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PHS303 ASSIGNMENT

QUESTIONS

1. Discuss the role of kidney in glucose homeostasis?

2. Discuss the process of micturition?

3. Explain juxtaglomerular apparatus?

4. Discuss the role of kidney in regulation of blood pressure?

5. Discuss the role of Kidney in Calcium homeostasis?

ANSWERS

QUESTION 1

The kidney has an important role in ensuring the energy needs during fasting periods. This organ has a vital role in absorbing the entire quantity of the filtered glucose. Having a glomerular filtration rate of 180 liters per day, it filters approximately 180 grams of glucose per day, bringing its contribution in maintaining normal fasting plasma glucose (FPG) levels. The reabsorption of glucose is ensured by the sodium-glucose cotransporter (SGLT) 2, responsible for the reabsorption of 90% of glucose, and SGLT1, that reabsorbs the remaining glucose.

Despite the large amount of data regarding the implication of the kidneys in glucose homeostasis, this organ is often overlooked as a key player in glucose metabolism. But the awareness of the renal mechanisms of glucose control is likely to increase due to the development of new types of glucose-lowering drugs that target this metabolic pathway.

The first researchers in this field, Bergman and Drury brought the first clues about the involvement of the kidney in glucose homeostasis in 1938. They used the glucose clamp technique in order to maintain euglycemia in two groups of rabbits – one functionally

hepatectomized and another one functionally hepatectomized and nephrectomized. In the group of hepatectomized and nephrectomized rabbits, the amount of glucose requested in order to maintain euglycemia was very high compared to the one required by the other group, These data led to the conclusion that the kidneys are an important source of plasma glucose
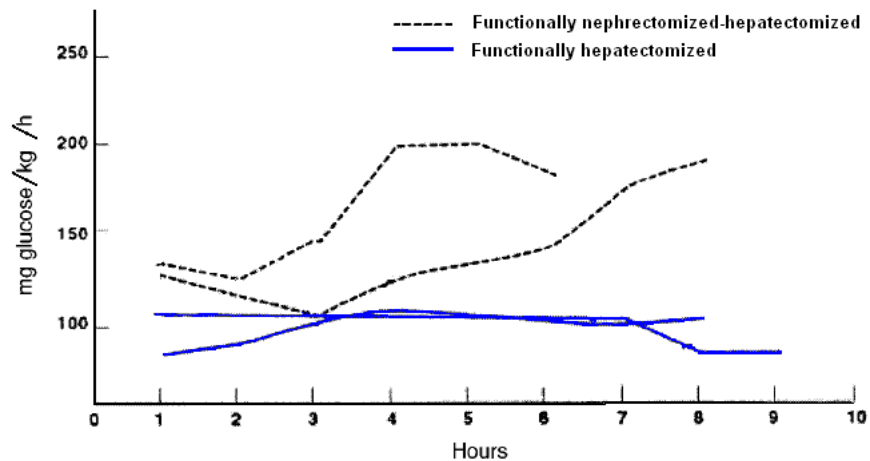

FIGURE 1. Effect of nephrectomy on glucose needs for maintaining euglycemia in hepatectomized rabbits

A few years later, the study was reproduced by Reinecke in rats. He also determined the arteriorenal venous glucose concentrations in the hepatectomized rats. He found that the glucose levels in renal vein exceeded the arterial levels when the animals became hypoglycemic proving that, under these conditions, the kidneys can release glucose into the circulation.

In other experiments, Teng proved that the renal cortex of the animal models with diabetes released glucose at a very high rate, but treatment of these animals with insulin could reverse this effect. A few years later, in 1960, Landau was able to prove, having a similar model, that gluconeogenesis from pyruvate was increased by the diabetic kidney.

The plasma glucose concentration is determined by the amount of glucose synthesized, and the one removed from the circulation and metabolized. This concentration must be maintained

within a relatively narrow range despite the wide daily fluctuations in glucose ingestion and glucose demands in various tissues [4]. Other substrates such as free fatty acids (FFAs), glycerol, lactate and ketone bodies have greater daily fluctuations. This can be explained by the need of the body to protect himself against hyper- and hypoglycaemia. Hyperglycaemia is associated with both chronic effects (such as nephropathy, retinopathy, neuropathy and premature atherosclerosis) and also acute complications (including diabetic ketoacidosis and hyperosmolar hyperglycaemic state that are associated with higher morbidity and mortality). Hypoglycaemia is also harmful because it can cause neurological events (including coma, seizures), cardiac arrhythmias and death

