Kidneys and Sports

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• Renal problems in athletes can range from
  – Benign hematuria to
  – Exercise-related acute renal failure.

• Hematuria
• Proteinuria
Hematuria

• Exercise-induced hematuria can be defined as,
  Gross or
  Microscopic
• Hematuria that occurs
  – After strenuous exercise and
  – Resolves with rest
  – In individuals with no apparent underlying urinary tract pathology.

• Hematuria is defined as,
  More than three red blood cells per high power field.

• A microscopic analysis of 10 to 15 mL of fresh centrifuged urine
  Is essential to confirm the diagnosis of hematuria.

• Presence of more than 50 red blood cells per micro-liter of urine is considered,
  Significant hematuria.
• Hematuria,
  – Macroscopic and
  – Microscopic
Can occur following exercise,
• Regardless of sport.
• The normal urine contains small numbers of red blood cells, which are *dismorphic* and originate from *glomeruli*.

• Microhematuria is prevalent in the general population, with even greater percentage in athletes.

• In a Mayo Clinic study, 13% of adult men and women (≥55 years of age) had asymptomatic microhematuria.

• The rates in athletes are even higher and vary greatly from
  – Marathons (20%) to
  – Football (55%) to
  – Swimming (80%).

• Gross hematuria following renal *trauma*, clearly requires aggressive follow-up to exclude significant renal tract disruption.
• Hematuria is common in long-distance runners. The incidence varies between 17% to 69%, with
  – The highest incidence being reported in ultra-marathon runners.

• Athletic psuedonephritis,
  The combination of
  – Hematuria with casts and
  – Proteinuria,
  May also occur in runners.

• The same rates of hematuria are seen in comparing men and women.

• Clean-catch urine needs to be obtained to differentiate
  Menstruation from hematuria.

• Sexually transmitted diseases can present with microhematuria;
  Therefore *infection* needs to be considered in sexually active athletes.
• Vegetable dyes
  – Such as beetroot and
• Medications such as
  – Nitrofurantoin and
  – Rifampicin and
  – Phenytoin
May discolor the urine.

Box 1. Causes and mechanisms of hematuria in athletes

• Relative renal ischemia: strenuous exercise results in increased blood flow to skeletal muscles at the expense of renal blood flow.
• Exercise-induced increase in catecholamines results in renal arteriolar vasoconstriction.
• Hypoxia and increased lactic acid cause damage to nephrons.
• Skeletal muscle damage from exercise combined with dehydration predisposes to rhabdomyolysis.
• Metabolic myopathies can cause rhabdomyolysis and myoglobinuria.
• Nonsteroidal anti-inflammatory drug use is associated with hematuria in half of the athletes.
- **Foot-strike hemolysis:** repetitive trauma to the heel from running and jumping causes rupture of red blood cells and release of hemoglobin. Hemoglobin is excreted in urine once excess haptoglobin binding sites are saturated by excess hemoglobin.

- **Indirect trauma to bladder** is caused by repetitive jarring motions, especially of empty bladder.

- **Direct blunt trauma to kidneys** in contact/collision sports rarely occurs.

- **Dehydration:** increased blood viscosity leads to increased red blood cell and plasma osmolality, resulting in increased hemolysis of older red blood cells.

- **Decreased red blood cell membrane resistance** results from increased body temperature and circulation associated with strenuous exercise.

- **Free radical damage:** increased free radical production associated with exercise may contribute to renal tissue damage.

- **Lyssolecithin:** strenuous exercise is associated with increased catecholamines that cause spleen contraction and release of lysolecithin. Lyssolecithin causes destruction of red blood cells.
• **Benign** causes of hematuria:
  – Bladder traumas
  – Footstrike hemolysis
  – Hypoxic damage to the nephrons

  Have been correlated to *intensity* of exertion.

• In both swimmers and runners,
  The *longer* and *more strenuous* races
  • Produce greater *incidence* and *severity* of hematuria.

• Hemoglobinuria from the lysis of red blood cells,
  May likewise discolor the urine and
  • May occur due to repetitive *foot strike* in runners
    (“march hemoglobinuria”).

• Myoglobinuria may occur in isolation or in combination with hemoglobinuria,
  Discoloring the urine and producing a dipstick result positive for blood.
• Dipstick tests react with hemo-groups that may present as,
  – Intact red blood cells, or
  – Myoglobin, or
  – Free hemoglobin (hemoglobinuria).

