1. **The involvement of kidneys in glucose homeostasis**

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. 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. 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.

**Renal 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 [18] 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 postabsorptive period. If the duration of fasting is increased, the glycogen stores are depleted and gluconeogenesis produces all the glucose released into circulation. 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 aminoacids, 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 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. Other hormones, such as growth hormone, cortisol and thyroid hormones can stimulate hepatic glucose release over a great period of time. Their effects on the kidneys regarding glucose release in humans are not completely deciphered.

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. A new concept of hepatorenal glucose reciprocity emerged from the differences observed in regulation and interchange between renal and hepatic glucose release.This concept refers to the facts that a pathological or physiological reduction in glucose release by kidney or liver determines a compensatory increase in glucose release of the other one (liver or kidney) in order to avoid hypoglycaemia. This situation occurs in the anhepatic phase during liver transplantation, prolonged fasting, meal ingestion, acidosis and insulin overdoses in diabetes mellitus.

**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.

1. **PROCESS OF MICTURITION**

We depend on micturition (urination) to eliminate organic waste products, which are produced as a result of cell metabolism in the body. The urinary system also regulates the concentrations of sodium, potassium, chloride and other ions in the blood as well as helping to maintain normal blood pH, blood pressure and blood volume. At its most basic level, micturition is a simple reflex which is displayed by infants who are not toilet-trained.

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

Control of micturition

Children and adults have considerable control over when and where they pass urine. They can also increase or decrease the rate of flow and even stop and start again, so micturition is clearly more than just a simple reflex. This control is learnt in infancy and involves other sensory fibres in the bladder wall. These fibres convey information on the degree of bladder fullness via the spine to the higher centres of the brain, the thalamus and cerebral cortex. This causes us to become aware that we need to pass urine and of the urgency of the situation. These links between the spine and cerebral cortex are not established until about two years of age and it is suggested that toilet-training is therefore not physiologically possible until that time. The brain is able to override the micturition reflex by inhibiting the parasympathetic motor nerve fibres to the bladder and reinforcing contraction of the external sphincter. The internal sphincter will not open until the external sphincter does. The increase in bladder volume increases stretch receptor and nerve activity, making the sensation of pressure more acute. When it is convenient, the brain centres remove the inhibition and permit micturition under our conscious control. When the bladder contains about 500ml, pressure may force open the internal sphincter; this in turn forces open the external sphincter and urination occurs whether it is convenient or not.

We can increase the rate of urine flow by contraction of the abdominal muscles and by the performance of Valsalva’s manoeuvre (forced expiration against a closed glottis). Contraction of the strong pelvic floor muscles can stop urine in mid-flow. The sound of running water also encourages micturition but some people cannot urinate in the presence of others, no matter how great their need.

After micturition, less than 10ml of urine remains in the bladder and the cycle begins again.

**Potential problems associated with micturition**

For normal micturition to occur we need:

- Intact nerve pathways to the urinary tract;

- Normal muscle tone in the detrusors, sphincters and pelvic floor muscles;

- Absence of any obstruction to urine flow in any part of the urinary tract;

- Normal bladder capacity;

- Absence of environmental or psychological factors which may inhibit micturition

Loss of any of these normal functions may result in incontinence or urgency to micturate. Neurological disorders may include stroke, Alzheimer’s disease or any condition where nerve pathways to and from the spine and brain are blocked or injured. The neurotransmitter acetylcholine (ACh) is involved in the relaying of nerve signals in micturition. ACh can be blocked with the drug atropine, so the detrusor muscle will not contract and retention of urine will occur. Stress incontinence can occur at any age. It occurs when abdominal pressure rises, for example when sneezing or coughing. The normally acute angle between the bladder and urethra is lost when abdominal pressure rises slightly, causing pressure in the bladder to rise. Laxity and weakness of muscles at the bladder neck, around the urethra and in the pelvic floor will mean that incontinence occurs with relatively small pressure changes. Stress incontinence can occur in men following prostatectomy, and in women after childbirth and during the menopause due to decreased oestrogen secretions. Renal stones, inflammation and an enlarged prostate gland may all obstruct the flow of urine and may result in frequency of micturition and retention of urine. Bladder tumours and pregnancy also reduce normal bladder capacity. Environmental and psychological factors can also affect a patient’s ability to pass urine.

