**ABUBAKAR SADIQ KABIR**

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**PHYSIOLOGY ASSIGNMENT**

 **Renal Physiology Body Fluid and Temperature Regulation**

**QUESTION 1: Discuss the role of kidney in glucose homeostasis?**

**ANSWER:**

 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 regulation of fluid and electrolyte balance, body fluid osmolality, acid-based balance, excretion of metabolic waste and foreign chemicals, arterial pressure, hormone secretion, and, most relevant to this discussion, glucose balance. The 2 kidneys produce a total of approximately 120 mL/min of ultra-filtrate, yet only 1 mL/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 ultra-filtrate. Fluid filtered from the glomerular capillaries flows into the tubular portion, which is made up of a proximal tubule, the Loop of Henle, and the distal tubule, all of which assist in reabsorbing essential substances and converting filtered fluid into urine.

**Mechanisms of Glucose Homeostasis in the Kidneys**
 The maintenance of glucose homeostasis is crucial in preventing pathological consequences that may result from hyperglycemia or hypoglycemia. Chronically uncontrolled hyperglycemia leads to a higher risk of macro vascular and micro vascular complications, such as cardiovascular disease, nephropathy, neuropathy, and retinopathy. Hypoglycemia, on the other hand, may lead to a myriad of central nervous system complications (e.g. confusion, behavioral changes, seizures, loss of consciousness, and even death), since the brain is the body’s largest consumer of glucose in the fasting or “post absorptive” state. Maintenance of glucose homeostasis involves several complementary physiologic processes, including

1. Glucose absorption (in the gastrointestinal tract),

2. Glycogenolysis (in the liver),

3. Glucose reabsorption (in the kidneys),

4. Gluconeogenesis (in the liver and kidneys), and

5. Glucose excretion (in the kidneys).10,12

As alluded to previously, the kidneys are capable of synthesizing and secreting many important hormones (e.g. renin, prostaglandins, kinins, erythropoietin) and are involved in a wide variety of metabolic processes such as activation of vitamin D3, gluconeogenesis, and metabolism of numerous endogenous compounds (e.g. insulin, steroids). With respect to renal involvement in glucose homeostasis, the primary mechanisms include release of glucose into the circulation via gluconeogenesis, uptake of glucose from the circulation to satisfy the kidneys’ energy needs, and reabsorption of glucose at the level of the proximal tubule.

***Glycogenolysis and Gluconeogenesis***
 Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis. Glycogenolysis involves the breakdown of glycogen to glucose-6-phosphate from precursors (e.g. lactate, glycerol, amino acids) and its subsequent hydrolysis (via glucose-6-phosphatase) to free glucose. Conversely, gluconeogenesis involves formation of glucose-6-phosphate from those same precursors and subsequent conversion to free glucose. Interestingly, the liver and skeletal muscles contain most of the body’s glycogen stores, but only the liver contains glucose-6-phosphatase. As such, the breakdown of hepatic glycogen leads to release of glucose, whereas the breakdown of muscle glycogen leads to release of lactate. Lactate (generated via glycolysis of glucose by blood cells, the renal medulla, and other tissues) may be absorbed by organs and reformed into glucose.
 With regard to glucose utilization, the kidney may be perceived as 2 separate organs, with glucose utilization occurring predominantly in the renal medulla and glucose release limited to the renal cortex. These activities are separated as a result of differences in the distribution of various 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-phosphatase and other gluconeogenic enzymes, they cannot release free glucose into the circulation. On the other hand, renal cortex cells do possess gluconeogenic enzymes (including glucose-6-phosphatase), and therefore can make and release glucose into the circulation. But because these cells have little phosphorylating capacity, they cannot synthesize glycogen.

