

Objectives

1. Understand adaptation and its critical role in Chronic Kidney Disease (CKD) Stages 3 through 5.
2. Understand the adaptive mechanisms for handling sodium, potassium, and hydrogen ion. Understand the relevance of these to volume overload, hyperkalemia, and metabolic acidosis in CKD.
3. Understand the pathophysiology associated with abnormalities in mineral metabolism, and how they relate to renal osteodystrophy.
4. Review the development of anemia in CKD.
5. Appreciate the varied manifestations of the uremic syndrome as seen in CKD Stage 5.

Readings

Rose and Rennke, pages 276-300.
Rennke and Denker, pages 311-335.

I. Introduction

- A. With progressive nephron loss, clearance is reduced. As a result, there is a tendency for accumulation of solutes and nitrogenous wastes.
- B. In CKD Stages 3 to 5, remarkable adaptive processes allow the maintenance of near-normal body levels of these substances.
- C. Therapy in these stages is focused on achieving balance by controlling intake, maintaining the adaptive process, treating its shortcomings, and minimizing any toxicity.
- D. In CKD Stage 5, the adaptive processes become inadequate, leading to retention of solutes and nitrogenous wastes.
- E. Therapy at this stage is directed at restoring more normal balance through pharmacologic therapy and, when necessary, beginning treatment with dialysis or kidney transplantation.

Patient Presentation

A 35-year-old man has known CKD since correction of a urinary obstruction from bilateral ureteral stenosis in childhood. Over the past 10 years, his GFR has declined at a rate of approximately 6 ml/min/1.73m² per year. At his routine clinic visit, he feels quite well, noting only mild fatigue.

On physical exam, his blood pressure is 160/90, his jugular venous pressure is normal, his heart is regular without murmur or rub, his lungs are clear, and he has no leg edema.

Labs include: Na ⁺ 140	Ca ⁺⁺ 8.6	hemoglobin 10.5
K ⁺ 4.8	HPO ₄ ⁻ 5.2	hematocrit 31.5
Cl ⁻ 105	albumin 3.6	Urine pH 5.0
HCO ₃ ⁻ 20	alkaline phosphatase normal	
BUN 35	PTH 150 (normal 15-55)	
creatinine 2.2		
GFR estimate 34 ml/min/1.73 m ²		

He falls within CKD Stage 3.

Discussion Focus - Consider the adaptive processes for sodium, potassium, hydrogen ion, and phosphate that allow near-normal balance despite a fall in GFR from 120 ml/min down to 34 ml/min and a fall in functioning nephron number from about 2 million down to about 400,000. Despite a loss of 80% of his nephrons, the patient is barely symptomatic.

II. CKD Stage 3/4 – Adaptations of Solute Handling

- A. Potential consequence of nephron loss is solute overload.
- B. Adaptation is defined as the response of the surviving nephrons to continue to excrete the daily load of a given substance.
- C. The process of adaptation is consistent with the *intact nephron hypothesis* which states:
 1. As CKD advances, kidney function is supported by a diminishing pool of functioning (or hyper-functioning) nephrons, rather than a relatively constant number of nephrons each with diminished function.
 2. The sum of the function of the damaged nephrons correlates with the total kidney GFR.
 3. The chronically damaged kidney continues to regulate and responds to the needs of the organism in an organized, meaningful, and directed fashion.
- D. Evidence for this hypothesis is seen in epidemiological studies examining prevalence of anemia, hypertension, low calcium and high phosphate according to the level of GFR

E. Patterns of adaptation vary with importance of the given solute.

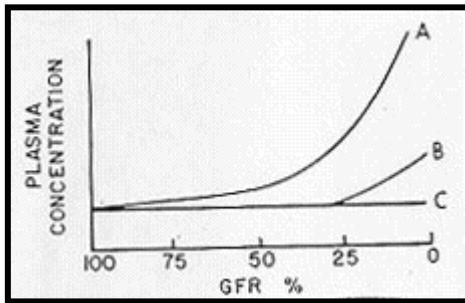


Figure 1:

Pattern A followed by nitrogenous wastes (i.e. BUN)

Pattern B followed by H^+ and phosphorus

Pattern C followed by K^+ and total body sodium

F. Mechanisms of adaptation

1. Hypertrophy - whole kidney vs. individual nephrons
2. Increased kidney blood flow by mild volume overload and hypertension
3. Increased GFR per residual nephron
4. Alterations in tubular reabsorption and/or secretion of solute.