• A false positive dipstick result can be caused by:
  – Vegetable peroxide
  – Bacterial enzymes
  – Other heme groups (myoglobinuria).
Due to this extreme sensitivity, the utility of urine dipstick testing for blood has been questioned. (It detects as few as $1 \times 10^6$ red blood cells in un-spun urine).

Urine microscopy therefore remains, the gold standard.

Microscopy should be performed on a centrifuged sample, and an intact red cell count of more than $100 \times 10^6$ /L is regarded as abnormal.

A positive result is considered, >3 RBC per high-powered field averaged over 21 fields.
• Any abnormal dipstick test, Should be repeated after 24 and 48 hours.

• Then followed by repeat, Urine microscopy
  • For red blood cells using morphology to attempt to distinguish
    – Glomerular
    – Nonglomerular

bleeding.

• Most athletes under 40 years of age will have a benign cause.

• Patients over 40 years of age have greater likelihood of, Significant urologic abnormality than do those who are younger, but

• Even young athlete with hematuria have been found with bladder malignancies.
• Important in both groups is, The persistence of hematuria,
• Sports hematuria is typically,
  – Short lived,
  – Clearing after 48 hours.

• It has been speculated that, A lack of urine in the bladder
• Facilitates trauma of the bladder walls.

• Nephron ischemia and hypoxia leads to
  – Increased glomerular permeability
  – Elevated filtration pressure and stasis,
Enhancing red blood cell and glomerular protein excretion.

• This mechanism probably also explains swimmer’s hematuria,
For which the magnitude also relates to the level of exertion.
• Hematuria may also arise from Perineal trauma
  • From bicycle seats and bumpy terrain among bicycle motocross and recreational cyclists.
  • This may be alleviated by, Angling the nose of the saddle downward.

• Hematuria may be a symptom of other medical conditions, such as:
  – Sickle cell disease
  – Schistosomiasis and
  – Von willebrand’s disease
  a through medical history is important.

• This history should include An accurate drug history, including,
  – Anticoagulants and
  – Nonsteroidal anti-inflammatory drugs (NSAIDs).

• NSAID usage of 54% was reported in a group of patients found to have idiopathic hematuria, Thus suggesting it may be a potential cause.
• Indomethacin has been shown to, *Compromise renal function* during sustained exercise and
• May itself potentiate the development of renal failure through,
Changes in renal blood flow.

• The exercise-related hematuria has been divided into different types:
  – Duration-related
  – Intensity related
  – Direct contact
  – Indirect contact
    • Indirect trauma is a part of the duration-related injuries in which the bladder or kidney is jarred during activity.
Causes of hematuria

<table>
<thead>
<tr>
<th>Categories</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration related</td>
<td>Footstrike hemolysis</td>
</tr>
<tr>
<td></td>
<td>Bladder/kidney trauma</td>
</tr>
<tr>
<td></td>
<td>Dehydration-related hematuria</td>
</tr>
<tr>
<td></td>
<td>Hyperexia hematuria</td>
</tr>
<tr>
<td>Intensity related</td>
<td>Ischemic insults</td>
</tr>
<tr>
<td></td>
<td>Hypoxic insults</td>
</tr>
<tr>
<td></td>
<td>Acidic insults</td>
</tr>
<tr>
<td></td>
<td>Toxic insults</td>
</tr>
<tr>
<td></td>
<td>Splenic lysis</td>
</tr>
</tbody>
</table>

- Hypoxic injury is due to decreased RBF during exercise.
- The damage is thought to be secondary to the spiral arteries to the renal papilla, having diminished flow and being starved of oxygen. This leads to fragility of the arterioles and bleeding on reperfusion postexercise.
- During childhood the spiral vessels are less tortuous, which would explain the decreased rate of hematuria in children.
• The use of NSAIDs, particularly Indomethacin,
• Has been shown to
  – Decrease RBF and
  – Increase FF
Which both of these changes will cause hematuria.

• Acidic insults (increased lactate)
• Toxic insult (myoglobinuria)

  Increase permeability of the glomeruli

• Intense exercise may cause
  Free radical production,
  That can cause destruction of RBC and hematuria.

• Another reason for RBC destruction is the hemolytic factor in the spleen (lysolecithin).

