Investigation of Renal Diseases
Clinical assessment of the renal patient

Investigation of Renal Disease – outline

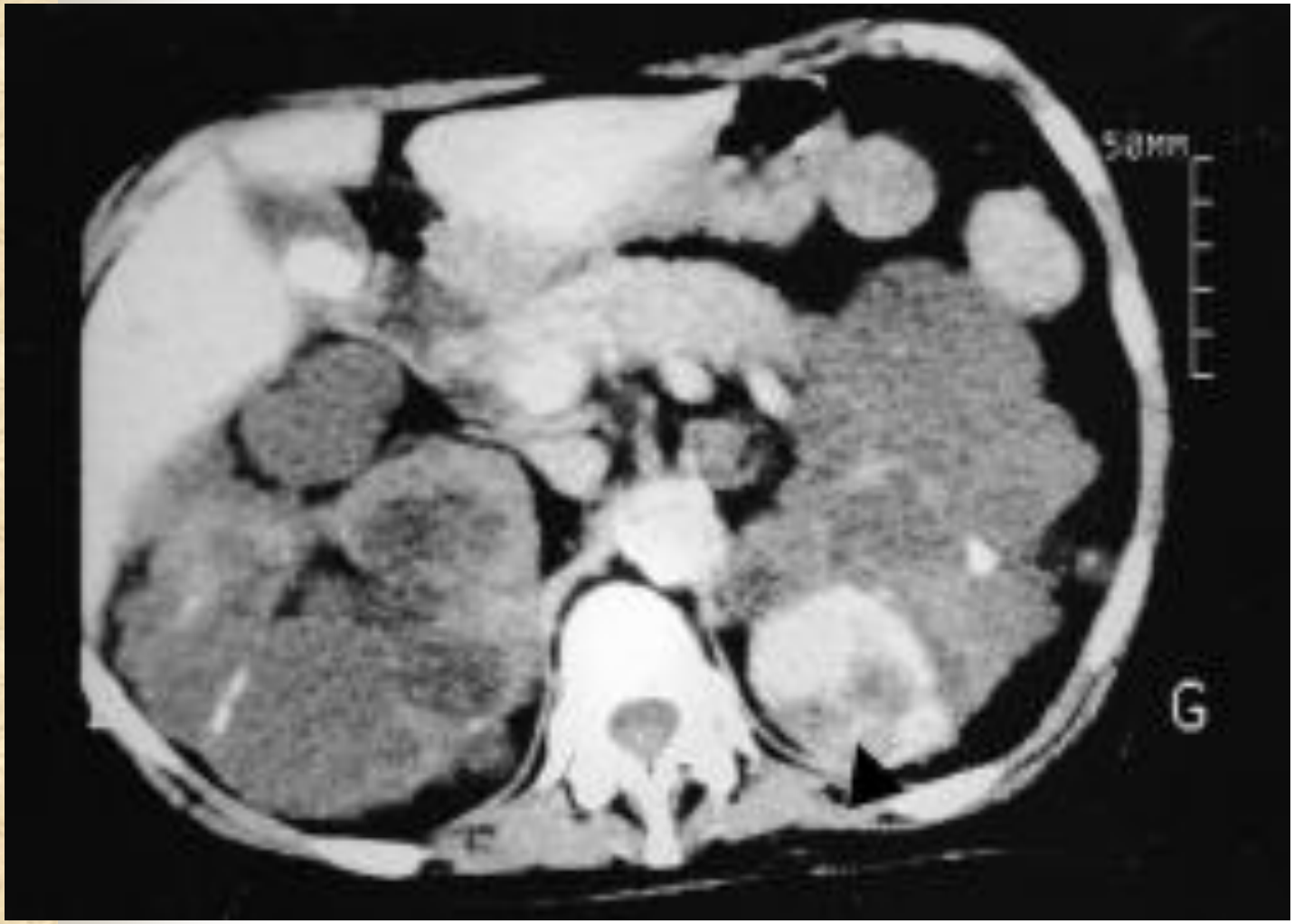
- I. Personal history and physical examination
- II. Blood laboratory findings (biochemistry, FBC, clotting, acid base balance..)
- III. Urinalysis (proteinuria, hematuria…)
- IV. Assessment of Renal Function (GFR…)
- V. Imaging (USS..)
- V. Renal Biopsy

