Physiology 1

Urinary System Components

- **Kidneys**: Main organs that filter blood, form urine, and regulate fluid/electrolyte balance.
- **Ureters**: Muscular tubes transporting urine from kidneys to bladder.
- **Urinary Bladder**: Stores urine until urination.
- **Urethra**: Passageway for urine excretion.

Kidney Anatomy

- Each kidney has a **hilum** (entry/exit for **renal artery, vein**, **ureter**, **lymphatics**, **nerves**).

The kidney is divided into:

- 1**Renal Cortex**: Outer layer.
- 2**Renal Medulla**: Inner region with renal pyramids and columns.
- 3**Papilla**: Tip of pyramid where urine drains into minor/major calyces.
- 4**Renal Capsule:** Protective outer covering.

Functions of the Urinary System (Mainly Kidneys)

1. Excretion of Waste Products: Removes nitrogenous wastes (urea, creatinine), drugs, and toxins via filtration, reabsorption, and secretion.

2. Conservation of Nutrients: Reabsorbs glucose, amino acids, and other valuable substances; can perform gluconeogenesis during fasting.

3. Regulation of Plasma Ion Levels: Controls sodium, potassium, chloride, and other ions in plasma by adjusting excretion/reabsorption.

4. Regulation of Blood pH: Adjusts excretion of hydrogen & bicarbonate ions to maintain acid-base balance, working with the **lungs**.

5. Regulation of Blood Volume and Pressure: Controls extracellular fluid volume; releases **renin** to activate RAAS, affecting blood pressure and sodium/water retention.

تقوم الخلايا المحببة (juxtaglomerular cells) في الكلى بإفراز الرينين عندما تستشعر انخفاض ضغط الدم، انخفاض نسبة الصوديوم (+Na) في الدم أو البول، بعد إفراز الرنين، الرينين يحوّل بروتينًا يُسمى الأنجيوتنسينوجين (Angiotensinogen) – الذي يُنتج في الكبد – إلى: أنجيوتنسين I (Angiotensin I) – غير نشط نسبيًا. في الرئتين، يقوم إنزيم يُسمى ACE (Angiotensin-Converting Enzyme) بتحويل أنجيوتنسين I إلى: أنجيوتنسين II (Angiotensin II) – وهو العنصر الفعّال. يعمل على انقباض الأوعية الدموية ← رفع ضغط الدم، تحفيز إفراز الألدوستيرون من الغدة الكظرية، يساعد على

إعادة امتصاص الصوديوم والماء في الكلى ← رفع حجم الدم والضغط، وتحفيز إفراز الهرمون المضاد لإدرار البول (ADH) ← لزيادة احتباس الماء

6. Regulation of RBC Production: Releases **erythropoietin** in response to hypoxia, stimulating red blood cell formation in bone marrow.
7. Urine Storage: Bladder stores urine produced by kidneys.
8. Urine Excretion: Urethra expels urine during micturition" urination".
9. **Hormone** Production/Secretion: Kidneys produce **calcitriol** (active vitamin D), **renin**, **prostaglandins/kinins** (modulate blood flow), and **erythropoietin**.

Kidney Blood Supply

- Receives about **25%** of cardiac output via the renal artery. مقدار كبير نسبه لحجمها
- ***Renal artery branches*** into ١**segmental**,٢ **interlobar**, ٣**arcuate**قوسية, and ٤**interlobular arteries.**
- **Afferent arteriole:** Brings blood to the glomerulus (capillary bed).
- **Efferent arteriole**: Drains glomerulus, then forms **peritubular** capillaries (cortical nephrons القشرية) **or vasa recta** (juxtamedullary nephrons).
- **Two** capillary beds in series (glomerulus للترشيح **and** peritubular/vasa recta لإعادة الإمتصاص وإفراز المواد) are crucial for **filtration** and **reabsorption**.

Nephron Structure and Types

- **Nephron**: **Functional unit** of the kidney (~1 million per kidney). يحدث فيه الإرتشاح والامتصاص والإفراز
- **Renal Corpuscle:** ١**Glomerulus** (capillaries) شبكة شعرات يحدث بها الارتشاح+٢ **Bowman's capsule** تجمع الراشح.
- **Renal Tubules**الأنابيب الكلوية: ١**Proximal convoluted tubule** الأنبوب الملتف القريب (PCT) امتصاص معظم الماء والأملاح والجلوكوز,

٢ **loop of Henle** (descendingللماء/ascendingفقط للأملاح limbs), ٣**distal convoluted tubule** (امتصاص اختياري وتنظيم للأيونات البعيد(DCT), ٤**collecting duct**(Transports urine toward the renal pelvis. Water reabsorption occurs here as needed, regulated by the hormone ADH).

Types of Nephrons:

- **Cortical Nephrons:** ~**85%**, mostly in cortex, **short** loop of Henle.
- **Juxtamedullary Nephrons:** ~15%, at cortex-medulla border, **long** loop of Henle, essential for urine concentration والحفاظ على توازن الماء والأملاح, surrounded by vasa recta الأوعية المستقيمة

Nephron Blood Supply & Urine Formation

- Blood Flow: **Afferent arteriole** → **glomerulus** (filtration) → **efferent** arteriole → **peritubular capillaries/vasa recta.**

❖ ***Urine Formation Mechanisms:***

1. **Filtration**: Passive process in glomerulus; filters plasma (except proteins/cells) into Bowman's capsule.
2. **Reabsorption**: Movement of substances **from** tubule back **into** blood.
3. **Secretion**: Active transport of substances **from** blood **into** tubule for excretion.
4. **Excretion**: Remaining filtrate is expelled as **urine**.

Clinical Notes

- Nephron loss is **irreversible;** about 10% lost per decade after age 40, but remaining nephrons compensate تحاول التعويض النفرونات المتبقيه.
- A person can live with **one healthy kidney.**

Special Notes

- Juxtamedullary nephrons and vasa recta are vital for the kidney's ability to **concentrate urine.**
- Prostaglandin inhibitors (e.g., COX inhibitors) can affect renal blood flow, especially in patients with kidney disease.

The renal corpuscle is the **initial blood-filtering unit** of the nephron, located in the kidney's cortex. It consists of two main parts: the glomerulus, a tuft of capillaries, and Bowman's capsule, a double-walled epithelial cup surrounding the glomerulus.

Structure:

- Bowman's capsule has an **outer parietal layer** of simple squamous epithelium and an **inner visceral layer** composed of podocytes, specialized cells with foot-like projections (pedicels) that wrap around glomerular capillaries to form filtration slits.
- The space between these layers, Bowman's space, collects the filtrate from blood plasma.
- The **glomerulus** is supplied by afferent arterioles and drained by efferent arterioles; its capillaries have fenestrated endothelium allowing selective filtration of plasma while retaining blood cells and large proteins.

- The filtration membrane includes fenestrated endothelium, a basement membrane acting as a selective barrier, and podocyte filtration slits.

Supporting cells:

- **Mesangial cells**, located between afferent and efferent arterioles, are contractile and regulate blood flow within the glomerulus.
- **Juxtaglomerular cells**, modified smooth muscle cells in the arteriole walls near the macula densa, form the juxtaglomerular apparatus with the macula densa, which regulates glomerular filtration rate via renal autoregulationUser text.

Renal tubules:

- After filtration, fluid passes through the proximal convoluted tubule (simple cuboidal with brush border), loop of Henle (thin squamous and thick cuboidal segments), distal convoluted tubule, and collecting ducts (with principal and intercalated cells involved in hormone response and pH regulation) .

Micturition:

- Urine flows from kidneys through ureters to the bladder, which stores 700-800 ml. Stretch receptors trigger a spinal reflex causing detrusor muscle contraction and relaxation of internal and external urethral sphincters, allowing voluntary control of urination.

In summary, the **renal corpuscle** filters blood plasma through a specialized filtration barrier formed by glomerular capillaries and podocytes, initiating urine formation. The juxtaglomerular apparatus regulates filtration rate, and the filtrate proceeds through renal tubules for further processing before excretion.

- الخلايا المجاورة للكبيبة **(Juxtaglomerular cells)** توجد في جدار الشُرَين الوارد (afferent arteriole) عند دخوله الكبيبة (glomerulus) في الكلية، وتحديدًا عند النقطة التي تلامس فيها هذه الشعيرة الجزء القريب من الأنبوب الملتف البعيد (distal convoluted tubule). وتكون هذه الخلايا جزءًا من جهاز يُدعى الجهاز المجاور للكبيبة (juxtaglomerular apparatus)، الذي يتكوّن من:

1. الخلايا المجاورة للكبيبة (Juxtaglomerular cells): خلايا عضلية ملساء متخصصة تُفرز الرينين (renin). 2 البقعة الكثيفة (macula densa): خلايا متخصصة من الأنبوب الملتف البعيد تراقب تركيز الصوديوم. 3 الخلايا خارج الكبيبة (extraglomerular mesangial cells): تعمل كوسيط بين الخلايا الأخرى.

