1. Chronic Kidney Disease Signs and Symptoms: Adaptation to Red...

**Chronic Kidney Disease Signs and Symptoms:**

**Adaptation to Reductions in Kidney Function**

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2. Objectives

**Objectives**

- Examine the clinical manifestations of the kidney’s adaptations to chronic kidney disease in humans
- Understand the mechanisms which underlie the signs and symptoms of CKD Stages 3 to 5
  - Sodium $\rightarrow$ hypertension and volume overload
  - Potassium $\rightarrow$ hyperkalemia
  - Hydrogen ion $\rightarrow$ acidosis
  - Mineral metabolism balance $\rightarrow$ osteodystrophy
  - Erythropoietin $\rightarrow$ anemia
- Appreciate the varied manifestations of the uremic syndrome as seen in CKD Stage 5

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3. Patient with CKD

**Patient with CKD**

- A 35-year-old man presents with known CKD since correction of a urinary obstruction from bilateral ureteral stenosis in childhood.
- Over the past 10 years, his GFR has declined at the rate of approximately 6 ml/min per 1.73 m² 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.

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4. Patient's Laboratory Results

**Patient’s Laboratory Results**

- Creatinine 2.2 mg/dl
- eGFR 34 ml/min per 1.73 m² → **CKD Stage 3**

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<td>Albumin</td>
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<td>PTH</td>
<td>150 pg/ml</td>
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5. Discussion Focus

**Discussion Focus**

Normal GFR 100 ml/min/1.73 m². Therefore, this patient’s GFR of 34 ml/min/1.73 m² represents 2/3’s loss of kidney function.

Despite the loss of 2/3’s of GFR and multiple biochemical abnormalities, the patient is barely symptomatic. How does this happen? Why are not all of the biochemical parameters abnormal? Are there trade-offs to this adaptation process?

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6. Determinants of GFR

**Determinants of GFR**

\[
\text{GFR} = N \times SNGFR \\
\]

\[
SNGFR = K_f \times P_{UF} \\
SNGFR = S \times k \times (\Delta P - \Delta \Pi)
\]

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7. Adaptation

**Adaptation**

**Definition:** The response of surviving nephrons to continue to excrete the daily load of a given substance.

**Description:**
- 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 diminishing function.
- Chronically damaged kidney continues to regulate and responds to the needs of the organism in an organized, meaningful, and directed fashion, leading to normal or near normal levels of most solutes and total body water.
- Total Kidney GFR is correlated with overall extent of damage and adaptation.
- These adaptations are maladaptive, further glomerular injury, thereby causing progression of renal disease. Ultimately, therefore, uremia develops.

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8. Adaptation: Maintenance of Regulation

**Adaptation: Maintenance of Regulation**

**Glomerular-Tubular Balance**

- **Glomerular**
  - Hypertrophy
  - Increased kidney blood flow
  - Increased GFR per residual nephron

- **Tubular**
  - Alterations in tubular reabsorption and/or secretion of solute

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9. Sodium Excretion in CKD

Sodium Excretion in CKD

- Total body sodium remains near-normal until late stages
- ANP plays a major role in pressure natriuresis. Therefore, with volume (salt) load:
  - sodium excretion per residual nephron rises
  - distal tubular sodium reabsorption is suppressed
- However, hypertension occurs in 85 to 90% of patients with CKD

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10. Mechanisms of Hypertension in CKD

Mechanisms of Hypertension in CKD

1. Salt retention
2. Kidney injury
   - Activation of renin-angiotensin system
   - Activation of sympathetic nervous system
   - Impaired nitric oxide synthesis and endothelium-mediated vasodilatation
3. Complications of CKD and their treatment
   - Secondary hyperparathyroidism → higher intracellular calcium concentration
   - Erythropoietin treatment leads to higher hemoglobin
4. Aortic stiffness

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11. Chronic Kidney Disease - Adaptation: Slide 11

12. Potassium Excretion in CKD

Potassium Excretion in CKD

- Avoiding hyperkalemia is critical for cell functioning
- Adaptation in CKD is same as adaptation to K load in people with normal kidney function
- Increased K excretion after load is so efficient that normal people can maintain K balance even if K intake is increased from 60 meq/day to 500 meq/day
13. K Adaptation

K Adaptation

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14. K adaptation: Mechanisms

K Adaptation: Mechanisms

- Kidney
  - Increase in K secretion via the Na⁺-K⁺ ATPase activity of principal cells in CCT
  - Reduction in reabsorption by loop of Henle
  - Requires aldosterone and distal flow
- Non-kidney:
  - Increased colonic secretion
  - Increased absorption into non-renal cells
  - Aldosterone dependent

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Clinical States Associated with Hyperkalemia

- Aldosterone deficiency
  - Hyporenin – hypoaldosteronism states
  - NSAID
  - ACE inhibitors
  - Potassium-sparing diuretics
  - Heparin
- Oliguria

H+ Secretion in CKD

In early stages of CKD:
- H+ balance and HCO₃⁻ remain normal due to increases in:
  - H+ secretion per residual nephron
  - NH₃ (buffer) production increases

In late stages of CKD:
- Metabolic acidosis develops due to decreased:
  - NH₃ generation****
  - HCO₃⁻ reabsorption
  - Excretion of hydrogen ions
- HCO₃⁻ levels falls to 12 to 20 and then stabilizes due to bone buffering
17. Chronic Kidney Disease - Adaptation: Slide 17

![Graph showing the adaptation of kidney function in Chronic Kidney Disease (CKD) compared to normal conditions.]