• Hematuria is different from proteinuria,
  Which doesn't occur if the intensity of exercise is below 50% of \( \text{vo}_2\text{max} \).
• Footstrike hemolysis,  
  Is probably the most recognizable cause of exercise hematuria.

• Running up hill,  
  Which has less heel strike than running down hill,  
• Has less hematuria.

• The rupture of RBCs in the heel due to impact  
  Causes the release of hemoglobin.

• If the repeated trauma is excessive,  
  Then haptoglobin binding of free Hgb is overwhelmed,  
  and,  
• Hemoglobin is excreted in the urine.

• This theory is supported by the finding of  
  Decreased plasma haptoglobin with hematuria.
• Hyperexia can cause lysis of RBCs, causing hemoglobinemia, 
The cause may be due to an increase in membrane fragility.

• This resulting hemolysis and lead to Acute renal failure.

• Care should be taken while exercising in the heat.

• Proper hydration is important in maintaining plasma volume and preventing hemolysis.

• Kidney trauma has been described as a cause of hematuria, either
  – By a direct blow (football, boxing) or
  – By jarring of the kidney (jumping, soccer, and basketball).
• Infection (cystitis, urethritis, prostatitis)
  – Accounts for 25% of all cases of atraumatic hematuria

• Stones
  – Representing another 20%

• No cause
  – Found in 10%

Evaluation

• The athlete with hematuria needs a thorough history and physical to evaluate whether the cause is exercise related.

• If there are no other ominous signs,
  Then a repeat urinalysis at 24-72 hours can be done.
• If repeat urinalysis is negative, The athlete may return to exercise with no known long-term detriment to renal function.

• The athlete should be well hydrated before exercise to prevent the decrease in RBF.

• Athletes with known metabolic disease, Such as sickle cell trait,
• Need further workup to eliminate the possibility of hemolysis.

• A consultation with a nephrologist is recommended for,
  – Asymptomatic athletes who have Persistent hematuria for 2 weeks or more,
  – As well as for athletes with a history of familial renal disease and Associated signs and symptoms, such as
    • Proteinuria,
    • Edema,
    • High blood pressure, and
    • Anemia.
• An athlete over age 40 needs further consideration,
  Since the likelihood for
  – Renal or bladder tumors with painless hematuria is greatly increased.

• Chronic cases of repeated exercise-related hematuria can cause
  Macrocytic anemia and further evaluation is warranted.

• The workup for hematuria should involve microscopy to evaluate for whole or fragmented RBCs.

• If no RBCs are seen, then myoglobinuria should be considered.

• Bailey found myoglobinuria in 1.6% of athletes from various sports.

• It’s more common in untrained individuals.

• For myoglobinuria, plasma CPKs should be measured, and the athlete should have aggressive fluid replacement.
Hematuria workup

Hematuria

Follow table

Repeat positive at 24-48 hours

Culture

Positive nitrate or L.E.
symptoms

Negative

Repeat positive at 24-48 hours

IVP/CT

Further workup

Abnormal

Cystoscopy

Further workup

Abnormal

24 hour Cr Cl & Pro

<1.5 grams pro

Normal Cr Cl

Close follow up

Further workup

Abnormal

Further workup

Normal

Treat

Further workup

Normal

CT scan of kidneys

Renal contusion or renal cancer

CT scan of kidneys

Urine culture, IVP, CT

Kidneys stones, trauma, or pyelonephritis

Glomerular disease

Serum screen for complement

Bladder tumor

Cystoscopy

Another cause of hematuria

More thorough history

Renal tumor

CT scan with contrast

Table: Hematuria; further workup

<table>
<thead>
<tr>
<th>Finding</th>
<th>Reason for workup</th>
<th>Important test to perform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuation of hematuria &gt;24-72 hours</td>
<td>Renal contusion or renal cancer</td>
<td>CT scan of kidneys</td>
</tr>
<tr>
<td>Flank pain</td>
<td>Kidneys stones, trauma, or pyelonephritis</td>
<td>Urine culture, IVP, CT</td>
</tr>
<tr>
<td>Urinary casts</td>
<td>Glomerular disease</td>
<td>Serum screen for complement</td>
</tr>
<tr>
<td>Recurrent episodes</td>
<td>Bladder tumor</td>
<td>Cystoscopy</td>
</tr>
<tr>
<td>Mild, short-duration exercise</td>
<td>Another cause of hematuria</td>
<td>More thorough history</td>
</tr>
<tr>
<td>Age over 40 years</td>
<td>Renal tumor</td>
<td>CT scan with contrast</td>
</tr>
</tbody>
</table>
Proteinuria

- Proteinuria is defined as,
  - More than 150 mg of protein per 24 hours.