Investigation of native kidney, transplanted kidney, hyperparathyreodism, secondary hypertension

Personal history

- Family history: Hereditary and Congenital Diseases
  - Autosomal Dominant Polycystic Kidney Disease
  - Alport´s syndrome
- Past medical history:
  - Diabetes mellitus
  - Arterial Hypertension
  - Systemic Diseases
  - Atherosclerosis, Gout
  - Stones disease, prostate
  - Infections: cystitis, pyelonephritis, HBV, HCV, chronic bacterial diseases
  - Tumours

Hereditary Disease of Kidney



- APKD

  Carcinoma of the left kidney

Vasculitis

- Typical appearance of nasal collapse in Wegener's granulomatosis.

Scleroderma

- The limited form of scleroderma (Microstoma)

Personal history 2

- Drugs, other nephrotoxins:
  - diuretics, ACEI, ARB : prerenal failure
  - NSA, antibiotics: Acute hypersensitivity intersticial nephritis
  - Penicillamine, Gold: Membranous GN
  - Analgesic Nephropathy
  - Cytostatics – cisplatin: ATN
  - Immunosupressants – CyA: prerenal failure, ATN, chronic intersticial disease
  - X-ray contrast agents: ATN
  - Lithium: tubular dysfunction
  - Ethylenglycol: tubular crystal formation
- Gynecological History:
  - Pregnancy: Pre-Eclampsia, Asymptomatic Bacteriuria, Right-Sided Pyelonephritis

Possible symptoms of kidney disease

- Fever, Chills, Suprapubic Pain, Loin Pain (Pyelonephritis, Cystitis)
- Haematuria
- Oedema (Nephrotic syndrome)
- Dyspnea
- Changes in Color and Volume of Urine (Diabetes Mellitus, IgA GN)
- Low urinary tract symptoms (obstructive or filling – urgency)
- Palpitation (arrhytmias - hyperkalemia)

- Failure of visual acuity, deafness (Alport syndrome, HT)
- Photosensitivity, Fevers, Night sweats, Painfull joints, myalgia (SLE)
- Epistaxis, Hematemesis (WG, HT)

Physical examination

- Oedema
- Dyspnea
- Arterial Hypertension
- Epigastric Bruit (Renal Artery Stenosis),
- Pericardial Friction Rub (Uremia, SLE)
- Kidney and (Liver) Enlargement (ADPKD)

- Swolen joints, Skin Rashes, Raynaud phen., Fever, Hair loss (Systemic Diseases)
- Pallor (Chronic Renal Failure, Systemic Diseases)
- Foetor ex Ore

Plasma laboratory findings

- urea, creatinine, Na, K
- Ca, PO3, parathormone
- pH, HCO3
- CRP, FW, leucocytosis
- anemia, trombocytopenia
- D dimers
- haptoglobin, myoglobin

- immunology: autoantibodies – ANCA, antiGBM, ANA, antidsDNA, complement

Urinalysis

- Physical Characteristics of Urine (Color, Turbidity, Density, Odour)
  - red – blood, beetroot ingestion, haemoglobin, myoglobin
  - orange – rifampicin
  - brown – blood, hyperbilirubinaemia, nitrofurantoin

- Chemical Characteristics of Urine

  * urinary test strips (dipstics): spccific gravity, pH, blood, albumin, leucocytes, nitrites, glucose, urobilinogen, bilirubin, ketones
  - > 2 erythrocytes
  - > 150 mg/l protein

  * 24 hour collection (quantitative proteinuria, creatinine clearance..)

- Urine Microscopy – e.g. bacteriuria, phase-contrast

Proteinuria

- major manifestation of renal disease
- risk factor for deterioration of renal function, of cardiovascular morbidity and mortality
- > 150 mg of protein /day in adults and > 140 mg/m^2 in children

- detection by dipstick - semiquantitative- detects only albumin
- 24 hour collection: concentration measured by turbidimetry after precipitation with sulfosalicylic acid
- selectivity of proteinuria – electrophoresis in polyacrylamide gel
- albumin / creatinine ratio (ACR) or protein / creatinine ratio (PCR)
  - quantitative measurement on a single early morning urine sample
  - ACR > 3 mg/mmol .. microalbuminuria
  - ACR > 30 mg/mmol .. overt proteinuria
  - ACR > 350 mg/mmol.. nephrotic range
  - PCR < 0,2 mg /mmol = 22 mg/mg = urine protein <0,2g /24h

