Question 1:

ROLE OF KIDNEY IN GLUCOSE HOMEOSTASIS

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 . 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.

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.

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.

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. The cells in the renal medulla can use only glucose for their needs (like the brain) and they have enzymes capable of glucose-phosphorylation and glycolysis. They can therefore phosphorylate important amounts of glucose and accumulate glycogen but, because these cells do not have glucose-6-phosphatase or any other gluconeogenic enzymes, they are unable to release glucose into the bloodstream. Moreover, the cells in the renal cortex have gluconeogenic enzymes and they can produce and release glucose into the circulation. However these cells cannot synthesize glycogen because they have little phosphorylating capacity.

After a 16-h overnight fast, approximately 10 µmol ⁄ (kg /min) of glucose is released into the circulation. Almost 50% of this is the result of glycogenolysis from the liver stocks and the other half is produced by liver and kidney gluconeogenesis. The renal cortex (like the liver) contains gluconeogenic enzymes and it can synthesize glucose-6-phosphate from precursors (lactate, glutamine, glycerol and alanine). Because it contains glucose-6-phosphatase, it is able to release glucose into the blood stream and the human liver and kidneys are the only organs that can perform gluconeogenesis. Therefore, after an overnight fast, the liver produces 75–80% of glucose released into the circulation and the remaining 20–25% is derived from the kidneys.

Several studies have indicated that human kidneys and liver provide approximately the same amounts of glucose through gluconeogenesis in post absorptive period. If the duration of fasting is increased, the glycogen stores are depleted and gluconeogenesis produces all the glucose released into circulation.

In the postprandial state the situation changes significantly. Postprandial glucose levels in the plasma are determined by insulin and glucagon levels. After glucose ingestion, plasma glucose levels reach the peak in 60–90 minutes and they return to post-absorptive levels in almost 3–4 h. The plasma insulin increases four times and the plasma glucagon levels decrease by 50%. Meyer et al. indicated that endogenous glucose release is reduced by almost 60% and hepatic glycogenolysis drops to zero in the 4- to 6-h period after meal ingestion .This is happening because this period determines the refilling of hepatic glycogen stores and inhibition of endogenous glucose release is able to limit postprandial hyperglycaemia. There is also a reduction in hepatic gluconeogenesis by 82% and glucose molecules generated through hepatic gluconeogenesis are also directed into hepatic glycogen, not only released in the circulation.

Renal gluconeogenesis can increase by approximately twofold and it can represent ~60% of endogenous glucose production in the postprandial state. This mechanism is believed to facilitate the repletion of glycogen stocks in the liver.

GLYCOGENOLYSIS

Glycogenolysis is the breakdown of glycogen to glucose-6-phosphate and a hydrolysis reaction (using 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 and helps regenerating glucose.

GLUCOSE REABSORPTION

Apart from the important role in gluconeogenesis and the role of renal cortex in glucose uptake, 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 180 grams 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 a 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 the maximum capacity, can vary from 260 to 350 mg/min/1.73 m2 in healthy subjects. It corresponds to blood glucose levels of 180-200 mg/dL. When the blood glucose is very high and the TmG is reached, the transporters cannot reabsorb all the glucose and glucosuria 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 hyperfiltration (eg. pregnancy), but as a consequence of hyperfiltration and not of significant hyperglycemia. In a given day, the kidneys can produce, via gluconeogenesis, 15–55g glucose and it can metabolize 25–35g glucose. Regarding the glucose metabolic pathways, it is obvious that 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 .

Question 2:

PROCESS OF MICTURITION

Micturition or urination is the process of emptying urine from the storage organ, namely, the urinary bladder. The detrusor is the smooth or involuntary muscle of the bladder wall. The urethral muscles consist of the external and internal sphincter. The internal sphincter and detrusor muscle are both under autonomic control. The external sphincter, however, is a voluntary muscle under the control of voluntary nerves.

The bladder normally accommodates up to 300-400 ml in adults. When the bladder is distended it sends signals to the brain, which is perceived as the ‘full bladder’ sensation.

The process of emptying the urine into the urethra is regulated by nervous signals, both from the somatic and the autonomic nervous system. The autonomic nervous system comprises both the sympathetic and the parasympathetic nervous system.

The bladder has two states of function; the storage and emptying phases.