وظيفة خلايا JG: إفراز الرينين استجابة لانخفاض ضغط الدم أو انخفاض تركيز الصوديوم، ما يؤدي إلى تنشيط نظام الرينين-أنجيوتنسين-ألدوستيرون لرفع ضغط الدم

Physiology 2

- The kidneys are the main organs of the renal system, with other organs serving as passageways or storage.
- Functions extend beyond filtration and waste elimination; **kidneys are also endocrine organs** (producing erythropoietin and calcitriol), regulate fluid and blood pressure (via renin), and control acid-base balance.

Basic Mechanisms of Urine Formation

Excretion = Filtration – Reabsorption + Secretion❗

1. **Filtration**: Passive لا تحتاج طاقة , variable, not very selective except for proteins; about **20%** of renal plasma flow is filtered.
2. **Reabsorption**: Highly variable حسب حاجة الجسم and selective; most electrolytes and nutrients are reabsorbed, while waste products are poorly reabsorbed.
3. **Secretion**: Highly variable; important for excreting certain waste products, drugs, and toxins rapidly.

Nephron Structure and Blood Supply

- Each kidney contains about 1 million nephrons, each with a **vascular** and a **tubular** part.
- Blood enters via the afferent arteriole into the glomerulus (a tuft of capillaries with fenestrations), surrounded by Bowman's capsule (a balloon-like structure).

Steps of Urine Formation

1. **Filtration**: 20% of plasma is filtered into Bowman's capsule, excluding proteins. This is a passive, size-selective process.
2. **Reabsorption**: Selective reuptake of important substances (e.g., amino acids, glucose) back into circulation.
3. **Secretion**: **Active** removal of substances (e.g., H+, toxins) that need rapid excretion.
4. **Excretion**: Final urine output after the above processes.

Filtration Membrane Structure

•Three main barriers:

1. **Fenestrated endothelial cells:** Negatively charged, size-limited pores.
2. **Basal lamina:** Negatively charged proteoglycans.
3. **Podocytes** with pedicels: Negatively charged, create filtration slits for small molecules.

- All barriers prevent protein filtration due to size and negative charge.

Handling of Water and Solutes

- **Water**: 180 L/day filtered, most reabsorbed, only ~1 L excreted.
- **Glucose**: 180 g/day filtered, **completely reabsorbed** under normal conditions; appears in urine if reabsorption capacity is exceeded (e.g., diabetes).
- **Creatinine**: 1.8 g/day filtered, **not** reabsorbed, **fully excreted** (may be slightly higher due to secretion).
- **Na+**: 25,560 mmol/day filtered, most reabsorbed; excretion varies with intake.

	• In all nephrons	• In all nephrons	• In all nephrons
	Filtration	reabsorption	excretion
L/day Water	180	179	1
Na+ mmol/day	25,560	25,410	150
Glucose gm/day	180	180	0
Creatinine gm/day	1.8	0	1.8

Renal Handling Scenarios

Four ways kidneys handle different substances:

- Filtration **only**: No natural substance fits exactly, but **creatinine** is close.
- Filtration & **partial reabsorption**: **Water, Na+, Cl-.**
- Filtration & **complete reabsorption: Glucose, amino acids.**
- Filtration & **secretion**: Toxins, exogenous substances, para-aminobenzoic acid.

Urinary System Functions

- Conserves nutrients: Prevents loss of glucose, amino acids, etc.
- Regulates plasma ion levels: Adjusts Na+, K+, Cl-, and other ions in urine.
- Gluconeogenesis: Kidneys can generate **glucose** from **glutamine**.

Sodium Intake and Excretion Experiment تجربة تناول الصوديوم

- Experiment: Increasing Na+ intake **10-fold** leads to gradual increase in Na+ excretion due to **hormonal regulation**ك الألدوستيرون.

Key points:

- Na+ is vital for fluid and blood volume homeostasis.
- Kidneys adjust excretion gradually, not instantly.
- When intake returns to normal, excretion decreases gradually as well.
- Demonstrates kidneys' robust ability to maintain electrolyte balance.

Factors Affecting Filterability

- **Size** and **charge** affect filterability across the glomerular membrane.
- Larger molecules = lower filterability.
- Positive charge = higher filterability. لان الغشاء الكبيبي شحنته سالبة
- Negative charge = lower filterability.
- **Dextran experiment**: Used to study **effects of size & charge on filtration.**

Clinical Application: Filtration Disorders

- **Edema**: Damage to glomerular capillaries increases permeability to proteins, raising Bowman's capsule colloid pressure, drawing more water into the capsule, reducing blood volume, and causing edema.
- **Albuminuria**: Normally, **albumin** (despite being smaller than the smallest pore) is **not** filtered due to negative charge. Loss of this charge (e.g., in **minimal change disease**) leads to albumin in urine.
- **Minimal Change Disease**: Loss of membrane charge (**not structure**) allows albumin leakage.

Physiology 3

Review of Previous Concepts

- Main Functions of Urinary System: Filtration, regulation, waste removal.
- Filtration Membrane Histology: Damage (**loss** of negative charges or podocytes) leads to protein leakage.
- Clinical Significance: **Early sign of renal disease** is **microalbuminuria** (**30–150** mg/day albumin in urine), important for early detection, especially in **diabetes** and **hypertension**.
- **Pregnancy**: **Proteinuria**/ albuminuria is significant, especially in preeclampsia. -> **hypertension**

Glomerular Filtration Function

- **Filtration Rate**: 180 L/day (entire plasma filtered ~**60 times/day**).
- Purpose: Efficient waste removal and rapid plasma regulation.
- **Kidney Blood Flow:** Receives 20% of cardiac output (CO), much higher than metabolic demand-necessary for filtration.

- **Filtrate Composition:** Similar to plasma, except for large proteins (mainly albumin) due to filtration barrier properties.

- **Filtration Fraction (FF)**: GFR" Glomerular Filtration Rate"125 mL/min | "Renal **P**lasma Flow" (RPF) 625 mL/min ≈ **20%.** من البلازما التي تصل الكليه يتم ترشيحها يقيّم كفاءة الكلية بالترشيح -> FF= GFR / RPF
- النسبة المتبقية (حوالي 80%) تمر عبر الشعيرات الدموية الكلوية دون أن تُرشَّح، وتذهب للأنابيب المحيطة لتتم فيها عمليات الامتصاص والإفراز.

***Determinants* of Glomerular Filtration**

Types of Pressure:

- **Hydrostatic Pressure:** Exerted by fluids.
- **Oncotic (Colloid) Pressure**: Exerted by plasma proteins.

Net Filtration Pressure (NFP)

Calculation:

- **NFP = (Glomerular Hydrostatic Pressure + Bowman's Capsule Oncotic Pressure) – (Bowman's Capsule Hydrostatic Pressure + Glomerular Oncotic Pressure)**

Example: (60 + 0) – (18 + 32) = 10 mmHg (drives filtration). هذا يعني أن هناك ضغطًا صافياً مقداره 10 ملم زئبقي يدفع السائل من الدم إلى محفظة بومان، ما يسمح ببدء تكوين البول

- Physiological Impact: Filtration is directly proportional to NFP.

✓ كلما زاد NFP، زاد معدل الترشيح الكبيبي (GFR) والعكس صحيح.

Renal Blood Flow Calculations

- Plasma is **55%** of blood.
- Renal Blood Flow: **RBF = RPF / 0.55** ≈ 1140 ml/min.
- Kidney receives 20% of Cardiac output for normal GFR.

Importance of Normal GFR

- **High GFR**: Excessive loss of needed substances and water.
- **Low** GFR: Inefficient waste removal, possible reabsorption of wastes.
- **Homeostasis**: GFR must be tightly regulated.

Filtration Coefficient (Kf)

- Definition: **GFR = NFP × Kf.**

أي أن GFR يتناسب طرديًا مع Kf: إذا زاد Kf، زاد GFR (طالما أن NFP ثابت).

- Kf in Kidneys: ~12.5 ml/min/mmHg (much higher than other tissues).
- Reasons for High Kf❓: Large surface area, high permeability, high renal blood flow.

- Pathological Changes: Diabetes, hypertension, glomerulonephritis can reduce Kf by damaging the membrane.
- Kf is **not** physiologically regulated but can change in disease. نتيجة تغيرات هيكلية بالكبيبة و فقدان بالمساحة

Bowman's Capsule Hydrostatic Pressure

- **Not** a physiological regulator of GFR.
- *Pathological* Increase: **Obstruction** (stones, tumors) increases pressure, reduces GFR.