The regulation of endogenous production of glucose is determined by hormonal and neural factors. In the acute phase, glucoregulatory mechanisms involve insulin, glucagon and catecholamines and they can effect changes in plasma glucose levels in a matter of minutes. Insulin is able to suppress glucose release in both the kidney and liver by direct enzyme activation ∕ deactivation and by reducing the availability of gluconeogenic substrates. Glucagon has no effect on the kidneys, but it stimulates glycogenolysis and gluconeogenesis in the liver [16]. Catecholamines also have multiple acute actions. They can stimulate renal glucose release and glucagon secretion and inhibit insulin secretion

The kidneys are involved in maintaining glucose homeostasis through three different mechanisms: 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.

The kidneys' contributions to maintaining glucose homeostasis are significant and include such functions as

- Release of glucose into the circulation via gluconeogenesis,

- Uptake of glucose from the circulation to satisfy their energy needs, and reabsorption of glucose at the level of the proximal tubule.

- Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis, respectively involving the breaking down and formation of glucose-6-phosphate from precursors (eg, lactate, glycerol, amino acids). With regard to renal reabsorption of glucose, the kidneys normally 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.

The process of renal glucose reabsorption is mediated by active (sodium-coupled glucose cotransporters) and passive (glucose transporters) transporters. In hyperglycemia, the kidneys may play an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, which in turn contributes to chronic glycemic burden and the risk of microvascular consequences.

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 ultrafiltrate, 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 ultrafiltrate. 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.

Evaluation of renal function is an important part of care, and with that, creatinine clearance (CrCl) or glomerular filtration rate (GFR), most frequently estimated (eGFR), are considered

most useful in determining the degree of renal insufficiency and the stage of chronic kidney disease in accordance with the National Kidney Foundation classification system. Since alterations in all renal functions (i.e., filtration, secretion, reabsorption, endocrine and metabolic function) have been associated primarily with GFR, this quantitative index may be used to measure any functional changes that result from kidney-related disease progression, therapeutic intervention, or toxic insult.

Mechanisms of Glucose Homeostasis

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 macrovascular and microvascular 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 "postabsorptive" state. Maintenance of glucose homeostasis involves several complementary physiologic processes, including glucose absorption (in the gastrointestinal tract), glycogenolysis (in the liver), glucose reabsorption (in the kidneys), gluconeogenesis (in the liver and kidneys), and glucose excretion.

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

1. 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.

2. 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.

The magnitude of renal glucose release in humans is somewhat unclear, with inconclusive evidence regarding the contribution of the kidneys to total body gluconeogenesis. One analysis of 10 published studies concluded that the renal contribution to total body glucose release in the postabsorptive state is approximately 20%. Based on the 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.2 Taking into consideration the potential contribution of renal gluconeogenesis, the kidneys appear to play a substantial role in overall glucose release in normal as well as pathophysiologic states (e.g., hepatic insufficiency, counter

regulation of hypoglycemia). To this point, evidence suggests that in patients with T2DM, renal glucose release is increased in both the postprandial and postabsorptive states, implicating the kidneys' contribution to the hyperglycemia that characterizes this condition. Insulin resistance (known to suppress renal/hepatic insulin release), increased free fatty acid (FFA) concentrations (FFAs stimulate gluconeogenesis), greater availability of gluconeogenic precursors, and increased glycogenolysis.3 Again, it is clear that there is a renal contribution to glucose output in the body, but the actual contribution in individual patients with T2DM is still controversial.

<u>Glucose Reabsorption</u>

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.4 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.4 Once the TmG (the threshold) is reached and transporters are unable to reabsorb all the glucose (as in T2DM), glucosuria ocurrs.7,15 The correlation between the degree of hyperglycemia and degree of glucosuria becomes linear when blood glucose concentrations have increased beyond a threshold.4 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.4 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 hyperfiltration (e.g., pregnancy), but as a consequence of hyperfiltration rather than significant hyperglycemia.

QUESTION 2

Micturition or urination is the process of expelling urine from the bladder. This act is also known as voiding of the bladder. The process of micturition is governed by both the nervous and muscular systems. Within the nervous system, the process is governed by the autonomous nervous system and the somatic system. Once the urinary bladder reaches its maximum capacity, the stretch receptors in the walls of the bladder send an impulse via the pelvic nerve to the brain via the spinal cord.

