NAME: FADIPE NAOMI INEMESIT

MATRIC NO: 17/MHS01/131

COURSE TITLE: RENAL PHYSIOLOGY, BODY FLUID AND TEMPERATURE REGULATION

COURSE CODE: PHS 303

QUESTION 1: Discuss the role of kidney in glucose homeostasis

ANSWER: Glucose homeostasis means the process by which glucose is regulated in the body. The kidneys synthesize glucose from amino acids and other precursors during prolonged fasting, a process referred to as gluconeogenesis. The kidneys' capacity to add glucose to the blood during prolonged periods of fasting rivals that of the liver. The kidney absorbs the entire quantity of filtered glucose. It has a glomerular filtration rate of 180litres/day and it filters approximately 180grams of glucose per day, bringing its normal contribution in maintaining normal fasting blood glucose (FBG) levels. Insulin can suppress glucose release in both kidney and liver by direct enzyme activation/deactivation and by reducing the availability of gluconeogenic substrates. The main roles of kidneys in glucose homeostasis include:

- Gluconeogenesis
- Glucose uptake from the blood for its own energy requests and
- Reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy

1. GLUCONEOGENESIS: The kidney is considered as 2 different organs from the point of view of glucose utilization. The renal medulla is characterized by glucose utilization and the renal cortex is responsible for glucose release. The release of renal glucose is as a result of glycogenolysis and gluconeogenesis. Glycogenolysis involves breakdown of glycogen to glucose-6-phosphate from precursors (lactate, glutamine, glycerol and alanine). Because it contains glucose-6-phosphatase, it is able to converts precursor to glucose through subsequent hydrolysis and release into bloodstream. Only liver and kidneys can perform gluconeogenesis. Gluconeogenesis involves formation of glucose-6-phosphate from the same precursor and subsequent conversion to free

glucose.Therefore, after an overnight fast, liver produces 75-80% of glucose released into the circulation and remaining 20-25% is derived. Kidney prefers glutamine as its precursor for glucose. Insulin suppresses glucose release in both organs. Catecholamines have a direct effect on renal glucose increase. During the 4 to 6-h after meal ingestion, there is a reduction in hepatic gluconeogenesis by 82% and renal gluconeogenesis increases by two-fold and it represents approximately 60% of endogenous glucose production in the postprandial state.

2. GLUCOSE UPTAKE FROM THE BLOOD FOR ITS OWN ENERGY REQUESTS: The renal cortex takes glucose from the blood for its energy requirement. Glucose in blood that is as a result of glycogenolysis and other means are absorbed by renal cortex for energy.

3. GLUCOSE REABSORPTION: Kidneys, under normal conditions, retrieve as much glucose as possible, rendering the urine virtually glucose free. The absorption takes place at region of proximal tubules. The glomeruli filter from plasma approximately 180grams/day, all of which s reabsorbed through glucose transporter proteins that are present in the cell membranes within the proximal tubules. If capacity of these transporters is exceeded, glucose appears in the urine. Maximum capacity, tubular maximum for glucose (TmG), ranges from 260 to 350mg/min/1.73m^2 in healthy adults and children, and corresponds to a plasma glucose level of approximately 200mg/dL. Once the TmG is reached and transporters are unable to reabsorb all the glucose, GLUCOSURIA occurs.

   N.B.: The main glucose transporter used is SGLT2 and it is important because it is responsible for 90% of the glucose filtered at the glomerulus. The other 10% is reabsorbed in proximal tubule is ensured by SGLT1. The GLUT2 is a major transporter and it releases into circulation the glucose reabsorbed in the proximal tubular cells.

