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**DEPARTMENT: MEDICINE AND SURGERY**

**COURSE: RENAL PHYSIOLOGY, BODY FLUID AND TEMPERATURE REGULATION**

**ASSIGNMENT**

1. **Discuss the role of kidney in glucose homeostasis?**

While not traditionally discussed, 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. This article provides an extensive review of the kidneys’ role in normal human physiology, the mechanisms by which they contribute to glucose regulation, and the potential impact of glucose imbalance on the kidneys.

Published studies over the last 60 years have provided considerable evidence regarding the ability of the kidneys to make and release glucose under various physiologic conditions. Yet traditionally, the kidneys have not been considered an important source of glucose (except during acidosis or after prolonged fasting), with most clinical discussions on glucose dysregulation centering on the intestine, pancreas, liver, adipose tissue, and muscle. More recently, however, the full significance of the kidneys’ contribution to glucose homeostasis, under both physiologic and pathologic conditions, has become well recognized, and is thought to involve functions well beyond glucose uptake and release. Besides the liver, the kidney is the only organ capable of generating sufficient glucose (gluconeogenesis) to release into the circulation, and it is also responsible for filtration and subsequent reabsorption or excretion of glucose. These findings have provided considerable insight into the myriad of pathophysiologic mechanisms involved in the development of hyperglycemia and type 2 diabetes mellitus.The kidneys’ role in normal human physiology, the mechanisms by which they contribute to glucose regulation, and the potential impact of glucose imbalance on the kidneys.

**OVERVIEW OF RENAL PHYSIOLOGY**

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 (ie, 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.

**MAINTENANCE OF GLUCOSE HOMEOSTASIS IN THE KIDNEYS**

The 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 (eg, 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 (in the kidneys).

As alluded to previously, the kidneys are capable of synthesizing and secreting many important hormones (eg, 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 (eg, 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**

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 (eg, 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.

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 (eg, hepatic insufficiency, counterregulation of hypoglycemia). To this point, evidence suggests that in patients with Type 2 diabetes mellitus, renal glucose release is increased in both the postprandial and postabsorptive states, implicating the kidneys’ contribution to the hyperglycemia that characterizes this condition. In one study, a 3-fold increase in renal glucose release was observed in patients with diabetes versus those without.14 In contrast, hepatic glucose release increased by only 30% in the diabetic state. Potential mechanisms involved in excessive renal glucose release in Type 2 diabetes mellitus include fasting gluconeogenesis, decreased postprandial insulin release, 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. Again, it is clear that there is a renal contribution to glucose output in the body, but the actual contribution in individual patients with Type 2 diabetes mellitus is still controversial.

**GLUCOSE REABSORPTION**

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

**RENAL GLUCOSE TRANSPORTERS**

The transport of glucose (a polar compound with positive and negative charged areas, making it soluble in water) into and across cells is dependent on specialized carrier proteins in 2 gene families: the facilitated glucose transporters (GLUTs) and the sodium-coupled glucose cotransporters (SGLTs). These transporters control glucose transport and reabsorption in several tissue types, including the proximal renal tubule, small intestine, blood-brain barrier, and peripheral tissues. GLUTs are involved in the passive transport of glucose across cell membranes, facilitating its downhill movement as it equilibrates across a membrane. SGLTs, on the other hand, mediate active transport of glucose against a concentration gradient by means of cotransport with sodium. Of the various SGLT proteins expressed in the kidneys, SGLT2 is considered most important; based on animal studies, it is responsible for reabsorbing 90% of the glucose filtered at the glomerulus. SGLT1 contributes to the other 10% of glucose reabsorbed in the proximal tubule. This predominant role of SGLT2 in renal reabsorption of glucose raises the prospect of therapeutically blocking this protein in patients with diabetes. Of the various GLUT proteins expressed in the kidneys, GLUT2 is the major transporter, releasing into circulation the glucose reabsorbed by SGLTs in the proximal tubular cells.