Proteinuria 2

- Prerenal (overflow) Glomerular Tubular Secretory

- Prerenal - secondary to increased production of low-molecular weight proteins, such as
  - immunoglobulin light chains (myeloma)
  - myoglobin (rhabdomyolysis)

- Glomerular - due to increased glomerular permeability to proteins, in primary and secondary GN
  - *Selective* – albumin (e.g. minimal-change disease)
  - *Non-selective* - albumin + higher molecular-weight proteins such as gammaglobulins (e.g.membranous nephropathy)

Proteinuria 3

- Tubular - due to decreased tubular reabsorption of proteins (e.g.tubular and interstitial diseases)
- Secretory – from urinary tract (bladder tumours, prostatitis)

Urine microscopy

- **Erythrocytes**

  Dysmorphic - irregular shapes and contours, from glomeruli

  Nonglomerular (isomorphic) : regular, from the excretory systém

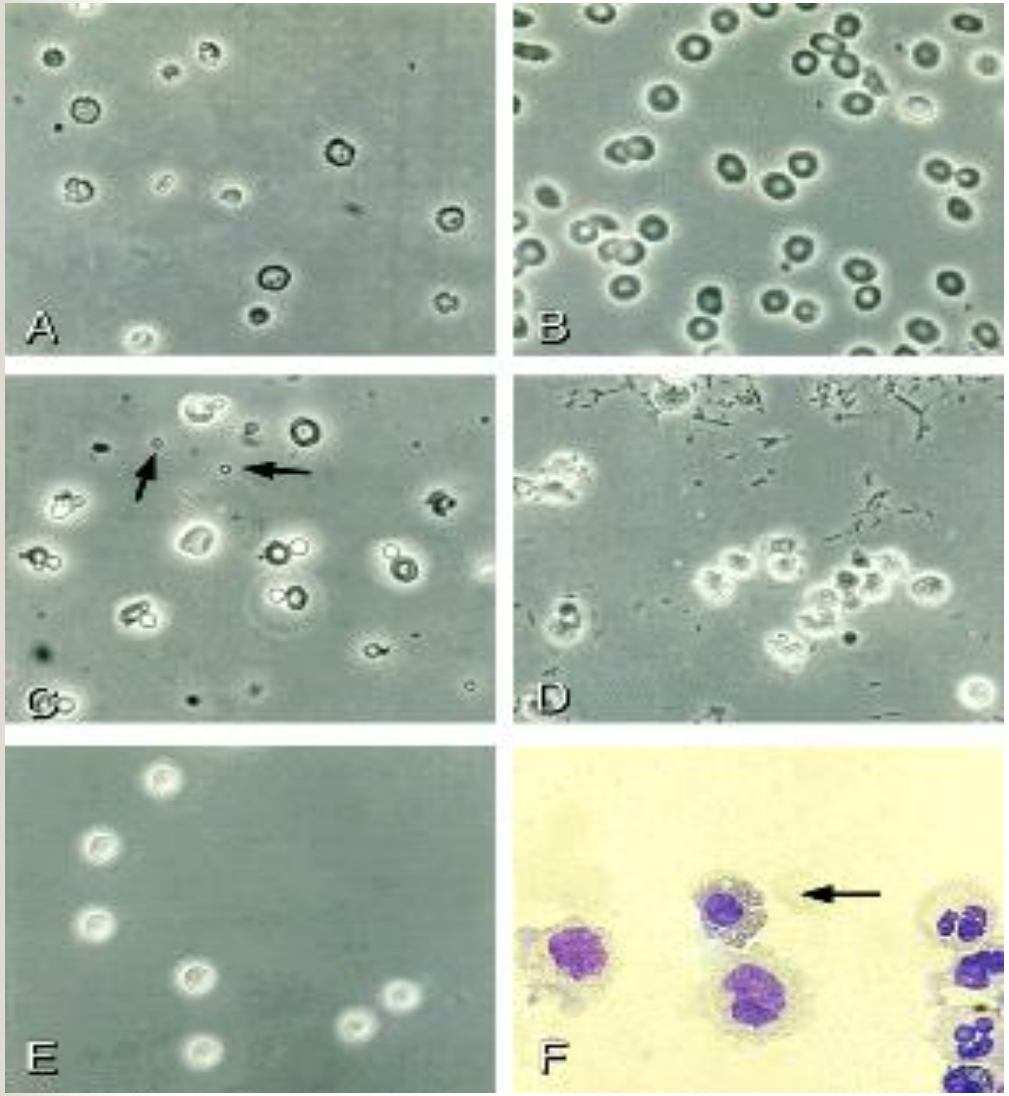
- Leucocytes (neutrophiles, lymphocytes, eosinophils
- Casts – plugs of Tamm-Horsfall mucoprotein,