Glomerular Capillary Oncotic Pressure

Factors:

- **Arterial oncotic pressure** (depends on albumin).
- Increases from afferent to efferent end due to filtration.
- **F**iltration **F**raction (FF): Higher FF increases oncotic pressure يزداد فقدان الماء من الشعيرات ويزيد تركيز البروتين فيرتفع الضغط.
- **Not** a physiological regulator of GFR, but changes with GFR/RPF.

إذا انخفض RPF (تدفق البلازما)، فإن FF يرتفع، ما يؤدي إلى زيادة الضغط، وبالتالي يقلل GFR، وإذا زاد RPF، فإن FF يقل، فيقل الضغط الأونكوبي، مما يسمح بزيادة GFR.

Glomerular Hydrostatic Pressure (PG)

- **Main physiological regulator of GFR.** ❗
- Affected by: **Mean arterial blood pressure.**
- **Autoregulation**: Between 60–140 mmHg, PG and GFR remain constant due to kidney's intrinsic mechanisms.

عضلية (Myogenic response): تتفاعل الأوعية مع التمدد أو الانقباض، و(Tubuloglomerular feedback): تُراقب الكلية تركيز الصوديوم وتعدّل قطر الشريان الوارد

- Loss of Autoregulation: In kidney disease, GFR becomes dependent on arterial pressure.

Effect of Arteriolar Resistance

- **Afferent Arteriole Constriction**: Decreases PG, RBF, and GFR.
- **Efferent Arteriole Constriction**: Increases PG (up to a point), decreases RBF.

- Kidney Adjusts Resistance: Main method for physiological GFR regulation❗ .

Effect	Afferent Arteriole Constriction	Efferent Arteriole Constriction
Glomerular Pressure (PG)	Decreases	Increases (then decreases if severe)
Renal Blood Flow (RBF)	Decreases	Decreases
Glomerular Filtration Rate (GFR)	Decreases	Increases slightly, then decreases

Autoregulation and Urine Output

- GFR and RBF: **Plateau** (stable) between 60–140 mmHg arterial pressure.
- Urine Output لا يبقى ثابتاً بل يرتفع بارتفاع الضغط : Increases with blood pressure (**no** plateau), due to RAAS يتم تثبيطه عند ارتفاع ضغط الدم & reabsorption mechanisms-> يقل امتصاص الماء والصوديوم ويزيد طرحهما بالبول.

Determinant	Physiological Regulator?	Pathological Impact?	Notes
Net Filtration Pressure (NFP)	Yes	Yes	Main driver of filtration
Filtration Coefficient (Kf)	No	Yes	Changes in disease, not physiologically regulated
Bowman's Capsule Hydrostatic Pressure	No	Yes	Increases with obstruction
Glomerular Capillary Oncotic Pressure	No	Yes	Increases with FF, not directly regulated
Glomerular Hydrostatic Pressure (PG)	Yes	Yes	Main physiological regulator
Arteriolar Resistance	Yes	Yes	Adjusts GFR via afferent/efferent arterioles

Physiology 4

Afferent and Efferent Arteriolar Resistance & GFR

- **Afferent Arteriole:** Increased resistance (constriction) ↓ reduces blood flow into the glomerulus, ↓ decreasing glomerular filtration rate (GFR).
- **Efferent Arteriole:** Constriction has a **bi**phasic effect:
- **Moderate** increase in resistance ↑ raises GFR due to increased glomerular hydrostatic pressure.

مثل أنك تضيق مخرج خزان ماء قليلاً، فيرتفع الضغط داخله فيدفع الماء بقوة أكبر.

- **Severe** increase causes ↓ GFR to decrease because the resulting high oncotic pressure (from retained proteins) overcomes the hydrostatic pressure, reducing net filtration.

- يصبح الخروج من الكبيبة صعب جدًا.
- يتباطأ تدفق الدم بشكل كبير ← فيبقى لفترة أطول في الكبيبة.

- هذا يؤدي إلى زيادة تركيز البروتينات (لأن الماء يُرشّح والبروتين لا) ← فيرتفع الضغط الأونكوبي الكبيبي.
- هذا الضغط يسحب السائل للداخل ويُعارض الترشيح.
- النتيجة: ينخفض GFR بالرغم من أن الضغط الهيدروستاتيكي قد يكون ما زال مرتفعًا.

- Both types of constriction **decrease** overall renal blood flow (RBF) because they impede blood flow.

Determinants of GFR

GFR is determined by:

- Hydrostatic pressure in glomerular capillaries (**PG**)
- Oncotic (colloid osmotic) pressure in glomerular capillaries (ΠG)
- Bowman's capsule pressure (PB)
- Filtration coefficient (**Kf**)
- Filtration fraction (**FF**) = GFR / Renal Plasma Flow (RPF)
- **Resistance in afferent** (RA) and **efferent** (RE) arterioles directly affects GFR.

Renal Blood Flow (RBF) & **Oxygen Consumption**

- High RBF is necessary to support high GFR.
- Most renal oxygen consumption is linked to active sodium reabsorption in renal tubules, not to the metabolic needs of kidney tissue itself.

Control of GFR and RBF: Mechanisms

- **Neurohumoral** Control: Involves systemic hormones and nerves.
- **Local** (**Intrinsic**) Control الأهم : Autoregulation within the kidney is the most important for maintaining stable GFR and RBF.

➢ ***Neurohumoral Regulation***

1. **Sympathetic** Nervous System/**Catecholamines**:

- Strong activation (e.g., severe hemorrhage) **increases** both afferent and efferent resistance, with a **greater effect on afferent**, leading to decreased GFR and RBF.
- Mild activation increases both resistances equally, so GFR remains **un**changed.

2. **Angiotensin II:**

- Released in response to low blood pressure **or** low sodium.
- Preferentially constricts the **efferent arteriole,** increasing GFR (or preventing its fall) and raising systemic blood pressure.
- Net effect: Restores GFR to normal if it was decreased.❗

3. **Prostaglandins**:

- Cause **vasodilation**, especially of the **a**fferent arteriole.
- Increase RBF and GFR; act as protective factors during conditions that threaten GFR (e.g., volume depletion).
- **NSAIDs** inhibit prostaglandin synthesis, potentially lowering GFR- important in patients with already compromised renal function❗ خطير عليهم

4. **Endothelial-Derived Nitric Oxide** (EDRF/NO):

- Vasodilates **a**fferent arteriole, increasing RBF and GFR.
- Deficiency (e.g., in atherosclerosis) increases risk of excessive GFR reduction during stress.

5. **Endothelin**:

- Potent **vasoconstrictor**, especially of the **a**fferent arteriole, reducing GFR and RBF.
- Endothelin antagonists may help in certain kidney diseases.

Neurohumoral Effects:

Factor	Effect on RBF	Effect on GFR
Sympathetic/Catecholamines	↓	↓ or ↔
Angiotensin II	↓	↑ or ↔
Prostaglandins	↑	↑
EDRF (NO)	↑	↑
Endothelin	↓	↓

➢ **Local (Intrinsic)** Control/**Autoregulation**

1. **Myogenic Mechanism**:

- Smooth muscle in afferent arteriole contracts in response to increased pressure, preventing excessive increases in RBF and GFR.
- Protects glomerulus from damage due to high blood pressure.

2. **Tubuloglomerular Feedback** (**Macula Densa Feedback**):

- Macula densa cells in the distal tubule sense NaCl concentration.
- High NaCl (from increased GFR) triggers signals to constrict afferent arteriole, reducing GFR.
- Low NaCl stimulates **renin release**, activating RAAS and increasing GFR.
- This feedback loop helps keep GFR stable despite changes in blood pressure or flow.

Regulation of Renin Secretion

Stimulated by:

- Low perfusion pressure in afferent arteriole
- Increased sympathetic nerve activity ينشط مستقبلات بيتا ١
- Low NaCl delivery to macula densa
- Renin release leads to activation of angiotensin II, which helps restore GFR and blood pressure.

Renal Autoregulation in Practice

- Kidneys maintain stable GFR and RBF over a wide range of arterial pressures (about ~80–180 mmHg).
- Sudden changes in blood pressure cause rapid, temporary changes in GFR and RBF, but autoregulatory mechanisms restore them to normal within minutes, even if blood pressure remains abnormal.

Clinical Applications

- **NSAIDs** can lower GFR in patients at risk (volume depletion, heart failure, cirrhosis).
- **Endothelin antagonists** may help in certain renal pathologies.
- **Angiotensin II blockers** (e.g., ACE inhibitors) can impair GFR autoregulation, especially in patients with low renal perfusion.

Agent	Effect on GFR	Mechanism / Clinical Note
NSAIDs	↓ GFR	Inhibit prostaglandin synthesis → ↓ afferent arteriole dilation → ↓ renal blood flow & GFR.
Endothelin Antagonists	↑ GFR (in some cases)	Block vasoconstrictive effect of endothelin → may improve renal perfusion in certain diseases.
ACE inhibitors / ARBs	↓ GFR (in low perfusion states)	Inhibit angiotensin II → ↓ efferent arteriole constriction → ↓ glomerular pressure.

