1. What are the major fuels used by kidney for energy production in different metabolic states?

2. What are the different roles of the kidney in carbohydrate, lipid & protein metabolism?

3. How does the kidney involved in the production of ammonia and control of acid base balance?

4. What are the endocrine functions of the kidney?

5. What is the normal urine composition?

6. How the renal glomerulus membrane structure affect the renal function?
Our kidneys are incredible organs that get rid of toxins, retain substances needed by our bodies, and maintain the right balance of electrolytes, minerals, and water; absorption of glucose, amino acids, and other small molecules; regulation of blood pressure; production of various hormones, such as erythropoietin; and activation of vitamin D.
What are the major fuels used by kidney for energy production in different metabolic states?
During **Well fed state** major fuels is **GLUCOSE**.

During **Starvation state** major fuels are **FATTY ACIDS AND KETONE BODIES**.
What are different roles of the kidney in carbohydrate, lipid & protein metabolism?
I-CARBOHYDRATE
METABOLISM
A-Glucose oxidation

RENAL CORTEX

richly supplied with oxygenated blood and thus oxidize glucose completely into CO2 and H2O by aerobic glycolysis and TCA cycle

RENAL MEDULLA

poorer blood supply thus oxidize glucose anaerobically into lactic acid by anaerobic glycolysis
REGULATION OF GLUCOSE HOMEOSTASIS

- Uptake of glucose from the circulation
- Reabsorption of filtered glucose and pumping it back in to circulation
- Release of glucose into the circulation during starvation via gluconeogenesis
- 90% of filtered glucose is reabsorbed in the first part (S1) of the proximal tubule SGLT2.
- The remaining 10% is reabsorbed in the distal (S2/S3) part of the tubule SGLT1.
- Glucose is released into the circulation through GLUTs at the basolateral membrane of the epithelial cells lining the proximal tubules.
N.B.

Specific SGLT2 inhibitors are being developed as a novel means of controlling hyperglycemia in T2DM by increasing glucose excretion in urine.
GLUCONEOGENESIS

Occur in renal cortex.

Kidney in Long-Term Fasting

Kidney expresses the enzymes of gluconeogenesis.
The renal cortex has the gluconeogenic enzymes, synthesize glucose-6-phosphate from: precursors and is able to release glucose into the blood stream via glucose-6-phosphatase.

What are these precursors?
- **Lactate**: Its sources are RBCs exercising skeletal muscles from anaerobic glycolysis.
- **Glycerol**: Its source is degradation of TAG by lipolysis of adipose tissue (Liver and kidney has active glycerol kinase).
- **Glutamine**: During starvation, protein carbon becomes the major source for glucose.
During starvation, a major site of glutamine metabolism is the kidney

- **Glutamine has 2 important functions:**
  - The nitrogen of this glutamine is eliminated as ammonium ions in urine
  - The carbon chain is utilized for gluconeogenesis.
Kidney in Long-Term Fasting

1. Kidney expresses the enzymes of gluconeogenesis.

2. Kidney also provides compensation for the acidosis that accompanies the increased production of ketone bodies.

3. The glutamine released from the muscle's metabolism is taken up by the kidney and acted upon by renal glutaminase and glutamate dehydrogenase, producing α-ketoglutarate that can enter the TCA cycle, plus ammonia.

   N.B. The ammonia picks up H+ from ketone body dissociation, and is excreted in the urine as NH4+, decreasing the acid load in the body.
Why a patient with renal failure may develop hypoglycemia during prolonged fasting?
After an overnight fast (14-16hrs):

- 75-80% of glucose released into the circulation derives from the liver.
- The remaining 20-25% derives from the kidneys.
- As the duration of fasting increases after 18 hrs, the hepatic glycogen stores become depleted so all the glucose released into the circulation is derived from gluconeogenesis.
As the kidney make a larger % contribution to circulating blood glucose level the liver cannot compensate for the kidney to preserve normoglycemia in patient with renal insufficiency during prolonged fasting.
II-LIPID METABOLISM
Renal cortex: richly supplied with oxygenated blood and thus can oxidize:

- Fatty acid through beta oxidation pathway
- Ketone bodies through ketolysis
II-PROTIEN METABOLISM
A-GAMMA GLUTAMYL CYCLE

- ALLOWS ABSORPTION OF AMINO ACIDS FROM GLOMERULAR FILTRATE

- $\gamma$-Glutamyl transpeptidase
- $\gamma$-Glutamylcysteine synthetase
- Glutathione synthetase
Steps of gamma glutamyl cycle
The nephrotoxicity of cisplatin, a chemotherapy drug

The binding of cisplatin to glutathione

Metabolism of the cisplatin-glutathione complex via a gamma glutamyl transpeptidase (ggt)-dependent pathway in the proximal tubules

