

Solutions to [Laxative Abuse, Electrolyte Disorders, and Nephrolithiasis](#)

1. B: There is a paucity of cases reporting nephrolithiasis in patients with eating disorders. Even though patients with eating disorders have risk factors for stone formation such as decrease urine output and hypokalemia, eating disorders also have stone-inhibiting effects. The most important stone-inhibiting effect of eating disorders is low urinary calcium excretion. Low urinary calcium excretion is thought to be due to increased proximal tubular re-absorption of calcium triggered by the volume depletion caused by vomiting or laxative abuse commonly seen in this group of patients. Eating disorders by themselves are generally insufficient to precipitate stones, and when nephrolithiasis develops another factor is usually present (ie, idiopathic hypercalciuria).

2. C: Hypocitraturia is a [risk factor](#) for the development of nephrolithiasis. Low urine pH increases citrate uptake and decreases urinary citrate excretion. Hypokalemia induces intracellular acidosis which stimulates the mitochondrial enzyme aconitase and the cytosolic enzyme adenosine triphosphate citrate lyase, enzymes responsible for citrate metabolism in proximal tubular cells. This lowers the cell citrate concentration, creating a more favorable gradient for citrate reabsorption. Additionally, hypokalemia has been shown to stimulate NaDC-1.

3. B: [Ammonia](#) is primarily produced in the proximal tubule from the metabolism of glutamine (Glu). Glu is transported into the proximal tubule across the basolateral membrane via the glutamine transporter SN1. Glutamine is subsequently transported into the mitochondria where it is metabolized by glutaminase (GA) into glutamate and NH_4^+ . Deamination of glutamate yields α -ketoglutarate and an additional NH_4^+ by glutamate dehydrogenase (GDH) in mitochondria. Further metabolism of α -ketoglutarate produces bicarbonate and malate. Malate is transported into the mitochondria, and then converted to oxaloacetate and finally to phosphoenolpyruvate and bicarbonate by phosphoenolpyruvate carboxykinase (PEPCK). Therefore, complete metabolism of Glu yields two NH_4^+ ions and two new bicarbonates. Two-thirds of ammonia is then excreted in the urine. Ammonia that is not excreted in the urine is returned to the systemic circulation and metabolized by the liver to urea via a process that consumes bicarbonate. Ammonia produced in the proximal tubule

is secreted into the lumen through the action of the apical Na^+/H^+ exchanger (NHE-3). Secreted NH_4^+ travels down the tubule where it is reabsorbed in the thick ascending limb into the medullary interstitium. The apical $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ cotransporter 2 (NKCC2) and basolateral $\text{Na}^+ - \text{H}^+$ (NH_4^+) exchanger 4 (NHE4) play a critical role in the ammonia transport in the thick ascending limb. The collecting duct then secretes ammonia into the urine. Although collecting duct NH_3 transport was initially thought to involve diffusive movement across the plasma membrane, recent studies have shown that Rh glycoproteins (Rhg) play an important role in collecting duct ammonia secretion. Metabolic acidosis and hypokalemia are associated with increased ammoniogenesis and urinary ammonia excretion. Both acidosis and hypokalemia stimulates glutamine uptake and the expression of ammoniogenic enzymes GA, GDH, and PEPCK in the proximal tubule. Expression of NKCC2 and NHE4 differ in response to acidosis and hypokalemia. Acidosis increases expression of NKCC2 and NHE4, and hypokalemia decreases NKCC2 expression and has no effect on NHE4. Both acidosis and hypokalemia stimulate Rhg expression in the collecting duct.

4. D: Long-standing hypokalemia has important consequences in a multitude of organs. In the kidney, hypokalemia induces mild reduction in renal plasma flow, glomerular filtration rate, and proteinuria. Hypokalemia causes nephrogenic diabetes insipidus through downregulation of aquaporin-2 expression, which is aggravated by the development of central polydipsia that accentuates polyuria independent of impaired urinary concentration. Hypokalemia stimulates proximal tubule bicarbonate reabsorption and ammoniogenesis. Plasma renin and angiotensin levels are invariably elevated in chronic hypokalemia. Potassium deficiency also contributes to hypertension. The mechanism is not completely understood, but vasoconstriction and sodium retention have been implicated. In animals, potassium deficiency stimulates renal enlargement because of cellular hypertrophy and hyperplasia. Finally, if chronic hypokalemia is sustained, the development of cysts, chronic interstitial nephritis, and progressive loss of kidney function can occur, the so-called [hypokalemic nephropathy](#).

5. D: Many factors have been implicated in the pathogenesis of hypokalemic nephropathy. One of the main factors implicated is hypokalemia-induced renal ammoniogenesis. Chronic metabolic acidosis also induces renal ammoniogenesis. Ammoniogenesis has been

associated with the activation of the alternative pathway of complement and the development of progressive tubulointerstitial injury. [A recent study](#) found that treatment of metabolic acidosis with bicarbonate supplementation in patients with chronic kidney disease slowed the progression of kidney disease. Potassium deficiency is also associated with excessive renal growth but impaired body growth. These changes seem to be mediated by abnormalities in the expression of several growth factors including IGF-I, IGFBP-1, and TGF β . The renin-angiotensin system seems to be implicated in the pathogenesis of hypokalemic nephropathy. Renin and angiotensin II levels are invariably elevated in this disorder. High intrarenal angiotensin II levels have been associated with vasoconstriction, ischemia, and upregulation of osteopontin, macrophage infiltration, and stimulation of TGF β synthesis, ultimately resulting in progressive renal fibrosis.