  - non-cellular : nonspecific

  - cellular : red-cell or epithelial casts (GN), white-cell casts (TIN),
- Organisms: Bacterias, Fungi, Trichomonas, Schistosoma haematobium

- Renal Tubular Cells, Epithelia

Erythrocyturia – phase contrast microscopy



- A dysmorphic erythrocytes
- B isomorphic erythrocytes
- C acanthocytes with typical spikes extending from ring-shaped cell
- D neutrophiless
- E lymphocytes
- F eosinophil

Erythrocyturia

- ‘glomerular’ – at least 75 % dysmorphic
- ‘non glomerular’ - at least 75 % isomorphic
- ‘mixed’ - the two types of cells are approximately in the same proportion

Assessment of Renal Function

- Functions of the kidney:
  - Glomerular Filtration
  - Tubular function (Na, K handling, concentrating/diluting capacity)
  - Acid-base balance
  - Endocrine function (RAA system, erythropoetin, vitamin D, parathormone)

Glomerular filtration rate

- reliably reflects the eliminatory function of kidneys
- glomerular filtrate = filtrate of plasma that crosses the glomerular barrier into the urinary space
- GFR represents the sum of filtration rates in all functionning nephrons = a surrogate for amount of functioning renal tissue

- **GFR expressed as renal clearance (C) : the volume of plasma from which a substance is completely removed by the kidney in a given amount of time**

- **$C = U_a \times V / P_a$**
  - V = urine volume per time (ml/s, ml/min)
  - Ua = urine concentration of a substance
  - Pa = plasma concentration of the substance

GFR 2

- The most important parameter
- Useful for

- measurement of kidney function
- monitoring progression of CKD
- forecasting the need for RRT
- determining appropriate drug dosing in CKD
- may correspond to the functioning mass of the kidney

- Ideal clearance substance:
  - safe, cheap, easy to measure
  - freely filtered at glomerulus (not protein bound)
  - not reabsorbed, secreted or metabolized by the kidney
  - no extrarenal elimination

Estimation of GFR in clinical practice

- s-creatinine
- Formulae based on s-creatinine
- Creatinine clearance
- Isotopic clearance (EDTA, DTPA)

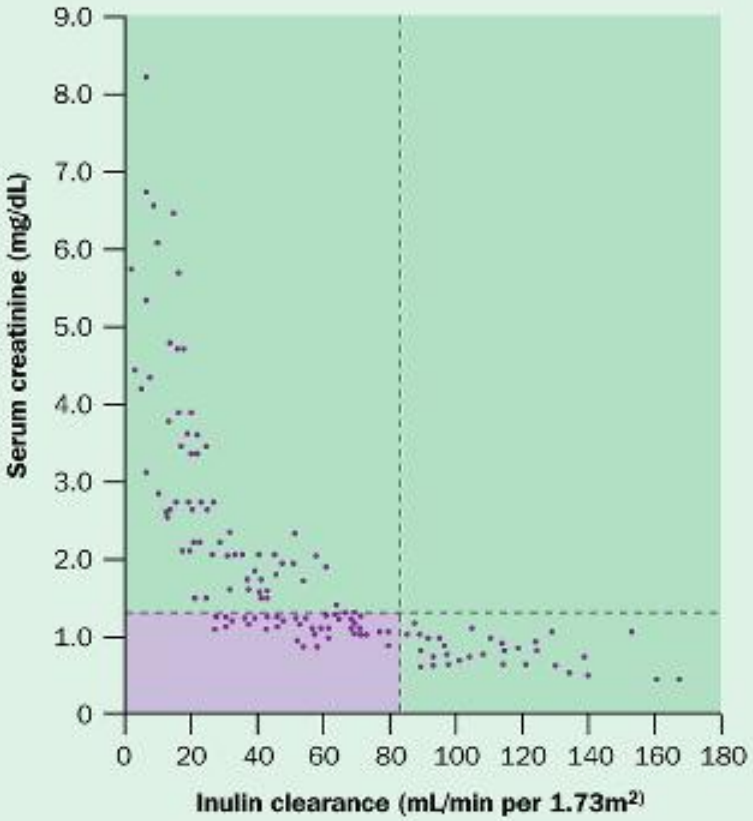
- Inulin clearance – gold standard
  - requirs a continuous infusion

