College of pharmacy

Clinical laboratory training

Fifth stage

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Lecture: 3

Blood urea, Blood creatinine, Creatinine clearance, Uric acid

Lecture 3 **Dr. Maytham Ahmed**

Creatinine

Creatinine is derived from the metabolism of creatine and phosphocreatine, the bulk of which is in muscle. Creatine and creatine phosphate exist in a reversible equilibrium in skeletal muscle. Since creatinine is chiefly excreted by glomerular filtration, serum creatinine levels **reflects changes** in glomerular filtration rate (GFR).

Serum creatinine affected partly by:

1- The amount of muscle tissue you have. Men tend to have **higher** levels of blood creatinine because they have more *skeletal muscle tissues* than women and children and infants have **lower** serum creatinine concentrations than adults.

2- Protein in diet. Vegetarians have been shown to have lower creatinine levels in blood. Serum creatinine values are low when the muscle mass is decreased, as in malnutrition.

Creatinine is widely used and a **good indicator** of impaired renal function. Serum creatinine concentration is an **insensitive index** of renal function, as it may not appear to be elevated until the GFR has fallen below 50% of normal, thus a normal serum creatinine does not necessarily indicate normal renal function. Serum creatinine is a more specific and a **better indicator than** urea for assessment of impaired renal function.

Normal Reference Values

Adult men: 0.9–1.3 mg/dL, **Adult women**: 0.6–1.1 mg/dL

Serum creatinine concentration in patients with untreated end-stage renal disease **(ESRD)** may exceed 1000 µmol/L (11 mg/dL). **To convert** plasma creatinine in µmol/L to mg/dL, multiply by 0.011.

Clinical Implications

1. ***Increased blood creatinine levels*** occur in the following conditions:

Impaired renal function, chronic nephritis, obstruction of urinary tract, muscle disease, congestive heart failure, shock, dehydration, rhabdomyolysis (skeletal muscle tissue breakdown), hypothyroidism.

2. ***Decreased creatinine levels*** occur in the following conditions:

Decreased muscle mass, advanced and severe liver disease, inadequate dietary protein, pregnancy (0.4–0.6 mg/dL is normal; 0.8 mg/dL is abnormal and should be noted).

Interfering Factors with creatinine

1. High levels of ascorbic acid and cephalosporin antibiotics can cause a falsely increased creatinine level; these agents also interfere with the BUN-to-creatinine ratio.

2. Drugs that influence kidney function can cause a change in the blood creatinine level. Some drugs including trimethoprim and cimetidine inhibit creatinine secretion, reducing creatinine clearance and elevating serum creatinine without affecting the GFR.

3. A diet high in meat can cause increased creatinine levels.

4. Creatinine is falsely decreased by bilirubin, glucose, histidine, and quinidine compounds.

5. Ketoacidosis may increase serum creatinine substantially.

Specimen

The methods described are suitable for the measurement of creatinine in **serum**, **plasma**, or **diluted urine**. Such specimens are stable for at least 7 days at 4°C. Serum creatinine is also stable during long-term frozen storage and after repeated thawing and refreezing.

Principle: Most chemical methods for measuring creatinine are primarily based on the reaction with alkaline picrate. In this reaction, **creatinine** reacts with **picrate ion** in an **alkaline medium** to yield an equimolar orange-red complex.

Urea

Urea is synthesized in the liver as the final product of amino acid catabolism. It is the major form of nitrogenous waste in mammals, having a very high solubility in water. More than 90% of urea is excreted through the kidneys, with the remainder mainly lost across the gastrointestinal tract and skin. In the kidney, it is freely filtered at the glomerulus; 40 % to 50% is **reabsorbed** in the proximal tubules.

Normal Reference Values

The normal value of **blood urea** is 15 - 40 mg per 100 ml.

To convert plasma urea in mmol/L to mg/dL, multiply by 6.

As a kidney function test, serum urea is inferior to serum creatinine because:

1- Urea varies directly with dietary protein intake. High protein diet increases urea formation. Gastrointestinal bleeding also increase urea formation.

2- Any condition of ↑ proteins catabolism *(Cushing syndrome, diabetes mellitus, starvation, thyrotoxicosis, severe infections, tissue breakdown, trauma, use of large doses of corticosteroids)* →↑ urea formation.

