**Lec 10 Renal Function & Morphology Dr. Ihab Alkhalifa**

**Introduction**

Most people are familiar with one important function of the kidneys—to rid the body of waste materials that are either ingested or produced by metabolism. The kidneys perform their most important functions by filtering the plasma and removing substances from the filtrate at variable rates, depending on the needs of the body.

**It is important to recognize that the kidneys serve multiple functions, including the following:**

1- Excretion of metabolic waste products and foreign chemicals

2- Regulation of water and electrolyte balances

3- Regulation of body fluid osmolality and electrolyte concentrations

4- Regulation of arterial pressure ( body blood pressure )

5- Regulation of acid-base balance ( pH of the blood )

6- Secretion, metabolism, and excretion of hormones, as :

A- production of renin ( control of blood pressure)

B- Erythropoietin (control of red blood cells production)

C- 1, 25-dihydroxycholecalciferol ( calcitriol ) , active form of vitamin D ,which stimulate calcium & phosphate absorption in the intestine and promoting bone deposition .

7- Gluconeogenesis : ( synthesis of glucose ) during fasting or starvation state

**Components of the urinary system:**

1- Two kidneys .

2- Two ureters carries urine from kidney to bladder .

3- urinary bladder

4- Urethra which carries urine from the bladder to the outside of the body and is expelled to the exterior by the process of urination, or micturition.

**The kidneys**

The kidneys, are paired organs , bean-like reddish collared organs located behind the peritoneal lining of the abdominal cavity .

Kidneys, located between the level of last thoracic and third lumbar vertebrae.

The kidney is divided into an outer layer called cortex , while the inner called the medulla .

The medulla contains eight to ten cone shaped structures called renal pyramid , drain in large passage which drain into single funnel shaped passage called renal pelvis which is then narrowed to form the ureter , pass thr filtered fluid ( urine) to bladder and then to urethra .

The basic and functional unit of the kidney is the nephron , which is composed of :

A- Glomerulus

B- Renal tubules

**Basic renal processes for urine formation**

In the kidneys, a fluid that resembles plasma is converted into urine by four processes

1- Filtered through the glomerular capillaries into the renal tubules **by Glomerular Filtration ( filtrate with no protein no blood cells ) .**

As this glomerular filtrate passes down the tubules, its volume is reduced and its composition altered by the processes of:

2- **Tubular Reabsorption** which involve removal of water and useful solutes from the tubular fluid back to the blood .

3-**Tubular secretion**  : involve the secretion of solutes into the tubular fluid to form the urine that enters the renal pelvis as wastes .

4- **Concentration**: removes water from the urine and concentrate the wastes .

 It emphasizes the manner by which water and important electrolytes and metabolites are conserved while wastes are eliminated in the urine.

**Urine :** is the final fluid as result of the previous processes , excreted from the kidney containing organic wast products as urea, creatinin , as well as excess of ions as Na, K,CL,HCO3, and H .

 Furthermore, the composition of the urine can be varied to maintain whole body fluid homeostasis (extracellular fluid [ECF] ). This is achieved via many homeostatic regulatory mechanisms that function to change the amount of water and solutes in the urine.

**THE NEPHRON**

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**THE NEPHRON**

The nephron is the functional unit of the kidney , consist of 2 major parts ( Fig. 38-1)

 1- The glomerulus

2- The tubule .

**The glomerulus** : which is about 200 mm in diameter, is formed by the invagination of a tuft of capillaries into the dilated, blind end of the nephron **(Bowman's capsule).**

 The capillaries are supplied by an **afferent arteriole** and drained by a slightly smaller **efferent arteriole** (Figure 38–2), and it is from the glomerulus that the filtrate is formed. Two cellular layers separate the blood from the glomerular filtrate in Bowman's capsule:

**Bowman s capsule : consist of two lyers ,**  the capillary endothelial cells and the specialized epithelium of the capsule called **podocytes**.

 **The endothelium of the glomerular capillaries is fenestrated, with pores .**



**Fig.(38-2) Glomerulus & Bowman s capsule**

**( juxtaglomerular apparatus ) الرسم مطلوب**

**Function:** the glomerular membrane permits the free passage of neutral substances up to 4 nm in diameter and almost totally excludes those with diameters greater than 8 nm., as plasma proteins and retained within the capillaries .