The micturition reflex is ultimately generated from the level of the spinal cord after it receives
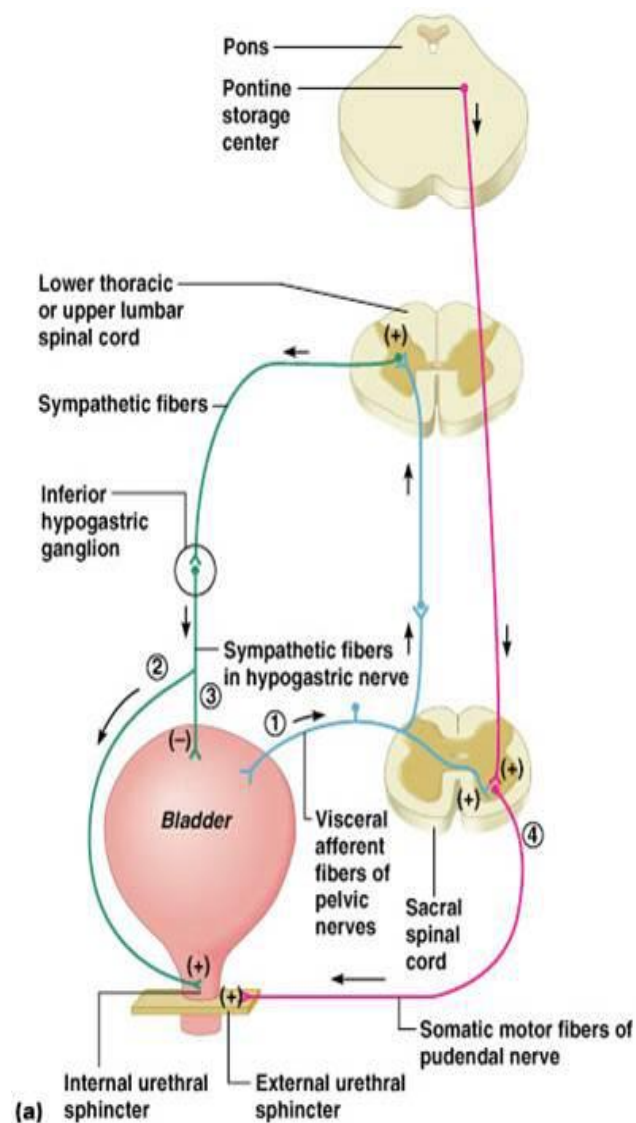
reflexes from the pontine region in the brain. Once the bladder and the urethra receive the

signals to empty the bladder, the two sphincters relax and the detrusor muscle causes the contractions of the bladder.

Along with these muscles, the muscles of the abdomen also play a role by putting pressure on the bladder wall. This leads to complete emptying of the bladder.

Excretion is a life process which is as important as nutrition. In animals, including humans, as a part of metabolism, many waste products are produced. Animals excrete them in different forms, such as urine, sweat, faeces, and tears. Among these, the usual form of excreta, urine, is produced and discarded from our body as fluid.

The excretory system in humans includes a pair of kidneys, two ureters, a urinary bladder and a urethra. The kidneys filter the urine and it is transported to the 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 urethra. The urinary bladder can store around 350-400ml of urine before it expels it out.

The urinary bladder has two distinct stages or phases:

1. Resting or filling stage
2. Voiding stage

Resting or filling stage:

It is in this phase of the bladder that the urine is transported from the kidneys via the ureters into the bladder. The ureters are thin muscular tubes that arise from each of the kidneys and extend downwards where they enter the bladder obliquely.

The oblique placement of the ureters in the bladder wall serves a very important function. The opening of the ureter into the urinary bladder is not guarded by any sphincter or muscle. Therefore, this oblique nature of opening prevents the urine from re-entering the ureters. 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.

The urethra is controlled by two sets of muscles: The internal and external urethral sphincters. The internal sphincter is a smooth muscle whereas the external one is skeletal. Both these sphincters are in a contracted state during the filling stage.

QUESTION 3

Juxtaglomerular apparatus: The prefix "juxta-" comes from the Latin preposition meaning near, nearby, close. The juxtaglomerular apparatus is a collective term referring to the cells near a structure called the glomerulus in the kidney. The juxtaglomerular cells are specialized cells that stimulate the secretion of the adrenal hormone aldosterone and play a major role in renal auto-regulation, the kidney's self-governance. The JGA is also important in the regulation of salt excretion.

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 juxtaglomerular apparatus consists of three cell types.