III. Excretion and Adaptation of Major Solutes

A. Sodium (Na^+)

1. Primary regulator of ECF volume. Careful regulation of sodium balance is critical. Sodium content is assessed by physical exam – edema, skin turgor, jugular venous pressure, lung crackles, and blood pressure. No lab test can assess.
2. Total body sodium content is near normal until the late stages of CKD as adaptation nearly follows line of complete compensation (line C).
3. With fewer nephrons, Na^+ excretion per residual nephron must rise if Na^+ intake remains constant. There is an inverse relationship between the fractional excretion of sodium and GFR
 - a. Typically, 95% of filtered Na^+ reabsorbed
 - b. May fall to 50% or less in advanced kidney disease
4. Secretion plays no role in Na^+ handling – sodium is handled by filtration and tubular reabsorption.
5. Proximal tubular reabsorption is not suppressed. The reduction in reabsorption occurs in the distal nephron: the collecting tubule and collecting duct.

- a. Aldosterone is not suppressed, and remains a dynamic participant in sodium homeostasis.
 - b. Atrial natriuretic peptide (ANP) appears to play a major regulatory role in tubular adaptation. With increased atrial stretch from sodium retention and hypervolemia, circulating ANP levels rise and suppress tubular sodium reabsorption. Natriuresis occurs, bringing body sodium stores back toward normal.
6. Mild increases in total body sodium (do not confuse with Na^+ concentration, which is regulated by ADH and water balance) assist in maintaining kidney blood flow, often at the expense of hypertension. Sodium restriction and anti-hypertensive therapy play an important role in treatment.

B. Potassium (K^+)

1. Avoidance of hyperkalemia is critical because of its potential impact on trans-membrane potential and cellular function.
2. Like Na^+ , K^+ adaptation is nearly complete. Serum K^+ tends to remain normal until late in CKD Stage 5.
3. Increased K^+ excretion per residual nephron is accomplished by increased secretion in the collecting tubule/duct. Increased activity of the Na^+-K^+ ATPase on basolateral surface of principal cells is responsible for this.
4. Aldosterone is felt to play a permissive role in K^+ handling, as major reductions in aldosterone cause hyperkalemia disproportionate to the degree of CKD.

Examples:

- a. Syndrome of hyporenin - hypoaldosteronism
- b. NSAIDs
- c. ACE Inhibitors
- d. K^+ sparing diuretics – i.e. spironolactone
- e. (Heparin)

C. Hydrogen ion (H^+)

1. Progressive H^+ retention as GFR falls would produce a life-threatening acidosis.
2. Early in CKD, plasma HCO_3^- and pH are near normal.
3. To accomplish elimination of the daily acid load, tubules must not only secrete H^+ by acidifying the urine, but also produce adequate titratable acid (NH_3) to allow H^+ elimination in bulk.
4. Adaptation of H^+ secretion does occur, but not completely. Compensated acid excretion in the setting of fewer nephrons requires increased tubular generation of NH_3 . The residual nephrons can increase ammonia production up to four-fold.
5. With further GFR decline during CKD Stage 3, the increased NH_3 generation is unable to compensate for the number of tubules lost. A new steady state HCO_3^- of appropriately 12-18 mEq/L is achieved. The pH remains near normal (7.3) due to respiratory compensation and bone buffering.
6. As GFR falls to less than 20 ml/min/1.73m², retention of unfiltered organic anions (sulfates, urates, phosphates) leads to an expansion of the anion gap, creating an anion gap metabolic acidosis.
7. Impact of metabolic acidosis includes:
 - a. Bone buffering leads to loss of calcium (demineralization) and subsequent osteopenia.
 - b. Metabolic acidosis can lead to skeletal muscle breakdown and decreased albumin synthesis.
 - c. Adaptive increase in NH_3 production per nephron can lead to tubulointerstitial damage.
8. $NaHCO_3$ is often prescribed for patients with CKD once HCO_3^- is less than 18-20 mEq/L to prevent positive H^+ balance. However, care must be used with this therapy to avoid inducing a positive sodium balance (volume overload).

