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**Question**  
Q1. Discuss the role of kidney in glucose homeostasis?

Q2. Discuss the process of micturition?

Q3. Explain juxtaglomerular apparatus?

Q4 Discuss the role of kidney in regulation of blood pressure?

Q5. Discuss the role of Kidney in Calcium homeostasis?

**ANSWERS**

1. The role of kidney in glucose homeostasis:

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 co-transporters) 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. 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).

**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. 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 T2DM, 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 T2DM 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.3 Again, it is clear that there is a renal contribution to glucose output in the body, but the actual contribution in individual patients with T2DM is still controversial.  
  
***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. 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.

1. 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 are essential for the process of micturition.

Micturition reflex is the reflex by which micturition occurs. 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 fibers of pelvic (parasympathetic) nerve. Motor (efferent) impulses produced in spinal cord, travel through motor fibers 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 (Fig. 57.5). Once urine enters urethra, the stretch receptors in the urethra are stimulated and send afferent impulses to spinal cord via pelvic nerve fibers. Now the impulses generated from spinal centers 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.

1. JUXTAGLOMERULAR apparatus:

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

* Macula densa : 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. Macula densa secretes thromboxane A2.
* Extraglomerular mesangial cells: Extraglomerular mesangial cells of juxtaglomerular apparatus secrete cytokines like interleukin-2 and tumor necrosis factor.
* Juxtaglomerular cells: Juxtaglomerular cells are also called granular cells because of the presence of secretary granules in their cytoplasm. Juxtaglomerular cells form a thick cuff called polar cushion or polkissen around the afferent arteriole before it enters the Bowman capsule.
* Besides extraglomerular mesangial cells there is another type of mesangial cells situated in between glomerular capillaries called **glomerular mesangial or intraglomerular mesangial cells.** Glomerular mesangial cells support the glomerular capillary loops by surrounding the capillaries in the form of a cellular network. These cells play an important role in regulating the glomerular filtration by their contractile property.

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

Juxtaglomerular apparatus secretes two hormones:

* Renin
* Prostaglandin.
* **Renin:** Juxtaglomerular cells secrete renin. Renin is a peptide with 340 amino acids. Along with angiotensins, renin forms the renin-angiotensin system, which is a hormone system that plays an important role in the maintenance of blood pressure. Stimulants for renin secretion Secretion of renin is stimulated by four factors: i. Fall in arterial blood pressure ii. Reduction in the ECF volume iii. Increased sympathetic activity iv. Decreased load of sodium and chloride in macula densa. Renin-angiotensin system When renin is released into the blood, it acts on a specific plasma protein called angiotensinogen or renin substrate. It is the α2-globulin. By the activity of renin, the angiotensinogen is converted into a decapeptide called angiotensin I. Angiotensin I is converted into angiotensin II, which is an octapeptide 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 has a short half-life of about 1 to 2 minutes. Then it is rapidly degraded into a heptapeptide called angiotensin III by angiotensinases, which are present in RBCs and vascular beds in many tissues. Angiotensin III is converted into angiotensin IV, which is a hexapeptide . Actions of Angiotensins Angiotensin I Angiotensin I is physiologically inactive and serves only as the precursor of angiotensin II. Angiotensin II Angiotensin II is the most active form. Its actions are**:**

**On blood vessels**: i. Angiotensin II increases arterial blood pressure by directly acting on the blood vessels and causing vasoconstriction. It is a potent constrictor of arterioles. Earlier, when its other actions were not found it was called hypertensin. ii. It increases blood pressure indirectly by increas ing the release of noradrenaline from postganglionic sympathetic fibers. Noradrenaline is a general vasoconstrictor.

**On adrenal cortex**: It stimulates zona glomerulosa of adrenal cortex to secrete aldosterone. Aldosterone acts on renal tubules and increases retention of sodium, which is also responsible for elevation of blood pressure.

**On kidney**: i. Angiotensin II regulates glomerular filtration rate by two ways: a. It constricts the efferent arteriole, which causes decrease in filtration after an initial increase. b. It contracts the glomerular mesangial cells leading to decrease in surface area of glomerular capillaries and filtration ii. It increases sodium reabsorption from renal tubules. This action is more predominant on proximal tubules.

