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**Assignment Title:** Renal Physiology   
**Course Title:** Renal Physiology Body Fluid and Temperature Regulation   
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**College:** Medicine and Health Sciences (MHS)

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Assignment Question

1. Discuss the role of kidney in glucose homeostasis?
2. Discuss the process of micturition?
3. Explain juxtaglomerular apparatus?
4. Discuss the role of kidney in regulation of blood pressure?
5. Discuss the role of kidney in calcium homeostasis?

AnswersConsiderable data have accumulated over the past 20 years, indicating that the human kidney is involved in the regulation of glucose via gluconeogenesis, taking up glucose from the circulation, and by reabsorbing glucose from the glomerular filtrate. In light of the development of glucose-lowering drugs involving inhibition of renal glucose reabsorption, this review summarizes these data. Medline was searched from 1989 to present using the terms ‘renal gluconeogenesis’, ‘renal glucose utilization’, ‘diabetes mellitus’ and ‘glucose transporters’. The human liver and kidneys release approximately equal amounts of glucose via gluconeogenesis in the post-absorptive state. In the postprandial state, although overall endogenous glucose release decreases substantially, renal gluconeogenesis increases by approximately twofold. Glucose utilization by the kidneys after an overnight fast accounts for ∼10% of glucose utilized by the body. Following a meal, glucose utilization by the kidney increases. Normally each day, ∼180 g of glucose is filtered by the kidneys; almost all of this is reabsorbed by means of sodium–glucose co-transporter 2 (SGLT2), expressed in the proximal tubules. However, the capacity of SGLT2 to reabsorb glucose from the renal tubules is finite and, when plasma glucose concentrations exceed a threshold, glucose appears in the urine. Handling of glucose by the kidney is altered in Type 2 diabetes mellitus (T2DM): renal gluconeogenesis and renal glucose uptake are increased in both the post-absorptive and postprandial states, and renal glucose reabsorption is increased. Specific SGLT2 inhibitors are being developed as a novel means of controlling hyperglycaemia in T2DM.Diabet. Med. 27, 136–142 (2010)

1. Role Of Kidney In Glucose Homeostasis

IntroductionKeywords: gluconeogenesis, kidney, sodium glucose co-transporter 2, Type 2 diabetes mellitus

The kidney’s involvement in glucose homeostasis was first described in the 1930s [1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4232006/#b1). Despite the large body of evidence amassed over the ensuing years, the kidney is still often overlooked as an important player in glucose metabolism. However, awareness of renal mechanisms of glucose homeostasis is likely to increase in the near future because novel glucose-lowering drugs are being developed that target one aspect of renal glucose handling, namely reabsorption of glucose from the glomerular filtrate [the sodium–glucose co-transporter 2 (SGLT2) inhibitors]. This article reviews our current understanding of the role of the kidney in normal glucose homeostasis and abnormalities in patients with Type 2 diabetes mellitus (T2DM). Medline was searched from 1989 to present using the terms ‘renal gluconeogenesis’, ‘renal glucose utilization’, ‘diabetes mellitus’ and ‘glucose transporters’

Overview of renal glucose homeostasis

The human kidney is involved in the regulation of glucose homeostasis and in abnormalities found in diabetes mellitus via three different mechanisms: (i) release of glucose into the circulation via gluconeogenesis;

(ii) Uptake of glucose from the circulation to satisfy its energy needs; and

(iii) Reabsorption into the circulation of glucose from glomerular filtrate to conserve glucose carbon.

Plasma glucose concentrations are determined by the relative rates of glucose entry into, and removal from, the circulation. Normally, despite wide daily fluctuations in the rate of delivery of glucose into the circulation (e.g. meal ingestion) and in the demands of tissues for glucose (e.g. during exercise), plasma levels are maintained within a relatively narrow range throughout the day. Maximal plasma concentrations following meal ingestion are usually < 9.0 mmol/l and minimal concentrations, after moderate fast or exercise, are usually > 3.0 mmol/l. This is in contrast to other substrates such as glycerol, lactate, free fatty acids (FFAs) and ketone bodies, for which daily fluctuation is much greater [5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4232006/#b5). Teleologically, this can be explained by the fact that, on the one hand, the body must defend itself from hyperglycaemia, which is associated with both chronic effects (including retinopathy, neuropathy, nephropathy and premature atherosclerosis) and acute effects (including diabetic ketoacidosis and hyperosmolar hyperglycaemic state, which have significant associated morbidity and mortality); on the other hand, the body must also defend itself against hypoglycaemia, which can cause cardiac arrhythmias, neurological dysfunction, coma, seizures and death. Brain function is particularly dependent on having adequate levels of plasma glucose because the brain is unable to either store or produce glucose and alternative sources of energy are either in short supply (e.g. ketone bodies) or are unable to pass the blood–brain barrier (e.g. FFAs).

The precise regulation of plasma glucose concentrations is mainly determined by hormonal and neural factors, which regulate endogenous production of glucose. Acute glucoregulatory mechanisms involve insulin, glucagon and catecholamines, which can effect changes in plasma glucose levels over a matter of minutes. Insulin suppresses glucose release in both the liver and kidney by direct enzyme activation/deactivation, as well as by reducing the availability of gluconeogenic substrates and actions on gluconeogenic activators. Glucagon has no effect on the kidney, but increases both gluconeogenesis and glycogenolysis in the liver. Catecholamines have multiple acute actions, including stimulation of renal glucose release, inhibition of insulin secretion, stimulation of glucagon secretion, and increases in gluconeogenic substrate supply, stimulation of lipolysis and reduced tissue glucose uptake.

