiency (Addison's disease), or by the administration of drugs that either inhibit angiotensin-stimulated aldosterone secretion (e.g., antihypertensive angiotensin-converting enzyme inhibitors) or inhibit the distal tubular K-secretory mechanism (e.g., spironolactone). Significant hyperkalemia does not usually occur among patients with progressive kidney disease until near-terminal renal failure develops. However, occasional patients with only moderately advanced kidney failure (creatinine clearance 15–60 mL/min) may exhibit hyperkalemia either because of reduced renal renin synthesis, resulting in reduced plasma renin activity and thus reduced angiotensin-mediated aldosterone secretion (43), or a state of decreased tubular responsiveness to aldosterone, or both. Impaired renal excretion of acid, and thus reduced plasma bicarbonate concentrations, may also be present. Plasma aldoster-

one (in ng/L) divided by plasma K (in mmol/L) may be <30 in such patients (43, 44).

**Metabolic Acidosis**

Overall biochemical reactions of metabolism result each day in the production of "fixed" acids (45), which are buffered principally by bicarbonate in body fluids. The bicarbonate consumed in that process is regenerated by the excretion of acid by the kidney. In addition to the reabsorption of nearly all of the filtered bicarbonate, the kidney excretes additional acid (the regenerated acid) by the protonation of filtered buffers, chiefly phosphate, and by protonation of \( NH_3 \) produced by renal tubular cells to urinary \( NH_4^+ \). Net renal acid excretion equals urinary titratable acid plus urine \( NH_4^+ \) minus urinary bicarbonate. Most urinary acid is excreted as \( NH_4^+ \).

In patients with metabolic acidosis— a low blood pH caused by a primary decrease in plasma bicarbonate concentration—the decrease in bicarbonate may be the result of (a) an increase in the rate of acid addition to body fluids, as in diabetic ketoacidosis; (b) fecal losses of bicarbonate in diarrheal disorders; or (c) impaired excretion of acid by the kidney. Assessment of the renal response to metabolic acidosis permits differentiation of these mechanisms causing acidosis.

When serum bicarbonate concentrations are <23 mmol/L (the lower limit of the normal range), urine pH among healthy subjects without kidney disease should be <6.0 (Figure 13). Higher urinary pH values, in the absence of infection of the urine by urease-producing bacteria, imply defective urinary acidification as in classic (type I) distal renal tubular acidosis.

Urinary pH reflects only free hydrogen ion activity, not the prevailing rate of total acid excretion. That assessment requires direct or indirect measurement of urinary \( NH_4^+ \). Urinary \( NH_4^+ \), divided by creatinine to correct for intersubject variations in body mass, increases among healthy subjects as plasma bicarbonate and urine pH decrease (Figure 14). Because metabolic acidosis from increased rates of acid production is accompanied by increased renal \( NH_4^+ \) production and urinary \( NH_4^+ \) excretion when kidney function is nor-

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**Fig. 12.** Range of \( U_K \) V/GFR in relation to simultaneous plasma K concentration among healthy adults eating diets providing 50–90 mmol or <3 mmol of K per day
From data in refs. 41 and 42

**Fig. 13.** Relationship between urine pH and plasma bicarbonate in healthy adults
Adapted from refs. 45–49
Fig. 14. Relationship between urine ammonium per unit GFR and plasma bicarbonate (upper panel) and urine pH (lower panel) in healthy adults
Adapted from refs. 45–51. Note logarithmic vertical scales

Fig. 15. Relationships in fasting healthy subjects between urine UCa/V/GFR and serum total Ca concentrations (top), urine UPO4/V/GFR and serum PO4 concentrations (middle), and urine Umg/V/GFR and serum Mg concentrations (bottom)
Expanded from data in refs. 41, 42, 51, and 54

normal, urinary NH4+/creatinine >10 mmol/mmol is expected when metabolic acidosis is the result of increased rates of acid addition to body fluids. If the urinary NH4+/creatinine ratio is significantly lower, impaired renal acid (NH4+) excretion must be present and contribute to the development of the metabolic acidosis. Such abnormalities occur among patients with all types of diffuse parenchymal kidney disease and in patients with renal tubular acidosis. Urinary NH4+ can be measured directly by using a modification of the assay for plasma NH4+ (52). Alternatively, urinary NH4+ may be accurately estimated by calculating the urinary anion gap: urinary NH4+, mmol/L = 24 - 0.4 ([Na] + [K] - [Cl]), mmol/L (r = 0.72) (53).

Other Minerals

Estimates of the urinary excretion of UCa/V/GFR, UPO4/V/GFR, and Umg/V/GFR in relation to their respective plasma concentrations may also be of use in the initial evaluation of patients with above-normal or below-normal plasma concentrations of these ions. The ranges of these relationships in health, for subjects eating various diets, are illustrated in the panels of Figure 15. As total Ca concentrations in serum vary across the normal range from 2.20 to 2.60 mmol/L, fasting UCa/V/GFR is <0.033 mmol/L (Figure 15, upper panel). Hypercalcemia is accompanied most often by increases in UCa/V/GFR, as in hyperparathyroidism, hypercalcemia related to neoplasia, or sarcoïdosis and other granulomatous diseases. However, occasional patients have familial hypocalciuric hypercalcemia, wherein UCa/V/GFR is normal despite hypercalcemia, related to enhanced renal tubular Ca reabsorption by a yet unknown mechanism (55). Other disorders of Ca metabolism, e.g., osteomalacia, osteoporosis, or Paget’s disease, are not assessed by plasma or urinary measurements alone and are reviewed in detail elsewhere (56). Fasting urine UPO4/V/GFR increases as serum PO4 concentrations increase (Figure 15, middle panel). When kidney function is normal, dietary PO4 deprivation is accompanied by rapid renal PO4 conservation within a few days (54), a response temporally and quantitatively similar to renal Na conservation in response to reduced Na intake. Thus, patients deprived of PO4 or who have lost PO4 in diarrheal stools would be expected to exhibit a urine UPO4/V/GFR <0.1 mmol/L when their serum PO4 concentration is <0.9 mmol/L. Inappropriately normal rates of UPO4/V/GFR, despite hypophosphatemia, may reflect the effects of parathyrin
to inhibit renal tubular reabsorption of PO₄ in patients with hyperparathyroidism or indicate intrinsic defects in renal tubular PO₄ absorption in patients with Fancconi syndrome or with hypophosphatemic rickets. Conversely, UPO₄/V/GFR is normal despite hyperphosphatemia in children during growth, in acromegalis, and among patients with tumoral calcinosis, because of enhanced PO₄ reabsorption. Fasting urine U₄/Mg/V/GFR also increases as serum Mg concentrations increase (Figure 15, lower panel). Urinary Mg excretion also decreases rapidly when dietary Mg intake is restricted (57). Thus, patients deprived of Mg intake or who have lost Mg in diarrheal stools would be expected to exhibit a urine U₄/Mg/V/GFR <0.02 mmol/L when serum Mg concentrations are <0.75 mmol/L. However, U₄/Mg/V/GFR can be expected to be inappropriately normal when hypomagnesaemia is an occasional toxic side effect of cis-platinum therapy for patients with cancer. The regulation of renal excretion of Ca, Mg, and PO₄ is reviewed in greater detail elsewhere (58).

In conclusion, an array of laboratory measurements is required for the full evaluation of kidney function in health and disease. Appropriately collected and analyzed plasma specimens, as well as either random (untimed) or accurate 24-h urine collections, provide these data. The clinical laboratory will, therefore, continue to contribute critical information for the care of patients with kidney disease.

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