3- Prerenal factors that decreases renal perfusion and GFR, such as dehydration, causes an increase in blood urea levels.

4- Unlike creatinine, urea production rates are not constant, being dependent on the activity of the urea cycle enzymes.

5- Significantly lower urea concentration may indicate acute tubular necrosis or decreased urea production due to low protein intake, starvation, or severe liver disease. High blood urea concentration with a normal creatinine concentration may be seen in pre-renal states leading to raised urea (i.e., decreased renal blood flow or increased urea production).

6- About 50 % or more of urea filtered at the glomerulus is passively reabsorbed by the renal tubules. The amount reabsorbed depends on flow rate. Less urea is reabsorbed when urine flow rates are high, so lower blood urea concentrations are seen in pregnancy. Conversely, reduced renal perfusion (e.g., with dehydration or cardiac failure) leads to increased blood urea concentrations.

Therefore urea is less accurate than creatinine as an estimate of GFR.

In the US and a few other countries, plasma or serum urea concentration is expressed as the amount of urea nitrogen, blood urea nitrogen (BUN).

The test for BUN, which measures the nitrogen portion of urea, is used as an index of glomerular function in the production and excretion of urea.

Blood urea nitrogen normal value is between 6 and 20 mg per 100 ml

The conversion is blood urea nitrogen × 2.14 = blood urea.

A normal level of blood urea is often mistakenly regarded to indicate normal kidney function. In a steady state the blood urea may not rise beyond the upper range of normal (40mg/dl) even when 75% of the renal function is lost.

Azotemia: **Increase** in the blood levels of **non-protein nitrogen compounds** (NPN) as creatinine, urea, uric acid is referred to as azotemia & is the hallmark of kidney failure.

Interfering Factors with blood urea nitrogen

1. A combination of a low-protein and high-carbohydrate diet can cause a decreased BUN level.

2. The BUN is normally lower in children and women than adult men.

3. Decreased BUN values normally occur in late pregnancy because of increased plasma volume (physiologic hydremia).

4. Older persons may have an increased BUN.

5. The IV feedings may result in over hydration and decreased BUN levels.

6. Many drugs may cause increased or decreased BUN levels.

Control of blood urea

- **Correct intake of protein**: If kidneys can't do their work properly, extra protein will increase the workload on kidneys. On the contrary, lack of protein may lead to malnutrition. Under this circumstance, it is necessary to restrict the amount of protein intake to 0.6-0.8 g/kg every day.
- **Supplement enough calories**: This can reduce the consumption of protein in the body.

Principle: Most of the enzymatic methods use urease to convert urea to ammonia; the methods may then be classified by the method used to quantify the ammonia generated. The generation of ammonia (ammonium ions in aqueous solution) may be monitored chemically, enzymatically, electrochemically, or using pH indicators.

Specimen

Serum and lithium heparin **plasma** can be used for most methods. No difference in measured urea has been reported for serum samples collected in plain tubes or gel-separator tubes. Fluoride inhibits the urease reaction, so fluoride-oxalate samples are

unsuitable; ammonium heparin cannot be used for any method dependent on ammonia measurement. Urea in separated serum or plasma is stable for 1 week at 4°C or at least 6 months at −20°C.

Estimation of blood urea & serum creatinine are useful. These tests are less sensitive than the clearance tests.

Clearance as an assessment of glomerular filtration rate

The **clearance** is used to **assess GFR** and it is a useful index for the assessment of severity of kidney damage. The concept of clearance is based upon the fact that the rate of removal of a substance from the plasma must equal its simultaneous rate of excretion in urine.

Clearance: is the volume of plasma that could be completely cleared from substance in 1 minute. The unit of clearance is ml/min

$$\textbf{Clearance} = U_x \times V/P_x$$

- U_x = urine concentration of x (mg/dL)
- P_x = plasma concentration of x (mg/dL)
- V = urine output (mL/min)

✓ If X is neither reabsorbed nor secreted, clearance = GFR (Inulin clearance)

✓ If X is reabsorbed, clearance < GFR (Urea clearance)

✓ If X is secreted, clearance > GFR (Creatinine clearance)

The best substance to use for glomerular clearance is that it is filtered completely through the glomerulus and not reabsorbed through the nephron tubule and not affected by endogenous and exogenous factors.

