**OKE SUCCESS OLUWASEYI**

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**MEDICINE AND SURGERY**

**QUESTION 1: ROLE OF KIDNEY IN GLUCOSE HOMEOSTATIS**

The kidneys are essentially designed to filter large quantities of plasma, reabsorb substances that the body must conserve and secrete substances that must be eliminated. These basic functions are critical to the regulation of fluid and electrolyte balance, blood osmolality, acid-base balance, excretion of metabolic waste and foreign chemicals, arterial pressure, hormone secretion and glucose balance.

The 2 kidneys produce a total of approximately 120mL/min of ultrafiltrate , yet only 1mL/min of urine is produced. The basic urine-forming unit of the kidney is the nephron, which serves to filter water and small solutes from plasma and reabsorb electrolytes, amino acids, glucose and protein. The nephron, of which there are approximately 1 million in each kidney, consists of a filtering apparatus (**THE** **GLOMERULUS**) that is connected to a long tubular portion that reabsorbs and conditions the glomerular ultrafiltrate. Fluid filtered from the glomerular capillaries flows into the tubular portion, which is made up of a proximal tubule, Loop of Henle, a distal tubule, all of which assist in reabsorbing essential substances and converting filtered fluid into urine.

CREATININE CLEARANCE (CrCl) or GLOMELURULAR FILTRATION RATE (GFR), most frequently ESTIMATED (eGFR) are considered most useful in determining the degree of renal insufficiency and stage of chronic kidney disease.

**MECHANISMS OF GLUCOSE HOMEOSTASIS IN THE KIDNEYS**

Maintenance of glucose homeostasis is crucial in preventing pathological consequences that may result from hyperglycemia or hypoglycemia. Maintenance of glucose homeostasis involves several complimentary physiologic processes, including glucose absorption (in the GIT), glycogenolysis (in the liver), glucose reabsorption (in the kidneys), gluconeogenesis (in the liver and kidneys) and glucose excretion (in the kidneys).

With respect to renal involvement in glucose homeostasis, the primary mechanisms include release of glucose from the circulation to satisfy the kidneys’ energy needs, reabsorption of glucose at the level of the proximal tubule.

**RENAL GLUCONEOGENESIS**

From the point of view of glucose utilization, the kidney is considered as 2 separate organs; the renal medulla is characterized mainly by glucose utilization and the renal cortex is responsible for glucose release. The separation of these activities represents the consequence of differences in the distribution of numerous enzymes along the nephron. To this point, cells in the renal medulla (which, like the brain, are obligate users of glucose) have significant glucose- phosphorylating and glycolytic enzyme activity, and can therefore phosphorylate and accumulate glycogen. However, since these cells lack glucose-6-phosphate and other gluconeogenic enzymes, they cannot release free glucose into the circulation.

But because these cells have little phosphorylating capacity, they cannot synthesize glycogen. The magnitude of renal glucose release in humans is somewhat unclear, with inconclusive evidence regarding the contribution of the kidneys to total body gluconeogenesis. Based on assumption that gluconeogenesis accounts for approximately half of all circulatory glucose release during the fasting state, renal gluconeogenesis is projected, although not conclusively proven, to potentially be responsible for approximately 40% of all gluconeogenesis. The kidneys appear to play a substantial role in overall glucose release in normal as well as pathological states (e.g, hepatic insufficiency etc.)

To this point, evidence suggests that in patients with Type 2 Diabetes Miletus, renal glucose release is increased in both postprandial and postabsorptive states, implicating the kidneys’ contribution to the hyperglycemia that characterizes this condition.

**GLYCOGENOLYSIS**

Glycogenolysis is the breakdown of glycogen to glucose-6-phosphate and hydrolysis reaction (glucose-6-phosphatase) in order to free glucose. The liver is the only organ that contains glucose-6-phosphatase. So, the cleavage of hepatic glycogen releases glucose, while the cleavage of glycogen from other sources can release only lactate. Lactate, that is generated via glycolysis, is often absorbed by other organs which help in regenerating glucose.

**GLUCOSE REABSORPTION**

The kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. In normal conditions, the kidneys can reabsorb as much glucose as possible, the result being a virtually glucose free urine.

Approximately 180grams of glucose are filtered by the glomeruli from plasma, daily but all of this quantity is reabsorbed through glucose transporters that are present in cell membranes located in the proximal tubules.

These glucose transporters have limited capacity of reabsorption. If this capacity is exceeded, glucose usually appears in the urine. The tubular maximum for glucose (TmG), the term used for maximum capacity, can vary from 260 to 350mg/min/1.73m2 in healthy individuals. It corresponds to blood glucose levels of 180-200m/dL. When the blood glucose is very high and TmG is reached, the transporters cannot reabsorb all the glucose and glucusoria occurs.