Growth hormone, thyroid hormone and cortisol influence glucose levels over a period of hours by altering the sensitivity of the liver, kidney, adipose tissue and muscle to insulin, glucagon and catecholamines, and by altering the activity of key enzymes, which effect glycogen stores and availability of gluconeogenic precursors (lactate, glycogen and amino acids). In the post-absorptive state, glucose uptake by tissues is largely dependent on tissue needs and the mass-action effects of the ambient plasma glucose concentration and, to a lesser extent, on the permissive actions of insulin and counter-regulatory hormones (e.g. thyroid hormones, growth hormone, catecholamines and cortisol). In these circumstances, most uptake of glucose occurs in tissues that do not require insulin (e.g. brain, gastrointestinal tract, renal medulla). However, in the postprandial state, although insulin and other hormones exert greater influence on tissue uptake of glucose, changes in hepatic and renal glucose release into the circulation are still quite important

Renal gluconeogenesis

The post-absorptive state

After a 14- to 16-h overnight fast, glucose is released into the circulation at a rate of approximately 10 μmol/(kg min). Approximately 50% of this is the result of the breakdown of glycogen (glycogenolysis) stored in the liver and the other half is because of the production of new glucose molecules from precursors such as lactate, glycerol, alanine and other amino acids (gluconeogenesis) by liver and kidneys. The kidney is unable to release glucose through glycogenolysis because it contains very little glycogen and those renal cells that are able to synthesize glycogen lack the enzyme glucose-6-phosphatase and therefore cannot release glucose. In humans, only the liver and kidney contain significant amounts of the enzyme glucose-6-phosphatase and therefore are the only organs that are able to perform gluconeogenesis. Research over the last 15–20 years has established that the human liver and kidneys provide about equal amounts of glucose via gluconeogenesis in the post-absorptive state. Consequently, after an overnight fast, 75–80% of glucose released into the circulation derives from the liver and the remaining 20–25% derives from the kidneys. As the duration of fasting increases, glycogen stores in the liver become further depleted until, after 48 h, virtually all the glucose released into the circulation is derived from gluconeogenesis. Consequently, as the length of fast increases, the proportion of overall glucose release accounted for by renal gluconeogenesis increases.

With respect to hormonal influences, insulin suppresses glucose release by both organs with roughly comparable efficacy, whereas glucagon normally stimulates hepatic glucose release only, mainly via an early action on glycogenolysis. Catecholamines normally exert a direct effect on renal glucose release only, although they may indirectly affect both hepatic and renal glucose release by increasing availability of gluconeogenic substrates and by suppressing insulin secretion. Cortisol, growth hormone and thyroid hormones have long-term stimulatory influences on hepatic glucose release (over a period of days). Their effects on renal glucose release in humans have yet to be determined.

The postprandial state

Classically, metabolic studies have usually been undertaken in the post-absorptive state (i.e. 12–16 h after the last meal). However, most of the day people are in the postprandial state as this includes 4–6 h on three occasions during the day.

Postprandial plasma glucose levels are critically influenced by insulin and glucagon levels. Following ingestion of glucose, plasma glucose levels peak in 60–90 min and slowly return to post-absorptive levels after 3–4 h. This profile is mirrored by a fourfold increase in plasma insulin and a reciprocal suppression of plasma glucagon levels of ∼50%*.* (2002) demonstrated that, after meal ingestion, overall endogenous glucose release decreases by ∼61%, with hepatic glycogenolysis virtually ceasing in the 4- to 6-h period. Teleologically, this is understandable because this period is responsible for replenishment of hepatic glycogen stores. Furthermore, suppression of endogenous glucose release limits postprandial hyperglycaemia. Hepatic gluconeogenesis also decreases by ∼82% and glucose molecules generated through this pathway are not generally released in the circulation, but are largely directed into hepatic glycogen. Perhaps surprisingly, renal gluconeogenesis actually increases by approximately twofold and accounts for ∼60% of endogenous glucose release in the postprandial period. This has been hypothesized to facilitate efficient repletion of glycogen stores in the liver.

These differences in regulation and reciprocal change in renal and hepatic glucose release have led to the concept of hepatorenal glucose reciprocity. This concept refers to the situations in which a physiological or pathological decrease in glucose release by kidney or liver is associated with a compensatory increase in glucose release by liver or kidney so as to prevent hypoglycaemia or to optimize homeostasis. Examples of this include the anhepatic phase after liver transplantation, prolonged fasting, acidosis, meal ingestion and insulin overdoses in diabetes mellitus

Renal glucose utilization

In the post-absorptive setting after an overnight fast, the kidneys utilize approximately 10% of all glucose utilized by the body. After meal ingestion their glucose utilization increases in an absolute sense. In terms of whole-body glucose economy, normally approximately 45% of ingested glucose is thought to be converted to glycogen in the liver, ∼30% is taken up by skeletal muscle and later converted to glycogen, ∼15% is taken up by the brain, ∼5% is taken up by the adipose tissue and ∼10% is taken up by the kidney. The metabolic fate of glucose is different in different regions of the kidney. Because of its low oxygen tension, and low levels of oxidative enzymes, the renal medulla is an obligate user of glucose for its energy requirement and does so anaerobically. Consequently, lactate is the main metabolic end product of glucose taken up in the renal medulla, not carbon dioxide (CO2) and water. In contrast, the renal cortex has little glucose phosphorylating capacity but a high level of oxidative enzymes. Consequently, this part of the kidney does not take up and use very much glucose, with oxidation of FFAs acting as the main source of energy. A major energy-requiring process in the kidney is the reabsorption of glucose from glomerular filtrate in the proximal convoluted tubule.