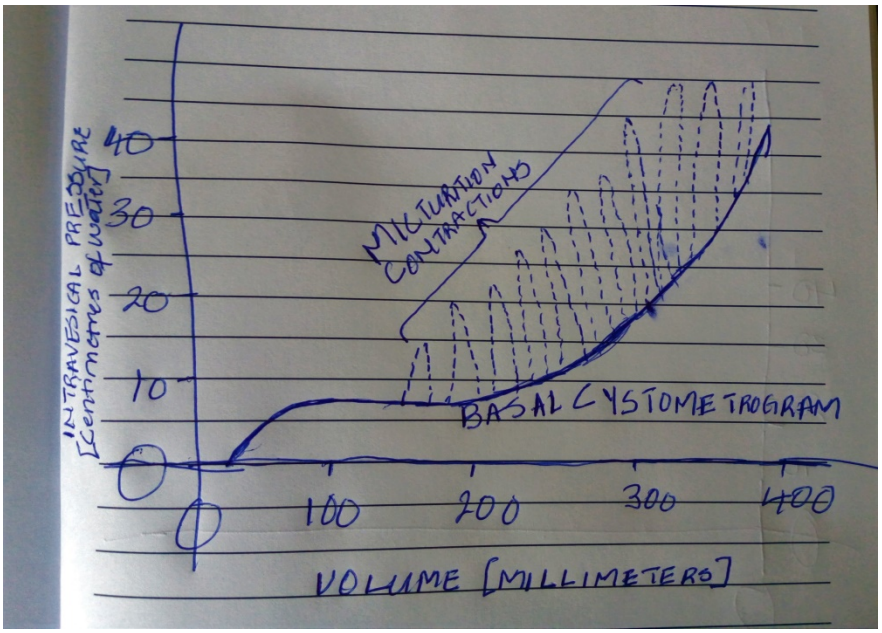
QUESTION 2: Discuss the process of micturition

ANSWER: Micturition is the process by which the urinary bladder empties when it becomes filled. Micturition is a voluntary action as the external sphincter is made up of skeletal muscle. This involves two main steps:

First, the bladder fills progressively until the tension in its walls rises above a threshold level; this elicits the second step, which is a nervous reflex called the micturition reflex that empties the bladder or, if this fails, at least causes a conscious desire to urinate. Although the micturition reflex is an autonomic spinal cord reflex, it can also be

inhibited or facilitated by centers in the cerebral cortex or brain stem.

MICTURITION REFLEX



This is a normal cystometrogram showing acute pressure waves [dashed spikes] caused by micturition reflexes.

Referring to the diagram above, one can see that as the bladder fills many superimposed micturition contractions begin to appear, as shown by the dashed spikes. They are the result of a stretch reflex initiated by sensory stretch receptors in the bladder wall, especially by the receptors in the posterior urethra when this area begins

to fill with urine at the higher bladder pressures. Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves and then reflexively back again to the bladder through the parasympathetic nerve fibers by way of these same nerves. When the bladder is only partially filled, these micturition contractions usually relax spontaneously after a fraction of a minute, the detrusor muscles stop contracting, and pressure falls back to the baseline. As the bladder continues to fill, the micturition reflexes become more frequent and cause greater contractions of the detrusor muscle. Once a micturition reflex begins, it is "self-regenerative." That is, initial contraction of the bladder activates the stretch receptors to cause a greater increase in sensory impulses from the bladder and posterior urethra, which causes a further increase in reflex contraction of the bladder; thus, the cycle is repeated again and again until the bladder has reached a strong degree of contraction. Then, after a few seconds to more than a minute, the self-regenerative reflex begins to fatigue and the regenerative cycle of the micturition reflex ceases, permitting the bladder to relax. Thus, the micturition reflex is a single complete cycle of:

(1) Progressive and rapid increase of pressure

(2) A period of sustained pressure, and

(3) Return of the pressure to the basal tone of the bladder.

Once a micturition reflex has occurred but has not succeeded in emptying the bladder, the nervous elements of this reflex usually remain in an inhibited state for a few minutes to 1 hour or more before another micturition reflex occurs. As the bladder becomes more and more filled, micturition reflexes occur more and more often and more and more powerfully. Once the micturition reflex becomes powerful enough, it causes another reflex, which passes through the pudendal nerves to the external sphincter to inhibit it. If this inhibition is more potent in the brain than the voluntary constrictor signals to the external sphincter, urination will occur. If not, urination will not occur until the bladder fills still further and the micturition reflex becomes more powerful.