Final filtrate from the glomerulus contain water, solutes and only small amounts of proteins which are readily reabsorbed in the proximal tubule , while the filtrate is free from blood cells and plasma proteins

**Juxtaglomerular apparatus :** Specialized structure , located near the glomerulus composed of :

 1- **The macula Densa : which are modified epithelial cells forming part of the distal tubule**

**2- Renin-Secreting juxtaglomerular cells ( also called granular cells since cytoplasm contain granules containing renin ) which are modified endothelial cells of the afferent arteriole , form the juxtaglomerular apparatus** (see Figure 38–2).

This apparatus plays an important role in blood volume & pressure control through release of renin upon reduced blood volume or filtrate reaching it .

**Functional divisions of renal tubule**

1- The human **proximal convoluted tubule :** which is mean proximal the bomann capsule is about 15 mm long and 55mm in diameter. Its wall is made up of a single layer of cells that interdigitate with one another and are united by apical tight junctions. The luminal edges of the cells have a striate **brush border** due to the presence of many microvilli, it starts from the end of Bormann’s capsule , carry the fluid filtered in the glomerulus to the rest of the tubule .

The convoluted proximal tubule straightens and the next portion of each nephron is:

2- The **loop of Henle: consist of two parts ( Descending**  **& Ascending** **parts** )

**The descending portion** of the loop and the proximal portion of the ascending limb are made up of thin, permeable cells.

 On the other hand, the thick portion of the ascending limb (Figure 38–1) is made up of thick cells containing many mitochondria.

The thick end of the ascending limb of the loop of Henle reaches the glomerulus of the nephron, there is Specialized cells at the end form the **macula densa** (Figure 38–2).

The thick portion returns to the cortex giving rise to distal tubule .

3- The **Distal convoluted tubule,** ( means distal to the bomann capsule ) which starts at the macula densa, is about 5 mm long. Its epithelium is lower than that of the proximal tubule, and although a few microvilli are present, there is no distinct brush border. The distal tubules coalesce to form **collecting ducts**

4- **Collecting ducts**  that are about 20 mm long and pass through the renal cortex and medulla to empty into the pelvis of the kidney at the apexes of the medullary pyramids. The epithelium of the collecting ducts is made up of **principal cells (P cells)** and **intercalated cells (I cells).**

**The P cells**,. They are involved in Na+ reabsorption and vasopressin-stimulated water reabsorption ( Antidiuretic Hormone (ADH) .

**The I cells**, which are present in smaller numbers and are also found in the distal tubules. They are concerned with acid secretion and HCO3– transport.

Cells in the kidneys that appear to have a secretory function include not only the juxtaglomerular cells but also some of the cells in the interstitial tissue of the medulla.

 These cells are called **type I medullary interstitial cells.** They contain lipid droplets and probably secrete prostaglandins, predominantly PGE2. PGE2 is also secreted by the cells in the collecting ducts; prostacyclin (PGI2) and other prostaglandins are secreted by the arterioles and glomeruli.

**Blood Vessels**

Although the kidneys are small organ but received about 21% of the cardiac output ( 1,2 liters / minute ) The renal circulation is diagrammed in Figure 38–3.

A **renal artery** ( arising from aorta ) forming straight branches of the **interlobular arteries**  , forming The **afferent arterioles**,

Each afferent arteriole supplies blood to single nephron, which is subdivided to form round cluster of capillaries called a **glomerulus**

 The glomerulus is supplied by afferent arteriole which is subdivided into glomerular capillaries , thses capillaries recombine to form **efferenr arterioles** through which the blood leaves the glomerulus by **renal vein** drain into **inferior vena cava .**

Each efferent arteriole soon divides into branches forming network surrounding the tubule , then finally rejoin to form the veins by which the blood leaves the kidneys .

 **Lymphatics**

The kidneys have an abundant lymphatic supply that drains via the thoracic duct into the venous circulation in the thorax.

**Capsule**

The renal capsule is thin but tough. If the kidney becomes edematous, the capsule limits the swelling, and the tissue pressure **(renal interstitial pressure)** rises. This decreases the glomerular filtration rate and is claimed to enhance and prolong anuria in acute renal failure.