Renal glucose reabsorption

In addition to releasing glucose into the circulation by synthesizing new glucose molecules via gluconeogenesis and its utilization of glucose, the kidney can also influence glucose homeostasis by returning glucose to the circulation via the reabsorption of glucose from glomerular filtrate. Normally, approximately 180 l of plasma are filtered by the kidneys each day. As the average plasma glucose concentration throughout a 24-h period is ∼5.5 mmol/l (100 mg/dl), ∼180 g of glucose is filtered by the kidneys each day. In healthy individuals, virtually all of this is reabsorbed into the circulation and the urine is essentially free from glucose. To put this into perspective, in a given day, the kidneys produce 15–55 g glucose via gluconeogenesis and metabolize 25–35 g glucose. Therefore, in terms of glucose economy, it is clear that renal reabsorption is the primary mechanism by which the kidney influences glucose homeostasis. Alterations in renal tubular glucose reabsorption may therefore be expected to have a considerable impact on glucose homeostasis.

Reabsorption of glucose from glomerular filtrate occurs by means of sodium–glucose co-transporters (SGLTs) in the proximal convoluted tubulae. There are six members of this family. In animal models, approximately 90% of glucose is reabsorbed by SGLT2, a high-capacity low-affinity glucose transporter (Km ∼10 mmol/l; Vmax ∼10 nmol/(min mg) protein). SGLT2 is thought to be located exclusively on the luminal surface of the epithelial cells lining the S1 and S2 segments of the proximal tubule. Transport of sodium and glucose by SGLT2 occurs in a 1:1 ratio. The remaining ∼10% of glucose reabsorption is mediated by SGLT1, a high-affinity, low-capacity glucose/galactose transporter (Km ∼0.2 mmol/l; Vmax ∼10 nmol/(min mg) protein; sodium:glucose coupling ratio = 2:1) located on the luminal surface of epithelial cells lining the S3 segment of the proximal tubule. SGLT1 is also extensively expressed in the small intestine and in other tissues. Glucose reabsorbed from the proximal tubules by SGLTs is then released into the circulation through the action of facilitative glucose transporters (GLUTs) at the basolateral membrane of the epithelial cells lining the proximal tubules (GLUT2 in the S1/2 segments and GLUT1 in the S3 segment). SGLT-mediated glucose transport is an active process, moving glucose against a concentration gradient, utilizing energy derived from the sodium electrochemical potential gradient across the brush border membrane and maintained by the transport of intracellular sodium into the blood via sodium:potassium adenosine triphosphatase (ATPase) pumps at the basolateral membrane. In contrast, GLUTs facilitate passive transport (equilibration) of glucose across membranes and do not require an energy source.

The renal threshold for glucose is decreased in individuals with a rare condition known as familial renal glucosuria (FRG), caused by a range of mutations to the *SLC5A2* gene, which encodes SGLT2. Depending on the nature of the mutations, these individuals have varying degrees of glucosuria, but in the most severe form (so-called ‘Type 0’ disease) they can lose > 100 g glucose per day to the urine. Interestingly, the large majority of patients exhibit no symptoms and their condition is only identified incidentally. Typically, they do not become hypoglycaemic or dehydrated and have no electrolyte imbalance or increased risk of urinary tract infections. Even the most severe form of the condition appears to carry a favourable prognosis (although it should be noted that only small numbers of patients have been described in the literature). In contrast, patients with SGLT1 gene mutations have low levels of glucosuria but suffer from glucose–galactose malabsorption in the gut, which can be associated with life-threatening severe diarrhoea and dehydration unless a glucose- and galactose-free diet is carefully followed

2. PHYSIOLOGY OF MICTURITION

Micturition is the process by which urinary bladder empties when filled. The main physiological events in the process of micturition are:

* Filling of urinary bladder and
* Emptying of urinary bladder.

FILLING OF URINARY BLADDER

Transport of urine into urinary bladder through ureters

As urine collects in the renal pelvis, the pressure in the pelvis increases and initiates a peristaltic contraction beginning in the pelvis and spreading along the ureter to force urine towards the bladder.

Capacity of the bladder

Physiological capacity of the bladder varies with age, being 20–50 mL at birth, about 200 mL at 1 year, and can be as high as 600 mL in young adult males. In all cases, the physiological capacity is about twice that at which the first desire to void is felt.