BLADDER FILLING AND THE GUARDING REFLEX

The filling phase is characterized by voluntary contraction of the external urethral sphincter, with sympathetic contraction of the inner urethral sphincter. The sympathetic nervous system also enables the detrusor to distend without reflex contractions, unlike that which happens in most voluntary muscles.

Urethral reflexes, called ‘the guarding reflex,’ also play a part in inhibiting involuntary bladder emptying during this process. The afferents are all conveyed through the pelvic nerves to initiate a spinal reflex.

BLADDER EMPTYING AND MICTURITION REFLEX

The micturition or emptying phase displays a coordinated relaxation of the inner and outer urethral sphincters, under sympathetic and somatic regulation respectively, with strong contractions of the detrusor muscle due to parasympathetic impulses.
Micturition is thus characterized by:

* relaxation of the striated sphincter (somatic innervation)
* relaxation of the smooth muscle sphincter and opening of the bladder neck (sympathetic innervation)
* detrusor contraction (parasympathetic innervation)

The distension of the urinary bladder wall causes wall tension to rise very slightly. However, when the bladder is almost full, at about 300-400 ml, the inherent contractility of the detrusor causes reflex contractions to occur, which are less powerful than the voiding contraction. Afferent firing frequency increases with filling, but cortical control still overrides the micturition reflex until voluntary voiding is determined upon.

During micturition, urinary flow is assisted by additional detrusor contractions and external sphincter relaxation which further lowers resistance to the passage of urine. The abdominal wall and pelvic floor musculature also participates by increasing the force on the bladder to help achieve complete emptying.



## SPINAL REFLEX ARCS

The act of micturition is an autonomic reflex at the level of the spinal cord. This reflex also helps to complete micturition when the act is voluntarily initiated, or when it follows a period of inhibition by the brain, by relaxing the external sphincter.

The control of this process is mediated via afferent signals from stretch and volume receptors in the bladder, as well as from the muscles of the pelvic floor, the vagina/penis, and the rectum, which informs the brain about the extent of filling, initiating several spinal reflexes. These serve to inhibit micturition until filling is complete, while activating the voluntary external urethral sphincter via the pudendal nerve. At the same time, detrusor activity is inhibited and the internal urethral sphincter is stimulated via sympathetic activity. Impulses from the filling bladder are carried to the spinal cord via the pelvic and hypogastric nerves, whereas the pudendal and hypogastric nerves carry impulses from the neck of the bladder and the urethra

## PONTINE MICTURITION CENTER

The pontine micturition center (PMC) in the brainstem is activated via afferent signals from the urinary bladder as it is filling. This center sends inhibitory impulses to the spinal reflex arcs to enable bladder voiding.

In the absence of any other regulation, the afferents from the bladder and urethra to the midbrain and pons and the efferents to the spinal cord would act as an on-off switch, to cause either reflex voiding or storage depending only on the urine volume stored in the bladder. This means that during the filling or storage phase, the voiding reflex is off, but it is switched on to the highest level when the bladder is distended beyond a critical point, activating the tension receptors in the wall.

Question 3:

JUXTAGLOMERULAR APPARATUS

Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron. Juxtaglomerular apparatus is formed by three different structures:

* Macula densa
* Extraglomerular mesangial cells
* Juxtaglomerular cells.

MACULA DENSA

Macula densa is the end portion of thick ascending segment before it opens into distal convoluted tubule. It is situated between afferent and efferent arterioles of the same nephron. It is very close to afferent arteriole. Macula densa is formed by tightly packed cuboidal epithelial cells.

EXTRAGLOMERULAR MESANGIAL CELLS

 Extraglomerular mesangial cells are situated in the triangular region bound by afferent arteriole, efferent arteriole and macula densa. These cells are also called agranular cells, lacis cells or Goormaghtigh cells.

 JUXTAGLOMERULAR CELLS

Juxtaglomerular cells are specialized smooth muscle cells situated in the wall of afferent arteriole just before it enters the Bowman capsule. These smooth muscle cells are mostly present in tunica media and tunica adventitia of the wall of the afferent arteriole. Juxtaglomerular cells are also called granular cells because of the presence of secretary granules in their cytoplasm.