In examining disorders involving renal glucose transport, gene mutations within SGLTs lead to inherited disorders of renal glucosuria, including familial (primary) renal glucosuria (FRG) and glucose-galactose malabsorption (GGM). FRG, an autosomal recessive or autosomal dominant disorder resulting from several different SGLT2 mutations, is characterized by persistent glucosuria in the absence of hyperglycemia or general renal tubular dysfunction. Because the majority of patients with FRG have no clinical manifestations, FRG is commonly described as a “nondisease” and is synonymous with the condition known as benign glucosuria. Even the most severe form of FRG (type O), where nonfunctioning mutations within the SGLT2 gene result in a complete absence of renal tubular glucose reabsorption, is associated with a favorable prognosis. Because FRG is generally asymptomatic, affected individuals are identified through routine urinalysis.

GGM, a more serious autosomal recessive disease caused by mutation of the SGLT1 transporter, is characterized by intestinal symptoms that manifest within the first few days of life and result from failure to absorb glucose and galactose from the intestinal tract. The resultant severe diarrhea and dehydration may be fatal if a glucose- and galactose-free diet is not initiated. In some patients with GGM, glucosuria is present but typically mild, while in others, no evidence of abnormal urinary glucose excretion exists, affirming the minor role of SGLT1 in renal glucose reabsorption of glucose.

Gene mutations involving GLUTs are associated with more severe consequences, as these transporters are more widespread throughout the major organ systems. Compared with SGLT2 and SGLT1, which are present mostly in the renal system, GLUT2 is a widely distributed facilitative glucose transporter that has a key role in glucose homeostasis through its involvement in intestinal glucose uptake, renal reabsorption of glucose, glucosensing in the pancreas, and hepatic uptake and release of glucose.4 Mutations of the gene encoding this protein result in Fanconi-Bickel syndrome, a rare autosomal recessive glycogen storage disease that encompasses a multitude of complications (glucose and galactose intolerance, postprandial hyperglycemia, fasting hypoglycemia, tubular nephropathy, hepatomegaly, renomegaly, rickets, and stunted growth). Because GLUT2 is involved in the tubular reabsorption of glucose, glucosuria is a feature of the nephropathy.

**IMPACT OF HYPERGLYCEMIA ON THE KIDNEYS**

While renal glucose reabsorption is a glucose-conserving mechanism in normal physiologic states, it is known to contribute to hyperglycemia in conditions such as T2DM. Renal glucose reabsorption tends to increase with plasma glucose levels, up to plasma concentrations of 180 mg/dL to 200 mg/dL.7 Among patients with diabetes, an excess of approximately 13 grams of glucose is taken up from the systemic circulation, of which 85% is attributed to increased renal glucose uptake. Evidence suggesting a higher TmG in patients with diabetes compared with healthy controls attests to the increased state of renal glucose reabsorption seen in chronic hyperglycemia, which in turn can increase the risk of microvascular complications. Over time, the glomeruli become damaged and are unable to filter blood efficiently and glomerular membranes leak protein (more than 50% of the protein is albumin) into the urine. In patients with diabetes, the kidneys may be particularly susceptible to the effects of hyperglycemia, as many kidney cells are unable to sufficiently decrease glucose transport rates to prevent intracellular hyperglycemia in states of increased glucose concentration.

**DIABETIC NEPHROPATHY**

Diabetes has become the most common single cause of endstage renal disease (ESRD) in the United States and Europe; this is most likely due to several evolving factors, including an increased prevalence of type 2 diabetes mellitus longer life spans among patients with diabetes, and better formal recognition of renal insufficiency. Based on the most current (2008) US statistics from the American Diabetes Association, diabetes accounted for more than 40% of new cases of kidney failure, with 48,374 patients with diabetes beginning treatment for ESRD, and 202,290 people with diabetes-related ESRD on chronic dialysis or undergoing a kidney transplant. Compared with patients with type 1 diabetes mellitus, a considerably smaller fraction of those with type 2 diabetes mellitus progress to ESRD, but due to the much higher prevalence of T2DM, these individuals constitute over half of those with diabetes on dialysis. Considerable racial/ethnic variability exists in this regard, with Native Americans, Hispanics (especially Mexican Americans), and African Americans at much greater risk of developing ESRD than non-Hispanic whites with type 2 diabetes mellitus.

Dialysis is a very expensive therapy, costing more than $50,000 per patient per year. Total medical spending for the approximately 400,000 patients with ESRD (representing those with and without diabetes) was $22.8 billion in 2001, an almost 3-fold increase over the 1991 to 2001 decade. ESRD spending represents 6.4% of the total Medicare budget, a 33% increase from 4.8% in 1991. The epidemic growth in ESRD cases has led to skyrocketing utilization of healthcare resources.

