

Sandwell and West Birmingham Hospitals NHS

# The Kidneys

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## Overview

- ▶ Renal physiology
- ▶ Renal pathophysiology
  - Acute kidney injury
  - Chronic kidney disease
- ▶ Assessing renal function
  - GFR
  - Proteinuria
  - Tubular function
- ▶ Effect on other biochemical analyses

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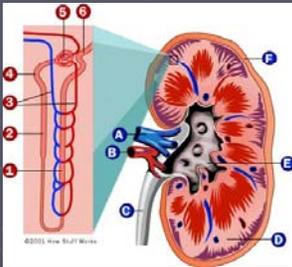
## Functions of the kidney

- ▶ Elimination of water-soluble waste products
- ▶ Water balance
- ▶ Electrolyte balance
- ▶ Acid-base balance
- ▶ Blood pressure control
- ▶ Vitamin D metabolism

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## The Nephron

▶ Functional unit of the kidney (~1 million/kidney)



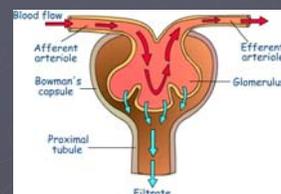
1 Ascending limb of loop of Henle	4 Renal vein
2 Descending limb of loop of Henle	5 Renal artery
3 Peritubular capillaries	6 Ureter
4 Proximal tubule	7 Medulla
5 Glomerulus (Bowman's capsule + Glomerular capillaries)	8 Pelvis
6 Distal tubule	9 Cortex

## Formation of Urine

- ▶ Over 150 L of plasma filtered / day
- ▶ Most fluid (containing vital constituents, i.e., electrolytes, nutrients, water) recovered by absorptive mechanisms and returned to blood
- ▶ Leaves 1-2 L of fluid containing water-soluble waste products to be excreted as urine
- ▶ Amounts of water and electrolytes excreted regulated by variety of mechanisms

## Glomerular Filtration

- ▶ Proportion of blood flowing through kidney is filtered (120 mL/min)
- ▶ Barrier consists of capillary wall, basement membrane and podocytes
- ▶ Filtrate contains all constituents of plasma except for plasma proteins



## Recovery of vital constituents 1

- ▶ Nutrients (glucose, amino acids)
- ▶ Electrolytes (Na, K, Cl, Ca) , bicarbonate, water
- ▶ Proximal Convolved Tubule
  - Bulk of absorption takes place (70% water & electrolytes)
  - Mostly obligatory absorption – no hormonal control
  - Variety of absorptive mechanisms: carrier-mediated transport, passive transport (osmosis, diffusion)

## Recovery of vital constituents 2

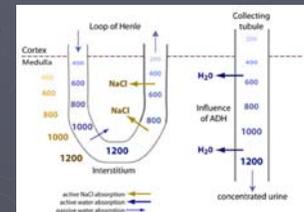
- ▶ Loop of Henle
  - Active absorption of electrolytes (25%) (without water)
  - A large difference in osmotic pressure created between renal cortex and medulla - increases ability of kidney to reabsorb water in the collecting ducts

## Recovery of vital constituents 3

- ▶ Distal Convoluted Tubule
  - Adjusts amount of electrolytes, water and H<sup>+</sup> ions excreted to maintain homeostasis
  - Hormonal control mechanism:
    - Aldosterone – increases recovery of NaCl in exchange for K<sup>+</sup> and H<sup>+</sup>

## Recovery of vital constituents 4

- ▶ Collecting ducts
  - Hormone ADH increases permeability of collecting ducts (and distal tubule) to water, allowing increased absorption by osmosis and production of a concentrated urine



## Acute Kidney Injury (AKI)

- ▶ Rapid reduction in kidney function resulting in failure to maintain fluid, electrolyte and acid-base homeostasis
- ▶ KDIGO definition ([www.renal.org](http://www.renal.org))

One of the following criteria must be met  
 Serum creatinine rises by  $\geq 26\mu\text{mol/L}$  within 48 hours **or**  
 Serum creatinine rises  $\geq 1.5$  fold from the reference value, which is known **or**  
 presumed to have occurred within one week **or**  
 urine output is  $< 0.5\text{ml/kg/hr}$  for  $>6$  consecutive hours  
 The reference serum creatinine should be the lowest creatinine value recorded within 3 months of the event

## Acute Kidney Injury (AKI)

- ▶ Pre-renal (poor blood flow to kidneys)
  - Dehydration, haemorrhage, sepsis, cardiac failure
- ▶ Intrinsic renal disease
  - Glomerular (e.g., glomerulonephritis, Goodpasture's disease, SLE); Tubular (e.g., pre-renal cause leading to tubular damage, drug nephrotoxicity); Misc (e.g., contrast nephropathy, rhabdomyolysis)
- ▶ Post renal (obstruction)
  - Bladder outflow obstruction, renal calculi, prostate cancer