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18. Reasons to Treat Metabolic Acidosis in CKD

**Reasons to Treat Metabolic Acidosis in CKD**

* Not pH (usually around 7.3)*

1. Without treatment, bones will serve as a buffer, which will lead to loss of bone calcium and subsequently osteopenia
2. Metabolic acidosis can lead to skeletal muscle breakdown and decreased albumin synthesis
3. Adaptive increase in NH₃ production per nephron can lead to local activation and to tubulointerstitial damage

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19. Mineral Metabolism

Mineral Metabolism
(Calcium, Phosphate, Parathyroid hormone)
Renal Osteodystrophy

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20. CKD

CKD

↓ Pi excretion ➔ HYPERPHOSPHATEMIA
↓ hydroxylat’n Vit D ➔ ↓ CALCITRIOL

HYPOCALCEMIA

HYPERPARATHYROIDISM

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21. Chronic Kidney Disease - Adaptation: Slide 21

Hyperparathyroidism

↑Bone Resorption (Ca release)  ↑Tubular phosphate excretion

Normo-Calcemia

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22. Prevention of Secondary Hyperparathyroidism

Prevention of Secondary Hyperparathyroidism

- Dietary restriction of phosphate
- Phosphate binders (calcium, lanthenum, sevelamer, aluminum)
- Calcitriol (1, 25 – Vitamin D)

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23. Treatment

![Diagram showing treatment for renal pathophysiology]

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24. Anemia in CKD

**Anemia in CKD**

- Decreases in hemoglobin level trigger erythropoietin production → erythropoiesis in the bone marrow
- Kidney senses decrease in oxygen saturation → increased transcription of erythropoietin gene in the peritubular fibroblast within kidney interstitial space

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25. Adaptation to Anemia

Adaptation to Anemia

- Similar to anemia of all etiologies:
  - Increased cardiac output
  - Left ventricular hypertrophy and cardiac symptoms
  - Decrease in vascular resistance
  - Maintenance of blood delivery & oxygenation

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26. Other Factors Involved in Development of Anemia in CKD

Other Factors Involved in Development of Anemia in CKD

- Iron deficiency
- Inflammation causing ‘anemia of chronic disease’
- Other causes of anemia related to underlying kidney disease (e.g. HUS, malignant hypertension, lupus) or nutritional deficiencies
- Reduction in red cell survival
- Erythropoietin resistance due to “uremic toxins” or to hyperparathyroid-induced bone marrow fibrosis

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27. Case - Follow-up

**Case - Follow-up**

- The patient was not seen in follow-up for many years. He returns at the age of 43 and reports feeling weak and "not himself."
- He notes difficulty concentrating and sleeping, irritability, muscle cramps, dry skin, generalized itching, occasional hiccups, a foul taste in his mouth, loss of appetite, and complains of 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. Blood pressure is 170/105. He has an abnormal breath odor (uremic fetor) and dry, exoriated 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.

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28. Patient’s Laboratory Results

**Patient’s Laboratory Results**

Creatinine 6.0 mg/dl  
eGFR 10 ml/min per 1.73 m²  ⇒ CKD Stage 5

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29. Discussion Focus

Discussion Focus

- The patient’s GFR has fallen progressively, now down to 10% of normal.
- 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 level of BUN and creatinine) 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.

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30. The Uremic Syndrome

The Uremic Syndrome

Symptoms
- Fatigue, metallic taste, drowsiness/insomnia, anorexia, nausea/vomiting, delirium/seizures

Signs
- General appearance - thin (anorexia), irritability
- Skin - grey skin, bruises, pruritis
- Vitals – dypnea, hypertension
- Face – pallor, uremic frost, uremia smell
- Neck – elevated JVP
- Chest – crackles, pleural effusions
- Heart - CHF, pericardial friction rub
- MSK - Bone pain, muscle weakness, paresthesias, twitching, cramps
- Heme: uremic platelets, anemia

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Summary

- CKD represents decline in GFR. Adaptive changes maintain electrolyte and solute balance.
- **Sodium balance** is maintained by suppression of tubular reabsorption. However, hypertension is prevalent and has a multifactorial etiology.
- **Hyperkalemia** is prevented primarily by increased secretion per nephron. Aldosterone plays a permissive role; inhibition leads to hyperkalemia.
- **H⁺ excretion** is partially adapted. Adaptation is limited by ammonium production, and anion retention.
- **Phosphate retention, and reductions in activated Vitamin D**, lead to **hypocalcemia, increased PTH**, and multiple toxicities – especially osteodystrophy and tissue calcification.
- The **uremic syndrome** represents the protean manifestations of waste retention

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