- The maculadensa, a part of the distal convoluted tubule of the same nephron.
- Juxtaglomerular cells, which secrete renin.
- Specialized smooth muscle cells of the afferent arteriole, which supplies blood to the glomerulus.

QUESTION 4

The kidney plays a central role in the regulation of arterial blood pressure. A large body of experimental and physiological evidence indicates that renal control of extracellular volume and renal perfusion pressure are closely involved in maintaining the arterial circulation and blood pressure. Renal artery perfusion pressure directly regulates sodium excretion-a process known as pressure natriuresis-and influences the activity of various vasoactive systems such as the renin-angiotensin-aldosterone system. As a result, many researchers argue that identifying any marked rise in blood pressure requires resetting of the relationship between arterial blood pressure and urinary sodium excretion, which can occur by an array of systemic or local mechanisms. Almost all of the monogenic forms of hypertension affect sites in the kidney associated with sodium handling and transport. Experimental models of spontaneous hypertension, such as the Dahl salt-sensitive rat, have been used to study the effects of kidney transplantation on blood pressure. Results from studies of kidney transplantation indicate that pressure sensitivity to sodium intake 'follows' the kidney, meaning that the recipient of a 'salt-resistant kidney' acquires sodium resistance, and that the recipient of a 'salt-sensitive kidney' acquires pressure sensitivity. The examples above and discussed in this Review demonstrate that it should come as no surprise that most disorders that affect the kidney or the renal vasculature commonly lead to secondary forms of hypertension.

Blood pressure and hypertension

Hypertension is one of the most common chronic diseases of human, affecting more than one billion people worldwide [6]. Although elevated blood pressure does not typically cause overt symptoms, the consequences of chronic hypertension, including cardiac hypertrophy, heart failure, stroke, and kidney disease, are responsible for substantial morbidity and mortality. Treatments that effectively reduce blood pressure can prevent these complications. However, in recent times, blood pressures were reduced to target levels in less than 50% of patients receiving hypertension treatment, and this rate was under 40% in individuals who also had chronic kidney disease (CKD).

The reasons for these poor outcomes include health services issues around processes of care, compliance, and patient education. Moreover, the precise cause of hypertension is not apparent in the vast majority of patients with hypertension. Limitations in understanding of hypertension pathogenesis in individual patients are an obstacle to applying individualized approaches for prevention and treatment and to identifying new, specific therapies.

The kidneys and their influence on blood pressure

The kidneys play a central role in the regulation of arterial blood pressure. A large body of experimental and physiological evidence indicates that renal control of extracellular volume and renal perfusion pressure are closely involved in maintaining the arterial circulation and blood pressure. Renal artery perfusion pressure directly regulates sodium excretion; a process known as pressure natriuresis, and influences the activity of various vasoactive systems such as the renin–angiotensin–aldosterone (RAS) system [9]. Along with vessel morphology, blood viscosity is one of the key factors influencing resistance and hence blood pressure. A key modulator of blood viscosity is the renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS), a hormone system that regulates blood pressure and water balance.

The blood pressure in the body depends upon:

• The force by which the heart pumps out blood from the ventricles of the heart - and this is dependent on how much the heart muscle gets stretched by the inflowing blood into the ventricles.

• The degree to which the arteries and arterioles constrict-- increases the resistance to blood flow, thus requiring a higher blood pressure.

• The volume of blood circulating round the body; if the volume is high, the ventricles get more filled, and the heart muscle gets more stretched.

The kidney influences blood pressure by:

• Causing the arteries and veins to constrict

•Increasing the circulating blood volume

Specialized cells called macula densa are located in a portion of the distal tubule located near and in the wall of the afferent arteriole. These cells sense the Na in the filtrate, while the arterial cells (juxtaglomerular cells) sense the blood pressure. When the blood pressure drops, the amount of filtered Na also drops. The arterial cells sense the drop in blood pressure, and the decrease in Na concentration is relayed to them by the macula densa cells. The juxtaglomerular cells then release an enzyme called renin.

Renin converts angiotensinogen (a peptide, or amino acid derivative) into angiotensin-1. Angiotensin-1 is thereafter converted to angiotensin-2 by an angiotensin-converting enzyme (ACE), found in the lungs. Angiotensin-2 causes blood vessels to contract -- the increased blood vessel constrictions elevate the blood pressure. When the volume of blood is low, arterial cells in the kidneys secrete renin directly into circulation. Plasma renin then carries out the conversion of angiotensinogen released by the liver to angiotensin-1. Angiotensin-1 is subsequently converted to angiotensin-2 by the enzyme angiotensin converting enzyme found in the lungs. Angiotensin-2m a potent vasoactive peptide causes blood vessels to constrict, resulting in increased blood pressure. Angiotensin-2 also stimulates the secretion of the hormone aldosterone from the adrenal cortex.