***Glucose Reabsorption***
 In addition to their important role in gluconeogenesis, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. Under normal conditions, the kidneys retrieve as much glucose as possible, rendering the urine virtually glucose free. The glomeruli filter from plasma approximately 180 grams of D-glucose per day, all of which is reabsorbed through glucose transporter proteins that are present in cell membranes within the proximal tubules. If the capacity of these transporters is exceeded, glucose appears in the urine. This maximum capacity, known as the tubular maximum for glucose (TmG), ranges from 260 to 350 mg/min/1.73 m2 in healthy adults and children, and corresponds to a plasma glucose level of approximately 200 mg/dL. Once the TmG (the threshold) is reached and transporters are unable to reabsorb all the glucose (as in T2DM), glucosuria occurs. The correlation between the degree of hyperglycemia and degree of glucosuria becomes linear when blood glucose concentrations have increased beyond a threshold. It should be noted that slight differences between individual nephrons and the imprecise nature of biological systems may alter this linear concentration/reabsorption curve, as indicated by a splay from the theoretical as the TmG is approached. As such, glucosuria may potentially develop before the expected TmG is reached. Glucosuria may also occur at lower plasma glucose concentrations in certain conditions of hyper-filtration (e.g. pregnancy), but as a consequence of hyper-filtration rather than significant hyperglycemia.

 The regulation of glucose production, uptake, reabsorption, and elimination is handled by several organs, most notably (historically) the pancreas and liver. While not traditionally discussed, the kidneys’ contributions to maintaining glucose homeostasis are multifaceted and include such functions as gluconeogenesis and glucose reabsorption, the latter being mediated by active (SGLT) and passive (GLUT) transporters. Under normal circumstances, glucose filtered by glomeruli is completely reabsorbed, but in conditions of hyperglycemia or reduced resorptive capacity, glucosuria may occur. In hyperglycemia, the kidneys may play an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, and subsequently to pancreatic β-cell failure, insulin resistance, and decreased glucose uptake. Hyperglycemia in turn detrimentally affects the kidneys by damaging glomeruli, ultimately causing microalbuminuria and nephropathy. Knowledge of the kidneys’ role in glucose homeostasis and the effect of glucose dysregulation on the kidneys is critical to optimal management of T2DM and prevention of associated renal complications

**QUESTION 2: Discuss the process of micturition?**

**ANSWER:**

**THE PROCESS OF MICTURITION**

Micturition is a process by which urine is voided from the urinary bladder. It is a reflex process. However, in grown up children and adults, it can be controlled voluntarily to some extent.

There are two kidneys which are bean-shaped and are approximately 10cm long, 5.5cm wide and 3cm thick. Each kidney weighs about 150g and has a marked indentation medially - the hilus - where the renal artery and renal nerves enter and the renal vein and ureter leave. Between them, the kidneys make approximately 30ml or more of urine every hour. Approximately 25 per cent of the cardiac output goes to the kidneys where organic waste products are removed in the million or so nephrons in each kidney. Normal urine production, therefore, depends on normal blood flow to the kidneys. The nephron is the functional unit of the kidney. Nephrons permit the passage of some substances out of the body but restrict the passage of others, for example, blood cells and large proteins.

* FILTRATION

As blood flows through the glomerulus (a capillary network that forms part of the nephron), much of the fluid and waste products in the blood are forced out through the walls of the capillaries, filtered, and then flow into the Bowman’s capsule. The Bowman’s capsule is a double-walled endothelial cup that surrounds the glomerulus. This glomerular filtrate (about 125ml per minute) consists of water, glucose, waste salts such as sodium and potassium, and urea.  Urea is the most abundant waste product excreted by the kidneys and is formed from ammonia, a highly toxic substance. Ammonia is formed in the liver from the breakdown of amino acids.

* ABSORPTION

Much of the glomerular filtrate, including most of the water, is reabsorbed into the capillaries surrounding the proximal and distal convoluted tubules, the loop of Henle and the collecting tubules. All of the glucose will be reabsorbed unless blood glucose levels are high - more than 8.9 millimoles per litre (mmol/l) or 160 milligrams per decilitre (mg/dl) - in which case some glucose will be excreted in the urine. Sodium is also reabsorbed but the amount varies, depending on how much the body requires to maintain a constant concentration of sodium ions in the blood.

* SECRETION

This is the final stage of urine formation, and occurs at the distal and collecting tubules. Substances either diffuse or are actively transported out of the capillaries and into the collecting tubules to be excreted in the urine. Hydrogen ions, potassium ions, ammonia and some drugs are all secreted at this stage and the kidneys play an important role in maintaining the acid-base balance within the body.

Final composition of urine

The final composition of urine is the result of filtration, absorption and secretion by the nephrons. The kidneys produce, on average, one and a half litres of urine each day - this is mostly composed of water, is straw coloured and has a specific gravity of 1.005 to 1.030.

