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Urinary Indices: Their Diagnostic Value in Current Nephrology

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Abstract

Urinary indices consist basically of urinary concentration, urine/serum ratio or fractional excretion of electrolytes or nitrogen products. They are useful for the decision making process for handling renal diseases such as acute kidney injury, chronic kidney disease, or nephrotic syndrome, as well as for internal milieu disorders such as hyponatremia, dyskalemia, metabolic alkalosis, and hyperchloremic metabolic acidosis. The main urinary indices used in clinical practice are: fractional excretion of sodium and urea which are used for interpreting acute renal injury and hyponatremia; fractional excretion of potassium, and transtubular potassium concentration gradient for evaluating dyskalemias, fractional excretion of uric acid for interpreting hyponatremia, as well as urine chloride for evaluating acid-base disorders such as metabolic alkalosis, and hyperchloremic metabolic acidosis. In conclusion, urinary indices are effective tools for the decision making process involved in treating renal diseases and internal milieu disorders.

Keywords: Urinary indexes; Acute renal injury; Hyponatremia; Nephrotic syndrome; Chronic kidney disease

Introduction

Urinary electrolytes and their derived urinary indices are very useful in clinical nephrology to diagnose renal diseases and internal milieu disorders, as well as for guiding their treatment [1]. Basically, these indices consist of the urinary concentration value, urine/serum ratio or fractional excretion of different electrolytes (sodium, potassium, chloride, etc.) or nitrogen products (urea and uric acid) [2,3] (Table 1).

Urinary indices based their utility on the fact that they are inexpensive, simple to obtain, and reliable markers of diverse physiologic and pathophysiologic mechanisms, particularly for evaluating renal tubule-interstitial pathologies [2,4].

It is worth mentioning that, since urinary indices values result from the interaction of many variables such as patient´s diet composition, age, intestinal and renal function, their normal values depend on the whole patient´s circumstances [5].

In the present review, an update of the role that main urinary indices have for handling acute renal injury, chronic kidney disease, nephrotic syndrome, and internal milieu disorders, is presented.

	Equations
FENa (%)	[urine sodium × serum creatinine/serum sodium × urine creatinine] × 100
FEU (%)	[urine urea × serum creatinine/serum urea × urine creatinine] × 100
FEUA (%)	[urine uric acid × serum creatinine/(serum uric acid × 0.8) × urine creatinine] ×100
FEK (%)	[urine potassium × serum creatinine/serum potassium × urine creatinine] × 100
TTKG	urine potassium × serum osmolality/serum potassium × urine osmolality
FENa: Fractional Excretion of Sodium; FEU: Fractional Excretion of Urea; FEUA: Fractional Excretion of Uric Acid; FEK: Fractional Excretion of Potassium; TTKG: Transtubular Potassium Concentration Gradient	

Table 1: Urinary indeces equations.

Acute renal injury

Acute kidney injury (AKI) is defined as an abrupt decrease in the glomerular filtration rate that occurs over a period of 7 days or less, and persists for a period less than 90 days. This entity is associated with high morbidity and mortality, and its early recognition is crucial in order to achieve an adequate treatment, such as limiting fluids or starting renal replacement therapy. AKI diagnosis is usually based on the medical history, physical examination, as well as urinalysis and urinary indices evaluation.

Traditionally, acute renal failure (ARF) was usually classified based on its possible pathophysiological mechanism [1,6-9]:

• **Pre-renal ARF (prerenal azotemia):** It is induced by renal hypoperfusion before the appearance of any parenchymal damage. AKI improvement after renal hypoperfusion resolution is the gold standard for its diagnosis.

• **Renal ARF:** It is induced by renal parenchymal damage (acute tubular necrosis).

• **Post-renal ARF:** It is induced by urinary tract obstruction.