Aldosterone causes the tubules of the kidneys to increase the reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases blood pressure. If the renin-angiotensin-aldosterone system is too active, blood pressure will be too high. Many drugs interrupt different steps in this system to lower blood pressure. These drugs are one of the main ways to control high blood pressure (hypertension), heart failure, kidney failure, and harmful effects of diabetes. It is believed that angiotensin-1 may have some minor activity, but angiotensin-2 is the major bioactive product. Angiotensin-2 has a variety of effects on the body: throughout the body, it is a potent vasoconstrictor of arterioles.

How the kidneys increase circulating blood volume

Angiotensin-2 also stimulates the adrenal gland to secrete a hormone called aldosterone. Aldosterone stimulates more Na reabsorption in the distal tubule, and water gets reabsorbed along with the Na. The increased Na and water reabsorption from the distal tubule reduces urine output and increases the circulating blood volume. The increased blood volume helps stretch the heart muscle and causes it to generate more pressure with each beat, thereby increasing the blood pressure. The circulating blood volume is directly proportional to the stretch of the heart muscle.

The actions taken by the kidney to regulate blood pressure are especially important during traumatic injury, when they are necessary to maintain blood pressure and conserve the loss of fluids. The body stores calcium in the bones, but also maintains a constant level of calcium in the blood. If the blood calcium level falls, then the parathyroid glands in the neck release a hormone called parathyroid hormone. Parathyroid hormone increases calcium reabsorption from the distal tubule of the nephron to restore the blood calcium level. Parathyroid hormone aside from stimulating calcium release from bone also causes calcium absorption from the intestine.

Vitamin D is also required by the body to stimulate calcium absorption from the kidney and intestine. Vitamin D is found in milk products. A precursor to vitamin D (cholecalciferol) is made in the skin and processed in the liver. The last phase in the conversion of an inactive form of cholecalciferol into active vitamin D takes place in the proximal tubule of the nephron. Once activated, vitamin D stimulates calcium absorption from the proximal tubule and from the intestine, thereby increasing blood calcium levels.

Kidney stones are abnormalities usually caused by problems in the kidney's ability to handle calcium. In addition, the kidney's role in maintaining blood calcium is important in the bone disease osteoporosis that afflicts many elderly people, especially women.

The kidneys therefore function in the body to:

• Control the composition of the blood and eliminate wastes by filtration/reabsorption/secretion

• Influence blood pressure by renin secretion

• Help regulate the body's calcium by vitamin D activation

If for any reason, the kidneys fail to function, then renal dialysis methods (artificial filtration methods) becomes the only alternative to assist the patient to survive by cleansing the blood. This is especially necessary when both kidneys fail.

QUESTION 5

Hypocalcemia refers to low blood calcium concentration. Clinical signs of this disorder reflect increased neuromuscular excitability and include muscle spasms, tetany and cardiac dysfunction.

Hypercalcemia indicates a concentration of blood calcium higher than normal. The normal concentration of calcium and phosphate in blood and extracellular fluid is near the saturation point; elevations can lead to diffuse precipitation of calcium phosphate in tissues, leading to widespread organ dysfunction and damage.

Preventing hypercalcemia and hypocalcemia is largely the result of robust endocrine control systems.

There are three major pools of calcium in the body:

1. Intracellular calcium: A large majority of calcium within cells is sequestered in mitochondria and endoplasmic reticulum. Intracellular free calcium concentrations fluctuate greatly, from roughly 100 nM to greater than 1 uM, due to release from cellular stores or influx from extracellular fluid. These fluctuations are integral to calcium's role in intracellular signaling, enzyme activation and muscle contractions.

2. Calcium in blood and extracellular fluid: Roughly half of the calcium in blood is bound to proteins. The concentration of ionized calcium in this compartment is normally almost

invariant at approximately 1 mM, or 10,000 times the basal concentration of free calcium within cells. Also, the concentration of phosphorus in blood is essentially identical to that of calcium.

3. <u>Bone calcium:</u> A vast majority of body calcium is in bone. Within bone, 99% of the calcium is tied up in the mineral phase, but the remaining 1% is in a pool that can rapidly exchange with extracellular calcium.