✓ GFR and RBF are tightly regulated by a combination of vascular resistance (afferent/efferent arterioles), neurohumoral factors (sympathetic, angiotensin II, prostaglandins, NO, endothelin), and intrinsic mechanisms (myogenic, tubuloglomerular feedback).

- The kidney's autoregulation is crucial for protecting against fluctuations in systemic blood pressure and maintaining stable filtration and excretion functions.
- Clinical interventions (drugs, disease states) affecting these pathways can significantly impact renal function.

Physiology 5

Renal Autoregulation and GFR

Angiotensin II Blockade:

- **ARBs** (Angiotensin Receptor Blockers) and **ACE inhibitors** impair the kidney's ability to autoregulate GFR (glomerular filtration rate).
- Normally, Ang II helps maintain a stable GFR despite changes in blood pressure by constricting **efferent** arterioles.
- Blockade leads to loss of this plateau in the GFR curve; renal blood flow may increase, but GFR regulation is lost.

Macula Densa Feedback Mechanism:

- A drop in arterial pressure leads to decreased GFR and less Na+/Cl- delivery to the macula densa.
- This triggers renin release, increasing Ang II, which constricts efferent arterioles and restores GFR.
- This mechanism normalizes GFR, not arterial pressure.

Other Factors Influencing GFR

- Fever/Pyrogens & Glucocorticoids: Increase GFR.
- Aging: GFR **decreases** by **10%** per decade after age 40 due to nephron loss.
- Hyperglycemia (Diabetes Mellitus): Increases GFR.
- Dietary Protein: High protein intake increases GFR; low protein decreases it.

Protein and Glucose Ingestion Effects

High-Protein Meals:

- **Increase** amino acids in blood, **reabsorbed** with Na+ in the proximal tubule.
- Less Na+ reaches macula densa, triggering feedback to decrease afferent arteriole resistance and increase GFR.

- ↓ وصول الصوديوم إلى البقعة الكثيفة (macula densa).
- البقعة الكثيفة تفسر هذا كأن الضغط الترشيحي منخفض ← تُرسل إشارة لتوسيع الشريان الوارد.

- النتيجة: ↑ GFR (معدل الترشيح الكبيبي).

Hyperglycemia:

- Similar mechanism as protein, with <u>increased glucose reabsorption decreasing Na+ at the macula densa</u>, **raising GFR.**

1. ↑ الجلوكوز في الدم → ↑ جلوكوز في الراشح الكبيبي (filtrate).
2. الجسم يحاول إعادة امتصاص الجلوكوز بسرعة في الأنبوب القريب.
3. هذا الامتصاص <u>يتم بمرافقة Na^+.</u> <u>SGLT"Sodium-Glucose Co-Transporters"</u>
4. النتيجة: كمية أكبر من Na^+ يتم امتصاصها مبكرًا.
5. Na^+ ↓يصل إلى الـ macula densa(وهي التي تراقب تركيز الصوديوم).
6. الماكولا دينسا تفسر هذا على أنه ↓ في GFR → فتقوم بتحفيز توسّع الشريان الوارد → ↑ GFR.

Importance of Autoregulation

Scenarios:

- Poor Autoregulation: Increases in arterial pressure cause parallel increases in GFR and massive urine output, risking dehydration.
- Good Autoregulation (No Adaptive Reabsorption): GFR changes less, but urine output still increases significantly.
- Good Autoregulation + Adaptive Reabsorption: Small changes in GFR cause minimal changes in urine output-ideal for homeostasis.

. **Urine Formation by the Kidneys: Tubular Reabsorption** and **Secretion**

Basic Mechanisms:

- **Ultrafiltration**: **Non**selective, filters ~180 L/day.
- **Re****absorption**: <u>Highly selective</u>, returns most filtered substances to blood; requires energy.
- **Secretion**: Moves waste from blood to tubule for excretion, often faster than filtration alone.
- **Excretion**: What remains in tubules becomes urine <u>(1-2 L/day).</u>

Mathematical Formula:

- Excretion = Filtration – Reabsorption + Secretion

Mechanisms of Tubular Reabsorption

➢ **Proximal Tubule Structure:**

- Lined with epithelial cells with brush border for increased surface area.
- **Na+/K+ ATPase** on basolateral membrane maintains low intracellular Na+, creating a gradient for Na+ reabsorption.

Routes of Reabsorption:

- **Para**cellular: Between cells via leaky tight junctions (allows water and ions).
- **Trans**cellular: Through cells, via channels or transporters (can be active **or** passive). Glucose,amino acids
- Solvent Drag: Water reabsorbed **para**cellularly can drag along cations like K+ and Ca2+. الماء بمر وبسحب معه أيونات

Osmosis and Water Reabsorption

Driven by Osmolarity:

- Reabsorption of solutes (especially Na+) lowers tubular osmolarity, driving water reabsorption by osmosis through **aquaporins** and **para**cellular routes.
- **Not** all nephron segments are equally permeable to water (e.g., distal tubule is **less** permeable).

Role of Sodium (Na+)

Key Transporter:

- Na+ is the principal cation in extracellular fluid and filtered fluid.
- Na+/K+ ATPase pump is essential for Na+ reabsorption and creates an electrical gradient.
- Na+ reabsorption drives reabsorption of other solutes and water.

Proximal Tubule Reabsorption

Extensive NaCl Reabsorption:

- About **70%** of filtered NaCl is reabsorbed here.
- **Active** transport is the **main mechanism.**
- Water follows Na+ by osmosis, both transcellularly and paracellularly.
- Solvent Drag: Water reabsorbed paracellularly drags other cations along.

The proximal tubule of the nephron is a critical site for reabsorption and secretion, handling about 65-70% of filtered water, sodium, chloride, potassium, bicarbonate, glucose, and amino acids.

Water and Solvent Drag

Water is reabsorbed isosmotically following solute reabsorption, creating an osmotic gradient that drives water movement. This water flow can drag along other cations like potassium and calcium, a process known as solvent drag.

Sodium Reabsorption

Approximately 70% of filtered sodium is reabsorbed here. Sodium enters epithelial cells via co-transporters and ion channels, then is pumped out basolaterally by the sodium-potassium ATPase, maintaining a low intracellular sodium concentration and electrochemical gradient that drives reabsorption.

Glucose and Amino Acid Reabsorption

Nearly all filtered glucose and amino acids are reabsorbed in the **proximal tubule.** **Glucose** reabsorption occurs **mainly via secondary active transport using sodium-glucose co-transporters (SGLT)** on the apical membrane, powered by the sodium gradient maintained by the sodium-potassium ATPase. Glucose then exits *basolaterally* through **GLUT** transporters by **facilitated** diffusion. Amino acids follow a similar secondary active transport mechanism.

Transport Maximum and Threshold

Glucose and amino acids have a transport maximum due to limited transporter numbers. When plasma glucose exceeds about 180 mg/dL, some nephrons reach saturation earlier, causing glucose to appear in urine (threshold). The full transport maximum is around 375 mg/min filtered load, beyond which glucose spills into urine, as seen in diabetes.

Hydrogen Ion Secretion

The **proximal tubule** also secretes hydrogen ions via a **sodium-hydrogen exchanger (NHE),** exchanging intracellular hydrogen for luminal sodium. This helps remove excess acid and maintain acid-base balance, contributing to acidic urine.

Chloride and Urea Reabsorption

Chloride is passively reabsorbed paracellularly driven by the negative potential created by sodium reabsorption. Water reabsorption concentrates urea in the tubular fluid, facilitating its passive reabsorption in the proximal tubule.

Summary

- The **proximal tubule reabsorbs** ~67% of filtered water, sodium, chloride, potassium, bicarbonate, and nearly 100% of glucose and amino acids (if below transport maximum).
- **Sodium-potassium ATPase** on the basolateral membrane is the key driver of reabsorption processes.
- **Secondary active transport** mechanisms couple sodium movement to glucose and amino acid reabsorption.
- Solvent drag enables water to carry along other ions like potassium and calcium.
- Transport maximum limits reabsorption of glucose and amino acids, leading to urinary excretion when exceeded.
- Hydrogen ions are secreted to maintain acid-base balance.
- **Chloride** and **urea** are passively reabsorbed following sodium and water reabsorption.

✓ Reabsorption and secretion are highly selective and energy-dependent processes essential for homeostasis.

- Sodium reabsorption is central to the movement of many other substances and water in the nephron.
- Diet, aging, and disease states (like diabetes) can significantly influence GFR and renal handling of solutes.