However, since there is no standard criterion to precisely define prerenal azotemia or acute tubular necrosis in daily

practice (clinical definition is highly subjective, and renal histopathology is not usually performed), therefore a new classification for acute renal injury (ARI) has been currently proposed, which is based now on the duration of the AKI [10,11]:

• **Subclinical AKI:** The AKI diagnoses are based only on the increased levels of renal injury biomarkers before any clinical manifestation: serum creatinine elevation and/or oliguria.

• **AKI:** The clinical manifestation of renal injury which lasts less than 7 days, and depending on its duration can be "transient" (≤ 48 hours), or "persistent" (>48 hours).

• **Acute renal disease (ARD):** The clinical manifestation of renal injury which lasts between 7 to 90 days.

• **Chronic kidney disease (CKD):** The renal injury which lasts more than day 90 from the acute event.

In order to establish some similarity between these two classifications, the current transient AKI could correspond to the classical pre-renal ARF, while the current persistent AKI and ARD could correspond to the classical renal ARF. However, this correspondence is not absolute do to the following reasons: Firstly, transient AKI may occasionally involve limited but significant renal damage that remain undetected by urinary indices and even some urinary biomarkers [10].

Secondly, clinical manifestation of AKI can be of short duration if the surrounding uninjured parenchyma regains function while the injured tubules are healing [11]. Thirdly, it has been documented that a significant period of warm renal ischemia is not sufficient in humans to trigger clinical AKI, so just a major renal blood flow (RBF) reduction seems to be insufficient to initiate AKI [12]. Conversely, AKI occurs despite significant elevation in RBF in hyperdynamic models of sepsis, while creatinine clearance is decreased even in milder hyper dynamic sepsis not associated with systemic hypotension [11,12]. This suggests that an imbalance between pre-glomerular and post-glomerular resistance, and/or intrarenal shunting is required to develop AKI [12]. Urinary indeces can help to distinguish between early AKI and established AKI. A combination of both tests (FEU and FENa) might increase diagnostic sensitivity and specificity in the differential diagnosis of AKI [13].

However, these indices may be affected by diuretic agents or sepsis. Besides, little information is available on their performance for distinguishing transient AKI from persistent AKI in critically ill patients [8].

a) Urinary sodium (UNa) and fractional excretion of sodium (FENa)

The UNa is an index traditionally used for classifying AKI, since values lower than 10-20 mmol/L are suggestive of renal hypoperfusion with preserved tubular sodium reabsorption capability, whereas values higher than 40 mmol/L are suggestive of established AKI with reduced sodium reabsorption capability. However, UNa values can be highly variable in some clinical settings and it often performs poorly for discriminating early AKI from established AKI. For instance: In septic shock, AKI characteristically has low UNa value (<20 mmol/L), but it has not been found to reliably predict worsening AKI, need for renal replacement therapy (RRT), or renal recovery in critically ill patients [14].

The FENa has been traditionally used to discriminate between pre-renal ARF (FENa<1%) and renal ARF (FENa>1%) [6] (Table 1). It has been reported that, this diagnosis urinary index has 62% sensitivity and 75% specificity in oliguric AKI patients, while it has 67% sensitivity and 89% specificity in non-oliguric AKI patients [8]. However, some situations different from pre-renal azotemia, such as glomerulophritis, myoglobinuric renal failure, contrast nephropathy, renal transplant rejection, acute interstitial nephritis, and acute urinary tract obstruction usually run with low FENa (<1%) [6,15].

Moreover, the clinical utility of FENa in critically ill patients with AKI has been challenged since it can be modified by fluid resuscitation, use of vasoactive drugs or diuretics. It is worth mentioning that a low FENa can often be found in circumstances of established AKI which has suffered a heterogeneous parenchyma injury with tubular function preservation in some regions. Interestingly, two studies performed in critically ill septic patients with AKI found temporal declines in FENa from about 1.5% to less than 1% over a period of 24 hours, despite most of the patients received fluid resuscitation, or were on vasopressor and/or diuretic treatment [14].