D. Mineral Metabolism: Calcium, Phosphate, and Parathyroid Hormone

1. Abnormalities in mineral metabolism are related to:
 - a. decreased phosphate (HPO_4^{--}) excretion
 - b. decreased hydroxylation of vitamin D
2. HPO_4^{--} is handled like sodium, by glomerular filtration and tubular reabsorption.
 - a. As GFR falls, HPO_4^{--} retention ensues.
 - b. Hyperphosphatemia causes a fall in plasma calcium due to precipitation of Ca^{++} x HPO_4^{--} crystals in soft tissues.
3. PTH release is stimulated:
 - a. By a fall in serum calcium concentration
 - b. Directly by Hyperphosphatemia
 - c. A decrease in Vitamin D levels (see below)
4. Vitamin D is absorbed through the GI tract or synthesized in the skin as cholecalciferol. In the liver, it is hydroxylated to become 25-hydroxycholecalciferol (Vitamin D2). It only becomes the active hormone after further hydroxylation to 1, 25 dihydroxyvitamin D (calcitriol).
 - a. 1, 25 Vitamin D has four major functions:
 - i. increase calcium and phosphate reabsorption in the small intestine
 - ii. increase calcium and phosphate release from the bone through osteoclast stimulation (in the presence of PTH)
 - iii. decrease phosphate and calcium excretion in the kidney
 - iv. inhibit release of PTH
 - b. Reduced synthesis of 1, 25 Vitamin D (calcitriol) by the kidney due to reduced kidney mass leads to hypocalcemia from:
 - i. decreased calcium absorption from the GI tract,
 - ii. impaired bone turnover
 - iii. increased calcium loss from the kidney.

5. A fall in plasma Ca^{++} leads to the release of PTH. PTH mobilizes Ca^{++} from bone and suppresses tubular reabsorption of HPO_4^- . The decrease in Vitamin D also releases the inhibition on PTH release (relevance for treatment and over-treatment implications). All together, these phenomenon lead to normalization of both Ca^{++} and HPO_4^- in the plasma at the “expense” of an increased PTH level.

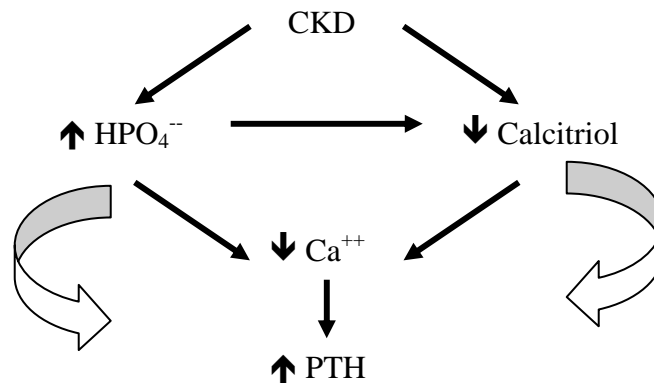


Figure 2

6. There is a wide spectrum of bone disease associated with CKD
7. Other manifestations of secondary hyperparathyroidism in CKD Stages 3 and 4 include pruritus, bone pain, radiographic osteopenia, abnormal bone histology, and muscle weakness.
8. Treatment
 - a. Dietary restriction of HPO_4^-
 - b. Oral binders to block absorption of dietary HPO_4^-
 - i. Aluminum hydroxide – should be used only in cases of severe hyperphosphatemia, as aluminum deposition in bone can result in abnormal bone turnover
 - ii. Calcium carbonate and calcium acetate
 - iii. Resin binders – sevelamer, lantheum
 - c. Cautious prescription of calcitriol when intact PTH > 2-3 x normal with normal HPO_4^- - watch for hypercalcemia and oversuppression of PTH