Renal clearance of ***INULIN*** is the gold standard for determination of GFR. Inulin meets all of the criteria for the ideal substance to measure

GFR. However, inulin does **not occur naturally** in the body and requires several hours of infusion to reach steady state concentration.

Creatinine clearance test

It measures the rate at which the kidneys are able to remove (to clear) a filterable substance creatinine from the blood. Creatinine clearance is a rough measure of the GFR

Normal range for male = 85 – 125 ml/min, female = 75 – 115 ml/min

In clinical practice creatinine clearance may be used to estimate GFR for the following reasons:

1. Inulin is not produced endogenously. Therefore, it must be infused intravenously if it is to be used in renal function tests. So, it is much more convenient to use a substance that is normally present in plasma.

2. Creatinine, a normal breakdown product of creatine, is an endogenous compound. Endogenous creatinine production is constant as long as the muscle mass remains constant. Because all creatinine filtered by the kidneys in a given time interval is excreted into the urine. Disorders of kidney function prevent maximum excretion of creatinine. In renal failure the kidney will not be able to excrete creatinine in urine leading to an elevation in serum creatinine level.

However, in humans, a small amount of creatinine is secreted into the urine in the proximal tubules. Consequently, the rate of excretion of creatinine exceeds its rate of filtration by 5 to 10%. The clearance of creatinine thus exceeds the true GFR by 5 to 10%.

Both serum creatinine and creatinine clearance are used in kidney function tests to :

1- Confirm the diagnosis of renal disease.

2- Give an idea about the severity of the disease.

3- Follow up the treatment.

Interfering Factors

1. Exercise may increase creatinine clearance and urine creatinine.

2. Pregnancy substantially increases creatinine clearance.

3. Many drugs decrease creatinine clearance.

4. The creatinine clearance overestimates the GFR when there is severe renal impairment. The serum creatinine is more indicative of the GFR in this situation.

5. A diet high in meat may elevate the urine creatinine concentration.

6. Proteinuria and advanced renal failure make creatinine clearance an unreliable method for determining GFR.

Limitations of creatinine clearance includes creatinine secretion, and may overestimate GFR when GFR is low (due to secretion).

Creatinine clearance is excellent for estimation of GFR in healthy individuals

Uric Acid

Uric acid is formed from the breakdown of nucleic acids and is an end product of purine (adenine and guanine) metabolism in the liver. Uric acid is transported by the plasma from the liver to the kidney, where it is filtered (the net urinary excretion of uric acid is 6% to 12% of the amount filtered). The remainder of uric acid is excreted into the gastrointestinal tract.

Clinical applications

Uric acid is measured to :

1- Diagnosis and monitor treatment of gout.

2- Diagnosis of renal calculi, and detection of kidney function.

3- Assess inherited disorders of purine metabolism.

4- Monitor if uric acid levels are too high after chemotherapy or radiation.

Normal Reference Values

Men: 3.4–7.0 mg/dL

Women: 2.4–6.0 mg/dL

To convert plasma uric acid (urate) in mmol/L to mg/dL, multiply by 17

Clinical Significance

1. **Disease states with increased plasma uric acid (hyperuricemia) include**: gout, increased catabolism of nucleic acids, renal disease, metabolic acidosis, diabetic ketoacidosis, leukemia, multiple myeloma, lymphoma, increased cell destruction, as after massive radiation or chemotherapy.
2. **Decreased levels of uric acid (hypouricemia) occur in the following conditions:** Fanconi's syndrome, SIADH, xanthinuria (deficiency of xanthine oxidase)

Interfering Factors with uric acid

1. Stress and strenuous exercise will falsely elevate uric acid.
2. Many drugs cause increase or decrease of uric acid. High levels of aspirin decrease uric acid levels.
3. Purine-rich diet (e.g., liver, kidney) increases uric acid levels. Low purine intake, coffee, and tea decrease uric acid levels.
4. Uric acid level should fall in patients who are treated with allopurinol and uricosuric drugs such as probenecid and sulfinpyrazone.

To control uric acid avoid eating foods high in purine. Limit alcohol intake because alcohol dehydrates the body. Keep your body hydrated with water.

The **device** routinely used for the biochemical evaluation of urea, creatinine and uric acid is **spectrophotometer**.