**On brain**: i. Angiotensin II inhibits the baroreceptor reflex and thereby indirectly increases the blood pressure. Baroreceptor reflex is responsible for decreasing the blood pressure.

* **Prostaglandin**: Extraglomerular mesangial cells of juxtaglomerular apparatus secrete prostaglandin. Prostaglandin is also secreted by interstitial cells of medulla called type I medullary interstitial cells.

1. Role of kidney in regulation of blood pressure:

Kidneys play an important role in the long-term regulation of arterial blood pressure by two ways:

i .**By regulating the volume of extracellular fluid** :When the blood pressure increases, kidneys excrete large amounts of water and salt, particularly sodium, by means of pressure diuresis and pressure natriuresis. Pressure diuresis is the excretion of large quantity of water in urine because of increased blood pressure. Even a slight increase in blood pressure doubles the water excretion. Pressure natriuresis is the excretion of large quantity of sodium in urine. Because 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.

ii. **Through renin-angiotensin mechanism**: Actions of Angiotensin II;When blood pressure and ECF volume decrease, renin secretion from kidneys is increased. It converts angiotensinogen into angiotensin I. This is converted into angiotensin II by ACE (angiotensin­converting enzyme). Angiotensin II acts in two ways to restore the blood pressure: i. 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. ii. 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. It increases the blood pressure to normal level.

Actions of Angiotensin III and Angiotensin IV; Like angiotensin II, the angiotensins III and IV also increase the blood pressure and stimulate adrenal cortex to secrete aldosterone.

1. Role of Kidney in Calcium homeostasis:

The role of the kidney in calcium homeostasis has been reshaped from a classic view in which the kidney was regulated by systemic calcitropic hormones such as vitamin D3 or parathyroid hormone to an organ actively taking part in the regulation of calcium handling. With the identification of the intrinsic renal calcium-sensing receptor feedback system, the regulation of paracellular calcium transport involving claudins, and new paracrine regulators such as klotho, the kidney has emerged as a crucial modulator not only of calciuria but also of calcium homeostasis. This review summarizes recent molecular and endocrine contributors to renal calcium handling and highlights the tight link between calcium and sodium reabsorption in the kidney. kidneys are major regulators of calcium homeostasis. This is illustrated by the profound and complex dysregulation of mineral metabolism appearing during chronic kidney disease (CKD) recognized as mineral and bone disorders in chronic kidney disease (MBD-CKD).

Fluxes of calcium between the small intestine (the place for calcium absorption), the bone (the main storage place for calcium), and the kidney (the main place of elimination of the absorbed calcium) are highly controlled by numerous transport mechanisms, hormones, and interconnected feedback loops. This is an absolute requirement to prevent unwanted biomineralization in tissues. Indeed, calcium is a highly reactive ion which has high propensity to form microcrystals in fluids and tissues. In mammals, the complex process of biomineralization takes place in a controlled manner in teeth and bones, in which the matrix is calcified with hydroxyapatite, a calcium-phosphate salt. As the calcification process necessitates interactions between matrix proteins and high local calcium and phosphate concentrations at a specific pH, keeping calcium in solution also demands significant effort. With plasma concentrations of ∼2.4 mmol/l for calcium and 1 mmol/l for phosphate, crystallization would spontaneously occur, if inhibitors of calcification, such as magnesium, fetuin A, osteoprotegerin, or matrix gla protein were not present in plasma. Thus the control of calcification in bone on the one hand and the preserved solubility of calcium salts in plasma on the other hand are both dependent on the tight control of plasma levels of calcium and phosphate and on the presence/absence of strong inhibitors.