Facilitation or Inhibition of Micturition by the Brain

The micturition reflex is an autonomic spinal cord reflex, but it can be inhibited or facilitated by centers in the brain. These centers include (1) strong facilitative and inhibitory centers in the brain stem, located mainly in the pons, and (2) several centers located in the cerebral cortex that are mainly inhibitory but can become excitatory. The micturition reflex is the basic cause of micturition, but the higher centers normally exert final control of micturition as follows:

1. The higher centers keep the micturition reflex partially inhibited, except when micturition is desired.
2. The higher centers can prevent micturition, even if the micturition reflex occurs, by tonic contraction of the external bladder sphincter until a convenient time presents itself.
3. When it is time to urinate, the cortical centers can facilitate the sacral micturition centers to help initiate a micturition reflex and at the same time inhibit the external urinary sphincter so that urination can occur.

The micturition reflex system is under both sympathetic and parasympathetic control. While the bladder is filling, the sympathetic nerves relax the smooth muscle of the bladder wall, accommodating the urine, and contract the internal urethral sphincter smooth muscle. When the bladder becomes “full,” mechanoreceptors signal a spinal reflex arc that stimulates parasympathetic contraction of the bladder (detrusor muscle) and relaxation of internal sphincters. The external urethral sphincter is skeletal muscle, and is voluntarily relaxed, allowing urination.

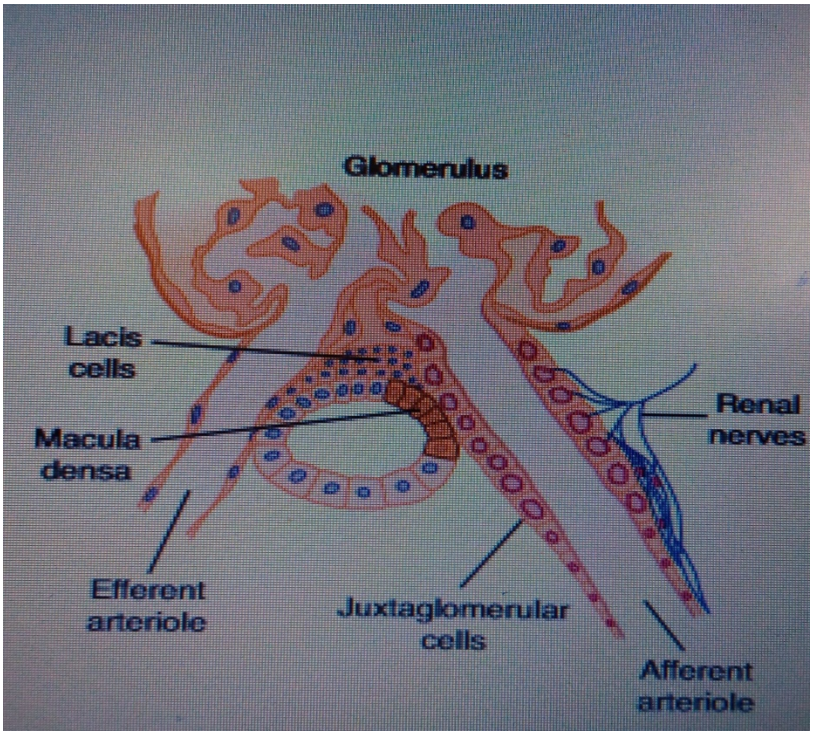
Voluntary urination is usually initiated in the following way: First, a person voluntarily contracts his or her abdominal muscles, which increases the pressure in the bladder and allows extra urine to enter the bladder neck and posterior urethra under pressure, thus stretching their walls. This stimulates the stretch receptors, which excites the micturition reflex and simultaneously inhibits the external urethral sphincter. Ordinarily, all the urine will be emptied, with rarely more than 5 to 10 milliliters left in the bladder.

QUESTION 3: Explain juxtaglomerular apparatus

ANSWER: This is an important structural and functional aspect of the kidney. This is the area where the distal convoluted tubule returns to its “parent” glomerulus. It consists of 1) lacis cells 2) juxtaglomerular cells and 3) macula densa. At this site, specialized macula densa cells are in contact with the distal convoluted tubule and afferent arteriole, forming the juxtaglomerular apparatus. The juxtaglomerular apparatus play a role in the maintenance of systemic arterial blood pressure during a reduction in vascular volume and decrease in filtration rate.