Volume and pressure changes in bladder during filling

The normal bladder is completely empty at the end of micturition and the intravesical pressure is equal to the intraabdominal pressure. As the bladder is filled up, it adjusts its tone and a fairly large volume of urine can be accommodated with minimal alterations in the intravesical pressure. This is possible because of the phenomenon of adaptation. The adaptation occurs because of the inherent property of plasticity, the smooth muscles of detrusor and because of law of Laplace.

Cystometry. This refers to the process of studying the relationship between the intravesical volume and pressure, the cystometrogram refers to a graphical record of this relationship.

Normal cystometrogram shows three phases of filling

Phase Ia. It is the initial phase of filling in which pressure rises from 0 to 10 cm H2O, when about 50 mL of fluid is collected in the bladder.

Phase Ib. It is the phase of plateau which lasts till the bladder volume is 400 mL. During this phase, the pressure in the bladder does not change much and remains approximately at 10 cm H2O. This is because of adaptation of urinary bladder by relaxation, as described above.

Phase II. This phase starts beyond 400 mL volume when the pressure begins to rise markedly, triggering the micturition reflex. Normally, the voiding contraction raises the intravesical pressure by about 20–40 cm H2O. If voiding is avoided (not initiated), the pressure rises from 10 cm H2O onward, as shown by dotted lines beyond the phase II. Beyond 600 mL, the urge to void urine becomes almost unbearable.

EMPTYING OF THE BLADDER

Emptying of the bladder is basically a reflex action called the micturition reflex, which is controlled by supraspinal centres and is assisted by contraction of perineal and abdominal muscles. Therefore, emptying of the urinary bladder focuses on:

* Micturition reflex,
* Voluntary control of micturition and
* Role of perineal and abdominal muscles in micturition

Micturition reflex

Initiation. Micturition reflex is initiated by the stimulation of the stretch receptors located in the wall of urinary bladder.

Stimulus. Filling of bladder by 300–400 mL of urine in adults constitutes the adequate stimulus for the micturition reflex to occur.

Afferents. The afferents from the stretch receptors in the detrusor muscle and urethra travel along the pelvic splanchnic nerves and enter the spinal cord through dorsal roots to S2, S3 and S4 segments to reach the sacral micturition centre.

Sacral micturition centre is formed by the sacral detrusor nucleus and sacral pudendal nucleus.

Efferents. Efferent arising from the sacral detrusor nucleus are the preganglionic parasympathetic fibres, which relay in the ganglia near or within bladder and urethra. The post-ganglionic parasympathetic fibres are excitatory to the detrusor muscle and inhibitory to the internal sphincter.

Response. Once micturition reflex is initiated, it is self-regenerative, i.e. initial contraction of the bladder wall further activates the receptors to increase the sensory impulses (afferents) from the bladder and urethra which cause further increase in the reflex contraction of detrusor muscle of the bladder. The cycle thus keeps on repeating itself again and again until the bladder has reached a strong degree of contraction. Once the micturition reflex becomes powerful enough, this causes another reflex which passes through pudendal nerves to external sphincter to cause its inhibition. If this inhibition is more potent than the voluntary constrictor signals from brain, then urination will not occur. If not so, urination will not occur unless the bladder fills still more and micturition reflex becomes more powerful.

Voluntary control of micturition

Role of supraspinal centres

The micturition reflex is fundamentally a spinal reflex facilitated and inhibited by higher brain centres (supraspinal centres) and, like defaecation, is subjected to voluntary facilitation and inhibition. In infants and young children, micturition is purely a reflex action. Voluntary control is gradually acquired as a learned ability of the toilet training. Once voluntary control is acquired, the supraspinal control centres exert final control of micturition by following means:

* The higher centres keep the micturition reflex partially inhibited all the time except when it is desired to micturate.
* When the convenient time to urinate present, the higher centres facilitate the sacral micturition centre (SMC) to initiate a micturition reflex and inhibit the external urinary sphincter so that urination can occur.

Supraspinal control centres which control the micturition reflex (a completely automatic cord reflex) include the pontine micturition centre (PMC) and suprapontine centres.

Pontine micturition centre, corresponds to the locus ceruleus of the rostral pons. Neurons from PMC descend in the reticulospinal tract and exert control over the SMC and thoracolumbar sympathetics. Function of PMC is coordination of detrusor contraction and sphincter relaxation, which is important for proper micturition. Suprapontine centres which relay their influence on the sacral micturition centre through the PMC are:

* Cerebral cortex
* Basal ganglion
* Limbic system

Role of perineal and abdominal muscles in micturition

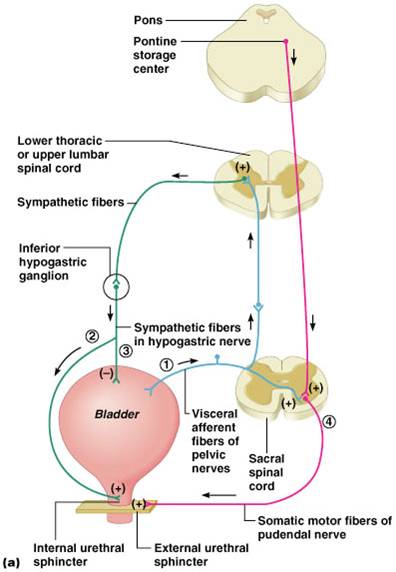
Certain muscular movements, which aid the emptying of bladder, but are not the essential component of micturition process are:

* At the onset of micturition, the levator ani and perineal muscles are relaxed, thereby shortening the post-urethra and decreasing the urethral resistance.
* The diaphragm descends and
* The abdominal muscles contract, accelerating the flow of urine by raising intra-abdominal pressure which in turn secondarily increase the intravesical pressure thereby increasing the flow of urine.