- A common finding on dip strip
  - Within 48 hours of exercise
  - Fewer than 2% of all cases having a serious urinary tract disorder.

- Common causes, (benign)
  - Dehydration, orthostasis, fever, heat or cold injury, emotional stress, vigorous exercise and acute illness.

- Pathologic causes,
  - Hypertension, diabetes, collagen vascular disease, cancer, infection or autoimmune disease.
• Post-exertion proteinuria occurs after both
  – Contact and
  – Non-contact sports.

• The etiology is complex and appears to be related to,
  Exercise intensity, not duration.

• Proteinuria is common during childhood and peaks in
  adolescence.
  The natural history is typically of a transient condition,
  Less than 1:1000 have anything other than a benign cause.

• For this reason, the utility of urinalysis during adolescent
  preparticipation examinations has been questioned.

• Considering the transient nature of this phenomenon,
  Routine screening is not recommended for this age group.
• There is not any difference in PEP between men and women.

• The effect of exertion on PEP is not altered by age or gender.

• In 1956 Gardner coined the phrase *Athletic pseudonephritis*

  • In an attempt to differentiate the condition from nephrotic syndrome.

  • The excess protein in the urine postexercise has been noted in many sports:
    – Rowing,
    – Bicycling,
    – Cross country skiing,
    – Running,
    – Swimming, and
    – Football.
• The term “orthostatic proteinuria” is used to define, 
  A condition characterized by the appearance 
  of proteinuria 
  – Upon standing or 
  – With physical exercise.

• It is generally nonselective and slight, 
  Though it may reach 1 g/24 h.

• Normal healthy athletes will excrete 
  Less than 50 mg of plasma proteins per day.

• At rest in the glomerulus, 
  – Proteins smaller than albumin are filtered from plasma 
  – With subsequent extensive proximal tubular reabsorption.
• During exercise,  
A glomerular pattern of protein loss occurs with enhanced glomerular filtration of macromolecules (principally albumin) due to,  
– Sluggish glomerular blood flow and  
– Increased glomerular basement membrane permeability.

• As exercise intensity increases,  
Tubular reabsorption of small proteins declines,  
– Leading to higher urinary concentration of low molecular weight proteins (β2-microglobulin) and thus,  
• Proteinuria of a mixed glomerular-tubular type.

• The increase in excretion of HMW proteins reflects  
A change in the glomerulus and that  
• The increase in the more readily filtered LMW proteins is due to  
An interference of the renal tubule reabsorption.  
Therefore,  
• Changes in the HMW proteins would reflect changes at the glomeruli and,  
• Increase of LMW proteins reflect changes at the renal tubules.
• Poortmans showed that the PEP changes with Type of exertion.

The 100 meter sprint (anaerobic) caused increase in albumin but not in beta-2-microalbumin. ??

• The longer events (aerobic) caused an increase in both proteins. ??

• They showed that PEP was correlated to the lactate level (r = 0.87).

Protein loss is
• Maximal within 30 minutes of stopping exercise and
• Should cease within 24 to 48 hours.

• Measuring serial urine postexercise, Poortmans showed that,
The half-life is 54 minutes and,
The peak is 20-30 minutes postexercise.

• Peak levels register 2+ or 3+ on dipstick testing or
• With quantitative measurement 100 to 300 mg.

• The extent of proteinuria and
• Speed of resolution
Differentiates exercise-induced proteinuria from more serious causes.
• Normal urine collected under resting conditions contains up to 200 mg per day of protein.

• Dipstick tests for proteinuria are sensitive and may detect and indicate “trace proteinuria” at urinary protein levels of 100 mg/L physiologic proteinuria.

• When daily output exceeds 2 liters, negative testing with dipstick occurs; more concentrated urine may register as positive, making this form of test a less reliable indicator of nonphysiologic proteinuria.

• Remembering that false-positive tests for proteinuria can occur,
  • It is important when assessing
    – Concentrated post exercise (spg over 1.025) or
    – Alkaline (pH more than 7.5) urine.