Creatinine Clearance

$$C_{cr} = \frac{U_{cr} x V}{P_{cr}}$$

- production of creatinine proportional to muscle mass + derived from dietary intake
- limitations of C_{cr}
  - creatinine secreted by the proximal tubule (GFR is overestimated)
  - extrarenal elimination by GI tract
  - competitive inhibition of tubular secretion (cimetidin, trimetoprim, spironolactone)

Relationship between serum creatinine and glomerular filtration rate



Example of creatinine clearance calculation

- P-Cr 200 umol/l
- U-Cr 4 mmol/l
- V: 2,4 l/24 hours

- C-Cr = U*V/P

  =(4x2400/24/60/60)/0,2= 0,55ml/s

  CAVE! Urine volume expressed in ml/s, not in l/24 hours

Cockroft-Gault formula for calculation of GFR in adults

- CCr = (140-age) x weight / 49 x S-Cr (umol/l)
  - x 0,85 in women
  - in U.S. CCr expressed in ml/min

  - S-Cr (mg/dl) x 72 → (umol/l)

MDRD

- the most recently advocated formula
- developed from data from Modification of diet in renal disease study
- CG tends to overestimate GFR, MDRD tends to underestimate
- abredged MDRD :

$$x = 32788 \times creatinine^{-1.154} \times age^{-0.203} \times constant$$

(x 0.742 if female)

Imaging

- **Conventional -** Plain film, IVU, retrograde pyelography, Antegrade pyelography, Cystography

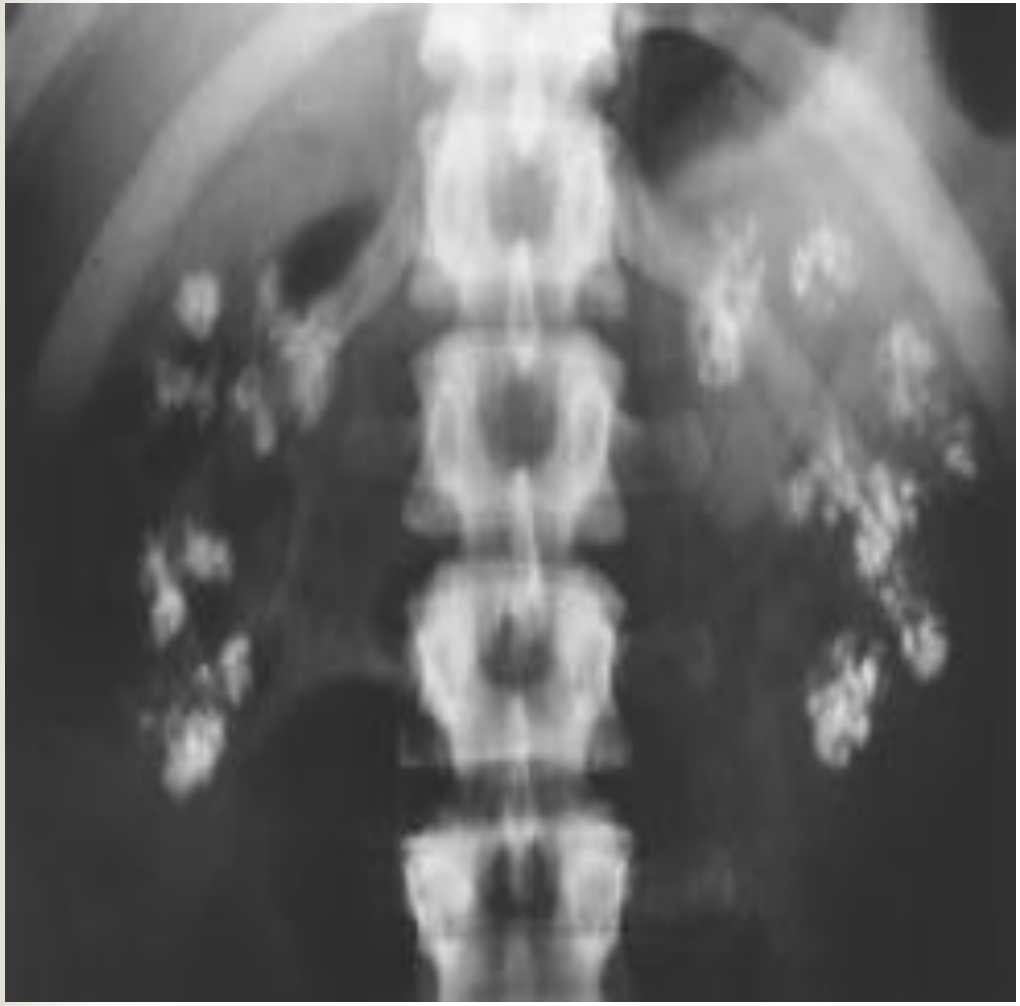
- Ultrasound
- Computed tomography
- Angiography
- Radionuclide evaluation
- Magnetic resonance imaging