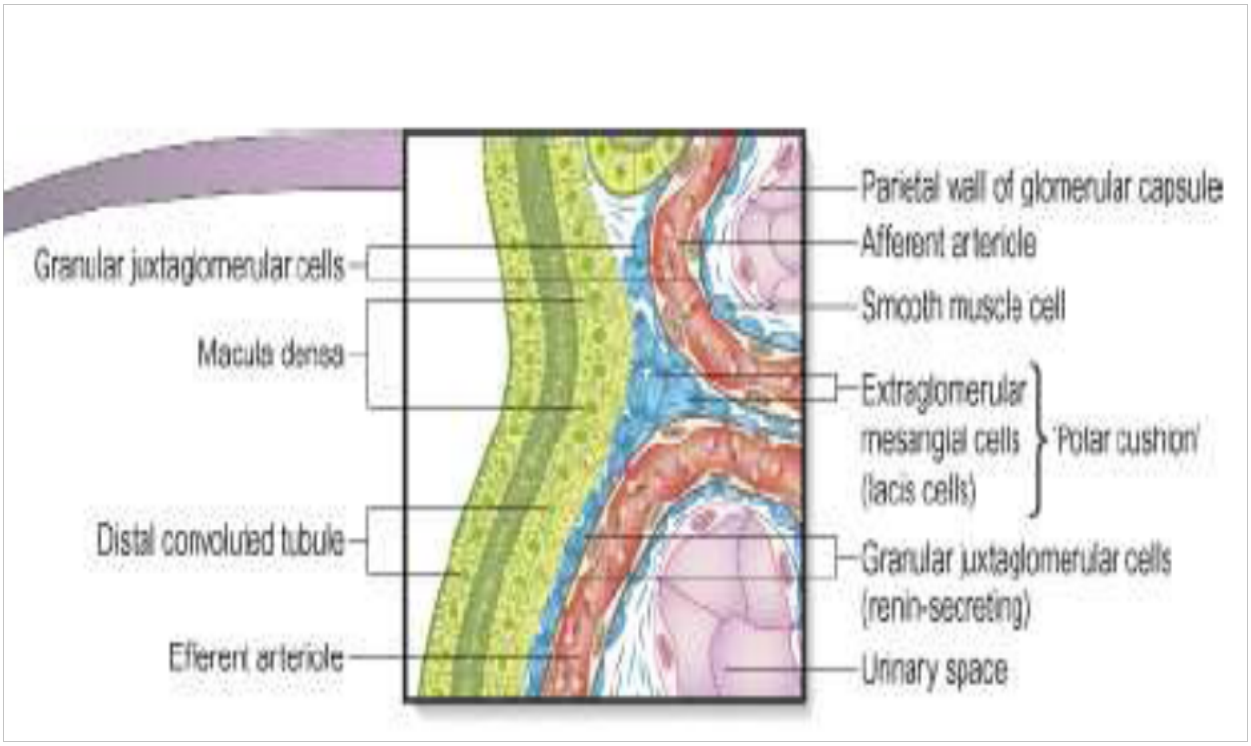
The macula densa cells of the juxtaglomerular apparatus are important in sensing tubular fluid flow and sodium delivery to the distal nephron, and because of their

proximity to the afferent arteriole, macula densa cells can regulate renal plasma flow and glomerular filtration rate (GFR) (auto regulation) and and can also monitor NaCl delivery to distal tubules. Macula densa cells also participate in the regulation of the release of the enzyme renin from juxtaglomerular cells adjacent to the afferent arterioles. The renin secretion aids in fluid and electrolyte homeostasis. Macula densa cells also receive input from adrenergic nerves through β1-receptors.



The arterioles of juxtaglomerular apparatus contain high pressure baroreceptor. The afferent and efferent arterioles at the vascular pole of a glomerulus and the macula densa of the distal tubule of the same nephron lie in close proximity, enclosing a small cone of tissue populated by extraglomerular mesangial (lacis) cells

The juxtaglomerular cells: They are modified smooth muscle cells of the tunica media of afferent and to lesser extent, efferent arterioles. They are different from normal smooth muscle cells. These cells are large, rounded cells and their cytoplasm contains many mitochondria and dense, renin-containing vesicles.