Urea, uric acid, creatinine, sodium chloride and potassium ions are all normal constituents of urine. Blood, ketones and glucose are not, and their presence may indicate disease.

**Storage of urine**

The bladder is a hollow, muscular sac which sits in the pelvis. In males, the base of the bladder lies between the rectum and pubic symphysis while in females the base is below the uterus and anterior to the vagina.

The bladder stores urine and can contain approximately one litre when full. It is held in position by the peritoneum surrounding it (though only its top surface lies within the peritoneum) and by strong umbilical ligaments.

The bladder is lined by mucosa. This is particularly thick in the area around the ureter openings and the junction with the urethra, where the mucosa acts as a funnel to channel urine into the urethra when the bladder contracts. During micturition, strong muscles in the bladder walls (the detrusor muscles) compress the bladder, pushing its contents into the urethra.

**Control of bladder emptying**

The opening, described as the neck of the bladder, between the bladder and the urethra, is closed by two rings of muscle - the internal and external sphincters. The internal sphincter contains smooth muscle fibres and the normal muscle tone of these fibres keeps it contracted; it is therefore not under voluntary control. The external sphincter is formed of a circular band of skeletal muscle which is supplied by the pudendal nerve and is under voluntary control. These fibres remain contracted, as a result of central nervous system stimulation, except during micturition when they relax.

**Micturition**

When the volume of urine in the bladder reaches about 250ml, stretch receptors in the bladder walls are stimulated and excite sensory parasympathetic fibres which relay information to the sacral area of the spine. This information is integrated in the spine and relayed to two different sets of neurones. Parasympathetic motor neurones are excited and act to contract the detrusor muscles in the bladder so that bladder pressure increases and the internal sphincter opens. At the same time, somatic motor neurones supplying the external sphincter via the pudendal nerve are inhibited, allowing the external sphincter to open and urine to flow out, assisted by gravity.

**QUESTION 3: Explain juxtaglomerular apparatus?**

**ANSWER:**

The juxtaglomerular apparatus is a specialized structure formed by the distal convoluted tubule and the glomerular afferent arteriole. It is located near the vascular pole of the glomerulus and its main function is to regulate blood pressure and the filtration rate of the glomerulus. The macula densa is a collection of specialized epithelial cells in the distal convoluted tubule that detect sodium concentration of the fluid in the tubule. In response to elevated sodium, the macula densa cells trigger contraction of the afferent arteriole, reducing flow of blood to the glomerulus and the glomerular filtration rate. The juxtaglomerular cells, derived from smooth muscle cells, of the afferent arteriole secrete renin when blood pressure in the arteriole falls. Renin increases blood pressure via the renin-angiotensin-aldosterone system. Lacis cells, also called extraglomerular mesangial cells, are flat and elongated cells located near the macula densa. Their function remains unclear.

**QUESTION 4: Discuss the role of kidney in regulation of blood pressure?**

**ANSWER:**

Kidneys play an important role in the long-term regulation of arterial blood pressure by two ways:

i. By regulating the volume of extracellular fluid

ii. Through **renin-angiotensin** mechanism.

***The renin-angiotensin system or RAS*** regulates blood pressure and fluid balance in the body. When blood volume or sodium levels in the body are low, or blood potassium is high, cells in the kidney release the enzyme, renin. Renin converts angiotensinogen, which is produced in the liver, to the hormone angiotensin I. An enzyme known as ACE or angiotensin-converting enzyme found in the lungs metabolizes angiotensin I into angiotensin II. Angiotensin II causes blood vessels to constrict and blood pressure to increase. Angiotensin II stimulates the release of the hormone aldosterone in the adrenal glands, which causes the renal tubules to retain sodium and water and excrete potassium. Together, angiotensin II and aldosterone work to raise blood volume, blood pressure and sodium levels in the blood to restore the balance of sodium, potassium, and fluids. If the renin-angiotensin system becomes overactive, consistently high blood pressure results.