Plain film

* Main role – identification of calcification, renal location and size
* Calcifications:

- calculi
- tuberculosis
- tumours,
- nephrocalcinosis due to : Hyperparathyroidism, Sarcoidosis, Idiopathic hypercalciuria, Milk-alkali syndrome, Hypervitaminosis D, Oxalosis, Distal renal tubular acidosis, Hyperoxaluria, Barrter´s syndrome,Medullary sponge kidney, Papillary necrosis, Cortical, Cortical necrosis, Chronic glomerulonephritis, trauma

Nephrocalcinosis

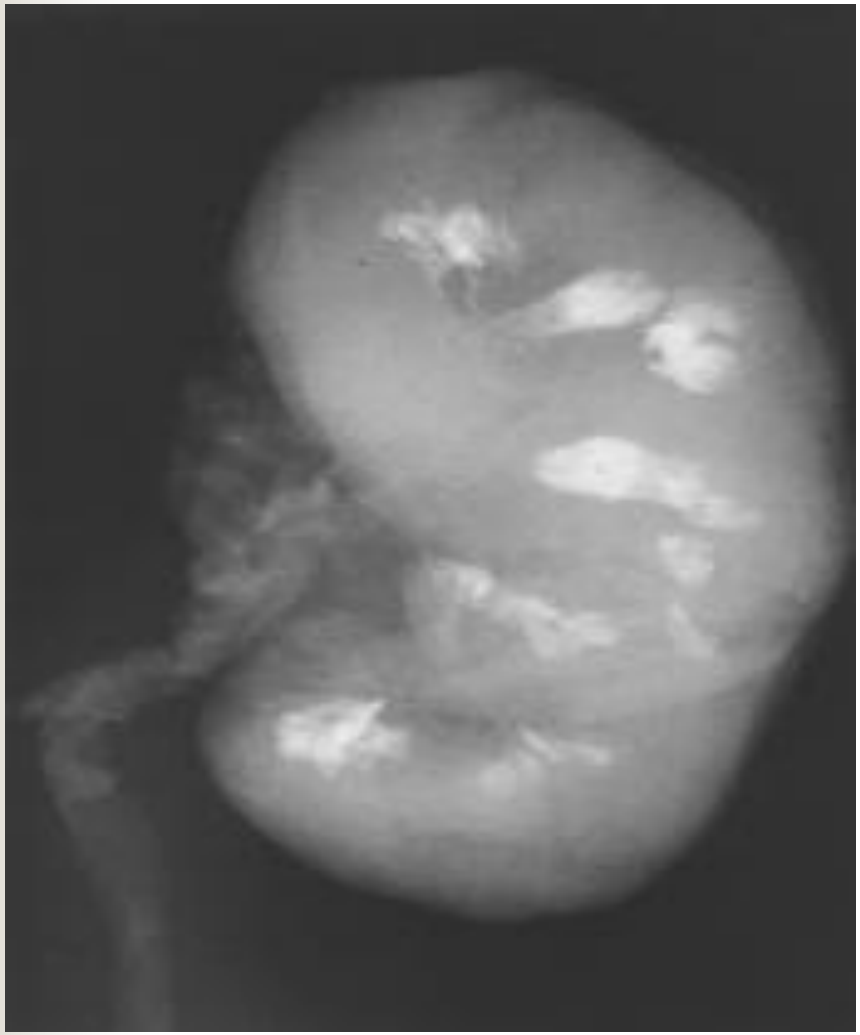


Medullary nephrocalcinosis in

a 25-year-old man with familial distal renal tubular acidosis.

