**17/MHS01/176**

**LAWAL FAREED OLADELE**

**Discuss the role of kidney in glucose homeostasis**

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

1. Gluconeogenesis and Glycogenolysis;
2. Glucose uptake from the blood for its own energy requests and
3. Reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy**.**

**Gluconeogenesis (Renal Gluconeogenesis):**

Inthis regard the kidney is considered as two separate organs; the renal medulla is characterized mainly by glucose utilization and the renal cortex is responsible for glucose release. This is a direct consequence of the distribution of enzymes along the nephron, the cells in the renal medulla can use only glucose for their needs and they have enzymes capable of glucose-phosphorylation and glycolysis and also glycogen formation and storage.

But as renal medullary cells do not possess gluconeogenic enzymes such as glucose-6-phosphatase, they are unable to release glucose into the bloodstream. However, the cells in the renal cortex have gluconeogenic enzymes and they can produce and release glucose into the circulation, these cells cannot synthesize glycogen because they have little phosphorylating ability.

After a 16 hour overnight fast, approximately 10 µmol ⁄ (kg /min) of glucose is released into the circulation, approximately 50% of this is the result of glycogenolysis from the liver stocks and the other half is produced by liver and kidney gluconeogenesis. The liver produces 75–80% of glucose released into the circulation and the remaining 20–25% is derived from the kidneys.

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. **The human liver and kidneys are the only organs that can perform gluconeogenesis.**

An important aspect is that kidney and liver use different gluconeogenic precursors and several hormones have different effects on their release of glucose. Lactate represents the predominant gluconeogenic precursor in both organs, but regarding the amino acids, the kidney prefers to use **glutamine**, whereas the liver preferentially uses **alanine.** Insulin can suppress glucose release in both organs with almost comparable efficacy, whereas glucagon stimulates hepatic glucose release only. Catecholamines (adrenaline) normally have a direct effect only on renal glucose release but their effect on both hepatic and renal glucose release may be indirect by increasing the quantity of gluconeogenic substrates available and by suppressing insulin secretion. Renal gluconeogenesis can increase by approximately twofold and it can represent approximately 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 release. In physiologic conditions, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose, the kidneys can reabsorb as much glucose as possible, the result being a virtually glucose free urine. Approximately 180 grams of D-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 (glucosuria). 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.

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 (e.g. pregnancy), but as a consequence of hyperfiltration and not of significant hyperglycemia.

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

**Discuss 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. The functional anatomy and nerve supply of urinary bladder and urethra are essential for the process of micturition.

**The urinary** **bladder** is a triangular hollow organ located in the pelvic cavity posterior to the pubic symphyses. It is of 3 layers:

1. Parietal peritoneum
2. Muscularis: the detrusor muscle (smooth muscle) which has 3 ill-defined layers
3. Mucosa: lined by transthelium, it is thrown into folds (rugae) when the bladder is relaxed but straightens out as the bladder fills up

At the posterior surface of the bladder wall is a triangular area called the **trigone**, which is like an inverted triangle, the upper angles of this inverted triangle formed by the entrance of the two ureters in to the bladder and the lower angle formed by the narrowing (neck) and continuation of the bladder with the urethra, the bladder and urethra are separated by the internal urethral sphincter, which is a circular band of muscle.

Male urethra has both urinary function and reproductive function. It carries urine and semen. Female urethra has only urinary function and it carries only urine. So, male urethra is structurally different from female urethra.

**Male urethra** is about 20 cm long. After origin from bladder it traverses the prostate gland, which lies below the bladder and then runs through the penis.

Throughout its length, the urethra has mucus glands called glands of Littre. Male urethra is divided into three parts:

1. Prostatic urethra
2. Membranous urethra
3. Spongy urethra.

**Female urethra** is narrower and shorter than male urethra. It is about 3.5 to 4 cm long. After origin from bladder it traverses through urogenital diaphragm and runs along anterior wall of vagina. Then it terminates at external orifice of urethra, which is located between clitoris and vaginal opening.