The primary mechanism by which the kidneys regulate blood volume is by adjusting the amount of water and sodium lost into the urine. At different sites along the proximal tubules, thick ascending limb of the loop of Henle, distal and collecting tubules, sodium transport is regulated by angiotensin II (Ang II), which increases sodium transport thereby leading to sodium retention. In the collecting tubules, another hormone (aldosterone) stimulates sodium transport from the tubular fluid into the interstitium. Together, Ang II and aldosterone provide a powerful mechanism for increasing sodium retention and consequently fluid volume in the body. A third hormone, antidiuretic hormone (ADH), increases water permeability in the late distal tubules and collecting tubules. This enables water to diffuse from the tubulular fluid into the hypertonic interstitium, thereby reducing urine volume and therefore water loss. Beside these hormone actions on sodium transport and water movement, changes in renal blood flow and glomerular filtration can affect the amount of sodium and water filtered at the glomerulus and entering the renal tubules. For example, increased blood volume increases arterial pressure, renal perfusion, and glomerular filtration rate. This leads to an increase in renal excretion of water and sodium that is termed pressure natriuresis. In certain types of renal disease, the pressure natriuresis relationship is altered so that the kidneys retain more sodium and water at a given pressure, thereby increasing blood volume.

Activation of the renin-angiotensin-aldosterone (RAAS) system causes increased sodium retention by the kidneys, which leads to reduced water loss into the urine and therefore blood volume expansion. RAAS activation occurs during heart failure, which leads to fluid retention in the body. RAAS activation also occurs with renal artery stenosis, which is one cause of secondary hypertension. Drugs that block the formation of angiotensin II (i.e., angiotensin converting enzyme inhibitors), or block aldosterone receptors (e.g., spironolactone) enhance sodium and water loss, and thereby reduce blood volume. Therefore, any mechanism or drug that alters the activity of the renin-angiotensin-aldosterone system will affect blood volume.

**How Blood Volume Affects Blood Pressure:**

Changes in blood volume affect arterial pressure by changing cardiac output. An increase in blood volume increases central venous pressure. This increases right atrial pressure, right ventricular end-diastolic pressure and volume. This increase in ventricular preload increases ventricular stroke volume by the Frank-Starling mechanism. An increase in right ventricular stroke volume increases pulmonary venous blood flow to the left ventricular, thereby increasing left ventricular preload and stroke volume. An increase in stroke volume then increases cardiac output and arterial blood pressure.

**QUESTION 5: Discuss the role of Kidney in Calcium homeostasis?**

**ANSWER:**

Kidneys play a role in the regulation of blood calcium level by activating 1,25-dihydroxycholecalciferol into **vitamin D.** Vitamin D is necessary for the absorption of calcium from intestine.

Plasma calcium concentration is maintained within a narrow range (8.5-10.5 mg/dL) by the coordinated action of parathyroid hormone (PTH), 1,25(OH)2D3, calcitonin, and ionized calcium (iCa2+) itself. The kidney plays a key role in this process by the fine regulation of calcium excretion. More than 95% of filtered calcium is reabsorbed along the renal tubules. In the proximal tubules, 60% of filtered calcium is reabsorbed by passive mechanisms. In the thick ascending limb, 15% of calcium is reabsorbed by paracellular diffusion through paracellin-1 (claudin-16). The calcium sensing receptor (CaSR) in the basolateral membrane of the thick ascending limb senses the change in iCa 2+ and inhibits calcium reabsorption independent to PTH and 1,25(OH)2D3. The fine regulation of calcium excretion occurs in the distal convoluted tubules and connecting tubules despite the fact that only 10-15% of filtered calcium is reabsorbed there. Transient receptor potential vanilloid 5 (TRPV5) and 6 (TRPV6) in the apical membrane act as the main portal of entry, calbindin-D28K delivers Ca2+ in the cytoplasm, and then Na2+/Ca2+ exchanger (NCX1) and plasma membrane Ca2+ -ATPase in the basolateral membrane serve as an exit. In the cortical collecting duct, TRPV6 is expressed, but the role might be negligible. In addition to PTH and 1,25(OH)2D3, acid-base disturbance, diuretics, and estrogen effect on these calcium channels. Recently, klotho and fibroblast growth factor 23 (FGF23) are suggested as new players in the calcium metabolism. Klotho is exclusively expressed in the kidney and co-localized with TRPV5, NCX1, and calbindin-D28K. Klotho increases calcium reabsorption through trafficking of TRPV5 to the plasma membrane, and also converts FGF receptor to the specific FGF23 receptor. FGF23:klotho complex bound to FGF receptor inhibits 1 –α hydroxylase of vitamin D, and contributes to calcium reabsorption and phosphate excretion in the kidney.