Polar Cushion or Polkissen Juxtaglomerular cells form a thick cuff called polar cushion or polkissen around the afferent arteriole before it enters the Bowman capsule.

FUNCTIONS OF JUXTAGLOMERULAR APPARATUS

Primary function of juxtaglomerular apparatus is the secretion of hormones. It also regulates the glomerular blood flow and glomerular filtration rate.

SECRETION OF HORMONES

Juxtaglomerular apparatus secretes two hormones:

* Renin
* Prostaglandin.

SECRETION OF OTHER SUBSTANCES

* Extraglomerular mesangial cells of juxtaglomerular apparatus secrete cytokines like interleukin-2 and tumor necrosis factor
* Macula densa secretes thromboxane A2. 

REGULATION OF GLOMERULAR BLOOD FLOW AND GLOMERULAR FILTRATION RATE

 Macula densa of juxtaglomerular apparatus plays an important role in the feedback mechanism called tubuloglomerular feedback mechanism, which regulates the renal blood flow and glomerular filtration rate

Question 4:

ROLE OF KIDNEY IN THE REGULATION OF BLOOD PRESSURE

The blood pressure in your body depends upon the following conditions:

* The force of contraction of the heart-- related to how much the heart muscle gets stretched by the incoming blood.
* The degree to which the arteries and arterioles constrict -- increases the resistance to blood flow, thus requiring a higher blood pressure.
* The circulating blood volume -- the higher the circulating blood volume, the more the heart muscle gets stretched by the incoming blood.

The kidney influences blood pressure by:

* Causing the arteries and veins to constrict
* Increasing the circulating blood volume

Specialized cells are located in a portion of the distal tubule located near and in the wall of the afferent arteriole. The distal tubule cells (macula densa) sense the Na in the filtrate, and the arterial cells (juxtaglomerular cells) sense the blood pressure. When the blood pressure drops, the amount of filtered Na also drops. The juxtaglomerular cells sense the drop in blood pressure and the decrease in Na 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 angiotensinI. Angiotensin I is then converted to angiotensin II by an angiotensin-converting enzyme (ACE), which is found mainly in the lungs. Angiotensin II causes blood vessels to contract -- the increased blood vessel constrictions elevate the blood pressure.

­­ Angiotensin II 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 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 your 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 also stimulates calcium release from bone and calcium absorption from the intestine.

In addition to parathyroid hormone, the body also requires vitamin D 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. However, the final step that converts an inactive form of cholecalciferol into active vitamin D occurs 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 often 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.

As you can see, the kidneys perform many functions that are important to the body:

* Controlling the composition of your blood and eliminate wastes -- filtration/reabsorption/secretion method
* Influencing blood pressure -- renin secretion
* Helping to regulate your body's calcium -- vitamin D activation

If the kidneys fail to function, then renal dialysis methods (artificial filtration methods) can be used to help you survive by cleansing the blood. This is especially necessary when both kidneys fail. Although you have two kidneys, it is possible to live with only one. One healthy kidney can be donated and transplanted into a compatible person with total kidney failure. Kidney transplants are a common way to help those people survive and live a normal life.

Question 5:

ROLE OF KIDNEY IN CALCIUM HOMEOSTASIS

Total serum calcium consists of ionized, protein bound, and complexed fractions (approximately 48%, 46%, and 7%, respectively). The complexed calcium is bound to molecules such as phosphate and citrate. The ultrafilterable calcium equals the total of the ionized and complexed fractions. Normal total serum calcium is approximately 8.9–10.1 mg/dl (about 2.2–2.5 mmol/l). Calcium can be bound to albumin and globulins.

In humans who have a GFR of 170 liters per 24 hours, roughly 10 g of calcium is filtered per day. The amount of calcium excreted in the urine usually ranges from 100 to 200 mg per 24 hours; hence, 98%–99% of the filtered load of calcium is reabsorbed by the renal tubules. Approximately 60%–70% of the filtered calcium is reabsorbed in the proximal convoluted tubule, 20% in the loop of Henle, 10% by the distal convoluted tubule, and 5% by the collecting duct. The terminal nephron, although responsible for the reabsorption of only 5%–10% of the filtered calcium load, is the major site for regulation of calcium excretion.