**Pressure in Renal Vessels**

The pressure in the glomerular capillaries has been measured directly in rats and has been found to be considerably lower than predicted on the basis of indirect measurements. When the mean systemic arterial pressure is 100 mm Hg, the glomerular capillary pressure is about 45 mm Hg.



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**Regulation of the Renal Blood Flow**

**1- Norepinephrine** (noradrenaline) **constricts the renal vessels**, with the greatest effect of injected norepinephrine being exerted on the interlobular arteries and the afferent arterioles.

 **2- Dopamine is made in the kidney and causes renal vasodilation and Natriuresis.**

 **3- Angiotensin II** exerts a **constrictor effect** on both the afferent and efferent arterioles.

**4- Prostaglandins** **increase blood flow** in the renal cortex and decrease blood flow in the renal medulla.

**5- Acetylcholine** also produces **renal vasodilation**.

A high-protein diet raises glomerular capillary pressure and increases renal blood flow.

**Innervation of the Renal Vessels**

The renal nerves travel along the renal blood vessels as they enter the kidney.

1- They contain many **postganglionic sympathetic** efferent fibers and a few afferent fibers.

2- There also appears to be a **cholinergic innervation via the vagus nerve**, but its function is uncertain.

The sympathetic preganglionic innervation comes primarily from the lower thoracic and upper lumbar segments of the spinal cord,

The sympathetic fibers are distributed primarily to the afferent and efferent arterioles, the proximal and distal tubules, and the juxtaglomerular cells (see Chapter 39). In addition, there is a dense noradrenergic innervation of the thick ascending limb of the loop of Henle.

Nociceptive afferents that mediate pain in kidney disease parallel the sympathetic efferents and enter the spinal cord in the thoracic and upper lumbar dorsal roots.

 **Functions of the Renal Nerves**

Stimulation of the renal nerves increases renin secretion by a direct action of released norepinephrine on B1- adrenergic receptors on the juxtaglomerular cells (see Chapter 39) and it increases Na+ reabsorption, probably by a direct action of norepinephrine on renal tubular cells.

The proximal and distal tubules and the thick ascending limb of the loop of Henle are richly innervated. While, Strong stimulation of the sympathetic noradrenergic nerves to the kidneys causes a marked decrease in renal blood flow. This effect is mediated by **α1-adrenergic** receptors and to a lesser extent by postsynaptic **α2**-adrenergic receptors.

**Glomerular Filtration**

**Glomerular filtration :** is the movement of plasma through the filtration membrane of the capsule , the portion that entering the nephron becomes “ filtrate “

An average of 21% of blood pumped by heart each minute flows through the kidneys . and about 180 liters of fluids are filtered every day, while 1400-1800 ml of urin is excreted per day ? Because , 99% of the fluid filtered is reabsorbed .

**Measuring GFR**

**The glomerular filtration rate (GFR)** : **is the amount of filtrate formed / minute By both kidneys** , it can be measured in intact experimental animals and humans by measuring the excretion and plasma level of a substance that is freely filtered through the glomeruli and neither secreted nor reabsorbed by the tubules.

The amount of such a substance in the urine per unit of time must have been provided by filtering exactly the number of milliliters of plasma that contained this amount. Therefore, if the substance is designated by the letter X, the GFR is equal to the concentration of X in urine (UX) times the **urine flow** per unit of time (V) divided by the **arterial plasma level** of X (PX).

 **PX** is, of course, the same in all parts of the arterial circulation, and if X is not metabolized to any extent in the tissues, the level of X in peripheral venous plasma can be substituted for the arterial plasma level.

**renal clearance of X is GFR= UX .V/PX.**

This value is called the clearance of X (CX).