Cisplatin-cysteinyl-glycine-conjugate which is a nephrotoxin.
Do you remember:

What is Carnitine?
B- Carnitine Homeostasis
Carnitine is crucial for energy production in tissues dependent upon fatty acid oxidation, such as cardiac and skeletal muscle. About 95 percent of carnitine is stored in muscle.
L-carnitine (LC) is an amino acid derivative that plays an essential role as it transports long-chain fatty acids into the mitochondrial matrix (carnitine shuttle), so they can be broken down through β-oxidation to acetyl CoA to obtain usable energy via the citric acid cycle.
Carnitine is derived from red meat and dairy products in the diet, biosynthesis is important to meet normal requirements in healthy individuals. The biosynthesis of carnitine occurs primarily in the liver and kidneys from the amino acids lysine and methionine then is released to other tissues.
Carnitine excretion in kidney

Carnitine is filtered at the glomerulus and over 90 percent undergoes tubular reabsorption back to conserve it.
A defect in the plasma membrane carnitine transporter in kidney and muscle.

Urinary carnitine wasting and intracellular carnitine accumulation.

Primary carnitine deficiency.

- Preterm neonates are at risk for developing carnitine deficiency because they have impaired reabsorption of carnitine at the level of the proximal renal tubule.
- Chronic renal failure may impair the biosynthesis of carnitine also patients with renal failure appear to lose carnitine via hemodialysis.
Symptoms of carnitine deficiency
Include symptoms of hypoglycemia which is a consequence of impaired fatty acid oxidation, muscular weakness and heart affection

Management:
L-carnitine supplementation
Hypoglycemia which is a consequence of impaired fatty acid oxidation

Why?
C- Creatine synthesis & excretion
CREATINE SYNTHESIS

- Arginine
- Ornithine
- Glycine

Guanidoacetate
- Glycine Arginine Amido transferase

SAM
- Methyl transferase

CREATINE
- Creatine kinase

ATP
- Creatine phosphate

Pi

H₂O

Excreted in Urine

Dr. N. Sivanjani
Creatine, is transported through the blood and taken up by tissues with high energy demands, such as the brain and skeletal muscle.

Importance

- Creatine phosphate is a high-energy compound which is a phosphorylated derivative of creatine found in muscle.
- Creatine is reversibly phosphorylated to creatine phosphate by creatine kinase, using ATP. The amount of creatine phosphate in the body is proportional to the muscle mass.
- The presence of creatine kinase (MB isozyme) in the plasma is indicative of heart damage and is used in the diagnosis of myocardial infarction.
ATP  \rightarrow  \text{creatine}

\text{CPK (mitochondrial)}

ADP  \leftarrow  \text{creatine phosphate}
CREATINE DEGRADATION

When muscle mass decreases for any reason (for example, from paralysis or muscular dystrophy), the creatinine content of the urine falls. Why?

excreted in the urine
Serum creatinine is an important indicator of renal health because it is an easily measured as it is excreted unchanged by the kidneys.

Any rise in blood creatinine is a sensitive indicator of kidney malfunction, because creatinine normally is rapidly removed from the blood and excreted.

Creatinine levels in blood and urine may be used to calculate the creatinine clearance (CrCl), which correlates with the glomerular filtration rate (GFR). The GFR is clinically important because it is a measurement of renal function.
D- Different disorders affecting amino acids metabolism that can affect the kidney function.
 PRIMARY HYPEROXALURIA
An autosomal recessive Transaminas deficiency that converts glyoxylate to glycine. Glyoxylate will accumulate. oxidized to oxalate, which, in the presence of calcium, will precipitate. Causes the formation of oxalate stones, and kidney damage.
The buildup of oxalate in the body causes increased excretion of oxalate, which in turn results in renal and bladder stones. Stones cause urinary obstruction (often with severe and acute pain), secondary infection of urine and eventually kidney damage.
Patients with alkaptonuria are usually asymptomatic until about age 40 years. Dark staining of diapers can indicate the disease in infants. Diets low in phenylalanine and tyrosine reduce the levels of HA and decrease the amount of pigment deposited in body tissues.
Cystinuria and cystinosis are disorders involving two different transport proteins for cystine.
An inherited defect in the transport protein that carries cystine, lysine, arginine, and ornithine into intestinal epithelial cells and that permits resorption of these amino acids by renal tubular cells.

Cystine, which is not very soluble in the urine, forms renal calculi (stones).
Symptoms of cystinuria:

- Renal colic caused by stones and perhaps urinary infection or the sequela of renal failure.
- Diagnosis of cystinuria is by measurement of cystine excretion in the urine.
- Treatment with increased fluid intake and alkalinization of the urine.
Cystinosis

- It is a rare disorder caused by a defective carrier that normally transports cystine across the lysosomal membrane from lysosomal vesicles to the cytosol.