The reabsorption of calcium in the proximal convoluted tubule parallels that of sodium and water. Proximal tubular calcium reabsorption is thought to occur mainly by passive diffusion and solvent drag. This is based on the observation that the ratio of calcium in the proximal tubule fluid to that in the glomerular filtrate is 1:1.2. The passive paracellular pathways account for approximately 80% of calcium reabsorption in this segment of the nephron. A small but significant component of active calcium transport is observed in the proximal tubules. The active transport of calcium proceeds in a two-step process, with calcium entry from the tubular fluid across the apical membrane and exit though the basolateral membrane. This active transport is generally considered to constitute 10%–15% of total proximal tubule calcium reabsorption and it is mainly regulated by parathyroid hormone (PTH) and calcitonin.

No reabsorption of calcium occurs within the thin segment of the loop of Henle. In the thick ascending limb of the loop of Henle, 20% of the filtered calcium is reabsorbed largely by the cortical thick ascending limb, through both transcellular and paracellular routes. In the thick ascending limb, the bulk of calcium reabsorption proceeds through the paracellular pathway and is proportional to the transtubular electrochemical driving force.

The apical Na+-K+-2Cl− cotransporter NKCC2 and the renal outer medullary potassium K+ (ROMK) channel generate the “driving force” for paracellular cation transport.In contrast with the proximal tubule and the thick ascending limb of the loop of Henle, the distal tubule reabsorbs calcium exclusively via the transcellular route. The distal convoluted tubule absorbs 5%–10% of the filtered calcium.

HORMONAL AND OTHER FACTORS

PARATHYROID HORMONE

Many physiologic, pharmacologic, and pathologic factors influence renal calcium absorption. The most important regulator is PTH, which stimulates calcium absorption. PTH is a polypeptide secreted from the parathyroid gland in response to a decrease in the plasma concentration of ionized calcium. Therefore, the major physiologic role of the parathyroid gland is to regulate calcium homeostasis. PTH acts to increase the plasma concentration of calcium in three ways:

* it stimulates bone resorption
* it enhances intestinal calcium and phosphate absorption by promoting the formation within the kidney of 1,25(OH)2D, and
* it augments active renal calcium absorption. These effects are reversed by small changes in the serum calcium concentration that lower PTH secretion.

VITAMIN D

The most important endocrine effect of 1,25(OH)2D in the kidney is a tight control of its own homeostasis through simultaneous suppression of 1α-hydroxylase and stimulation of 24-hydroxylase. An intact 1,25(OH)2D–vitamin D receptor system is critical for both basal and PTH-induced osteoclastogenesis. Mature osteoclasts release calcium and phosphorus from the bone, maintaining the appropriate levels of the two minerals in the plasma.

SERUM CALCIUM

Hypercalcemia is associated with an increase in urinary calcium excretion as a consequence of an increase in the filtered load and a decrease in the tubular reabsorption of calcium. Although hypercalcemia can decrease GFR by renal vasoconstriction, which tends to offset the increase in filtered load, hypercalcemia also causes a decline in tubular reabsorption of calcium by both PTH-dependent and -independent effects. Hypocalcemia decreases renal calcium excretion by decreasing the filtered load and enhancing the tubular reabsorption of calcium.

EXTRACELLULAR FLUID

Expansion of the extracellular fluid is associated with an increase in sodium, chloride, and calcium excretion, whereas reciprocal effects are seen with volume contraction. The mechanisms of this effect are interrelated with the effects of sodium reabsorption and compensatory changes that occur as a result of volume expansion.

METABOLIC ACIDOSIS

Acute and chronic metabolic acidosis can be associated with an increase in calcium excretion, independent of PTH changes. The calciuria may, in part, be due to the mobilization of calcium from bone, as the hydrogen ion is buffered in the skeleton; however, direct effects of acidosis on tubular calcium resorption also play a role.

DIURETICS

Loop diuretics decrease calcium absorption as a result of inhibition of the transport of sodium chloride at the NKCC2 transporter in the ascending loop of Henle. Thiazide diuretics, which act in the distal tubule, are associated with hypocalciuria. Two main mechanisms have been proposed to explain the effect of thiazides on calcium excretion:

* increased proximal sodium and water reabsorption due to volume depletion,
* increased distal calcium reabsorption at the thiazide-sensitive site in the distal convoluted tubule.