As with calcium, the majority of body phosphate (approximately 85%) is present in the mineral phase of bone. The remainder of body phosphate is present in a variety of inorganic and organic compounds distributed within both intracellular and extracellular compartments. Normal blood concentrations of phosphate are very similar to calcium.
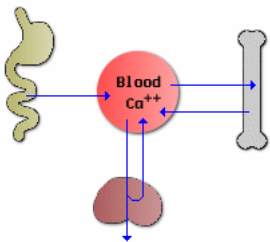
<u>Fluxes of Calcium and Phosphate</u>

Maintaining constant concentrations of calcium in blood requires frequent adjustments, which can be described as fluxes of calcium between blood and other body compartments.

Three organs participate in supplying calcium to blood and removing it from blood when necessary:

-   The small intestine is the site where dietary calcium is absorbed. Importantly, efficient absorption of calcium in the small intestine is dependent on expression of a calcium-binding protein in epithelial cells.

- Bone serves as a vast reservoir of calcium. Stimulating net resorption of bone mineral releases calcium and phosphate into blood, and suppressing this effect allows calcium to be deposited in bone.

- The kidney is critically important in calcium homeostasis. Under normal blood calcium concentrations, almost all of the calcium that enters glomerular filtrate is reabsorbed from the tubular system back into blood, which preserves blood calcium levels. If tubular reabsorption of calcium decreases, calcium is lost by excretion into urine.

Hormonal Control Systems

1. Maintaining normal blood calcium and phosphorus concentrations is managed through the concerted action of three hormones that control fluxes of calcium in and out of blood and extracellular fluid:

2. Parathyroid hormone serves to increase blood concentrations of calcium. Mechanistically, parathyroid hormone preserves blood calcium by several major effects:

   - Stimulates production of the biologically-active form of vitamin D within the kidney.

   - Facilitates mobilization of calcium and phosphate from bone. To prevent detrimental increases in phosphate, parathyroid hormone also has a potent effect on the kidney to eliminate phosphate (phosphaturic effect).

   - Maximizes tubular reabsorption of calcium within the kidney. This activity results in minimal losses of calcium in urine.

Vitamin D acts also to increase blood concentrations of calcium. It is generated through the activity of parathyroid hormone within the kidney. Far and away the most important effect of vitamin D is to facilitate absorption of calcium from the small intestine. In concert with parathyroid hormone, vitamin D also enhances fluxes of calcium out of bone.

Calcitonin is a hormone that functions to reduce blood calcium levels. It is secreted in response to hypercalcemia and has at least two effects:

- Suppression of renal tubular reabsorption of calcium. In other words, calcitonin enhances excretion of calcium into urine.

- Inhibition of bone resorption, which would minimize fluxes of calcium from bone into blood.

Although calcitonin has significant calcium-lowing effects in some species, it appears to have a minimal influence on blood calcium levels in humans.

A useful way of looking at how hormones affect tissues to preserve calcium homeostasis is to examine the effects of calcium deprivation and calcium loading. The following table summarizes body responses to conditions that would otherwise lead to serious imbalances in calcium and phosphate levels in blood.

	Calcium Deprivation	Calcium Loading
Parathyroid hormone	Secretion stimulated	Secretion inhibited
Vitamin D	Production stimulated by increased parathyroid hormone secretion	Synthesis suppressed due to low parathyroid hormone secretion
Calcitonin	Very low level secretion	Secretion stimulated by high blood calcium
Intestinal absorption of calcium	Enhanced due to activity of vitamin D on intestinal epithelial cells	Low basal uptake
Release of calcium and phosphate from bone	Stimulated by increased parathyroid hormone and vitamin D	Decreased due to low parathyroid hormone and vitamin D
Renal excretion of calcium	Decreased due to enhanced tubular reabsorption stimulated by elevated parathyroid hormone and vitamin D; hypocalcemia also activates calcium sensors in loop of Henle to directly facilitate calcium reabsorption	Elevated due to decreased parathyroid hormone-stimulated reabsorption.
Renal excretion of phosphate	Strongly stimulated by parathyroid hormone; this phosphaturic activity prevents adverse effects of elevated phosphate from bone resorption	Decreased due to hypoparathyroidism
General Response	Typically see near normal serum concentrations of calcium and phosphate due to compensatory mechanisms. Long term deprivation leads to bone thining (osteopenia).	Low intestinal absorption and enhanced renal excretion guard against development of hypercalcemia.
Summary		