There are two urethral sphincters in the urinary tract:

1. **Internal Urethral sphincter**: This sphincter is situated between neck of the bladder and upper end of urethra. It is made up of smooth muscle fibres and formed by thickening of detrusor muscle. It is innervated by autonomic nerve fibres. This sphincter closes the urethra when bladder is emptied.
2. **External Urethral sphincter**: External sphincter is located in the urogenital diaphragm. This sphincter is made up of circular skeletal muscle fibres, which are innervated by somatic nerve fibres.

**Nerve Supply to Urinary Bladder and Urethral Sphincters**

Urinary bladder and the internal sphincter are supplied by sympathetic and parasympathetic divisions of autonomic nervous system whereas, the external sphincter is supplied by the somatic nerve fibres

1. **Sympathetic Nerve Supply:** The stimulation of sympathetic (hypogastric) nerve causes relaxation of detrusor muscle and constriction of the internal sphincter. It results in filling of urinary bladder and so, the sympathetic nerve is called **nerve of filling**.
2. **Parasympathetic Nerve Supply:** Stimulation of parasympathetic (pelvic) nerve causes contraction of detrusor muscle and relaxation of the internal sphincter leading to emptying of urinary bladder. So, parasympathetic nerve is called the nerve of emptying or nerve of micturition. Pelvic nerve has also the sensory fibres, which carry impulses from stretch receptors present on the wall of the urinary bladder and urethra to the central nervous system.
3. **Somatic Nerve Supply**: Function of Pudendal Nerve Pudendal nerve maintains the tonic contraction of the skeletal muscle fibres of the external sphincter and keeps the external sphincter constricted always. During micturition, this nerve is inhibited. It causes relaxation of external sphincter leading to voiding of urine. Thus, the pudendal nerve is responsible for voluntary control of micturition.

**Filling of the Urinary Bladder**

Urine is continuously formed by nephrons and it flows into urinary bladder drop by drop through ureters. When urine collects in the pelvis of ureter, the contraction sets up in pelvis. This contraction is transmitted through rest of the ureter in the form of peristaltic wave up to trigone of the urinary bladder. The peristaltic wave moves the urine into the bladder.

After leaving the kidney, the direction of the ureter is initially downward and outward. Then, it turns horizontally before entering the bladder. At the entrance of ureters into urinary bladder, a valvular arrangement is present. When peristaltic wave pushes the urine towards bladder, this valve opens towards the bladder. The position of ureter and the valvular arrangement at the end of ureter prevent the back flow of urine from bladder into the ureter when the detrusor muscle contracts. Thus, urine is collected in bladder drop by drop.

**Micturition Reflex**

This reflex is elicited by the stimulation of stretch receptors situated on the wall of urinary bladder and urethra. When about 300 to 400 mL of urine is collected in the bladder, intravesical pressure increases. This stretches the wall of bladder resulting in stimulation of stretch receptors and generation of sensory impulses.

**Pathway for Micturition**

Reflex Sensory (afferent) impulses from the receptors reach the sacral segments of spinal cord via the sensory fibres of pelvic (parasympathetic) nerve. Motor (efferent) impulses produced in spinal cord, travel through motor fibres of pelvic nerve towards bladder and internal sphincter. Motor impulses cause contraction of detrusor muscle and relaxation of internal sphincter so that, urine enters the urethra from the bladder. Once urine enters urethra, the stretch receptors in the urethra are stimulated and send afferent impulses to spinal cord via pelvic nerve fibres. Now the impulses generated from spinal centres inhibit pudendal nerve. So, the external sphincter relaxes and micturition occurs. Once a micturition reflex begins, it is self-regenerative, i.e. the initial contraction of bladder further activates the receptors to cause still further increase in sensory impulses from the bladder and urethra. These impulses, in turn cause further increase in reflex contraction of bladder. The cycle continues repeatedly until the force of contraction of bladder reaches the maximum and the urine is voided out completely. During micturition, the flow of urine is facilitated by the increase in the abdominal pressure due to the voluntary contraction of abdominal muscles.