The earliest clinical evidence of nephropathy is the appearance of low, but abnormal, levels (≥30 mg/day or 20 μg/min) of albumin in the urine (referred to as microalbuminuria). Although the course for each patient with type 2 diabetes mellitus is different, once albumin is detected in the urine, the chance of progression to more persistent albuminuria, progressive decline in GFR, raised arterial blood pressure, and increased cardiovascular morbidity and mortality is increased. Since undetected may be present for many years, a higher proportion of individuals with type 2 diabetes mellitus (vs type 1 diabetes mellitus) have microalbuminuria and overt nephropathy shortly after diagnosis. Without specific interventions, 20% to 40% of patients with type 2 diabetes mellitus and microalbuminuria progress to overt nephropathy; however, within 20 years of onset of overt nephropathy, only 20% will have progressed to ESRD. This may be attributable to the greater risk of dying from associated coronary artery disease than progressing to ESRD among the older diabetic population. As interventions for coronary artery disease continue to improve, however, more patients with type 2 diabetes mellitus may survive long enough to develop renal failure.

Increasing evidence demonstrates that the onset and course of diabetic nephropathy may be significantly altered by several interventions (eg, tight glucose control, use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), all of which have their greatest impact if instituted early. As such, annual screening for microalbuminuria is critical since it leads to early identification of nephropathy. Well-known data from the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study established that intensive glycemic control may significantly reduce the risk of developing microalbuminuria and overt nephropathy. Recent research (eg, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE] trial) offers more perspective on the effects of tight glucose control and reduction of nephropathy. ADVANCE evaluated progression to major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy) in 11,140 patients with type 2 diabetes mellitus randomly assigned to undergo standard or intensive glucose control (glycated hemoglobin level ≤6.5%). After a median of 5 years, intensive glucose control produced a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a result of a 21% relative reduction in the risk of developing new or worsening nephropathy. The intensive glucose control group was also associated with a 9% reduction in new onset microalbuminuria, but a higher incidence of severe hypoglycemia (2.7% vs 1.5% in the standard control group). The observed reduction in nephropathy is important, since indices of renal impairment are strongly associated with future risk of major vascular events, ESRD, and death in patients with diabetes.

**CONCLUSION**

The regulation of glucose production, uptake, reabsorption, and elimination is handled by several organs, most notably (historically) the pancreas and liver. While not traditionally discussed, the kidneys’ contributions to maintaining glucose homeostasis are multifaceted and include such functions as gluconeogenesis and glucose reabsorption, the latter being mediated by active (SGLT) and passive (GLUT) transporters. Under normal circumstances, glucose filtered by glomeruli is completely reabsorbed, but in conditions of hyperglycemia or reduced resorptive capacity, glucosuria may occur. In hyperglycemia, the kidneys may play an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, and subsequently to pancreatic β-cell failure, insulin resistance, and decreased glucose uptake. Hyperglycemia in turn detrimentally affects the kidneys by damaging glomeruli, ultimately causing microalbuminuria and nephropathy. Knowledge of the kidneys’ role in glucose homeostasis and the effect of glucose dysregulation on the kidneys is critical to optimal management of type 2 diabetes mellitus and prevention of associated renal complications.

1. **Discuss the 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 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 MICTURICTION 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.

**CENTRAL NERVOUS SYSTEM REGULATION**

As the bladder fills, the conscious sensation is perceived and the cortical signals are triggered. This inhibits the purely involuntary firing of the voiding reflex and instead helps the individual to control voiding until the time and place are appropriate. This includes social, sensory, and emotional states, including the degree to which bladder stretching is sensed to be safe and tolerable. The cell group in the periaqueductal gray (PAG) plays a role in detecting the bladder distension, as well as in relaying bladder afferents to higher centers in the brain and enabling the person to feel the sensation. It also regulates the feed to the pontine center, while receiving afferents from higher brain centers such as the anterior cingulate and the prefrontal cortex. These help to inhibit the voiding reflex via suppression of PMC excitation.

The PMC neurons are released from inhibition and fire maximally once the voluntary signal for voiding is produced. This causes excitation of the sacral neurons which stimulate detrusor contractions and induce a sudden increase in turn of intravesical pressure, as well as relaxing the external or voluntary urethral sphincter. Once the intravesical pressure overcomes the urethral resistance, urine flows out through the urethra.