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1Changes in Concentration in the Proximal Tubule

- Solute Concentrations: The concentration of various solutes in the proximal tubule depends on their relative rates of reabsorption compared to water.
- **Ratio = 1:** Solutes like Na^+ and Cl^- are reabsorbed at the same rate as water.
- **Ratio > 1**: Solutes such as urea and creatinine are reabsorbed **less** than water, or not at all, leading to their concentration increasing along the tubule.
- **Ratio < 1**: Solutes like glucose, amino acids, and bicarbonate are reabsorbed more rapidly than water, so their concentration decreases.

• The concentration profile along the tubule reflects the **balance** between water and solute reabsorption.

2. **Loop of Henle**

Segments:

- **Thin Descending Limb**: Highly permeable to water (via aquaporins), not to solutes. About **15%** of filtered water is reabsorbed here due to the medullary osmotic gradient.
- **Thin Ascending Limb: Im**permeable to water, passive reabsorption of Na^+, K^+, and Cl^-.
- **Thick Ascending Limb: Im**permeable to water, active reabsorption of Na^+, K^+, Cl^- (about **25%** of filtered load), HCO_3^-, Ca^{2+}, and Mg^{2+}. Known as the "**diluting segment**." H^+ is secreted here.

Mechanisms

- **Active Transport: $Na^+/K^+/Cl^-$ cotransporter** (NKCC2) on the apical side and **Na^+/K^+ ATPase** on the basolateral side.
- **Furosemide** (Lasix): Blocks the NKCC2 channel, causing diuresis and potential hypokalemia.
- **Voltage Drag:** Backleak of K^+ creates a positive lumen voltage, driving paracellular reabsorption of cations (Mg^{2+}, Ca^{2+}, Na^+, K^+).

3. **Early Distal Tubule**

- **Diluting Segment:** Continues the dilution of tubular fluid due to active reabsorption of Na^+ and Cl^- via the Na^+/Cl^- cotransporter. Impermeable to water.
- **Thiazide Diuretics:** Inhibit the Na^+/Cl^- cotransporter, leading to increased sodium and water excretion (diuresis).
- **Macula Densa:** Part of the juxtaglomerular apparatus, involved in **tubuloglomerular feedback** for renal **autoregulation**.

4. **Late Distal Tubule** and **Collecting Duct**

Cell Types

Principal Cells:

- Na^+/K^+-ATPase (basolateral) and ENaC (apical): Reabsorb Na^+ and secrete K^+.
- **Aldosterone**: **Increases Na^+ reabsorption** and **K^+ secretion** by upregulating Na^+/K^+-ATPase and ENaC.
- Aldosterone Antagonists (e.g., spironolactone): Decrease Na^+ reabsorption, spare K^+ (potassium-sparing diuretics).
- ENaC Blockers (e.g., amiloride): Also spare K^+ by blocking Na^+ reabsorption.

Intercalated Cells:

- **Type A:** Secrete H^+ (via H^+-ATPase), reabsorb HCO_3^- (via HCO_3^-/Cl^- exchanger). Important for acid secretion and bicarbonate reabsorption.
- **Type B:** Secrete HCO_3^- and reabsorb H^+, important during **alkalosis**.
- **H^+/K^+-ATPase**: Exchanges H^+ and K^+ according to body needs.

Water Permeability

- **ADH** (Antidiuretic Hormone): Regulates water permeability by inserting aquaporins into cell membranes. Without ADH, these segments are **im**permeable to water; with ADH, they become permeable, allowing water reabsorption.

Urea Handling

- **Medullary Collecting Duct:** Becomes permeable to urea in the presence of ADH, **facilitating urea reabsorption** and contributing to the medullary osmotic gradient.

Summary

- **Proximal Tubule**: Bulk reabsorption of solutes and water.
- **Loop of Henle:** Countercurrent multiplication, water reabsorption (descending limb), solute reabsorption (ascending limb), creation of medullary osmotic gradient.
- **Distal Tubule:** Further dilution, active solute reabsorption, variable water permeability (depends on **ADH**).
- **Collecting Duct:** Fine-tuning of Na^+, K^+, H^+, and water reabsorption/secretion, regulated by **aldosterone** and **ADH**.

Key Points

- **Furosemide**: Inhibits NKCC2 in thick ascending limb (loop diuretic).
- **Thiazides**: Inhibit Na^+/Cl^- cotransporter in early distal tubule.
- **Aldosterone Antagonists** (Spironolactone): Block aldosterone effects in principal cells (potassium-sparing).
- **ENaC Blockers** (Amiloride): Block epithelial sodium channels in principal cells (potassium-sparing).

Acid-Base Regulation

- Type A Intercalated Cells: Secrete H^+, reabsorb HCO_3^- (combat **acidosis**).
- Type B Intercalated Cells: Secrete HCO_3^-, reabsorb H^+ (combat **alkalosis**).

Water Reabsorption and Concentration Changes

- In specific nephron segments, about 98% of filtered water is reabsorbed, leaving only 2% remaining in the tubule (1/50 of original filtrate).
- Solute concentration in tubular fluid changes depending on relative reabsorption of solutes vs. water; for example, inulin concentration increases if water is reabsorbed more than solutes.

Regulation of Tubular Reabsorption

- Multiple mechanisms regulate tubular reabsorption to maintain balance despite changes in filtration:
- Glomerulotubular Balance: Tubular reabsorption adjusts proportionally to changes in glomerular filtration rate (GFR) to keep reabsorption percentage stable, preventing large urine volume changes.
- Peritubular Physical Forces: Hemodynamic forces between tubule, interstitium, and peritubular capillaries influence reabsorption.
- Hormones: Aldosterone, angiotensin II, ADH, atrial natriuretic factor (ANF), and parathyroid hormone modulate reabsorption by regulating channels and transporters.
- Sympathetic Nervous System and Arterial Pressure (pressure natriuresis) also affect reabsorption rates.
- Osmotic factors contribute to the regulation.

Mechanisms of Tubular Reabsorption

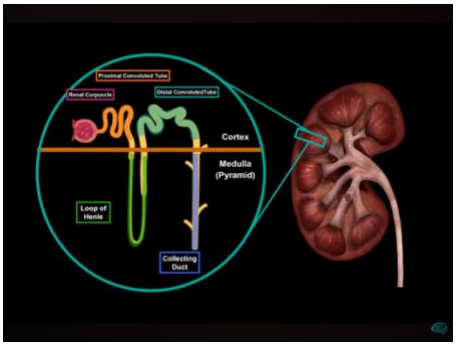
- Passive Transport: Movement of solutes down concentration gradients without energy.
- Active Transport: Energy-dependent transport against gradients, including:
- Primary active transport (e.g., Na+/K+ ATPase pump).
- Secondary active transport (e.g., Na+-glucose cotransport via SGLT2) relying on primary active transport gradients.
- Pinocytosis and Receptor-Mediated Endocytosis: Cells engulf fluids or proteins for reabsorption via vesicles.

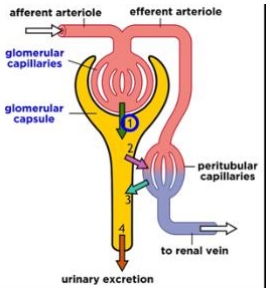
Phosphate Reabsorption in Proximal Tubule

- Proximal tubular phosphate (Pi) reabsorption is crucial for phosphate homeostasis and occurs via a secondary active Na-Pi cotransporter (type IIa) in the brush-border membrane.
- Regulation involves changes in transporter expression and membrane insertion/removal, influenced by hormones such as thyroid hormone, calcitonin, and lipophilic hormones.

Importance of Glomerulotubular Balance

- When GFR increases, tubular reabsorption increases proportionally to maintain urine volume and solute balance.
- Without this balance, increased GFR leads to decreased percentage reabsorption and increased urine output.





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Peritubular Capillary Reabsorption: The ***Driving Force***

- Reabsorption Process: After substances cross the tubular epithelium, they must enter the peritubular capillaries via **bulk flow** تدفق جماعي, driven by **hemodynamic forces.**

Main Forces:

Peritubular Capillaries:

- Hydrostatic pressure (-13 mmHg, opposes reabsorptionارتشاح)
- Oncotic pressure (+32 mmHg, favors reabsorption)

Interstitial Fluid: العكس

- Hydrostatic pressure (+6 mmHg, favors reabsorption)
- Oncotic pressure (-15 mmHg, opposes reabsorptionارتشاح)
- **Net Reabsorptive Pressure:** About +10 mmHg, favoring reabsorption.
- Clinical Note: If this pressure drops, reabsorption decreases, leading to fluid accumulation in the interstitial space and possible backleak into the tubule.