1. **Juxtaglomerular Apparatus**

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

1. **The Role of Kidney in Regulating Arterial Blood Pressure**

* Control of Blood Pressure: If a sudden change in blood pressure occurs it is controlled in the short term by the sympathetic nervous system which alters three things:
* Total peripheral resistance
* Capacitance
* Cardiac output

It is only in the long term in response to chronic changes in blood pressure that the kidney works to alter the balance between fluid intake and output in order to regulate blood pressure. Renal Regulation: Increased pressure has a direct effect on the kidney

#### Three mechanisms of Renal Regulation

##### Pressure Diuresis

* As arteriolar blood pressure increases, so flow through the kidneys also increases - see above formula
* This increases filtration rate
* This increases urinary output

##### Pressure Natriuresis

* If renal perfusion pressure is increased then sodium excretion increases
* I.e. sodium excretion increases when blood pressure increases
* If more sodium is excreted less water is reabsorbed therefore the ECF volume decreases and blood pressure decreases.
* The actual mechanism is not clear but it is thought to involve a direct effect of the pressure on the renal interstitium.

**Renin-Angiotensin-Aldosterone System**

* Specialized cells in the distal tubule called the macula densa sense the concentration of sodium and chloride.
* If blood pressure falls there is a reduction in concentration of sodium and chloride in the distal tubule which is sensed by the macula densa.
* The macula densa releases prostaglandins which act on the juxtaglomerular apparatus which releases renin into the bloodstream.
* The drop in blood pressure is also detected by baroreceptors in the aortic arch, carotid sinus and the afferent renal arteriole which stimulates renin release by the juxtaglomerular apparatus.
* Renin cleaves angiotensinogen into angiotensin 1 which in turn is cleaved by [**Angiotensin Converting Enzyme** (ACE)](https://en.wikivet.net/Angiotensin_Converting_Enzyme) into angiotensin 2.
* Angiotensin 2 is a potent vasoconstrictor and also stimulates the adrenal cortex to release [aldosterone](https://en.wikivet.net/Aldosterone).
* [Aldosterone](https://en.wikivet.net/Aldosterone) acts on the distal tubules and collecting ducts in the kidney causing retention of sodium and water.
* Blood pressure increases.

Regulation of Renal Blood Flow

It is essential that renal blood flow is maintained to ensure that adequate filtration of toxins from the blood takes place. Changes in pressure affect renal blood flow.

1. Discuss the role of Kidney in Calcium homeostasis?

About 50% of plasma calcium (ionized and complexed form; ultrafilterable fraction, excluding the protein bound form) is freely filtered through the renal glomerulus, and 99% of the filtered calcium is actually reabsorbed along renal tubules (Table 1). The excreted calcium in the final urine is about 200 mg per day in an adult person with an average diet. Several factors are involved in the regulation of calcium in renal tubules. PTH and activated vitamin D enhance calcium reabsorption in the thick ascending limb (TAL), distal convoluted tubule (DCT) and/or connecting tubule (CNT), and estrogen promotes calcium absorption in the DCT/CNT1, 2). Acidosis contributes to hypercalciuria by reducing calcium reabsorption in the proximal tubule (PT) and DCT, and alkalosis vice versa3). Diuretics like thiazide and furosemide also alter calcium absorption in the renal tubules; thiazide promotes calcium reabsorption and furosemide inhibits it4, 5). Plasma calcium itself also controls renal calcium absorption through altered PTH secretion as well as via binding to the calcium sensing receptor (CaSR) in the TAL. To facilitate Ca2+ reabsorption along renal tubules; (i) voltage difference between the lumen and blood compartment should be favorable for Ca2+ passage, i.e., a positive voltage in the lumen; (ii) concentration difference should be favorable for Ca2+ passage with a higher Ca2+ concentration in the lumen; (iii) an active transporter should exist if the voltage or concentration difference is not favorable for Ca2+ reabsorption. Each renal tubular segment has a different Ca2+ concentration difference or voltage environment for its unique mechanism for calcium reabsorption.