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## Pre-renal vs intrinsic renal failure

- ▶ Pre-renal failure
  - ↑ Urea
  - ↑ Creatinine
  - No proteinuria
  - Reversible if treated early, acute tubular necrosis if not
- ▶ Intrinsic renal failure
  - ↑↑ Urea
  - ↑↑ Creatinine
  - Proteinuria common

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## Chronic Kidney Disease (CKD)

- ▶ KDOQI Definition
  - Kidney damage for ≥3 months as defined by structural or functional abnormalities (i.e., abnormal imaging, haematuria, proteinuria), with or without decreased GFR
  - GFR <60 mL/min/1.73m<sup>2</sup> for ≥3 months, with or without kidney damage

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## Chronic Kidney Disease (CKD)

Stage	GFR*	Description	Treatment
1	90+	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease	Observation, control of blood pressure.
2	60-89	Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease	Observation, control of blood pressure and risk factors.
3A 3B	45-59 30-44	Moderately reduced kidney function	Observation, control of blood pressure and risk factors.
4	15-29	Severely reduced kidney function	Planning for endstage renal failure.
5	<15 or on dialysis	Very severe, or <b>endstage</b> kidney failure (sometimes called <b>established renal failure</b> )	Treatment choices.

\* All GFR values are normalized to an average surface area (size) of 1.73m<sup>2</sup>  
**Suffixes:**  
**p suffix:** the addition of **p** to a stage (e.g. 3Ap, 4p) means that there is significant proteinuria

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## Chronic Kidney Disease (CKD)

- ▶ Diabetic nephropathy
- ▶ Hypertensive nephropathy
- ▶ Glomerular disease (haematuria & proteinuria) e.g., IgA nephropathy, minimal change nephropathy, systemic lupus erythematosus (SLE)
- ▶ Acute interstitial nephritis, e.g., drugs (NSAID's, antibiotics), infections, Sjogren's disease
- ▶ Inherited, e.g., polycystic kidney disease
- ▶ Toxic nephropathy
- ▶ Monoclonal light chains e.g., myeloma, amyloid

## Assessing renal function

- ▶ GFR = Glomerular filtration rate
  - Gold standard for assessing kidney function
  - Reduced GFR always occurs before renal failure
- ▶ Proteinuria
- ▶ Tubular function

## Measuring GFR

- ▶ Ideal marker of GFR
  - Filtered at glomerulus
  - Neither absorbed or secreted in renal tubules
  - Endogenous production at constant rate
  - If exogenous - non toxic
  - Easy to measure
- Closest to ideal used in routine clinical chemistry
  - $^{51}\text{Cr}$ -labelled EDTA clearance

## Urea

- ▶ Produced in liver from protein metabolism
  - Rate of production depends on protein intake
- ▶ Filtered at glomerulus
- ▶ Flow rate dependent passive reabsorption in renal tubules
- ▶ **Very crude index of GFR**

## Creatinine

- ▶ Derived from muscle (creatin)
- ▶ Produced at a constant rate, dependent on muscle mass
- ▶ Fairly crude marker of GFR (better than urea)

$$\frac{1}{\text{Serum creat}} \propto \text{GFR}$$

## Creatinine as marker of GFR

- ▶ Creatinine secreted in renal tubules
- ▶ Serum creatinine – large variation between individuals (muscle mass)
- ▶ Insensitive at detecting mild renal impairment
- ▶ Affected by recent high protein intake

## Creatinine Clearance

- ▶ Requires serum creatinine result, 24 hour urine collection for urine creatinine output

$$\text{Creat Cl (mL/min)} = \frac{\text{Urine creat (mmol/L)} \times \text{Volume (mL)} \times 1000}{\text{Serum creat (\mu\text{mol/L})} \times \text{Time (min)}}$$

- Insensitive at detecting early stage CKD due to overestimation of GFR at reduced GFR
- Relies on collection of an accurate 24 hour urine

## Estimated GFR

- ▶ eGFR calculated from equation (4V-MDRD)
  - Includes serum creatinine conc, age, sex, ethnicity
- ▶ Improved detection of Stage 3 CKD (early)
- ▶ Inaccurate at normal GFR (report > 90 mL/min)
- ▶ Invalid in children <16 yr, paraplegic etc
  - In children use Schwartz Equation (includes height)
- ▶ Not validated in elderly, some ethnic groups

## Creatinine methods

- ▶ Jaffe reaction
  - Colourimetric method (alkaline picrate)
  - Problems with specificity (e.g. ketoacids)
  - Factor to match results from enzyme assay for calculating eGFR
- ▶ Enzyme method
  - Specific
  - More expensive