Conversely, high FENa values can be documented in pre-renal ARF in elderly individuals, patients on diuretics or suffering from chronic kidney disease (CKD) [6,9]. The FENa increases in patients on diuretics while fractional excretion of urea (FEU) results unaffected in this setting, due to urea is reabsorbed mainly at the proximal tubule (40% of urea filtered load) and most diuretics act at more distal segments. Conversely, FENa would be useless in patients on loop diuretics since its value increases over 1%, even if the patient is volume depleted since NaK_2Cl co-transporter blockade impairs sodium reabsorption [6,9].

However, Pepin et al. documented that the specificity for diagnosing transient AKI was 30% higher for FENa than for FEU, regardless of the diuretic use [6]. Additionally, despite diuretic intake, FENa values are usually lower in patients suffering from transient AKI than those with persistent AKI [6]. Finally, the type of diuretic used is also important because for example, loop diuretics (e.g.: furosemide) impair urine concentration inducing lower urine sodium concentration than thiazides [6]. Tubular sodium reabsorption capability is largely reduced during established AKI, usually leading to a FENa value higher than 3%, then a FENa higher than 1% is in favor of persistent AKI [6,9].

b) Fractional excretion of urea (FEU)

Prerenal azotemia occurs during states of water conservation, where serum urea raises more compare to serum creatinine, because urea is reabsorbed by two mechanisms: Firstly, the activation of the renin-angiotensin-aldosterone (RAAS), and the sympathetic nervous systems which lead to a greater sodium proximal reabsorption inducing passive urea

reabsorption in the proximal tubules. Secondly, urea is also reabsorbed at the papillary collecting ducts by vasopressin-dependant channels [6]. Consequently, FEU values are usually lower than 35-40% during pre-renal azotemia in young patients, while its value is above 50% in established AKI [6,9-11]. It has been reported that, FEU has 85% sensitivity and 61% specificity in non-oliguric AKI patients [8]. Additionally, it was recently reported that a lower value of FEU (<35%) was more sensitive and specific than a lower FENa (<1%) in order to differentiate between early and established AKI [6] (Table 1).

It is worth mentioning, that it has been proposed that endotoxemia and aging could induce urea transporters downregulation, explaining why FEU value increases in sepsis and elderly people, even during prerenal azotemia [9]. In this sense, FEU has been reported to be less effective in patients with infection, as cytokines interfere with the urea transporters in the kidney and colon [16]. However, a recent study has compared the urine biochemistry in septic and non-septic AKI, finding no significant difference in FEU value between the groups [16]. Finally, Musch et al found that age could influence FEU, while Dewitte et al. did not [11].

It has been documented that in septic critically ill patients suffering from early non-oliguric AKI, an average FEU value was below 35% over 24 hours despite the majority of the patients were on diuretics [10,11]. Carvounis et al. suggested the useful role of FEU in early AKI, particularly under diuretic intake, while Pepin et al. documented that FEU was not better than FENa for diagnosing prerenal azotemia, regardless the diuretic intake. This phenomenon has been attributed to the fact that there were many diabetic patients in this study, and therefore the osmotic diuresis induced by the hyperglycemia could have led to inappropriately high urea excretion [6,9]. Besides, Hall et al. have documented that FEU is a poor predictor of early AKI in patients undergoing cardiac surgery, since FEU value was 13.5% for all patients, with those worsening AKI having the lower FEU value compared to those without worsening AKI [10,11]. In CKD patients, the FEU values are usually similar to those observed at healthy conditions (over 40-50%) [9].

Studies have shown that FEU is significantly higher in patients with established AKI compared to those with prerenal azotemia at the time of presentation, since during persistent AKI tubules are damaged or dysfunctional and FEU should be high in this context [16]. However, there is some controversy regarding FEU reliability in AKI: On one hand, Darmon et al. also concluded that FEU is not helpful in differentiating transient from persistent AKI. On the other hand, Dewitte et al, in a single-center study concluded that an FEU lower than 40% was a sensitive and specific index for making this differentiation.