Nevertheless, there can be slight differences between the nephrons and the inaccurate nature of biological systems may potentially lead to the development of glucosuria when blood glucose is below TmG. Glucosuria may occur at lower plasma glucose levels in certain conditions of hyper filtration e.g. pregnancy, but as a consequence of hyperfiltration and not hyperglycemia. Renal reabsorption represents the main mechanism by which the kidney is involved in glucose homeostasis. Therefore, the change in tubular glucose reabsorption may have a considerable impact on glucose homeostasis.

**RENAL GLUCOSE TRANSPORTERS**

Glucose is a polar compound with positive and negative charged areas; therefore it is soluble in water. Its transport into and across cells is dependent on two specialized carrier protein families: the GLUTs (facilitated glucose transporters) and SGLTs (sodium-coupled glucose co-transporters). These transporters are responsible for glucose passage and reabsorption in several tissue types, including the proximal renal tubule, blood-brain barrier, small intestine. GLUTs are responsible for the passive transport of glucose across cell membranes, in order to equilibrate its concentrations across a membrane. SGLTs, on the other hand, are involved in active transport of glucose against a concentration gradient by means of sodium-glucose cotransport. There are six members of the SGLT family, SGLT1 , SGLT2 , SGLT4 , SGLT5 , SGLT6 , SMIT1 . With SGLT2 considered the most important because, based on animal studies, it is responsible for the reabsorption of 90% of the glucose filtered at the glomerulus. The other 10% of glucose reabsorbed in the proximal tubule is ensured in SGLT1. Of the family of GLUT proteins expressed in the kidneys, GLUT2 is the major transporter and it releases into circulation the glucose reabsorbed by SGLTs in the proximal tubular cells.

**QUESTION 2: PROCESS OF MICTURITION**

**Micturition or Urination** is a process where urine is expelled from the body. The excretory system in humans includes a pair of kidneys (plays an important role in the formation of urine), two ureters, a urinary bladder via the ureters where it is stored till its expulsion. The process of micturition is regulated by the nervous system and the muscles of the bladder and the urethra. The urinary bladder can store around 350-400ml of urine before it expels it out.

As the bladder becomes full, the stretch receptors increase their firing rate. This increase the urge to urinate and causes micturition reflex. It sometimes even causes involuntary urination. On a average, a normal adult excretes 1 to 1.5L of urine per day. Normal urine is a light yellow fluid majorly consisting of 95% water and 5% solid wastes. It is slightly acidic with a pH close to 6.

**STAGES OF MICTURITION**

1. Resting or Filling or Storage stage
2. Voiding stage

**RESTING OR FILLING OR STORAGE STAGE**

The urinary bladder is a balloon-shaped, hollow, muscular, organ that acts as the storage organ for urine and can store urine for 2 to 5 hours. It is in this phase of the bladder that the urine is transport from the via the ureters of the bladder. The ureters are thin muscular tubes that arise from each of the kidneys and extend downwards where they enter the bladder obliquely.

This oblique nature of opening prevents the urine from re-entering the ureters because the bladder is not guarded by any sphincter or muscle. At the same time, the main muscle of the urinary bladder, **the** **detrusor** **muscle**, is relaxing allowing the bladder to distend and accommodate more urine.

**VOIDING STAGE**

During this stage, both the urinary bladder and the urethra come into play together. The detrusor muscle of the urinary bladder which was relaxing so far starts to contract once the bladder’s storage capacity is reached. When the bladder is filled with urine, the nerves get triggered, which in turn stimulates the need to urinate. The brain signals the urinary bladder to contract. The receptors of the urinary bladder send a signal to the Central nervous system, in response to which the nervous system sends a signal that incites the contraction of the urinary bladder. Through the urinary opening at the urethra, the urine is eliminated, and the process is called **micturition**. The neural mechanism involved is called **MICTURITION** **REFLEX**

**QUESTION 3: JUXTAGLOMERULAR APPARATUS**

The Juxtaglomerular apparatus (a.k.a juxtaglomerular complex) is a structure in the kidney that regulates the function of each nephron, the functional units of the kidney. The juxtaglomerular apparatus is named because it is next to (juxta) the glomerulus. It is found between afferent arteriole and the distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and glomerular filtration rate. It consists of three types of cells:

1. The **MACULA** **DENSA**, a part of the distal convoluted tubule of the same nephron
2. **JUXTAGLOMERULAR** **CELLS**, (also known as granular cells) which secrete **renin**
3. **EXTRAGLOMERULAR MESANGIAL CELLS**

The cells of the macula densa represent a morphologically distinct region of the thick ascending limb. The region passes through the angle formed by the afferent and efferent arterioles of the same nephron. The cells of the macula densa are in contact with the extraglomerular mesangial cells and the granular cells of the afferent arterioles. Granular cells of the afferent arterioles are derived from metanephric mesenchymal cells. They contain smooth muscle myofilaments and they manufacture, store, and release renin.