The same reasoning can be applied to urine in which calcium has a concentration of ∼3 mmol/l and phosphate 10 mmol/l. Inhibitors and promoters of urine crystallization and stone formation have been extensively described , and calciuria appears to be a major promoter of crystallization and stone formation. Hypercalciuria, as defined either as excretion rate or as concentration, is contributing to Randall's plaque formation and to kidney stone formation. Thus control of calciuria is instrumental in reducing the risk of intrarenal biomineralization and kidney stone formation.In plasma, only ∼50% of calcium is freely available, the rest being bound to proteins or forming complexed salts. The concentration of free ionized calcium depends on plasma pH and plasma protein content and constitutes the calcium that is sensed and defended by the organism. It can be measured as ionized calcium.In the kidney, the only source of calcium reaching the tubules is ultrafiltrated calcium, consisting of ionized calcium and other calcium-containing salts filtered through the glomerulus. It represents ∼50% of the total plasma calcium, but it is impossible to be precisely measured in a clinical setting. This constitutes a major caveat when it comes to evaluating the fractional excretion of calcium. No secretion or backleak of calcium contributes to the calcium delivered to the tubular system and, consequently, the load of calcium filtered is the unique and major contributor of calcium reaching the proximal tubule (PT). Along the tubular system, complex transepithelial transport mechanisms allow a highly regulated reabsorption of ∼98% of filtrated calcium . In certain circumstances though, the tubular reabsorption system may be overwhelmed by the filtrated load, as seen in primary hyperparathyroidism or in vitamin D intoxication. In these two conditions, the calcium reabsorption machinery of the kidney is maximally stimulated but cannot counterbalance the filtered calcium load, leading to hypercalciuria.

Two main transepithelial calcium transport pathways have been described along the tubules of the kidneys: paracellular and transcellular. Paracellular pathways are dependent on transepithelial electrochemical gradients and can be regulated by specialized paracellular proteins, the claudins. The transcellular path implies the presence of a tight epithelium and a three-step transport with apical entry, transcytoplasmic transport, and basolateral extrusion mechanisms. The driving force is mainly provided by basolateral Ca- or Na-K-ATPases.

The following part of this review will address the way calcium is reabsorbed in the different parts of the tubular system.

**PT**

The PT reabsorbs ∼60–70% of the calcium filtered by the glomerulus. The majority of the calcium is reabsorbed by passive, hormone-independent, paracellular transport through the remarkably permeable epithelium of the PT. The mechanisms of calcium reabsorption in the PT are complex, due to the heterogenous architecture of the PT, that includes a first cortical convoluted part, displaying a short initial negative luminal transepithelial potential difference (PD), followed by a lumen-positive PD along the other segments of the PT . Calcium permeability in the proximal segment is globally high, but the tubular fluid over plasma filtrate calcium concentration ratio (TF/P) increases slightly in the late PT, maybe due to decrased paracellular transport compared with water in these segments or to formation of luminal calcium complexes. The passive transport is, however, heavily influenced by sodium, chloride, bicarbonate, and potassium availability and by sodium backleak.

**Mechanisms of transport*.***

Transcellular calcium reabsorption in the DCT-CNT occurs in three steps ( *1*) apical calcium entry through transient receptor potential cation channel subfamily V member 5 and/or 6 (TRPV5-6) is followed by *2*) intracellular buffering by calbindins *3*) at the basolateral side, calcium is exiting the DCT-CNT cell via the calcium-ATPase PMCA4 and the sodium-calcium exchanger NCX1.

The transport protein responsible for apical entry of calcium into the tubular cells of the distal nephron had long remained elusive, and the discovery of dihydropyridine (verapamil)-sensitive cardiac L-type calcium channels was once believed to fill the gap. However, disruption of one essential component of the channel (CACNB3) in mice induced only a minor phenotype and only after challenges by chlorthiazide treatment.

This changed when a calcium channel was cloned from rabbit kidney and named epithelial calcium channel 1 (ECaC-1). At the same time, the rat homolog was cloned from kidney and named calcium transporter 2 (CaT-2)). The now-called TRPV5 was found strongly expressed in the DCT and the CNT uniquely at the apical side .It was subsequently shown that TRPV5's expression is stimulated by 1,25(OH)2vitamin D and PTH and that TRPV5-mediated calcium reabsorption was activated by cellular hyperpolarization and by cytosolic calcium. The function of TRPV5 in vivo was demonstrated in mice deleted for *TRPV5*: they exhibited renal calcium wasting, increased intestinal calcium absorption, and a decreased bone mass . These mice displayed a sharp downregulation of calbindin binding protein (CaBP)-D28K, by an unknown vitamin D-independent mechanism, and an upregulation of the closely related calcium channel transporter TRPV6, which forms heterotetramers with TRPV5.