The different findings among these studies are probably caused by differences in study design, AKI definition and the characteristics of the studied population [16]. However, it was documented that FEU was low in some patients with AKI, possibly due to the fact that a number of nephrons remained undamaged and therefore retaining sodium and urea. Furthermore, urea secretion in the S3 segment has been shown to be an important mechanism too. Since acute tubular necrosis preferentially affects S3, the disruption of this mechanism could explain the reduced FEU documented in ischemic AKI [2].

Chronic kidney disease

It is known that the utility of the urinary indexes is reduced in chronic kidney disease (CKD) patients since their values are usually increased compared to those documented who have normal renal function [6,9]. This phenomenon can be explained by a combination of increased tubular excretion for compensating a reduced glomerular filtration rate (increased tubular secretion) and/or tubular dysfunction (reduced tubular reabsorption) [1,3].

Regarding potassium metabolism, hyperkalemia is one of the most serious complications of CKD, and the cause of potassium retention in not advanced CKD, is a reduction in urinary potassium excretion [17]. In a retrospective study involving patients with CKD, a significant decrease in UK was observed at CKD stage 4 compared to earlier stages; and this decrease progressed further at stage 5 [17]. High urinary potassium (UK) has been recently associated with a lower risk of death and cardiovascular events, and a reduced incidence of hypertension in general populations. Additionally, decreased UK excretion has been associated with an increased risk of death and cardiovascular events in CKD patients, particularly in stages 4 and 5 CKD, which could be explained due to their low potassium excretion (<38 mmol/L) [17].

Nephrotic syndrome

There are two different theories regarding the mechanisms of edema formation in nephrotic syndrome (NS): Firstly, it is the underfill mechanism where plasma volume reduction is due to a fall in plasma colloid osmotic pressure, effective hypovolemia induction, and consequently renin-angiotensin-aldosterone system activation (secondary sodium retention). Secondly, it is the overflow mechanism, where plasma volume expansion is due to primary tubule sodium retention by intrinsic activation of the Na+K+ATPase pump in the cortical collecting duct (primary sodium retention). To understand the inducing edema mechanism in this nephropathy is very useful, since it can help to predict the response to diuretics [1].

However, it is particularly difficult to clinically distinguish between these two pathophysiologic mechanisms. Moreover, plasma aldosterone level does not help to distinguish between these clinical settings because of its high cost and long waiting time for its result. In this sense, the combination of a urinary sodium reabsorption marker (FENa), and an indicator for sodium/potassium exchange induced by aldosterone in the distal nephron: The urine potassium/[urine potassium+urine sodium] index (UK/[UK+UNa]), could help [18].

Additionally, it has been reported a significant correlation between UK/[UK+K] and plasma aldosterone in

normal subjects and children suffering from NS [18]. Donckerwolcke et al. have postulated that primary sodium retention presented the pattern of the combination of low FENa (<0.5%) with low UK/[UK+UNa] index (<60%); while secondary sodium retention presents the combination of low FENa (<0.5%) with high UK/[UK+UNa] (>60%) [19]. The higher UK/[UK+UNa] value documented during secondary sodium retention can be explained since this index includes urinary potassium among its variables, whose secretion is stimulated by aldosterone hormone [3].

The FENa can also detect NS remission and relapse since it was found that there was significant difference in the FENa value between remission (0.45%) and relapse (0.24%) in NS [20]. This phenomenon can be explained since urinary sodium reabsorption trend is higher in NS relapse than in NS remission. Conversely, there was no significant difference in the UK/[UK+UNa] value between remission and relapse groups. Moreover, the FENa has not been found to be different in minimal change disease and nephrotic syndrome induced by different histological lesions [20].