Cystine accumulates in the lysosomes in many tissues and forms crystals, impairing their function especially the kidneys and eyes.
Cystinosis has three different forms known as

- Nephropathic cystinosis,
- Intermediate cystinosis
- Non-nephropathic (or ocular) cystinosis.

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Nephropathic cystinosis presents in infancy and is the most common and severe form.

Growth failure and renal Fanconi syndrome are usually the first noticeable complications of the cystinosis.

Diagnosis of cystinosis can be confirmed by measuring cystine levels in white blood cells.

Urinary examination may reveal excess loss of nutrients including minerals, electrolytes, amino acids, carnitine and water, which is indicative of renal Fanconi syndrome.

Treatment of cystinosis
Cysteamine drug is a cystine-depleting agent that can greatly lower cystine levels within cells.
How does the kidney involved in the production of ammonia and control of acid base balance?
The kidney produce ammonia ion in the renal tubules by the action of the enzymes:

*Glutaminase and L-glutamate dehydrogenase*

The produced ammonia combines with $H^+$ to form ammonium ions:

$$\text{NH}_3^+ + H^+ \leftrightarrow \text{NH}_4^+$$

which is excreted as ammonium ions.

NH$_4^+$ production in the tubular lumen accounts for about 60% excretion of hydrogen ions associated with a high protein diet, prolonged fasting, overproduction of normal metabolic acids, such as lactate, acetoacetate, or β-hydroxybutyrate.
What are the endocrine functions of the kidneys?
The Kidneys produce three important hormones:

- Erythropoietin
- Calcitriol (1,25-dihydroxycholecalciferol)
- Renin

- They also synthesize prostaglandins, which affect many processes in the kidneys.
- In addition to synthesis, the kidneys also contribute to the degradation of certain hormones – such as insulin (forms insulinase – cleaves insulin) or parathyroid hormone.
Low oxygen levels

The renal cortex produces a glycoprotein hormone called erythropoietin (EPO).

The bone marrow to make red blood cells
Vitamin D helps the body absorb calcium, which forms and maintains strong bones.

One of the major metabolic functions of the kidney is the formation of the active form of vitamin D (1,25-dihydroxyvitamin D).

The key regulatory enzyme in vitamin D activation is the 1α-hydroxylase enzyme which is found in the kidney.
VITAMIN D DEFICIENCY SECONDARY TO DEFECT IN 1-Α-HYDOXYLASE ENZYME ACTIVITY IN KIDNEY AS A RESULT OF:

• CONGENITAL CAUSE:
• VITAMIN D-DEPENDENT RICKETS TYPE I IS A CONGENITAL DISEASE OCCUR IN INFANT (FAILURE OF CONVERSION OF 25-HYDROXYVITAMIN D (25-OHD) TO 1,25-DIHYDROXYVITAMIN D DUE TO INHERITED MUTATION IN 1-Α-HYDROXYLASE ENZYME

Chronic renal disease
In patients with chronic kidney disease, calcitriol [1,25(OH)2D] production is low due to, loss of the 1-α-hydroxylase enzyme secondary to structural renal damage.
What is the normal urine composition?
COMPOSITION OF URINE

- 95% of volume of normal urine is due to water

**Organic components:**
- urea
- urobilinogen
- uric acid
- creatinine
- metabolites of hormones

**Inorganic components:**
- cations: Na$^+$, K$^+$, Ca$^{2+}$, NH$_4^+$
- anions: Cl$^-$, SO$_4^{2-}$, HCO$_3^-$, HPO$_4^{2-}$
How the renal glomerular membrane structure affect the renal function?
The primary components of the renal glomerular membrane are three proteins:

Three proteins: laminin, entactin, and type IV collagen

The GAG heparin or heparin sulfate.
Thick basal lamina of the renal glomerulus has an important role in glomerular filtration, regulating the passage of large molecules (most plasma proteins) across the glomerulus into the renal tubule.

The pores in the glomerular membrane are large enough to allow molecules up to about 8 nm to pass through.

Although albumin is smaller than this pore size, but it is prevented from passing by the negative charges of heparan sulfate and of certain sialic acid-containing glycoproteins present in the lamina.

These negative charges repel albumin and most plasma proteins, which are negatively charged at the pH of blood.
The normal structure of the glomerulus may be severely damaged in certain types of glomerulonephritis (e.g., caused by antibodies directed against various components of the glomerular membrane).

This alters the pores and the amounts and dispositions of the negatively charged macromolecules referred to above.

Massive amounts of albumin (and of certain other plasma proteins) can pass through into the urine, resulting in severe albuminuria.
Thank You