Micturition is thus under cortical control as well as mediated by the spinal reflex arc, which inhibits the pontine center until it is deemed appropriate to void. In addition, the motor cortex controls the voluntary muscle of the external urethral sphincter. The decision to void implies that the prefrontal cortex suppresses the tonic inhibition of the afferents from the PAG to the PMC.

**URETHRAL REFLEXES**

The flow of urine and the mechanical distension of the urethra together cause detrusor contractions to occur, which encourages complete bladder emptying.

1. **Explain juxtaglomerular apparatus**

It refers to the collection of specialized cells that are located very near to the glomerulus. It forms the major component of RENIN-ANGIOTENSIN ALDOSTERONE system. It comprises three types of cells.

- Juxtaglomerular cells

- Macula densa cells

- Mesangial cells

1. **JUXTAGLOMERULAR CELLS**

 They are specialised myoepithelial (modified vascular Smooth muscle) cells located in the media of the afferent arteriole in the region of

juxtaglomerular apparatus. They have well developed Golgi apparatus and

endoplasmic reticulum, abundant mitochondria and ribosomes. They

synthesize, stop and release an enzyme called renin. Renin is stored in the

secretory granules of juxtaglomerular cells and therefore, these are also

called GRANULAR CELLS. They act as baroreceptors( tension receptors)

afferent arterioles and the interstitium. They are densely innervated by the

sympathetic nerve fibres and release their renin content in response to the

sympathetic discharge. As these cells act as vascular volume receptors,

they monitor renal perfusion pressure and are stimulated by hypovolaemia

or decreased renal perfusion pressure.

**B) MACULA DENSA CELLS**

 It refer to the specialised renal tubular epithelial cells of a short

segment of the thick ascending limb of loop of Henle which passes

between the afferent and efferent arterioles supplying its glomerulus of

origin. They are not well adapted for reabsorption. They are not

innervated. These cells are in direct contact with the mesanglial cells and in

close contact with the juxtaglomerular cells. They act as chemoreceptors

and are stimulated by decreased NaCl concentration and thereby causing

increased renin release.

C) **MESANGIAL** **CELLS**

 They are the interstitial cells of the juxtaglomerular apparatus. They

are in contact with both the macula dense cells ( on one side) and

juxtaglomerular cells(on the other side). Functionally, these cells positly

relay the signals from macula dense to the granular cells after modulation

the signals. In this way, a decreased intraluminal Na+ load, Cl- load or

both in the region of macula dense stimulates the juxtaglomerular cells to

secrete renin.

NOTE: The combination of macula densa and juxtaglomerular cells is

known as the juxtaglomerular apparatus.

1. **The role of kidney in regulation of blood pressure**

**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. 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

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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.

1. **Discuss the role of kidney in calcium homeostasis**

Calcium balance are controlled primarily by parathyroid hormone and 1,25-(OH)2D. Approximately 60% of plasma calcium is available for filtration in the kidney. The remaining plasma calcium is protein- bound or complexed with anions. Because calcium is so important in the function of every cell in the body, the kidneys have very effective mechanisms to reabsorb calcium ion from the tubular fluid. More than 60% of calcium ion reabsorption is not under hormonal control and occurs in the proximal tubule. The hormonal control of calcium ion reabsorption occurs mainly in

the distal convoluted tubule and early in the cortical collecting duct. When plasma calcium is low, the secretion of parathyroid hormone (PTH) from the parathyroid gland increases. Parathyroid hormone situated the opening of calcium channels in these parts of the nephron, thereby increasing calcium ion reabsorption. Another important action of PTH in the kidney is to increase the activity of the 1-hydroxylase enzyme, thus activating 25(OH)-D to 1,25-(OH)2D, which then goes on to increase

calcium and phosphate ion absorption in the gastrointestinal tract. About half of the plasma phosphate is ionised and is filterable. Like calcium, most of the phosphate ion that is filtered is reabsorbed in the proximal tubule. Unlike calcium ion, phosphate ion reabsorption is decreased by PTH, thereby increasing the excretion of phosphate ion. Therefore when plasma calcium is low, and parathyroid hormone and calcium ion reabsorption are increased as a result, phosphate ion excretion is increased.