 **Normal GFR**

**The GFR in a healthy person of average size is approximately 125 mL/min**. Its magnitude correlates fairly well with surface area, but values in women are 10% lower than those in men even after correction for surface area. A rate of 125 mL/min is 7.5 L/h, or 180 L/d, whereas the normal urine volume is about 1 L/d. Thus, 99% or more of the filtrate is normally reabsorbed. At the rate of 125 mL/min,

Note/ asmall change in GFR will lead to an enumerous effect on the volume of the fluid filtered , therefore , GFR is regulated by many factors to keep it constant

**Factors that Control of GFR**

**The factors governing filtration** across the glomerular capillaries are the same as those governing filtration across all other capillaries :

1- the size of the capillary bed

2- the permeability of the capillaries

3- the hydrostatic and osmotic pressure gradients across the capillary wall. For each nephron

**Tubular Function**

**General Considerations**

The amount of any substance (X) that is filtered is the product of the GFR and the plasma level of the substance .

 **The tubular cells may add more of the substance to the filtrate (tubular secretion), may remove some or all of the substance from the filtrate (tubular reabsorption), or may do both.**

The amount of the substance excreted per unit of time equals the amount filtered plus the **net amount transferred** by the tubules.

This latter quantity is conveniently indicated by the symbol **TX**

**1- The clearance of the substance equals the GFR if there is no net Tubular secretion or Reabsorption, mean ( TX = GFR )**

**2- TX** > **GFR if there is net tubular secretion,**

 **3- TX** < **GFR if there is net tubular reabsorption**

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**Mechanisms of Tubular Reabsorption & Secretion**

1- Small proteins and some peptide hormones are reabsorbed in the proximal tubules by endocytosis.

2- Other substances are secreted or reabsorbed in the tubules by passive diffusion between cells and through cells by facilitated diffusion down chemical or electrical gradients or active transport against such gradients.

3- Movement is by way of ion channels, exchangers, cotransporters, and pumps. Many of these have now been cloned, and their regulation is being studied.

It is important to note that the pumps and other units in the luminal membrane are different from those in the basolateral membrane. It is this different distribution that makes possible net movement of solutes across the epithelia.

**Reabsorption**

Involves two steps :

1- the movement of solutes from tubular fluid into the interstitial fluid

2- From the interstitial fluid into peritubular capillaries

 **The plasma membrane** of tubule epithelial cells facing tubule lumen is called **apical or ( luminal membrane )** while that facing the interstitial fluid is called **basolateral membrane.**

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| **1- Mechanism of Na+ Reabsorption :** The net reabsorption of Na ions from the tubule lumen back into the blood three steps : 1- Na+ moves by cotransport or exchange from the tubular lumen into the tubular epithelial cells down its concentration and electrical gradients,2- then actively pumped from these cells into the interstitial space. Na+ is pumped into the interstitium by **Na, K ATPase in the basolateral membrane.** Thus, Na+ is actively transported out of all parts of the renal tubule except the thin portions of the loop of Henle. **It extrudes three Na+ in exchange for two K+ that are pumped into the cell.**3-. Normally about 60% of the filtered Na+ is **reabsorbed** in:a- **the proximal tubule**, primarily by **Na–H exchange**. **b-** Another 30% is absorbed via the Na–2Cl–K cotransporter in the **thick ascending limb** of the loop of Henle, c- and about 7% is absorbed by Na–Cl cotransporter in the **distal convoluted tubule**. d- The remainder of the filtered Na+, about 3%, is absorbed via the **ENaC** channels in the **collecting ducts**, and this is the portion that is **regulated by aldosterone in the production of homeostatic adjustments in Na+ balance** |
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| Transport Proteins Involved in the Movement of Na+ and Cl– Across the Apical Membranes of Renal Tubular Cells.a |

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| **Site** | **Apical Transporter** | **Function** |
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| Proximal tubule | Na/glucose CT  | Na+ uptake, glucose uptake  |
| Na+/Pi CT  | Na+ uptake, Pi uptake  |
| Na+ amino acid CT  | Na+ uptake, amino acid uptake  |
| Na/lactate CT  | Na+ uptake, lactate uptake  |
| Na/H exchanger  | Na+ uptake, H+ extrusion  |
| Cl/base exchanger  | Cl– uptake  |
| Thick ascending limb | Na–K–2Cl CT  | Na+ uptake, Cl– uptake, K+ uptake  |
| Na/H exchanger  | Na+ uptake, H+ extrusion  |
| K+ channels  | K+ extrusion (recycling)  |
| Distal convoluted tubule | NaCl CT | Na+ uptake, Cl– uptake  |
| Collecting duct | Na+ channel (ENaC)  | Na+ uptake  |