Note. Certain important facts about micturition are:

* A voiding contraction, once initiated, is normally maintained until all the urine has been discharged from the urinary bladder. This is a function of facilitating impulses from the higher centres. However, if required so, the micturition can be voluntarily stopped in between by inhibitory impulses from the higher centres.
* The bladder contracts in all directions like a toy balloon deflating from its neck.
* After urination, the female urethra empties by gravity, whereas the urine remaining in the urethra of male is expelled by several contractions of bulbospongiosus muscle.

Note. In the urinary bladder dysfunction, bladder contractions are insufficient to completely empty the bladder, therefore, some urine is left in the urinary bladder called residual urine.



ABNORMALITIES OF MICTURITION

EFFECT OF INTERFERENCE WITH NERVOUS CONTROL OF BLADDER

1. Transection of sympathetic supply following effects are produced:

* In man, the immediate effect would be the relaxation of ureteric reflexes, trigone and internal sphincter.
* Later, the internal sphincter may recover and closes completely, though it gives way easily when a catheter is passed.
* After an initial and inconstant period of frequency of micturition, bladder function is re-established in a comparatively normal way.

1. Effect of deafferentation or atonic bladder

* The destruction of sensory nerve fibres from the bladder to spinal cord prevents transmission of stretch signals from the bladder and therefore, also prevents micturition reflex contractions.

– In these conditions, the person loses all bladder control despite intact efferent fibres from the cord to the bladder and despite intact neurogenic connections with brain.

– Instead of emptying periodically, the bladder fills to capacity and overflows a few drops at a time through the urethra. This is called overflow dribbling.

Causes of atonic bladder are:

* Syphilis. It frequently causes constrictive fibrosis around the dorsal nerve root fibres where they enter the spinal cord and subsequently destroys these fibres.
* Crushing injuries to spinal cord. It damages the sensory roots.

1. Effect of denervation

When there is interruption with both afferent and efferent nerves of bladder, the following consequences are observed:

* The bladder is flaccid and distended for a while,
* Gradually, however, the muscle of decentralized bladder becomes active, with many contraction waves that expel dribbles of urine out of the urethra and
* The bladder becomes shrunken and the bladder wall hypertrophies.

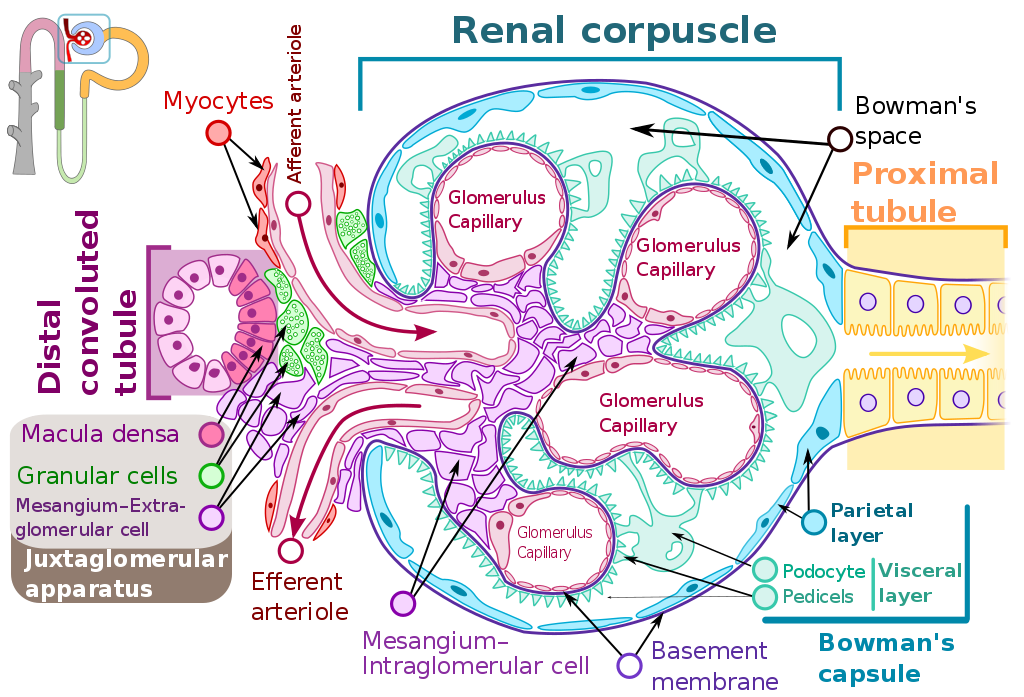
1. Effect of spinal cord transection

During spinal shock

* Voluntary micturition is completely abolished. The activity of detrusor muscle remains in abeyance for a long period, but sphincter now returns very soon. At this stage, bladder responds to filling in the same manner as the dead organ or an elastic bag. Retention of urine is therefore, complete from an early stage. If no catheter is passed the bladder becomes increasingly overstretched. The sphincter is finally forced open by a high intravesical pressure and small quantities of urine escape at frequent intervals—a condition of retention with overflow.
* The capacity is reduced and its walls become hypertrophied. This type of bladder is sometimes called spastic neurogenic bladder.