Spinal centres for micturition are present in sacral and lumbar segments. But, these spinal centres are regulated by **higher centres**. The higher centres, which control micturition are of two types, **inhibitory** centres and **facilitatory** centres.

**Inhibitory centres** **for micturition:** Centres in **midbrain** and **cerebral cortex** inhibit the micturition by suppressing spinal micturition centres.

**Facilitatory centres** **for micturition:** Centres in **pons** facilitate micturition via spinal centres. Some centres in **cerebral cortex** also facilitate micturition.

**Explain Juxtaglomerular Apparatus**

Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron. It is found between afferent arteriole and the distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and glomerular filtration rate.

The juxtaglomerular apparatus consists of three types of cells:

1. The macula densa, a part of the distal convoluted tubule of the same nephron
2. Juxtaglomerular cells, (also known as granular cells) which secrete renin
3. Extraglomerular mesangial cells (also called lacis cells)

Cells in the **macula densa** respond to changes in the sodium chloride levels in the distal tubule of the nephron via the tubuloglomerular feedback (TGF) loop, the macula densa cells trigger contraction of the afferent arteriole, reducing flow of blood to the glomerulus and the glomerular filtration rate.

**Juxtaglomerular cells/Granular cells:** Renin is produced by juxtaglomerular cells. These cells are similar to epithelium and are located in the tunica media of the afferent arterioles as they enter the glomeruli. The juxtaglomerular cells secrete renin in response to:

1. Stimulation of the beta-1 adrenergic receptor
2. Decrease in renal perfusion pressure (detected directly by the granular cells)
3. Decrease in NaCl concentration at the macula densa, often due to a decrease in glomerular filtration rate

Renin increases blood pressure via the renin-angiotensin-aldosterone system

**Extraglomerular mesangial cells/Lacis cells** are located in the junction between the afferent and efferent arterioles. These cells have a contractile property similar to vascular smooth muscles and thus play a role in regulating glomerular filtration rate by altering the vessel diameter. Renin is also found in these cells.

**Discuss the Role of the Kidney in Regulation of Blood Pressure**

Kidneys play an important role in the long-term regulation of arterial blood pressure. When blood pressure alters slowly in several days, months, years, the nervous mechanism adapts to the altered pressure and loses the sensitivity for the changes. It cannot regulate the pressure any more. In such conditions, the renal mechanism operates efficiently to regulate the blood pressure. Therefore, it is called long-term regulation. Kidneys regulate arterial blood pressure by two ways:

1. **By regulation of ECF volume:** When the blood pressure increases, kidneys excrete large amounts of water and salt, particularly sodium, by means of **pressure diuresis** and **pressure natriuresis.** Due of diuresis and natriuresis, there is a decrease in ECF volume and blood volume, which in turn brings the arterial blood pressure back to normal level. When blood pressure decreases, the reabsorption of water from renal tubules is increased. This in turn, increases ECF volume, blood volume and cardiac output, resulting in restoration of blood pressure
2. **Through renin­angiotensin mechanism:** When renin is released into the blood, it acts on a specific plasma protein called angiotensinogen or renin substrate. By the activity of renin, the angiotensinogen is converted into angiotensin I. Angiotensin I is converted into angiotensin II by the activity of angiotensin-converting enzyme (ACE) secreted from lungs. Most of the conversion of angiotensin I into angiotensin II takes place in lungs. Angiotensin II acts in two ways to restore the blood pressure:
3. It causes constriction of arterioles in the body so that the peripheral resistance is increased and blood pressure rises. In addition, angiotensin II causes constriction of afferent arterioles in kidneys, so that glomerular filtration reduces. This results in retention of water and salts, increases ECF volume to normal level. This in turn increases the blood pressure to normal level.
4. Simultaneously, angiotensin II stimulates the adrenal cortex to secrete aldosterone. This hormone increases reabsorption of sodium from renal tubules. Sodium reabsorption is followed by water reabsorption, resulting in increased ECF volume and blood volume which in turn increases the blood pressure to normal level.

**Discuss the role of Kidney in Calcium homeostasis?**

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.