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**2- Mechanism of Glucose & Amino acid Reabsorption**

Glucose, amino acids, and bicarbonate are reabsorbed along with Na+ in the early portion of the proximal tubule (Figure 38–9). Further along the tubule, Na+ is reabsorbed with Cl– .

other carrier protein combine sodium ions and amino acids in an efficient way to remove all glucose and amino acids from the filtrate into the tubule cells , by process called ( **co-transport ) , since transport of glucose occur secondary to sodium ions ( secondary active transport ) , The energy required is obtained from Na-k exchange pump**

**3- Mechanism of Proteins reabsorption**

**By process of pinocytosis** , the protein attached to the brush boarder of the luminal membrane in the proximal , then invaginate into the interior of the cells until it completely pinched off , forming vesicles containing the protein

2- This protein then digested into its constituents amino acids which are reabsorbed accompanied by Na ions as mentioned previouslyThe process of pinocytosis is considered type of active transport

**5- Mechanism of Urea reabsorption :**

**Reabsorbtion of urea follows water removal from the tubule** , creating concentration gradient allow urea to flow from tubular lumen ( high conc.) back to the blood , thus urea reabsorption is a passive diffusion dependent on water reabsorption

**Urea transport is mediated by urea transporters, presumably by facilitated diffusion**. There are at least four isoforms of the transport protein UT-A in the kidneys (UT-A1 to UT-A4);

**Kidneys usually removes half of filtered urea , keeping its blood level in safe rang of 10-20 mg/100 ml**

**6- creatinine** : is not reabsorbed at all , its too large molecule to diffuse through water channels and not have carrier proteins , **therefore all filtered load by the glomerulus is excreated in urine .**

**7- Mechanism of Water Transport**

There is two important facts:

1- At least 87% of the filtered water is reabsorbed,

2- The reabsorption of the remainder of the filtered water can be varied without affecting total solute excretion.

 Therefore, when the urine is concentrated, water is retained in excess of solute; and when it is dilute, water is lost from the body in excess of solute. Both facts have great importance in the regulation of the osmolality of the body fluids. A key regulator of water output is vasopressin acting on the collecting ducts.

**Proximal Tubule**

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| Active transport of many substances occurs from the fluid in the proximal tubule (Figure 38–9). at the basolateral and apical membrane of the proximal tubules and its presence allows water to move rapidly out of the tubule along the osmotic gradients set up by active transport of solutes, and isotonicity is maintained. **Loop of Henle**There is a graded increase in the osmolality of the interstitium of the pyramids in humans: The osmolality at the tips of the papillae can reach about 1200 mOsm/kg of H2O, approximately four times that of plasma. 1- The **descending limb** of the loop of Henle **is permeable** to water,**2- The Ascending limb is impermeable to water (Table 38–8).** Na+, K+, and Cl– are co transported out of the thick segment of the ascending limb. Therefore, the fluid in the descending limb of the loop of Henle becomes **hypertonic** as water moves out of the tubule into the hypertonic interstitium. 3- **In the ascending limb it becomes more dilute because of the movement of Na+ and Cl– out of the tubular lumen,** and when fluid reaches the top of the ascending limb (called the diluting segment) it is now **hypotonic** to plasma. In passing through the descending loop of Henle, another 15% of the filtered water is removed, so approximately 20% of the filtered water enters the distal tubule4- **In the thick ascending limb**, a carrier co transports one Na+, one K+, and 2Cl– from the tubular lumen into the tubular cells. This is another example of secondary active transport; the Na+ is actively transported from the cells into the interstitium by Na,K ATPase in the basolateral membranes of the cells, keeping the intracellular Na+ low.**Distal Tubule**The distal tubule, particularly its first part, is in effect an extension of the thick segment of the ascending limb. It is relatively impermeable to water, and continued removal of the solute in excess of solvent further dilutes the tubular fluid. **Collecting Ducts**The collecting ducts have two portions: **A cortical portion** and a **medullary portion**. The changes in osmolality and volume in the collecting ducts depend on the amount of vasopressin acting on the ducts. **This antidiuretic hormone** (ADH) from the posterior pituitary gland increases the permeability of the collecting ducts to water. The key to the action of vasopressin on the **collecting ducts is :Aquaporin-2.:**  In the presence of enough vasopressin to produce maximal antidiuresis, water moves out of the hypotonic fluid entering the cortical collecting ducts into the interstitium of the cortex, and the tubular fluid becomes isotonic. In this fashion, as much as 10% of the filtered water is removed. The isotonic fluid then enters the medullary collecting ducts, producing concentrated urine. |