## Cystatin C

- ▶ Low molecular weight protein synthesised by all nucleated cells
- ▶ Freely filtered at glomerulus
- ▶ Serum concentrations unaffected by muscle mass, gender, diet
- ▶ No extra-renal routes of elimination
- ▶ More sensitive and specific means of monitoring changes in GFR than serum creatinine, especially useful for detecting mild kidney impairment
- ▶ Measured using precise latex particle-enhanced turbidimetric or nephelometric immunoassays

## Proteinuria

- ▶ Urine should only contain very small amounts of protein (<150 mg/24h)
- ▶ Glomerular proteinuria – mainly albumin (+ transferrin, IgG)
- ▶ Tubular proteinuria – Low MW proteins:  $\beta$ 2 microglobulin, retinol binding protein
- ▶ Overflow proteinuria – Bence Jones Protein, myoglobulinuria

## Assessing proteinuria

- ▶ 24h urine collection
  - 24 h urine protein excretion (mg/24h)
  - Protein concentration (mg/L)
- ▶ Ratio with creatinine
  - Avoids difficulties collecting a 24h urine, adjusts for urine concentration and correlates well with 24h urine protein excretion
  - Protein:creatinine ratio (mg/mmol)
  - Albumin:creatinine ratio (mg/mmol)
- ▶ Urine dipstick

## Urine total protein

- ▶ Protein:creatinine ratio cut-offs (mg/mmol):
  - <15 Normal
  - 15-44 Trace
  - >45 Clinical Proteinuria
  - >450 Nephrotic Syndrome
- ▶ Method
  - Turbidimetry – add protein precipitant, measure increase in turbidity
- ▶ Issues
  - Poor precision at low protein concs
  - Non specific, insensitive
  - Poor between lab agreement at low concs

## Urine albumin

- ▶ Albumin:creatinine ratio cut-offs (mg/mmol)
  - $\leq 2.5$ (m) /  $\leq 3.5$  (f) Normal
  - 2.5/3.5 - 30 Microalbuminuria
  - $> 30$  Clinical proteinuria
- ▶ Method
  - Turbidimetric – uses specific antibodies
- ▶ Advantages
  - More specific than TP, detects only albumin
  - More sensitive, can detect microalbuminuria
- ▶ Issues
  - High antigen excess phenomenon
  - Analytical range up to 500 mg/L, target for lower limit of detection 5mg/L
  - Will not detect tubular / overflow proteinuria

## Microalbuminuria

- ▶ Pathological increase in albumin excretion below level detected by dipstick
- ▶ Diabetes mellitus
  - Increased risk of developing overt nephropathy, independent risk factor for CVD
- ▶ Monitor annually using albumin:creatinine ratio (early morning urine)
- ▶ NICE guidelines require at least 2 positive urine samples taken a month apart to classify as microalbuminuria

## Urine protein dipsticks

- ▶ Cut off at clinically significant proteinuria
  - $> 300$ mg/L
- ▶ More sensitive to albumin than other proteins (e.g., BJP)
- ▶ Variable performance at cut-off
- ▶ Operator dependent
- ▶ False positives
  - Concentrated urine, UTI, interference from bilirubin / drugs
- ▶ False negatives
  - Dilute urine

## Assessing tubular function

- ▶ Tubular proteinuria
  - Functional (filtered at glomerulus, reabsorbed in PCT)
    - ▶  $\beta 2$ -microglobulin, retinol binding protein
  - Due to cell damage
    - ▶ Tamm Horsfall glycoprotein, NAG
- ▶ Renal Tubular Reabsorption of Phosphate
  - Fraction of filtered phosphate reabsorbed by renal tubules
  - Used in investigation of hypophosphataemia
- ▶ Urine phosphate, bicarbonate, glucose, amino acids
  - Defective reabsorption in PCT - Fanconi Syndrome
- ▶ Urine pH
  - Renal tubular acidosis (failure to produce an acidic urine due to defect in bicarb reabsorption in PCT or  $H^+$  excretion in DCT)

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## Effect of renal disease on other biochemical analyses

- ▶ Raised potassium, phosphate
  - Impaired excretion of  $K^+$  and  $PO_4^{2-}$  ions
- ▶ Low bicarbonate, reflecting (increased anion gap) metabolic acidosis
  - Impaired excretion of organic acids
- ▶ Hypocalcaemia due to reduced  $1\alpha$ -hydroxylation of 25 OH vitamin D
  - Increased phosphate levels, reduced  $1\alpha$ -hydroxylase enzyme synthesis
  - Results in raised PTH
- ▶ Anaemia
  - Chronic disease, reduced erythropoietin synthesis

EVERYONE