Review of renal pathophysiology

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• 1st Editor KSAP, ASN
• Course Director, Homeostasis 2 (GI, endo, renal pathophysiology, required for all 1st HMS Pathways students)

• Clinical focus: transition to adult care, kidney disorders in context of HIV, electrolytes
• Nothing to disclose
Objectives

• Explore case vignettes to:
  – Review the components of the nephron and key roles in physiology and pathophysiology
In 2019, CREDENCE thrilled the nephrology community!

**CREDENCE**
(Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation)

- **Urinary albumin to creatinine ratio**
- **Change in eGFR from baseline**

V Perkovic NEJM 2019
Q1. Which of the following is the most likely cause of the findings seen in this study?

a) Efferent arteriolar vasoconstriction
b) Afferent arteriolar vasodilation
c) Thinning of the glomerular basement membrane
d) Afferent arteriolar vasoconstriction
Terminology

Determinants of glomerular filtration:

Single nephron Glomerular Filtration Rate

\[ \text{SNGFR} = K \times A \times (\Delta P - \Delta \pi) \]

- **K** = hydraulic conductivity
- **A** = surface area
Hydraulic pressure along the renal vasculature

Adapted from Brenner The Kidney 10th ed
Pressure in the glomerular capillary differs from a peripheral capillary.

Adapted from Rennke Denker 2007
Hydraulic and oncotic pressures along an idealized glomerular capillary.
The kidney must maintain filtration over a wide range of perfusion pressures.

Renal plasma flow (RPF) and glomerular filtration rate (GFR) are plotted against renal arterial mean pressure (mm Hg).
Glomerular filtration is regulated by:

1) flow to the arteriole

Low flow to the afferent arteriole leads to release of renin. Renal nerves can stimulate renin release or directly increase tone.

Efferent arteriole

Low flow to the afferent arteriole leads to release of renin.
Glomerular filtration and 2. tubuloglomerular feedback

Low flow can prompt release of vasodilatory Prostaglandins
Glomerular filtration and tubuloglomerular feedback

High flow in Distal nephron causes constriction of AA through adenosine
Hyperglycemia → Increased glucose in filtrate → Increased sodium reabsorption proximal tubule

Normal

Decreased NaCl delivery to macula densa
Activation of RAAS
Increased glomerular pressure

Blocking SGLT2 increases NaCl delivery distally and **theoretically** limits the increase in glomerular pressure and ultimately limits glomerular damage

**LOSS OF SODIUM** and water with the osmotic diuresis leads to a small weight loss, small decrease in BP
Kidokoro K. Circulation 2019

1st measurement of AA diameter

2nd measurement of AA diameter

catheterization

Empa 5 mg/kg

Before medication

30 min after medication

EA

G

AA

△diameter of afferent arteriole

vehicle

empa

And similar graph for SNGFR!
Q2. A 35-year-old man is evaluated for darkened urine. He is using PrEP (pre-exposure prophylaxis) for HIV for several years.

On exam, he appeared well with a BP of 116/82 mm Hg

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>138 mEq/L</td>
</tr>
<tr>
<td>Cl</td>
<td>114 mEq/L</td>
</tr>
<tr>
<td>K</td>
<td>3 mEq/L</td>
</tr>
<tr>
<td>HCO$_3$</td>
<td>16 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>20 mg/dl</td>
</tr>
<tr>
<td>Creat</td>
<td>1.6 mg/dl</td>
</tr>
<tr>
<td>Phos</td>
<td>2.3 mg/dl</td>
</tr>
<tr>
<td>Uric acid</td>
<td>2.8 mEq/L</td>
</tr>
</tbody>
</table>

Urine: pH 5 no blood, trace protein, + glucose

Urine protein to creatinine ratio is 1.0 mg/mg

Urine albumin to creatinine ratio is 250 mcg/mg

The most likely cause of the laboratory abnormalities is

a) Classic distal renal tubular acidosis  
b) Proximal renal tubular acidosis  
c) Type IV renal tubular acidosis
The proximal tubule is the site of reabsorption of most of the filtrate.
Proximal tubule plays a major role in bicarbonate reclamation

L. Lee Hamm et al. CJASN 2015;10:2232-2242
Proximal reclamation of $\text{HCO}_3^-$ relates to the plasma bicarbonate level (under normal circumstances).

Excretion of bicarbonate

Adapted from Pitts et al JCI 1949
The proximal kidney tubule is the target for tenofovir-associated nephrotoxicity

Atta MG et al. CJASN 2019;14:435-444

[Diagram showing transport mechanisms and stability of tenofovir (TFV) and tenofovir alafenamide (TAF) in the proximal tubule.]

TDF
\[ t \frac{1}{2} 0.4 \text{ min} \]
Unstable in plasma

TAF
\[ t \frac{1}{2} 90 \text{ min} \]
Stable in plasma

Most transported to target cells

[Annotations: MRP 2, MRP 4, MATE1, Mitochondria, OAT-1, OAT-3, OCT-2]
Q3. Cobisistat is in combination pills with tenofovir. In mild to moderate renal impairment, this leads to a decline in eGFR.