Calculation of Tubular Reabsorption and Secretion

Reabsorption Formula:

- **Reabsorption** = Filtration - Excretion
- **Filtration** = GFR × Plasma concentration (Ps)
- **Excretion** = **Urine** concentration (Us) × **Urine flow rate** (V)
- **Secretion** = Excretion **-** Filtration (when Excretion > Filtration)

Interpretation:

- If **filtered** load **>** excreted amount → net **re**absorption
- If **excreted** amount **>** filtered load → net secretion

Example: Sodium Handling

- Given: GFR = 100 ml/min, PNa = 140 mEq/L, Urine flow = 1 ml/min, Urine Na = 100 mEq/L

Calculations:

- Filtration Na = 14 mEq/min

- Excretion Na = 0.1 mEq/min
- Reabsorption Na = 13.9 mEq/min
- Conclusion: Net reabsorption of sodium, no net secretion.

الخطوة 1: حساب كمية الصوديوم المُرشّحة، نستخدم القانون:

Filtered Na = **GFR** × **PNa**

100 ml/min = 0.1 L/min: *L* إلى *GFR* نحوّل

Filtered Na = 0.1 L/min × 140 mEq/L = **14** mEq/min

الكلى تُرشّح 14 mEq من الصوديوم في الدقيقة.

الخطوة 2: حساب كمية الصوديوم المطروحة في البول، نستخدم القانون:

Excreted Na = **Urine Flow** × **Urine Na**

Excreted Na = 0.001 L/min × 100 mEq/L = **0.1** mEq/min

فقط 0.1 mEq من الصوديوم يُطرح في البول بالدقيقة.

الخطوة 3: حساب الصوديوم المعاد امتصاصه

Reabsorbed❓ = **Filtered** - ***Excreted***

= 14 - 0.1 = 13.9 mEq/min.الكلى تعيد امتصاص معظم الصوديوم

Transport Maximum (Tm) & Threshold

- هو الحد الأقصى الذي تستطيع النبيبات الكلوية إعادة امتصاص مادة معينة عنده
- Definition: Some substances have a maximum reabsorption rate due to **transporter saturation.**
- **Tm**: Point where all nephrons are saturated; excess appears in urine ذا زاد عن هذا الحد بظهر بالبول.
- **Threshold**: Tubular load at which some nephrons start to excrete the substance.
- Examples: Glucose, amino acids, phosphate, sulfate, urate, lactate.

- Note: Some secreted substances also display Tm.

Glucose Example: Tm and Threshold

- Case: **Uninephrectomized diabetic** patient, GFR = 90 ml/min, Plasma glucose = 2 mg/ml, Tm = 150 mg/min.

Calculation:

- Filtered load = 180 mg/min
- Tm = 150 mg/min
  - حساب الكمية المرشحة ، filterd load

Filtered load = GFR × Plasma glucose

90 ml/min × **2** mg/ml = **180** mg/min نقارنها مع قيمة Tm= 150 <-

إذاً الكلية تستطيع فقط إعادة امتصاص 150 mg/min الباقي يُطرح في البول:

Excreted glucose = 180 – 150 = **30** mg/min يطرح

- Excreted glucose = (filtered load – Tm)
- Clinical Relevance: **Glucosuria** occurs when **filtered load exceeds Tm**, **not due to secretion.**

Peritubular Capillary Reabsorption Equation

Formula:

- **Reabsorption** = **Net Reabsorptive Pressure** × **Filtration Coefficient** (Kf)
- Example: 10 mmHg × 12.4 ml/min/mmHg = 124 ml/min

Determinants:

- **Kf** (filtration coefficient)
- **Hydrostatic** and **oncotic pressures**

Determinants of Renal Reabsorption

- Hydrostatic Pressure: Increased pressure decreases reabsorption.
- Oncotic Pressure: Increased plasma proteins or filtration fraction increases reabsorption.

Afferent/Efferent Arteriolar Resistance:

- **Afferent:** ↑ resistance → ↓ glomerular/peritubular hydrostatic pressure → ↑ reabsorption
- **Efferent:** ↑ resistance → initially ↑ GFR, but ↓ peritubular hydrostatic pressure → ↑ reabsorption
- Key Equation: **Filtration Fraction** (**FF**) = **GFR** / **RPF** (renal plasma flow)

✓ ↑Afferent/Efferent Resistance → ↓RPF → عكسيه↑FF → ↑Oncotic Pressure → ↑Reabsorption

Effect of Hydrostatic/Colloid Osmotic Pressure

- Increased hydrostatic pressure or decreased oncotic pressure in peritubular capillaries **reduces reabsorption** ⬇. بزيد الارتشاح
- **Backleak**: Fluid may leak back into the tubule, reducing net reabsorption.

Hormonal Regulation: **Aldosterone**

- Action Sites: **Late** distal tubule, cortical and medullary collecting ducts (principal and intercalated cells).

Principal Cells:

- ↑ **Na+ re**absorption (ENaC channels and Na/K ATPase)
- ↑ K+ secretion

Intercalated Cells:

- ↑ **H+** secretion (acid-base regulation)
- Stimuli for Secretion: Angiotensin II (main), hyperkalemia (lesser extent)

Aldosterone Disorders

- ⬆ Excess Aldosterone (**Conn's Syndrome**):
- Na+ retention, hypokalemia, alkalosis, hypertension
- ⬇ Aldosterone Deficiency (**Addison's Disease**):
- Na+ wasting, hyperkalemia, hypotension

Control of Aldosterone Secretion

- Factors increasing secretion: **Angiotensin II** (main), hyperkalemia.

Renin-Angiotensin-Aldosterone System (RAAS) Blockade

- Drugs like **ACE inhibitors** (captopril, benazepril, ramipril), angiotensin II receptor blockers (**ARBs** such as losartan, candesartan, irbesartan), and direct renin inhibitors (aliskiren) **reduce angiotensin II levels.**
- This leads to **decreased aldosterone secretion**, resulting in less sodium and water reabsorption in the kidneys, causing **natriuresis** (sodium loss) and **diuresis** (water loss).
- Angiotensin II normally constricts efferent arterioles to maintain glomerular pressure; blocking it dilates these arterioles, increasing renal blood flow and reducing sodium/water reabsorption.
- Overall, **RAAS blockers lower** blood volume and blood pressure.

Antidiuretic Hormone (ADH) عند ارتفاع تركيز الأملاح يُحفز افرازه

- **ADH** (**vasopressin**) is synthesized in the hypothalamus and secreted by the posterior pituitary.
- It increases water permeability in the distal tubules and collecting ducts by inserting **aquaporin-2 channels**, allowing water reabsorption and urine concentration.
- ADH secretion is stimulated by **increased plasma osmolarity** detected by hypothalamic osmoreceptors.
- It plays a critical role in controlling extracellular fluid osmolarity.
- **Disorders** include **SIADH** (excess ADH causing hyponatremia انخفاض الصوديوم بالدم) and central **diabetes insipidus** (ADH deficiency causing **polyuria** and **hypernatremia**).

Atrial Natriuretic Peptide (ANP) عند ارتفاع الضغط أو حجم الدم

- Secreted by cardiac atria in response to stretch from **increased blood volume.**
- ANP **inhibits** sodium reabsorption in the nephron, suppresses renin and aldosterone release, **dilates afferent arterioles** to increase GFR, promoting natriuresis and diuresis.
- Acts as a **natural antihypertensive** to reduce blood volume.

Parathyroid Hormone (PTH)

- Released in response to **low extracellular calcium.** ⬇️

- Increases renal calcium reabsorption, enhances calcium absorption from the gut, decreases phosphate reabsorption, and increases magnesium reabsorption.
- Helps maintain extracellular calcium levels.

Sympathetic Nervous System Effects عند انخفاض حجم الدم أو التوتر

- Stimulates sodium reabsorption **directly** via **alpha-adrenergic receptors** on renal tubules.
- Promotes renin release, increasing angiotensin II and aldosterone.
- High sympathetic activity causes afferent arteriole vasoconstriction, reducing GFR and promoting fluid retention.
- Overall, it preserves blood volume and pressure during stress or volume depletion.

Pressure Natriuresis

- Increased arterial pressure **raises peritubular capillary hydrostatic pressure** and renal plasma flow, opposing sodium reabsorption.
- Elevated pressure inhibits renin and aldosterone secretion over time, enhancing sodium and water excretion.
- In **hypertensive patients**, RAAS is downregulated, so *pressure natriuresis is more pronounced.*

Osmotic Effects on Water Reabsorption

- Water reabsorption depends on osmotic gradients; unreabsorbed solutes like glucose (in diabetes mellitus) or mannitol دواء مدر للبول (osmotic diuretic) increase tubular osmolarity.

هذه المواد تبقى في الأنابيب وتجذب الماء نحوها، فلا يُمتص الماء بشكل طبيعي حتى لو كان الـADH موجودًا (الذي عادةً يساعد على امتصاص الماء).

- This reduces water reabsorption despite ADH presence❗, causing diuresis and water loss.
- This principle is exploited therapeutically with osmotic diuretics.