After spinal shock has passed, the voiding reflex returns, although there is no voluntary control. Some paraplegic patients train themselves to initiate voiding by pinching or stroking their thighs, provoking a mild mass reflex.

1. Juxtaglomerular Apparatus



DEFINITION

Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron (juxta = near).

STRUCTURE OF JUXTAGLOMERULAR APPARATUS

Juxtaglomerular apparatus is formed by three different structures:

1. Macula densa

2. Extraglomerular mesangial cells

3. Juxtaglomerular cells.

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

EXTRAGLOMERULAR MESANGIAL CELLS

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

Glomerular Mesangial Cells

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.

Glomerular mesangial cells are phagocytic in nature. These cells also secrete glomerular interstitial matrix, prostaglandins and cytokines.

JUXTAGLOMERULAR CELLS

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

Polar Cushion or Polkissen

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

FUNCTIONS OF JUXTAGLOMERULAR APPARATUS

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

SECRETION OF HORMONES

Juxtaglomerular apparatus secretes two hormones:

1. 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:

1. Fall in arterial blood pressure
2. Reduction in the ECF volume
3. Increased sympathetic activity
4. 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: 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:

1. 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.
2. ii. It increases blood pressure indirectly by increasing 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:

1. Angiotensin II inhibits the baroreceptor reflex and thereby indirectly increases the blood pressure. Baroreceptor reflex is responsible for decreasing the blood pressure
2. It increases water intake by stimulating the thirst center
3. It increases the secretion of orticotropin-releasing hormone (CRH) from hypothalamus. CRH in turn increases secretion of adrenocorticotropic hormone (ACTH) from pituitary
4. It increases secretion of antidiuretic hormone (ADH) from hypothalamus.

Other actions:

Angiotensin II: acts as a growth factor in heart and it is thought to cause muscular hypertrophy and cardiac enlargement.

Angiotensin III: increases the blood pressure and stimulates aldosterone secretion from adrenal cortex. It has 100% adrenocortical stimulating activity and 40% vasopressor activity of angiotensin II.

Angiotensin IV: It also has adrenocortical stimulating and vasopressor activities.

1. Prostaglandin

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

SECRETION OF OTHER SUBSTANCES

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

REGULATION OF GLOMERULAR BLOOD FLOW AND GLOMERULAR FILTRATION RATE

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

4 Role of Kidney in Blood Pressure

Introduction

That the kidney plays a role in hypertension is a knowledge that dates back almost 200 years some a researcher postulated that abnormalities in urine production by the kidney altered blood in such a way that tends to increase vascular resistance, leading to high blood pressure and increased cardiac mass. Many years later, Harry Goldblatt also induced malignant hypertension in dogs by obstructing one of the renal arteries. Arthur Guyton and colleagues also advanced a hypothesis suggesting that the kidney governs the level of blood pressure by regulating extracellular fluid volume in 1970. They argued that balance is normally achieved by matching urinary excretion of salt and water with dietary intake, thereby maintaining a constant extracellular fluid volume and blood pressure. They explained that when blood pressure increases for any reason, renal perfusion pressure also increases thereby enhancing sodium and water excretion, which Guyton referred to as pressure-natriuresis.

Based on the capacity for the kidney to excrete sodium, this blood pressure-altering mechanism should have sufficient advantage to limit intravascular volume and consequently lower blood pressure in response to a range of stimuli from elevated heart rate to increase peripheral vascular resistance. Furthermore, a permissive modification of the pressure-natriuresis response has been predictably required to perpetuate a chronic elevation in intra-arterial pressure, whereby the equilibrium point for salt and water excretion is shifted to a higher level of arterial blood pressure. Also, a series of kidney cross-transplantation studies have supported a key role for intrinsic functions of the kidney in the pathogenesis of hypertension. Genetically, compatible donor and recipient strains were used to circumvent rejection, with both native kidneys removed such that the full extent of excretory function is provided by the transplanted kidney.

Likewise, studies in spontaneously hypertensive rats and Milan hypertensive rats recapitulated these findings. The same principle seems to also hold true in humans where resistant hypertension can be alleviated after successful kidney transplantation. Collectively, these studies point to the fact that a defect in sodium excretion by the kidney confers susceptibility to elevated blood pressure.

Blood pressure and hypertension

Hypertension is one of the most common chronic diseases of human, affecting more than one billion people worldwide. Although elevated blood pressure does not typically cause overt symptoms, the consequences of chronic hypertension, including cardiac hypertrophy, heart failure, stroke, and kidney disease, are responsible for substantial morbidity and mortality. Treatments that effectively reduce blood pressure can prevent these complications. However, in recent times, blood pressures were reduced to target levels in less than 50% of patients receiving hypertension treatment, and this rate was under 40% in individuals who also had chronic kidney disease.

The reasons for these poor outcomes include health services issues around processes of care, compliance, and patient education. Moreover, the precise cause of hypertension is not apparent in the vast majority of patients with hypertension. Limitations in understanding of hypertension pathogenesis in individual patients are an obstacle to applying individualized approaches for prevention and treatment and to identifying new, specific therapies.