The pyramidal distribution of the clusters of nephrocalcinosis.

Nephrocalcinosis



Calcification of the renal papillae (necropsy specimen) in a 43-year-old woman, a pharmacy assistant who consumed large amounts of Rennies (calcium carbonate) and phenacetin.

Ultrasound

- the front-line investigation in renal disease
- documents 1-2 kidneys
- obstruction
- renal size
- cystic vs. solid renal masses
- polycystosis
- nephrocalcinosis + calculi
- bladder emptying, prostate size
- guiding renal biopsy
- Doppler USS to estimate blood flow

Ultrasound

Long-axis scan through the right upper quadrant, demonstrating a longitudinal section of the right lobe of the liver (L) and the right kidney (between the Xs). The right renal capsule, the low-level grey echoes of the renal cortex, the darker medullary pyramids, and the bright right renal sinus.

Intravenous urography

- overview of urinary tract: kidney – size, location, contour, pelvicalyceal system, ureters, calculi, bladder
- currently superseded by CT and US, used if USS is negative and CT not available
- includes: plain control film, bilateral nephrograms post-contrast (delayed- obstruction, poor perfusion, ATN, venous thrombosis), renal outline (scars, reflux, TB), further exposures after 5 + 10 min.: PC filling defects – stone, tumour, PC deformity – reflux), post-voiding film (bladder outflow)
- indications: flank pain (suspected renal colic), recurrent UTI, bladder outflow obstruction, painless hematuria
- contraindications: renal insufficiency, diabetes, dehydration,. allergy to iodinated contrast agents and pregnancy
- preparation: fluids, antiallergenic (Prednison 30 mg pre- + post)
- contrast media: non-ionic, iso-osmolar better tolerated
- risk of nephrotoxicity (ATN): DM, age, CCF, dehydration, ↓GFR

CT

- widespread use
- indication: renal, perirenal masses, cysts vs. tumours, tumour staging, abscesses, calculi, retroperitoneal diseases, obstruction, pyelonephritis
- CT angiography
- contraindications: renal insufficiency, diabetes, dehydration, allergy to iodinated contrast agents and pregnancy
- risk of nephrotoxicity (ATN): DM, age, CCF, dehydration, ↓GFR
- preparation: fluids, antiallergenic (Prednison 30 mg pre- + post)

CT

Small simple renal cyst of the left kidney following intravenous contrast injection; low density, lack of enhancement, indiscernible wall, sharp contour

CT

Necrotic malignant tumour: even thicker wall with irregular thickness (arrows)

Angiography

- Gold standard in renovascular disease
- Invasive - catheter via puncture of a. femoralis

- Indications: renovascular disease (percutaneous transluminal angioplasty), acute renal ischamia (thrombosis, traumatic occlusion, dissection, emboli..), unexplained haematuria (angioma?), guiding embolisation, intrarenal microaneurysms (polyarteritis nodosa), evaluation of donor of kidney before transplantation, identifying source of bleeding after kidney biopsy
- Contraindication same as CT

Angiography

Intravenous digital subtraction angiography (injection via a central venous catheter after selective renal vein sampling).

Angiography

Digital arteriography of a transplanted kidney. Stenosis of the external iliac artery and the origin of the renal artery at the site of the anastomosis (arrow)

Nuclear medicine

- non-invasive
- provides functional and structural information

3 types:

- GFR estimation (Cr-EDTA)
- Dynamic (Tc-DTPA, Tc-MAG 3)) – tracks renal uptake, transit and excretion of isotope
- Static (Tc-DMSA) – retained within functionning tissue – demonstrates scars

Nuclear medicine

Applications:

- DMSA: congenital abnormalities, chronic pyelonephritis, reflux, scarring, split function
- DTPA: split function, perfusion and obstruction of the transplanted kidney, arterial occlusion, captopril renography (assymetry of size and function, delayed time to peak activity, cortical isotope retention)