What happens with juxtaglomerular apparatus:

- decrease in blood volume causes a decrease in RBF and decrease Bp
- JG cells become sensitive to decrease in BP and secrete renin
- Renin act on angiotensinogen in the blood and convert it to angiotensin I
- Angiotensin I is converted to angiotensin II by ACE
- Angiotensin II increase vascular resistance which in turn increase BP

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

ANSWER: Regulation of blood pressure involves the short term, long term and intermediate control mechanism. Blood pressure is monitored at several points in the body and the juxtaglomerular apparatus in kidney is one of it. The arterioles of the juxtaglomerular apparatus of the kidneys also contain high-pressure baroreceptors; in this case, stretch results in release of the enzyme renin by the kidney. Renin enzymatically cleaves the plasma protein angiotensinogen (a liver product) to form

angiotensin I, which is converted to angiotensin II by endothelial angiotensin-converting enzyme. This mechanism is important in short-term regulation of blood pressure only during pathophysiologic states such as hemorrhage. Kidney secretes renin which has many effects in regulating blood pressure. In addition to evoking mechanisms for acute adjustment of blood pressure, changes in blood volume and pressure will also activate renal mechanisms for adjusting blood volume. Afferent arterioles in the renal juxtaglomerular apparatus which contain high-pressure baroreceptors are involved in regulation of renin release, and consequently, regulation of sodium and water balance, important in long-term regulation of blood pressure. Reduced blood volume (and therefore reduced arterial pressure) will stimulate the renin-angiotensin-aldosterone system, with the end result of sodium and water retention. Reduced blood pressure will also activate the sympathetic nervous system, which will stimulate renin secretion as well as have direct effects on the kidneys. On the other hand, increased volume will stimulate atrial natriuretic peptide (ANP) release by the heart. ANP has direct renal effects (natriuresis and diuresis) and also inhibits aldosterone release by the adrenal medulla. Thus, the effects of multiple hormones (ADH, angiotensin II, aldosterone) on sodium and fluid retention and water intake result in an increase in blood volume, which helps to maintain blood pressure.

QUESTION 5: Discuss the role of kidney in calcium homeostasis

ANSWER: Renal tubules convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D which acts on kidney, intestine ad bones which helps in regulating calcium homeostasis. Plasma calcium is tightly controlled with regulatory systems keeping levels at -2.4mEq/L or 9.4mg/dL. The intestines, kidneys and bones are integral to calcium regulation in body. In the kidneys, calcium is regulated by excreting about 100 to 200mg of it daily as about 100 to 200mg is absorbed daily. This is about 2% of filtered calcium load and it means that about 98% of calcium in body is reabsorbed daily.

Parathyroid hormone (PTH) regulates calcium concentration. It is main regulating mechanism of regulating calcium. It is a continually synthesized hormone. PTH is synthesized by chief cells of Parathyroid gland as a 110 preprohormone. Additional PTH is secreted into blood in response to small decreases in ionized calcium in the plasma. This PTH acts at kidney, intestines and bone to return plasma calcium to its normal levels. PTH stimulates cAMP (cyclic AMP) through its G protein– coupled receptors:

At the kidney:

1. To increase calcium reabsorption at the distal tubule, and to inhibit phosphate reabsorption at both the proximal and distal tubules; and

2. To increase the synthesis of 1,25-dihydroxycholecalciferol, the active metabolite of vitamin D.

This conversion is critical to producing active vitamin D, and loss of PTH or loss of kidney function can impair vitamin D metabolism and function. The actions at the kidney are rapid and are a main avenue for the rapid restoration of plasma calcium levels. The chief cells of the parathyroid gland have calcium sensors, which monitor plasma calcium concentration. This allows rapid response when plasma calcium decreases, and PTH can quickly mobilize calcium from bone and stimulate vitamin D production. PTH acts on kidney to increase Ca^{2+} reabsorption and decrease phosphate reabsorption and increase production of active vitamin D. Rapid effect of PTH increase Ca^{2+} in blood, restoring homeostasis.