Although this mouse model revealed a dramatic function of TRPV5 in vivo, with loss of function leading to severe hypercalciuria, no TRPV5 variant has been associated with hypercalciuria or kidney stone formation in humans so far.

CaBP-D28K is a cytosolic protein expressed in the DCT-CNT of the kidney able to buffer intracellular calcium. Its role in calcium handling is debated, however, as loss-of-function mouse models have only inconsistently shown hypercalciuria. This may be due to an alternative calcium-binding system (calbindin-9, parvalbumin) or regulation, although, when a double CaBP-D28K and CaBP-D9K KO mouse model was studied, disturbed calcium homeostasis with lower bone density was observed under a low-calcium diet.

Parvalbumin is an intracellular calcium-binding protein found in the early DCT , after it had long been known to be present in muscle fibers and neurons. A direct role for parvalbumin in distal tubular calcium reabsorption remains in question, but it was implicated in NCC regulation, and hypocalciuria was accentuated in parvalbumin KO mice compared with wild-type mice upon hydrochlorothiazide treatment. At the basolateral side of the DCT-CNT cells, two systems are involved in the exit of calcium: the calcium P-ATPases and the calcium/sodium exchanger NCX1. Two main types of calcium ATPases have been identified in the kidney: PMCA1 and PMCA4. For a while, PMCA1b was considered as quantitatively more important, but recent work has shown that PMCA4 is the main regulated calcium-transporting ATPase. This is based on two lines of evidence: *1*) PMCA4 is highly enriched in DCT-CNT tubular cells and *2*) PMCA4 is downregulated in TRPV5-KO animals, indicating that interference with calcium transport affects PMCA4 expression.

The sodium-calcium exchanger NCX1 (or *SLC8A1*) is a key molecule for basolateral calcium export but can also work in the reverse mode, depending on the electrochemical gradients. NCX1 is part of a widely distributed family of electrogenic solute antiporters that exchange sodium for calcium ions with different types of stoichiometry (3Na:1Ca in its main electrogenic mode) . One study showed that other members of the NCX family might be also expressed in the kidney (NCX2), but this was not reported by other studies.

The relative contributions of NCX1 and PMCA pumps for basolateral calcium export are debated, but a mathematical model of calcium reabsorption in the DCT/CNT proposed that NCX1 is the main regulated basolateral exit pathway, while PMCA has housekeeping functions. Moreover, NCX1 presents two specificities over PMCA: it is dependent on the transmembrane sodium gradient and on the transepithelial voltage in the DCT. Although calcium reabsorption in the distal nephron is rather sodium independent compared with the PT and TAL, NCX1 activity is an exception. Under normal conditions, NCX1 would increase intracellular sodium levels and depolarize the DCT-CNT cell, if its activity were not counterbalanced by the activity of the sodium/potassium ATPase, which pumps sodium out of the cell. If the sodium gradient is inversed in DCT cells, NCX1 exports sodium and imports calcium in the reverse mode. The link between NCX1 and the sodium/potassium ATPase was further confirmed in the developing heart: when the sodium/potassium ATPase is blocked, intracellular calcium levels rose in the presence of NCX1 but not in its absence.

Basolateral NCX1 activity also depends on sodium entry at the apical side of the distal tubular cell: Sodium is transported through the NCC in the early DCT, while it is reabsorbed through the epithelial sodium channel (ENaC) in the late DCT and CNT. The close connection between NCC and NCX1 activity has been studied by Nijenhuis et al. . Rats treated with hydrochlorothiazides, a blocker of NCC activity, have lower NCX1 mRNA levels compared with untreated rats, situations alike in which the rats were sodium depleted. The lowest NCX1 expression was found when both hydrochlorothiazide treatment and sodium depletion were combined. However, a direct connection between NCC and NCX1 is possible only in a short tubular segment, since colocalization of the two transporters only partially occurs at the end of DCT1 and beginning of DCT2. The interaction between NCC-mediated apical sodium entry and basolateral NCX1 activity is even more complex, as hydrochlorothiazide treatment was affecting not only NCX1 expression levels but also those of TRPV5 and calbindin-D28K. A direct interaction between ENaC and NCX1 or the effect of amiloride, the blocker of ENaC, on NCX1 activity has not been reported so far.