**Tubuloglomerular Feedback & Glomerulotubular Balance**

1- **Tubulo- glomerular feedback**

 Signals from the renal tubule in each nephron feed back to affect filtration in its glomerulus. **As the rate of flow through the ascending limb of the loop of Henle and first part of the distal tubule increases, glomerular filtration in the same nephron decreases, and, conversely, a decrease in flow increases the GFR (Figure 38–13).** This process, which is called **tubuloglomerular feedback,** tends to maintain the constancy of the load delivered to the distal tubule.

The sensor for this response is the **macula densa.** The amount of fluid entering the distal tubule at the end of the thick ascending limb of the loop of Henle depends on the amount of Na+ and Cl– in it.

 The Na+ and Cl– enter the macula densa cells , increased Na+ causes **afferent vasoconstriction and a resultant decrease in GFR. Presumably,** with decreases renin secretion by the adjacent juxtaglomerular cells in the afferent arteriole .

2- **Glomerulotubular balance**

 **Conversely, an increase in GFR causes** an increase in the reabsorption of solutes, and consequently of water, primarily in the proximal tubule, This process is called **glomerulotubular balance**, When the GFR is high, there is a relatively large increase in the oncotic pressure of the plasma leaving the glomeruli This increases the reabsorption of Na+ from the tubule.



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| **The Bladder****Filling**The walls of the ureters contain smooth muscle arranged in spiral, longitudinal, and circular bundles .Regular peristaltic contractions occurring one to five times per minute move the urine from the renal pelvis to the bladder, with each peristaltic wave. The ureters pass obliquely through the bladder wall and, although there are no ureteral sphincters as such, the oblique passage tends to keep the ureters closed except during peristaltic waves, preventing reflux of urine from the bladder.**Emptying**The smooth muscle of the bladder, like that of the ureters, is arranged in spiral, longitudinal, and circular bundles. Contraction of the circular muscle, which is called the detrusor muscle, is mainly responsible for emptying the bladder during urination (micturition). along the urethra is a sphincter of skeletal muscle,  **Micturition** is fundamentally a spinal reflex facilitated and inhibited by higher brain centers and, like defecation, subject to voluntary facilitation and inhibition. Urine enters the bladder without producing much increase in intravesical pressure until the viscus is well filled. During micturition, the perineal muscles and external urethral sphincter are relaxed, the detrusor muscle contracts, and urine passes out through the urethra. **The bands of smooth muscle** on either side of the urethra apparently play no role in micturition**, and their main function in males is believed to be the prevention of reflux of semen into the bladder during ejaculation.** |

 **Reflex Control**

The bladder smooth muscle has some inherent contractile activity; however, when its nerve supply is intact, stretch receptors in the bladder wall initiate a reflex contraction that has a lower threshold than the inherent contractile response of the muscle. Fibers in the pelvic nerves are the afferent limb of the voiding reflex, and the parasympathetic fibers to the bladder that constitute the efferent limb also travel in these nerves. The reflex is integrated in the sacral portion of the spinal cord.

In the adult, the volume of urine in the bladder that normally initiates a reflex contraction is about 300 to 400 mL. **The sympathetic nerves to the bladder** play no part in micturition, but in males they do mediate the contraction of the bladder muscle **that prevents semen from entering the bladder during ejaculation.**

The bladder can be made to contract by voluntary facilitation of the spinal voiding reflex when it contains only a few milliliters of urine. Voluntary contraction of the abdominal muscles aids the expulsion of urine by increasing the intra-abdominal pressure, but voiding can be initiated without straining even when the bladder is nearly empty.

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