• False-negative results occur with
  – Dilute urine (specific gravity more than 1.015) and
  – When the urinary proteins are non-albumin or low molecular weight.
• A clinical yardstick is to combine
  – The urinary specific gravity with
  – Protein dipstick estimates of trace or 1+ proteinuria
    (in cases where dip strip is 2+ or more, spg is less important)

The last two digits of the specific gravity an indicator of the upper limit of normal for that specimen of urine
(e.g., 1.030 spg = 30 mg/dl expected upper limit of normal for protein in that specimen).

<table>
<thead>
<tr>
<th>TABLE 58.1 Dip Strip Indices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>Color and appearance</td>
</tr>
<tr>
<td>Specific gravity</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>Protein</td>
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<tr>
<td>Glucose</td>
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<tr>
<td>Hemoglobin</td>
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<tr>
<td>Nitrite</td>
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<tr>
<td>Leukocytes</td>
</tr>
</tbody>
</table>

In rats,
• An angiotensin II infusion has been shown to increase albuminuria,
  Which is secondary to an increase in FF.
• The same mechanism would explain the PEP changes seen in humans.

• The runners have more proteinuria in the Warmer dehydrating weather with an increase in FF.
• There is a question of whether, The renin-angiotensin system (RAS) or Prostaglandins play a role in PEP.
  • Numerous studies have shown, ACE inhibitors decrease PEP.
  • This would support the role of RAS.
• Indomethacin has been shown to, Decrease RBF and Increase FF and,
  • Through this mechanism, increase proteinuria.
• A training effect exists with
  Reduced proteinuria for bouts of consistent exercise,
But any increase in
  – Workload or
  – Intensity
Further elevates urinary protein levels.

• Prone and upright samples may be necessary,
  To exclude benign orthostatic proteinuria.

Evaluation of athletes with proteinuria:

- Proteinuria
  - Repeat urinalysis (24-48 hrs)
    - ABNL
    - Upright and supine urinalysis
      - Supine ABNL
      - Serum creatinine and BUN
      - 24 urine for creatinine and protein
    - Urine protein electrophoresis
      - IVP/CT
        - Tubular protein
          - Evaluate for tubular disease
            - 1-2 gr/day proteinuria
            - Follow closely
          - Serum cholesterol, albumin, glucose, serology
            - Renal biopsy
          - >3 gr/day proteinuria
            - Evaluate for tubular disease
• When investigating proteinuria that doesn’t resolve,
  Other forms of benign and common causes need to be considered.

• The most common kind of proteinuria in adolescents is
  Benign positional proteinuria.

• This disorder, like PEP or fever-associated proteinuria, is
  Transient.
**Selected Investigations to Be Considered in Proteinuria**

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibody</td>
<td>Elevated in systemic lupus erythematosus</td>
</tr>
<tr>
<td>Antistreptolysin O titer</td>
<td>Elevated after streptococcal glomerulonephritis</td>
</tr>
<tr>
<td>Complement C3 and C4</td>
<td>Levels are low in glomerulonephritis</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>If normal, helps to rule out inflammatory and infectious causes</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>Elevated in diabetes mellitus</td>
</tr>
<tr>
<td>Hemoglobin, hematocrit, or both</td>
<td>Low in chronic renal failure that impairs hematopoiesis</td>
</tr>
<tr>
<td>HIV, VDRL, and hepatitis serologic tests</td>
<td>HIV, hepatitis B and C, and syphilis have been associated with glomerular proteinuria</td>
</tr>
<tr>
<td>Serum albumin and lipid levels</td>
<td>Albumin level decreased and cholesterol level increased in nephrotic syndrome</td>
</tr>
</tbody>
</table>

**Selected Investigations to Be Considered in Proteinuria**

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum electrolytes (Na⁺, K⁺, Cl⁻, HCO₃⁻, Ca²⁺ and PO₄²⁻)</td>
<td>Provide a screening examination for any abnormalities following renal disease</td>
</tr>
<tr>
<td>Serum and urine protein electrophoresis</td>
<td>Results are abnormal in multiple myeloma</td>
</tr>
<tr>
<td>Serum urate</td>
<td>In addition to stones, elevated urate can cause tubulointerstitial disease</td>
</tr>
<tr>
<td>Renal ultrasonography</td>
<td>Provides evidence of structural renal disease</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Can provide evidence of systemic disease (e.g., sarcoidosis)</td>
</tr>
</tbody>
</table>
• When the proteinuria is due to exercise alone,
It carries a benign prognosis with no long-term sequel.