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.

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.

How the kidneys increase circulating blood volume

Angiotensin-2 also stimulates the adrenal gland to secrete a hormone called aldosterone. Aldosterone stimulates more Na reabsorption in the distal tubule, and water gets reabsorbed along with the Na. The increased Na and water reabsorption from the distal tubule reduces urine output and increases the circulating blood volume. The increased blood volume helps stretch the heart muscle and causes it to generate more pressure with each beat, thereby increasing the blood pressure. The circulating blood volume is directly proportional to the stretch of the heart muscle.

The actions taken by the kidney to regulate blood pressure are especially important during traumatic injury, when they are necessary to maintain blood pressure and conserve the loss of fluids. The body stores calcium in the bones, but also maintains a constant level of calcium in the blood. If the blood calcium level falls, then the parathyroid glands in the neck release a hormone called parathyroid hormone. Parathyroid hormone increases calcium reabsorption from the distal tubule of the nephron to restore the blood calcium level. Parathyroid hormone aside from stimulating calcium release from bone also causes calcium absorption from the intestine.

Vitamin D is also required by the body to stimulate calcium absorption from the kidney and intestine. Vitamin D is found in milk products. A precursor to vitamin D (cholecalciferol) is made in the skin and processed in the liver. The last phase in the conversion of an inactive form of cholecalciferol into active vitamin D takes place in the proximal tubule of the nephron. Once activated, vitamin D stimulates calcium absorption from the proximal tubule and from the intestine, thereby increasing blood calcium levels.

Kidney stones are abnormalities usually caused by problems in the kidney’s ability to handle calcium. In addition, the kidney’s role in maintaining blood calcium is important in the bone disease osteoporosis that afflicts many elderly people, especially women.

The kidneys therefore function in the body to:

• Control the composition of the blood and eliminate wastes by filtration/reabsorption/secretion

• Influence blood pressure by renin secretion

• Help regulate the body’s calcium by vitamin D activation

If for any reason, the kidneys fail to function, then renal dialysis methods (artificial filtration methods) becomes the only alternative to assist the patient to survive by cleansing the blood. This is especially necessary when both kidneys fail.

Mechanisms of blood pressure control by the kidneys

Intra-renal actions of the renin-angiotensin system in blood pressure control

The renin-angiotensin system (RAS) is a potent modulator of blood pressure, and dysregulation of the RAS results in hypertension. Pharmacological blockade of the RAS with renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers effectively lowers blood pressure in a substantial proportion of patients with hypertension, reflecting the important role for RAS activation as a cause of human hypertension. While in rodents, deletion of RAS genes lowers blood pressure, overexpression causes hypertension.

While The distal tubule cells (macula densa) sense the Na in the filtrate, and the arterial cells (juxtaglomerular cells) sense the blood pressure. Studies have shown that chronic infusion of low doses of angiotensin II directly into the kidney caused hypertension with impaired natriuresis due to a shift of the pressure-natriuresis relationship. It is also believed that the existence of local and independent control of RAS activity within the kidney influencing sodium excretion and blood pressure regulation. In this hypothesis, increased circulating levels of angiotensin II are associated with accumulation of angiotensin peptides in the kidney, upregulated expression of angiotensinogen, the primary RAS substrate, in proximal tubule epithelium, and increased excretion of angiotensinogen and angiotensin peptides in urine. In this feed-forward pathway, angiotensin II acting via type 1 angiotensin (AT1) receptors in the kidney induces local activation of the RAS inside the kidney and increases generation of angiotensin II in the lumen of renal tubules, resulting in autocrine and paracrine stimulation of epithelial transporters.

Recent studies in support of this idea have verified the critical requirement of ACE within the kidney to fully manifest stimulation of sodium transporter expression, renal sodium reabsorption, and hypertension in the setting of RAS activation.

Salt Homeostasis

Salt sensitivity, defined as an exaggerated change in blood pressure in response to extremes in dietary salt intake, is relatively common and is associated with an increased risk for the development of hypertension. Classic Guytonian models suggest that a defect in sodium excretion by the kidney is the basis for salt sensitivity, with impaired elimination of sodium during high-salt feeding leading directly to expanded extracellular fluid volume, which promotes increased blood pressure. This model presumes that the two major components of extracellular volume within the intravascular and interstitial spaces are in equilibrium. As such, accumulation of sodium would be accompanied by commensurate retention of water to maintain iso-osmolality and would thereby proportionally expand the intravascular volume.