Physiology 8

Clearance: Definition and Importance

- **Clearance**: The rate at which substances are removed from plasma by the kidneys.

- Renal clearance: Volume of plasma completely cleared of a substance per minute.

Key points:

- Clearance is the kidney's most vital function.
- GFR is a constant property of healthy kidneys, indicating plasma filtered per unit time.
- Clearance varies by substance, depending on filtration, reabsorption (decreases clearance), and secretion (increases clearance).

Clearance Technique

- Formula:

Cs = (**Us** × V) / **Ps**

- Cs: Clearance of substance S
- Us: Urine concentration of S
- V: Urine flow rate
- Ps: Plasma concentration of S
- Interpretation: Renal clearance is the volume of plasma cleared of a substance per minute.

Clearance Values for Different Substances

Substance	Clearance (ml/min)
Glucose	0
Albumin	0
Sodium	0.9
Urea	70
Inulin	125
Creatinine	140
PAH	600

- **Glucose** and **albumin** have **zero clearance** (normally reabsorbed or not filtered).
- **Inulin's** clearance equals GFR.
- **PAH** clearance approximates renal plasma flow (RPF). لأنه تقريبا كله يزال من البلازما عندما يعبر من الكلية

GFR and RPF Calculations

- **Inulin**: **Ex**ogenous تحقن بالجسم, freely filtered, **not** reabsorbed/secreted clearance **equals GFR.**
- **Creatinine**: Endogenous, used clinically to estimate GFR (less precise but convenient).

- **PAH** (Para-Aminohippuric Acid): Syntheticمصنع, freely filtered and secreted, used to **estimate RPF.**

Inulin Clearance = GFR (Calculation Example)

- GFR = (**Uinulin** تركيزه بالبول× **V**) / **Pinulin** تركيز الإينولين بالبلازما

Example:

- Pinulin = 1.0 mg/100ml
- Uinulin = 125 mg/100ml
- V = 1.0 ml/min
- GFR = 125 ml/min

Estimating Renal Plasma Flow (RPF)

- **PAH** clearance **≈ RPF**
- PAH is filtered and actively secreted; nearly **all** PAH entering kidneys is excreted.
- Theoretical Maximum: If a substance is completely cleared, clearance = RPF.

Effective vs Actual Renal Plasma Flow

- **Actual RPF**الحقيقي: Total plasma through all kidney regions.
- **Effective RPF**الفعال (**E**RPF): Plasma through nephrons where PAH is fully cleared (mainly cortex).
- About 10% of PAH escapes secretion; ERPF underestimates actual RPF by ~10%.

- EPAH (extraction ratio) ≈ 0.9 (90% extracted)
- **Actual RPF** = **E**RPF / **E**PAH

مثال: إذا كان ERPF = 600 ml/min و EPAH = 0.9

فإن: Actual RPF=667

Calculating Tubular Reabsorption and Secretion

- Reabsorption: Filtration - Excretion
- Filtration = GFR × Ps
- Excretion = Us × V
- Secretion: Excretion - Filtration

Clearance Conceptual Questions

- **Max possible clearance** = Renal plasma flow (RPF), not GFR.
- GFR is only the filtered fraction (~20% of RPF); substances that are also secreted can have clearance rates exceeding GFR.

Interpreting Clearance Values

Substance	Clearance (ml/min)
Inulin	125
PAH	600
Glucose	0
Sodium	0.9
Urea	70

نقارن تصفية أي مادة (Cx) بتصفية الإينولين (Cinulin)، لأن الإينولين يُرشح فقط، ولا يُعاد امتصاصه أو يُفرز

- If Cx < Cinulin: Indicates reabsorption.
- If Cx = Cinulin: **Only filtration**, no reabsorption/secretion.
- If Cx > Cinulin: Indicates secretion.
- Creatinine clearance is used to estimate GFR in practice.

Effects of Reduced GFR on Creatinine

If GFR drops by 50%:

- Plasma creatinine doubles ↑. لأن الكلى لم تعد تطرح نفس الكمية من الكرياتينين، يتراكم في الدم

- Creatinine excretion rate returns to normal after a transient drop, as plasma creatinine increases.
- Steady State: Creatinine production = excretion, even with reduced GFR.

Clinical Use: Estimating GFR

- Plasma creatinine **inversely** reflects GFR.
- eGFR equations (not for memorization) are used in clinical practice.
- **Chronic Kidney Disease** (CKD): GFR estimation is used to stage CKD.

✓ Clearance is a measure of kidney function, reflecting how efficiently substances are removed from plasma.

- **GFR** is best measured by inulin clearance but estimated clinically using creatinine.
- **PAH** clearance is used to estimate renal plasma flow, with correction for incomplete extraction.
- Changes in GFR can be tracked using plasma creatinine.

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Control of Extracellular Osmolarity (NaCl Concentration)

- **ADH** (Antidiuretic Hormone): **Main controller of ECF osmolarity,** increases water reabsorption in the **d**istal convoluted tubules and collecting ducts, concentrating urine.
- **Thirst Center**: Osmo-receptors in the hypothalamus sense high osmolarity, stimulating thirst and ADH release, which together correct osmolarity by increasing water intake and reducing water output.

Urine Concentration and Dilution

- Maximal Urine Concentration: **1200-1400** mOsm/L (specific gravity ~1.030)
- Minimal Urine Concentration: **50-70** mOsm/L (specific gravity ~1.003)
- Urine concentration varies widely based on the body's needs and homeostasis.

Mechanisms of Water Diuresis (Dilute Urine Formation) تخفيف التركيز

After Water Intake:

- Urine osmolarity drops, urine flow rate increases, but plasma osmolarity changes only slightly.
- Selective excretion of water without significant change in solute excretion.
- ADH is inhibited بعد تخفيف التركيز, making distal tubules and collecting ducts impermeable to water, resulting in large volumes of dilute **urine**.

Mechanism of Dilute Urine Formation

1. **Filtration in Bowman's Capsule:** Osmolarity equals plasma (**300** mOsm/L).
2. **Proximal Tubule: 70%** of water and solutes reabsorbed; osmolarity unchanged.
3. **Loop of Henle:**

- **D**escending Limb: Permeable to **water**, water reabsorbed, urine becomes concentrated.
- **A**scending Limb: **Im**permeable to water, active solute reabsorption, urine becomes diluted.

4. **Distal Convoluted Tubule** and **Collecting Ducts:** In absence of ADH, these remain **im**permeable to water, further diluting urine to as low as 50 mOsm/L.

Relationship Between Urine Osmolarity and Specific Gravity

- Specific gravity rises by 0.001 for every 35-40 mOsm/kg increase in osmolarity.
- Not always directly proportional, as specific gravity is affected by **molecular weight of solutes** (e.g., glucose, proteins).

Mechanism of Concentrated Urine Formation

1. Continuous solute reabsorption (dilutes tubular fluid initially)
2. Presence of ADH (increases water reabsorption via aquaporins)
3. High osmolarity in the renal medullary interstitium (provides the gradient for water reabsorption)

Stepwise Process:

- Descending limb: Water reabsorbed, **urine concentrated.**
- Ascending limb: Solutes reabsorbed, **urine diluted.**
- Distal tubule and collecting duct: With ADH, water reabsorbed, concentrating urine up to 1200 mOsm/L.
- Urea reabsorption in the collecting duct further increases medullary osmolarity, enhancing water reabsorption.

Obligatory Urine Volume

- Definition: **Minimum urine volume** required to dissolve and excrete daily solute load.

Calculation Example:

-If max urine osmolarity is 1200 mOsm/L & 600 mOsm solute must be excreted:

- Obligatory urine volume = **600** mOsm / **1200** mOsm/L = 0.5 L/day

-If concentrating ability impaired (e.g., max 300 mOsm/L):

- Obligatory urine volume = **600** mOsm / **300** mOsm/L = 2.0 L/day ⬆
- Clinical Relevance: In **renal disease**, obligatory urine volume **increases** due to **impaired concentrating ability.**

Factors Contributing to High Medullary Osmolarity (Countercurrent Multiplier)

- Active transport of Na+, Cl-, K+ from **thick ascending limb** of Henle into medullary interstitium.
- Active ion transport from medullary collecting ducts.
- Passive urea diffusion from medullary collecting ducts (especially with high ADH).
- Minimal water diffusion into medullary interstitium (maintains high osmolarity).
- Low medullary blood flow prevents solute washout.

Countercurrent Mechanisms

- ❖ **Countercurrent Multiplier** (**Loop of Henle**):
  - Active solute transport in **a**scending limb creates osmotic gradient.
  - Water reabsorption in **d**escending limb equalizes osmolarity with interstitium.
  - Repeated cycles "**multiply**" the gradient, raising medullary osmolarity.
- ❖ **Countercurrent Exchanger** (**Vasa Recta**):
  - Maintains medullary gradient by minimizing solute washout while allowing exchange of water and solutes.