Renin is involved in the formation of **ANGIOTENSIN** **II** and ultimately in the secretion of aldosterone. The Juxtaglomerular apparatus is one component of the tubuloglomerular feedback mechanism that is involved in the autoregulation of the renal blood and the Glomerular filtration rate.

**QUESTION 4: ROLE OF THE KIDNEY IN REGULATION OF BLOOD PRESSURE**

The kidneys play a central role in the regulation of arterial pressure. Increased pressure has a direct effect on the kidney. Increasing salt intake increases blood pressure in the short term. It increases the osmolarity of the blood which therefore increases water movement from tissues to the blood causing an increased circulating volume. As a result of this, more Anti-Diuretic hormone is released as the osmoreceptors in the hypothalamus is triggered. This results in increased water retention in the kidneys further increasing the circulating volume. Secondary to the increase in salt, the thirst center is stimulated to increase fluid intake to try and counter act the increased osmolarity. This increases blood volume and there pressure temporarily until it is corrected by the compensatory mechanisms detailed below.

**PRESSURE** **DIURESIS**

As arteriolar blood pressure increases, so flow through the kidneys also increases. This increases filtration rate and urinary output

**PRESSURE** **NATRIURESIS**

If renal perfusion pressure is increased then sodium excretion increases i.e sodium excretion increases when blood pressure increases. If more sodium is excreted, less water is reabsorbed therefore the extracellular fluid volume decreases and blood pressure decreases.

**RENIN-ANGIOTENSIN SYSTEM**

Specialized cells in the distal tubule called the macula densa sense the concentration of sodium and chloride. If blood pressure falls there is reduction in concentration of sodium and chloride in the distal tubule which is sensed by the macula densa. This macula densa releases prostaglandins which act on the juxtaglomerular apparatus which releases renin into the bloodstream. The drop in blood pressure is also detected by baroreceptors in the aortic arch, carotid sinus and afferent renal arteriole which stimulates renin release by the juxtaglomerular apparatus.

Renin cleaves angiotensinogen into Angiotensin 1 which in turn is cleaved by the **Angiotensin converting enzyme (ACE )** into Angiotensin 2. Angiotensin 2 is a potent vasoconstrictor and also stimulates the adrenal cortex to release aldosterone. This then acts on the distal tubules and collecting ducts in the kidney causing retention of sodium and water. Blood pressure increases.

**REGULATION OF RENAL BLOOD FLOW**

It is essential that renal blood flow is maintained to ensure that adequate filtration of toxins from the blood takes place. Changes in pressure affect renal blood flow. Important auto-regulatory processes are responsible for this.

**QUESTION 5: ROLE OF KIDNEY IN CALCIUM HOMEOSTASIS**

About 50% of the plasma calcium (ionized and complexed form; ultrafilterable fraction, excluding the protein bound form) is freely filtered through the renal glomerulus, and 99% of the filtered calcium is actually reabsorbed along renal tubules. The excreted calcium in the final urine is about 200mg per day in an adult person with average diet. Several factors are involved in the regulation of calcium in renal tubules. PTH and activated vitamin D enhance calcium reabsorption in the thick ascending limb, distal convoluted tubule and/or connecting tubule and estrogen promotes calcium absorption in the distal convoluted tubule and connecting tubule.

Acidosis contributes to **hypercalciuria** by reducing calcium reabsorption in the proximal tubule and distal convoluted tubule, and alkalosis vice versa. To facilitate Ca2+ reabsorption along renal tubules,

1. Voltage difference between the lumen and blood compartment should be favourable for Ca2+ passage, i.e, a positive voltage in the lumen.
2. Concentration difference should be favourable for Ca2+ passage with a higher Ca2+ concentration in the lumen.
3. An active transporter should exist if the voltage or concentration difference is not favorable for calcium reabsorption.

Each renal segment has a different calcium concentration difference or voltage environment for its unique mechanism for calcium reabsorption. Although only 10-15% of filtered calcium is absorbed in the distal convoluted tubule and connecting tubule, these are the Min sites in which the fine regulation calcium excretion and the major action of PTH and activated vitamin D can occur, in the distal convoluted tubule and connecting tubule, the luminal voltage is negative and calcium concentration in the lumen is lower than that of the plasma. Several calcium transporting proteins are involved in this active transmembrane transport of calcium in the distal convoluted tubule and connecting tubule. Transcellular calcium reabsorption can occur by three steps;

1. Entry of calcium through the calcium channels in the apical membrane.
2. Binding of calcium with calcium binding protein (calbindin) and diffusion in the cytoplasm (which enables no significant change in the intracellular calcium)
3. Calcium extrusion via an ATP-dependent plasma membrane and an Na2+/Ca2+ exchanger in the basolateral membrane.

Each renal tubule has a unique environment and plays a different role in calcium reabsorption. The coordinated play of different renal tubules could Maintain harmony of renal calcium handling.