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The Role Of Kidney In Calcium Homeostasis

Control of Renal Calcium Excretion and Extracellular Calcium Ion Concentration

The mechanisms for regulating calcium ion concentration, along with the endocrinology of the calcium-regulating hormones parathyroid hormone (PTH) and calcitonin. Therefore, calcium ion regulation is discussed only briefly in this chapter. Extracellular fluid calcium ion concentration normally remains tightly controlled within a few percentage points of its normal level, 2.4 mEq/L. When calcium ion concentration falls to low levels (hypocalcemia), the excitability of nerve and muscle cells increases markedly and can in extreme cases result in hypocalcemic tetany. This is characterized by spastic skeletal muscle contractions. Hypercalcemia (increased calcium concentration) depresses neuromuscular excitability and can lead to cardiac arrhythmias. About 50 per cent of the total calcium in the plasma (5 mEq/L) exists in the ionized form, which is the form that has biological activity at cell membranes. The remainder is either bound to the plasma proteins (about 40 per cent) or complexed in the non-ionized form with anions such as phosphate and citrate (about 10 per cent). Changes in plasma hydrogen ion concentration can influence the degree of calcium binding to plasma proteins.With acidosis, less calcium is bound to the plasma proteins. Conversely, in alkalosis, a greater amount of calcium is bound to the plasma proteins. Therefore, patients with alkalosis are more susceptible to hypocalcemic tetany. As with other substances in the body, the intake of calcium must be balanced with the net loss of calcium over the long term. Unlike ions such as sodium and chloride, however, a large share of calcium excretion occurs in the feces. The usual rate of dietary calcium intake is about 1000 mg/day, with about 900 mg/day of calcium excreted in the feces. Under certain conditions, fecal calcium excretion can exceed calcium ingestion because calcium can also be secreted into the intestinal lumen. Therefore, the gastrointestinal tract and the regulatory mechanisms that influence intestinal calcium absorption and secretion play a major role in calcium homeostasis. Almost all the calcium in the body (99 per cent) is stored in the bone, with only about 1 per cent in the extracellular fluid and 0.1 per cent in the intracellular fluid. The bone, therefore, acts as a large reservoir for storing calcium and as a source of calcium when extracellular fluid calcium concentration tends to decrease.

One of the most important regulators of bone uptake and release of calcium is PTH.When extracellular fluid calcium concentration falls below normal, the parathyroid glands are directly stimulated by the low calcium levels to promote increased secretion of PTH. This hormone then acts directly on the bones to increase the resorption of bone salts (release of salts from the bones) and, therefore, to release large amounts of calcium into the extracellular fluid, thereby returning calcium levels back toward normal. When calcium ion concentration is elevated, PTH secretion decreases, so that almost no bone resorption now occurs; instead, excess calcium is deposited in the bones because of new bone formation. Thus, the day-to-day regulation of calcium ion concentration is mediated in large part by the effect of PTH on bone resorption. The bones, however, do not have an inexhaustible supply of calcium. Therefore, over the long term, the intake of calcium must be balanced with calcium excretion by the gastrointestinal tract and the kidneys. The most important regulator of calcium reabsorption at both of these sites is PTH. Thus, PTH regulates plasma calcium concentration through three main effects: (1) by stimulating bone resorption; (2) by stimulating activation of vitamin D, which then increases intestinal reabsorption of calcium; and (3) by directly increasing renal tubular calcium reabsorption (Figure 29–10). The control of gastrointestinal calcium reabsorption and calcium exchange in the bones is discussed elsewhere, and the remainder of this section focuses on the mechanisms that control renal calcium excretion.

Control of Calcium Excretion by the Kidneys

Because calcium is both filtered and reabsorbed in the kidneys but not secreted, the rate of renal calcium excretion is calculated as Renal calcium excretion = Calcium filtered - Calcium reabsorbed Only about 50 per cent of the plasma calcium is ionized, with the remainder being bound to the plasma proteins or complexed with anions such as phosphate. Therefore, only about 50 per cent of the plasma calcium can be filtered at the glomerulus. Normally, about 99 per cent of the filtered calcium is reabsorbed by the tubules, with only about 1 per cent of the filtered calcium being excreted. About 65 per cent of the filtered calcium is reabsorbed in the proximal tubule, 25 to 30 per cent is reabsorbed in the loop of Henle, and 4 to 9 per cent is reabsorbed in the distal and collecting tubules. This pattern of reabsorption is similar to that for sodium. As is true with the other ions, calcium excretion is adjusted to meet the body’s needs. With an increase in calcium intake, there is also increased renal calcium excretion, although much of the increase of calcium intake is eliminated in the feces. With calcium depletion, calcium excretion by the kidneys decreases as a result of enhanced tubular reabsorption. One of the primary controllers of renal tubular calcium reabsorption is PTH. With increased levels of PTH, there is increased calcium reabsorption in the thick ascending loops of Henle and distal tubules, which reduces urinary excretion of calcium. Conversely, reduction of PTH promotes calcium excretion by decreasing reabsorption in the loops of Henle and distal tubules. In the proximal tubule, calcium reabsorption usually parallels sodium and water reabsorption. Therefore, in instances of extracellular volume expansion or increased arterial pressure—both of which decrease proximal sodium and water reabsorption—there is also reduction in calcium reabsorption and, consequently, increased urinary excretion of calcium. Conversely, with extracellular volume contraction or decreased blood pressure, calcium excretion decreases primarily because of increased proximal tubular reabsorption. Another factor that influences calcium reabsorption is the plasma concentration of phosphate. An increase in plasma phosphate stimulates PTH, which increases calcium reabsorption by the renal tubules, thereby reducing calcium excretion. The opposite occurs with reduction in plasma phosphate concentration. Calcium reabsorption is also stimulated by metabolic acidosis and inhibited by metabolic alkalosis. Most of the effect of hydrogen ion concentration on calcium excretion results from changes in calcium reabsorption in the distal tubule.