E. Anemia

1. A normochronic, normocytic anemia is predictable in CKD. Its severity tends to mirror the loss of kidney function.
2. Erythropoietin deficiency is the major cause, due to its synthesis in functional kidney tissue.
3. Adaptation to anemia associated with CKD is similar to adaptation to anemia of other causes and includes cardiac and vascular changes to maintain adequate blood flow
4. Other causes of anemia in CKD:
 - a. Modest reduction in red blood cell half-life
 - b. Possible erythropoietin resistance due to retention of unidentified uremic toxins
 - c. Hyperparathyroid induced bone marrow fibrosis
 - d. Iron deficiency resulting from blood loss, including repeated blood taking
 - e. Inflammation or infection causing 'anemia of chronic disease'
 - f. Other causes of anemia related to underlying kidney disease (eg HUS, malignant hypertension, lupus) or nutritional deficiencies
5. Treatment involves Epo replacement. Weekly subcutaneous injections should be started when Hct < 33.

F. Nitrogenous Wastes

1. No tubular adaptation occurs, and levels of many toxins rise in proportion to the fall in GFR.
2. Need for medication dosage adjustment. Refer to pharmacy recommendations.

Patient Follow-up

This patient has not been seen in follow-up for many years after job placement in another city. He returns at the age of 43 and reports feeling weak and “not himself.” He has difficulty concentrating and sleeping, and feels irritable. He notes muscle cramps, dry skin, and generalized itching. He has occasional hiccups. He notes a foul taste in his mouth, a loss of appetite, and occasional nausea. He has leg swelling and dyspnea on exertion. He has begun to develop chest pain with deep inspiration.

On physical exam, he looks sallow and chronically ill. His weight has decreased 6 pounds since his last visit. Blood pressure is 170/105. He has an abnormal breath odor (uremic fetor) and dry, excoriated skin. His JVP is elevated. His lung exam is notable for reduced basilar breath sounds indicating pleural effusions, and dependent pulmonary crackles. A soft pericardial friction rub is heard at the apex, and his extremities show 3+ pitting edema, distal sensory loss, and asterixis.

Labs include: Na ⁺ 135	Ca ⁺⁺ 7.0	hemoglobin 8.5
K ⁺ 6.3	HPO ₄ ⁻ 8.0	hematocrit 25.5
Cl ⁻ 100	albumin 3.0	Urine pH 5.5
HCO ₃ ⁻ 13	alkaline phosphatase elevated	
BUN 80	PTH 350 (normal 15-55)	
creatinine 6.0		
GFR estimate 10 ml/min/1.73m ² .		

He now falls within CKD Stage 5.

Discussion Focus – This patient’s GFR has fallen progressively, now down to 10% of normal. The loss of functioning nephrons is even more profound. The processes of tubular adaptation are now insufficient to handle the daily loads of Na⁺, K⁺, H⁺, and HPO₄⁻. His anemia has worsened. Nitrogenous and other wastes, as indicated by the level of BUN and creatinine, which are not adapted, have accumulated progressively and caused widespread toxicity. Medication and dietary therapy may help to a certain degree, but dialysis should be instituted to prevent further clinical deterioration.

IV. Stage V CKD – Limits of Adaptation**A. Sodium (Na⁺)**

Hypertension, edema, lung congestion and dyspnea result from sodium accumulation. Despite maximal suppression of tubular sodium reabsorption by high ANP levels, the functioning nephron number becomes insufficient to excrete the daily sodium load. Tight salt restriction and intravenous diuretics might help, but dialysis will efficiently remove the excess salt and water by ultrafiltration (removal of the aqueous portion of plasma).

B. Potassium (K^+)

Despite increased K^+ secretion per residual nephron, nephron loss is overwhelming and K^+ retention has resulted. Conservative measures such as oral exchange resins could help lower the K^+ , but dialysis will accomplish this more efficiently by utilizing diffusion.