Net Effects of Countercurrent Multiplier

1. More solute than water is added to the medulla (**solute trapping**).
2. Ascending loop fluid is diluted; interstitium is concentrated.
3. Most water reabsorption occurs in cortex (proximal/distal tubules).
4. The horizontal solute gradient is multiplied by countercurrent flow.

Role of Urea

- Urea recycling from medullary collecting duct into interstitium is crucial for maintaining high medullary osmolarity, especially during high ADH states, enhancing the kidney's ability to concentrate urine.

Tubular Characteristics

Segment	Permeability to Water	Permeability to Solutes	ADH Sensitivity
Proximal Tubule	High	High	No
Descending Limb (Henle)	High	Low	No
Ascending Limb (Henle)	Low	High	No
Early Distal Tubule	Low	High	No
Late Distal/Collecting Duct	Variable (ADH)	High	Yes

Tubule Segment	Active NaCl Transport	Permeability H_2O	Permeability NaCl	Permeability Urea
Proximal	++	+++	+	+
Thin Desc.	0	+++	+	+
Thin Ascen.	0	0	+	+
Thick Ascen.	+++	0	0	0
Distal	+	+ADH	0	0
Cortical Coll.	+	+ADH	0	0
Inner Medullary Coll.	+	+ADH	0	+++

✓ This is achieved through tightly **regulated mechanisms** involving ADH, the countercurrent system, and urea recycling.

- ✓ Understanding these processes is essential for diagnosing and managing disorders of water and electrolyte balance.> diabetes insipidus,dehydration

    - Urea is a major nitrogen waste product formed from protein metabolism; its concentration in urine depends on dietary protein intake, affecting urine concentrating ability (**low protein → low urea → reduced concentration**).
    - After plasma filtration, urine initially contains 100% of filtered urea. About **50%** is passively reabsorbed in the descending loop of Henle, but high urea concentration in the medullary interstitium causes urea to diffuse back into the urine, restoring its concentration to near 100% in the descending limb.
    - The thick ascending limb, distal tubule, and cortical collecting duct are **im**permeable to urea, preserving urea concentration in the urine as it passes through these cortical segments.

    - In the medullary collecting duct, urea **permeability is high** (especially under antidiuretic hormone, **ADH**), allowing about 80% of urea to be reabsorbed into the medullary interstitium via facilitated urea transporters (UT-A1, UT-A3), increasing medullary osmolarity and aiding water reabsorption.
    - The reabsorbed urea recirculates back into the descending limb of Henle, maintaining a high urea concentration in the medulla, which is essential for creating the corticopapillary osmotic gradient that drives water reabsorption and urine concentration.

    - **ADH** regulates urea permeability by activating urea transporters (UT-1/UT-A1), enhancing urea recycling and water retention during antidiuresis; low ADH reduces urea reabsorption, promoting water loss.
    - Urea transporters vary along nephron segments: UT1 in terminal inner medullary collecting ducts, UT2 and UT3 in descending thin limbs and vasa recta, respectively, coordinate urea recycling and retention.

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Factors Contributing to Urine Concentrating Capability

- **High ADH:** Most important; increases water reabsorption in late distal tubules and collecting ducts.
- **High Osmolarity of Medullary Interstitium**: Achieved by:
    - Chloride buildup via countercurrent multiplier (**active** process).
    - Urea buildup and recirculation (**passive** process), contributing 40-50% of medullary osmolarity.

Urea Recirculation and Its Importance

Urea Handling:

- Filtered at glomerulus; about 50% reabsorbed in proximal tubule.

- Urea concentration increases in the proximal tubule due to more water reabsorption than urea.
- In the thin descending limb of the loop of Henle, water is reabsorbed, further concentrating urea.
- Urea is **secreted** into the tubular fluid from the interstitium, especially in the inner medullary region via **UTA2 transporters**.
- Thick ascending limb, early distal tubule, and cortical collecting tubules are **im**permeable to urea.
- In the inner medullary collecting duct (especially with high ADH), urea permeability increases (**UTA1**, **UTA3** transporters), leading to passive reabsorption into the medullary interstitium.
- Only about **20%** of filtered urea is excreted; **80% is reabsorbed** and recirculated.
- Significance: Urea recycling is crucial for conserving body fluid. Without it, more water would be needed to excrete urea, increasing obligatory urine output. يزيد الجفاف والحاجة لشرب الماء

Vasa Recta & Medullary Osmolarity

- Function: Vasa recta preserve **hyperosmolarity** of the renal medulla as countercurrent exchangers (not multipliers).
- Blood Flow: **Low** (1-2% of total renal blood flow), preventing solute washout.

Mechanism:

- **Descending limb**: Blood becomes concentrated as solutes enter, and water exits.
- **Tip**: Blood is most concentrated.
- **Ascending limb:** Solutes leave, water re-enters, blood becomes less concentrated. diluted
  - ✓ Vasa recta maintain but do not create the medullary osmotic gradient.

Effect of ADH on Tubular Fluid Osmolarity

- ADH Effect: Increases water permeability in late distal tubule, cortical, and medullary collecting ducts, concentrating urine up to 1200 mOsm/L and reducing urine volume.
- **Proximal Tubule:** 65% reabsorption, isosmotic.
- **Descending Loop:** 15% reabsorption, osmolarity increases.
- **Ascending Loop & Early Distal: No** water reabsorption, osmolarity decreases. بل يمتص الأملاح
- **Late Distal & Collecting Tubules:** ADH-dependent water reabsorption, osmolarity increases. ❗ اعلى تركيز

Free Water Clearance (CH_2O) كميه الماء الخالي من المذابات "مخفف"

Definition: Rate of solute-free water excretion.

Formula: $CH_2O = V - (Uosm \times V / Posm)$

- V = urine flow rate
- Uosm = urine osmolarity
- Posm = plasma osmolarity

Interpretation:

- **Positive** CH_2O: Dilute urine (water excreted in excess).
- **Negative** CH_2O: Concentrated urine.

الكلى تُفرز ماء زائد → الجسم يتخلص من ماء حر.	البول مخفف (Uosm < Posm)	موجب CH_2O
الكلى تحتفظ بالماء → الجسم يعاني من نقص ماء أو ADH مرتفع.	البول مركز (Uosm > Posm)	سالب CH_2O
لا يوجد ماء حر زائد أو ناقص.	البول مساوي في التركيز للبلازما	$CH_2O = 0$

Disorders of Urine Concentrating Ability

- **Central Diabetes Insipidus**: Failure to produce **ADH**.

الدماغ (تحديدًا تحت المهاد أو الغدة النخامية الخلفية) لا يُنتج كميات كافية من هرمون ADH، النتيجة: الكلى لا تتلقى الإشارة لإعادة امتصاص الماء، البول يكون كبير الحجم ومخفف جدًا، الأعراض: عطش شديد، تبول مفرط، جفاف.

- **Nephrogenic Diabetes Insipidus**: Kidney **un**responsive to ADH رغم وجوده (causes: loop diuretics مدرّات البول, lithium drug , analgesics, kidney diseases, malnutrition).
- **Malnutrition**: Low protein intake reduces urea, decreasing concentrating ability.
- **Chronic Renal Failure**: Nephron loss leads to **isosthenuria** يعني البول يصبح دائماً بتركيز ثابت كالبلازما ~٣٠٠ (urine osmolarity equals plasma osmolarity), losing ability to concentrate **or** dilute urine.

Regulation of Extracellular Osmolarity (NaCl Concentration)

- Key Regulators: **ADH** and **thirst**.
- Mechanism: Increased extracellular osmolarity stimulates ADH release (increases water reabsorption) and thirst (increases water intake).

ADH and Thirst Osmoreceptor System

- ADH Synthesis: In hypothalamic **magnocellular neurons**, released by posterior pituitary, acts on kidneys.

❖ **Stimuli for ADH Secretion:**

- Increased osmolarity (most sensitive).

- Decreased blood volume (cardiopulmonary reflexes)/pressure (arterial baroreceptors).
- Angiotensin II, nausea, nicotine, morphine, fear.

Decreased ADH Secretion: Decreased osmolarity, increased blood volume/pressure, alcohol, clonidine (antihypertensive drug) haloperidol (antipsychotic, Tourette's)

❖ **Thirst Stimuli:** Similar to ADH, plus mouth dryness.

Thirst **Inhibition:** Gastric distention and, decreased osmolarity, increased blood volume, Increased blood pressure, decreased angiotensin II

Maximal Urine Flow Rate and Water Excretion

- Max Water Excretion: 20-23 L/day (**not** exceeding 800-1000 **ml/hr**).
- **Water Intoxication:** ❗Occurs if intake exceeds excretion capacity, leading to **hyponatremia** and electrolyte imbalance.

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