Internal milieu disorders

a) Hypotonic hyponatremia

It has been classically described that hypotonic hyponatremia in a setting of real hypovolemia (eg: severe diarrhea) or effective hypovolemia (eg: heart failure, cirrhosis) characteristically present low UNa (≤ 10-20 mmol/L), FENa (<0.5%) and FEU (≤ 35%) while hypotonic hyponatremia in a setting of normal extracellular fluid (eg: syndrome of inappropriate antidiuretic hormone secretion) present high UNa (≥ 60 mmol/L), FENa (≥ 1%), and FEU (≥ 65%) [1]. However, it is worth mentioning that hyponatremic patients who are on a chronic low sodium diet could have low UNa and low FENa even when they are suffering from those causes of hyponatremia which characteristically have high UNA and FENa, such as syndrome of inappropriate antidiuretic hormone secretion (SIADH), renal/cerebral salt wasting syndrome (R/CSW) or reset osmostat (RO) [1]. For distinguishing these previously mentioned causes of hyponatremia, a more reliable urinary index has been described: fractional excretion of uric acid (FEUA) [20] (Table 1). Thus, a hyponatremic patient with a low value of FEUA (<4%) can be interpreted as secondary to hypovolemia (real or effective), while a hyponatremic patient with normal FEUA (4-11%) can be interpreted as secondary psychogenic polydipsia or RO. Finally, a hyponatremic patient with high FEUA (>11%) can be interpreted as secondary to SIADH or R/CSW. After treating this patient the FEUA normalizes in SIADH while it keeps high in R/CWS [21].

b) Dyskalemias and acid-base disorders

Urinary potassium (UK) concentration (spot or 24 hours urine sample), fractional excretion of potassium (FEK), and transtubular potassium concentration gradient (TTKG), are indices useful for evaluating if hypokalemia is induced (tubular dysfunction) or worsened (concomitant secondary hyperaldosteronism) by inadequate urinary potassium loss, or on the contrary if the kidney is trying to save potassium in this context of depletion. Urinary indices values such as UK (spot urine sample):<20 mmol/L, UK (24 hours urine sample):<15 mmol/day, FEK<6%, and TTKG<4 are all patterns of renal potassium saving [3,22-24]. However, it should be taken into account that TTKG is an unreliable urinary index in elderly people and chronic kidney disease patients [3] (Table 1).

In patients suffering from hyperkalemia, suboptimal TTKG (if GFR ≥ 80 ml/min/1.73 m²) or FEK (if GFR: 15-79 ml/min/1.73 m²) reflects an inadequate urinary potassium secretion capability. Conversely, an optimal TTKG or FEK value in a hyperkalemic patient reflects the presence of potassium shift from the intracellular compartment to the extracellular compartment [3,22-24].

Urine chloride (UC) plays an important role in some acid-base disorders evaluation. On one hand, as urine chloride in spot urine sample is useful for distinguishing between chloride sensitive metabolic alkalosis (UC<30 mmol/L), and chloride resistant metabolic alkalosis (UC>30 mmol/L). On the other hand, UC is one of the components of the urinary anion GAP (UAG) formula (UAG=[urinary sodium+urinary potassium]-urinary chloride), which constitutes an indirect method for estimating urinary ammonium excretion.

Thus, UAG (and consequently UC) is a useful urinary index for evaluation the causing mechanism of hyperchloremic metabolic acidosis (HMA). A low UC implies a low urine ammonium excretion (positive UAG) due to distal tubule acidification dysfunction. Conversely, a high UC value implies a high urine ammonium excretion (negative UAG), due to an adequate distal tubule acidification, then HMA can be secondary to proximal tubule acidification dysfunction or intestinal bicarbonate loss (eg: diarrhea).

Conclusion

Urinary indices, as markers of physiological and pathophysiological mechanisms, are effective tools in the decision making process for handling renal syndromes and internal milieu disorders.

Conflict of Interest

All the authors declare that they have no conflict of interest.

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