What is the mechanism of altered eGFR?

a) Proximal tubulopathy
b) Organic cation transporter inhibition
c) Effective arteriolar vasodilation
d) Tubular Intraluminal obstruction

Inhibition or competition at the organic cation transporters may ↑ serum creatinine without altering filtration (and therefore no change in GFR)

Dolutegravir (Marketed alone as Tivicay)  
(Or co-formulated with ABC+3TC as Triumeq)  
Bicetegravir (co-formulated with TAF +FTC as Biktarvy)  
No dose reduction to eGFR > 30 ml/min

Adapted from Atta
CJASN
Long-acting Cabotegravir and Rilpivirine (CAB+RPV LA, marketed as “Cabenuva”)

- Cabotegravir, a long-acting integrase inhibitor, does not appear to be a substrate for OCT but Rilpivirine may be (but creatinine increase not observed in phase 3 trials)

- No renal toxicity in phase 3 trials (no change in creatinine, eGFR, proteinuria, albuminuria) and those who switched from TDF had improvements (? 1 case report of nephrotic syndrome)

- Limited data on use in eGFR<30 ml/min (but it is 99% protein bound and therefore renal clearance is normally limited)
Q 4. A group of nephrology fellows celebrate COVID19 freedom by eating at a local restaurant but succumb to symptoms of norovirus with nausea and vomiting.

Several days later, one presents with malaise, weakness and vomiting.

Laboratory Data:
- Na 142 mEq/L
- Cl 110 mEq/L
- HCO₃ 30 mEq/L
- K 3.0 mEq/L
- BUN 34 mg/dL
- Creatinine 1.8 mg/dL

The most likely cause of the hypokalemia is
a) Shift of potassium out of the cells
b) Urinary loss with bicarbonaturia
c) Secondary hyperaldosteronism
d) Potassium loss in emesis
Electrolyte concentration in the gastric fluid of normal subjects

Riddell MJ et al. Exp Physiology 1960
When HCO$_3^-$ is not reabsorbed proximally, it is excreted with a cation.
Q5. a 68-year-old man is evaluated for management of hypertension and longstanding hyponatremia. He takes HCTZ, lisinopril and carbamazepine for a distant history of seizure disorder. His blood pressure is 150/88 mmHg and he has no edema. He is not willing to stop the carbamazepine. A trial without HCTZ does not improve his serum sodium and the urine Osm is 600 mOsm/kg. Which of the following is the next best intervention for this patient?

a) Restart the HCTZ
b) Prescribe chlorthalidone
c) Begin torsemide
d) Add amlodipine
e) Start tolvaptan
Production of a maximally concentrated urine requires:

1. Maintenance of the concentrated medulla

1. Activity of vasopressin
Q 6. Our fellow with vomiting is still feeling poorly and now back in the ED and BP is 90/70 mmHg.

Recall his laboratory data:

- Na     142 mEq/L
- Cl    110 mEq/L
- HCO$_3^-$ 30 mEq/L
- K     3.0 mEq/L
- BUN  34 mg/dL
- Creatinine 1.8 mg/dL

Which of the following is most likely to represent urinary electrolytes?
In the setting of volume depletion and RAAS activation, Ang II increases proximal tubule sodium reabsorption.
1. Na\(^+\) is absorbed

2. Lumen becomes electronegative

3. K\(^+\) is secreted

Hoenig, P Zeidel  ML CJASN 2014
Differential phosphorylation of the mineralocorticoid receptor in hyperkalemia vs. volume depletion contributes to the observations seen in the aldosterone paradox!
Q7. An 8-year-old boy is seen for evaluation and delayed growth. His blood pressure is 90/60 mmHg and his heart rate is 96 beats per minute. Screening laboratory studies are done:

<table>
<thead>
<tr>
<th>Na</th>
<th>138 mEq/L</th>
<th>Cl</th>
<th>114 mEq/L</th>
<th>K</th>
<th>2.8 mEq/L</th>
<th>HCO₃⁻</th>
<th>12 mEq/L</th>
<th>BUN</th>
<th>14 mg/dl</th>
<th>Creat</th>
<th>0.7 mg/dl</th>
<th>Ca²⁺</th>
<th>9.9 mg/dL (9.6-10.3)</th>
</tr>
</thead>
</table>

Urine pH 6.5 no blood, trace protein
Urine protein to creatinine ratio is 0.1 mg/mg
Urine Ca²⁺ to creat ratio 0.3 (normal <0.2)

What is the most likely cause of this patient’s laboratory abnormalities?

a) Hypocalcemic hypercalciuria
b) Classic distal renal tubular acidosis
c) Gitelman’s syndrome
d) Chronic diarrhea
Classic distal (type I) RTA

Intercalated cell defect

Ankita Roy et al. CJASN 2015;10:305-324
LOVE renal physiology? Learn along with us all year long!

A chapter by chapter recap of Burton Rose’s classic, The Clinical Physiology of Acid Base and Electrolyte Disorders

www.rosebookclub.com
Further reading


