Urinary indices in nephrotic syndrome

Nephrotic patients with edema may have variable volume status i.e. hypo, hyper or normovolemia. Volume-expanded patients may benefit with diuretics while volume-contracted patients need volume expansion, as shown in the study by Iyengar et al in this issue of the Journal.[1] Clinically it is not possible to differentiate severely edematous nephrotic syndrome (NS) patients with intravascular volume expansion (VE) from those with intravascular contraction (VC).[2] Hence urine indices may have some role in elucidating the volume status. Since severe hypoalbuminemia is commoner in children, these indices may be more important in the management of NS in the pediatric population.

Pathogenesis of Edema

It is important to be aware of the pathogenesis of edema in NS in order to understand the principle behind measurement of urinary indices. The historical theory of nephrotic edema generation postulates that stimulation of the renin-aldosterone axis (RAAS) in response to hypovolaemia mediates sodium retention through the following sequence of events: Low serum albumin with decreased plasma oncotic pressure results in an imbalance of Starling forces in capillaries leading to interstitial leakage of fluid, low oncotic pressure, hypovolaemia and stimulation of the RAAS system.[3] This is termed as the underfill hypothesis.

However, many workers do not support the underfill theory, and focus on the conceptually opposite idea, the so-called "overfill" hypothesis of primary sodium retention in at least some patients.[4] The classic studies by Chandra *et al.,*[5] demonstrated that proteinuria per se results directly in sodium retention. They showed that hypoalbuminemia and hypovolemia are not essential for sodium retention.

The site of increased sodium absorption in the kidney remains controversial. In the study by Ichikawa *et al.*[6] the collecting duct was found to be the main site for sodium reabsorption with increased sodium transport via epithelial sodium channel ENaC and sodium potassium adenosine triphosphatase (Na-K-ATPase).[7] Valentin *et al.* showed that cyclic guanosine monophosphate cGMP phosphodiesterase activity in the medullary collecting ducts is increased, leading to resistance to atrial natriuretic peptide actions thus causing sodium retention.[8] In contrast, some studies have supported the proximal tubule as the site of increased sodium reabsorption in NS with albumin directly stimulating NHE3 (sodium hydrogen exchanger 3).[9] Thus the relative importance of the role of the proximal tubule and collecting duct in sodium absorption is controversial.

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Even though the site of sodium reabsorption remains controversial, it is abundantly clear that edema in nephrotic patients may be associated with either low or increased intravascular volume and identification of volume status is important for therapy. In patients with intravascular volume depletion IV albumin may be needed while in edema associated with renal sodium retention diuretics are indicated.

Urine indices may be useful for determining the volume status associated with nephrotic edema. The common urine indices used for determining volume status are the following:

(1) Fractional excretion of sodium (Fe_{Na}) = ($S_{Cr} \times U_{Na}$) / ($S_{Na} \times U_{Cr}$) ×100 where S_{Cr} is serum creatinine (mg/dl), U_{Na} is urinary sodium (meq/l), S_{Na} is serum sodium (meq/l)and U_{Cr} is urine creatinine (mg/dl). Fe_{Na} is low $< 0.2 \pm 0.2$ % in the VC group in contrast to the VE group.[10]

(2) Urine Potassium index ($U_{K}^{+}/U_{K}^{+} + U_{Na}^{+}$). U_{K}^{+} is urine potassium in spot urine sample (meq/l) while U_{Na}^{+} is urine sodium (meq/l). In VC states due to associated secondary hyperaldosteronism urine potassium excretion is high. In contrast, patients with VE have low urine K excretion. Thus in VC states urine K index is >0.6 (or 60% if expressed as %) while in VE states urine K index is < 0.6.[11] A fresh second voided morning spot urine sample is recommended for albumin, sodium, potassium and

creatinine estimation. A simultaneous serum sample should be collected to measure sodium, potassium, albumin and creatinine values. Patients should be on normal salt and water intake. Diuretics, angiotensin enzyme inhibitors and angiotensin receptor blockers may interfere with urine indices and hence should not be used before the urine indices have been tested or diuretics should be discontinued for at least 8 h.

Other Indicators of Volume Status

VC patients may have postural hypotension; their serum albumin is generally <2 g/dl. In addition, VC patients have significantly higher blood urea nitrogen (BUN) and BUN/creatinine ratio compared with VE patients. Mean hemoglobin/hematocrit, urine osmolality, and urine-to-serum osmolality ratio (U_{Osm}/S_{Osm}), may be higher in the VC group compared with the VE group. VC patients have higher renin, aldosterone, and anti-diuretic hormone (ADH) concentration in comparison to the VE group. These tests are, however, expensive and not available at all centers. Hence, urine indices can be useful surrogate markers for volume status.

Limitations of Urine Indices

Use of diuretics or angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) may interfere with the use of urinary indices. Salt intake may influence the urinary indices hence the patients should be on normal salt diet during evaluation. The urine indices do not differentiate between minimal change disease and the non-minimal change variety of NS. Also, the urine indices cannot differentiate between the steroid responders and non-responders as has been highlighted in this issue of the journal.

Conclusion

Measurement of urine indices is a simple bedside tool, and can be used for volume assessment in nephrotic patients. Low sodium excretion coupled with high urinary potassium indicates hypovolemia. Such patients should not receive oral or intravenous diuretics, before correction of their intravascular volume with either crystalloids or colloids. Patients with edema and no clinical or laboratory features of hypovolemia (normal levels of blood urea, FeNa not <0.2% and urinary $K^+/ K^+ + Na^+$ <60%) can safely be treated with potent diuretics.

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