Enhanced colonic secretion may account for 30 to 50% of dietary K in patients with ESRD. Constipation in such patients may cause hyperkalemia

C. Hydrogen ion (H^+)

1. Despite greatly increased ammonia synthesis per nephron, inadequate buffer is synthesized due to the magnitude of nephron loss. H^+ ion retention leads to a fall in HCO_3^- and the development of a non-anion gap metabolic acidosis.
2. At the same time, a reduced clearance of organic acids including phosphate, sulfate, urate, and hippurate result in an anion gap acidosis.
3. Significant buffering of H^+ in bone prevents life-threatening acidosis at the expense of bone demineralization. $NaHCO_3$ often improves the metabolic acidosis, but worsens the sodium (and volume) overload. Dialysis will allow HCO_3^- to diffuse into the blood while also removing salt and water.

D. Mineral metabolism

Despite a progressive rise in PTH and reduced tubular HPO_4^{--} reabsorption, HPO_4^{--} retention occurred at a higher level of kidney function than Na^+ , K^+ , and H^+ retention. Hyperphosphatemia and progressive decreases in calcitriol result in hypocalcemia. The increased PTH can also produce pruritus. A rise in the $Ca^{++} \times HPO_4^{--}$ product above 75 puts patients at risk for soft tissue calcification. Abnormalities in Ca^{++} , HPO_4^{--} and PTH increase risk for vascular calcification (medial layer of artery, in contrast to intimal layer seen in atherosclerotic disease). Dialytic HPO_4^{--} removal is often needed in conjunction to HPO_4^{--} restriction, HPO_4^{--} binders, and calcitriol.

E. Anemia

Progressive anemia is usually responsive to erythropoietin and iron replacement

F. Nitrogenous Wastes

As progressive nitrogenous waste retention occurs with a falling GFR, a constellation of symptoms appears that is referred to as the uremic syndrome. The uremic syndrome affects multiple organ systems and has manifestations that vary in severity among individuals. BUN and creatinine are convenient markers, but a legion of other toxins accumulates, and themselves do not exhibit toxic effects. This requires medication dose adjustment as well.

1. Generalized

- a. Fatigue and malaise
- b. Malnutrition – manifested by hypoalbuminemia and weight loss

2. Neurologic

- a. CNS – Irritability, concentration impairment, insomnia, and asterixis can occur early. Later manifestations include mental status change, delirium, myoclonus, seizures, and EEG abnormalities.
- b. Peripheral – Weakness, sensory loss, cramps, myopathy.

3. Gastrointestinal

- a. Anorexia, nausea, vomiting, abnormal taste sensation, gastritis, and diarrhea
- b. Fetor uremicus is a foul odor due to urea metabolized to NH_3 in the mouth, and is a frequent sign of uremia.

4. Cardiopulmonary

- a. Pericarditis may present with a friction rub. Hemorrhagic effusions and cardiac tamponade can also occur.
- b. Pleuritis and pleural effusions may be present.
- c. CHF is a manifestation of sodium (and volume) overload

5. Skin

- a. Xerosis
- b. Excoriation
- c. Skin calcification, uremic “frost” (precipitated urea)

- 6. Platelets have a functional defect caused by uremic plasma. Although the platelet number is normal, abnormal aggregation can be assessed by an increased bleeding time. It is often correctable with dialysis or DDAVP.

Summary

1. CKD represents progressive destruction of functioning nephrons. Adaptive changes assist in maintaining electrolyte and solute balance.
2. Sodium balance is maintained in CKD by the suppression of tubular reabsorption. ANP probably plays a major role after moderate volume expansion develops. Major or abrupt increases or reductions in intake can be problematic.
3. Hyperkalemia is prevented by increased secretion per nephron, mediated by intrinsic tubular cell anatomic and enzymatic change. Aldosterone plays a permissive role; inhibition leads to hyperkalemia.
4. H⁺ excretion is partially adapted. Adaptation is limited by ammonium secretion (reduction in buffers), phosphate and sulfate retention, and other processes. Bone buffering is a last resort in the prevention of progressive acidosis.
5. Phosphate retention, and reductions in activated Vitamin D, lead to hypocalcemia, increased PTH, and multiple toxicities – especially osteodystrophy and tissue calcification.
6. The uremic syndrome represents the protean manifestations of waste retention and resembles an intoxication.