¨ ---- *In renal artery stenosis ACEI blocks afferent arteriolar constriction*

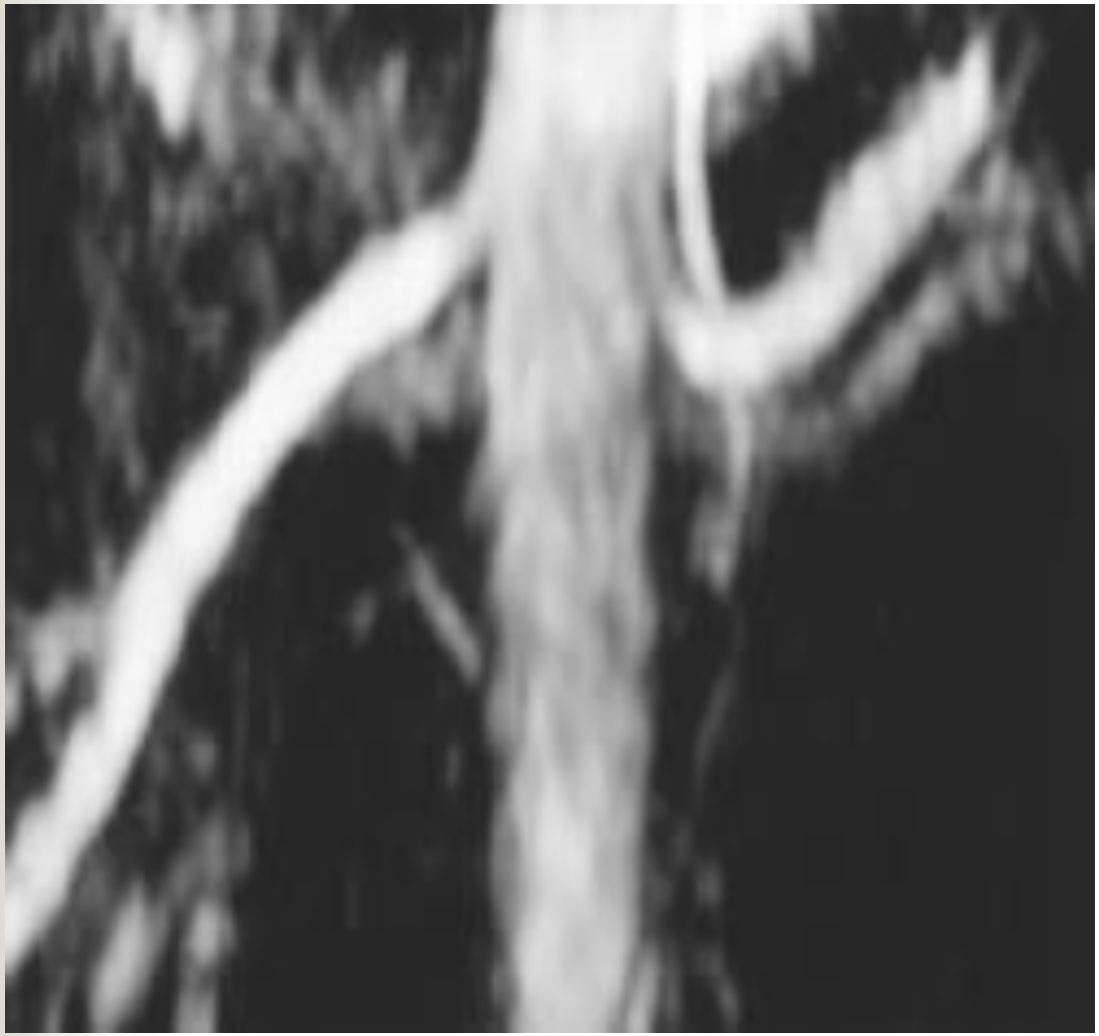
Radionuclide evaluation

[99Tcm]DMSA scan showing the effect of reflux into a lower moiety of a duplex kidney on the left and a lower pole scar in the right kidney

Magnetic resonance

- Evaluation of a renal mass and tumour staging
- Not the first-line investigation method – expensive and not allways available
- Advantages - direct multiplanar imaging, excellent soft-tissue contrast, can be used in renal insufficency (gadolinium less nephrotoxic and not allergenic), in pregnancy
- Disadvantages - claustrophobic pts may be uncooperative
- Contraindication – patients with some types of internal metallic hardware (pacemacer) cannot undergo MRI
- MR urography – equivalent of an IVU
- MR angiography – dg. of renovascular disease

MR



MR angiography of renal arteries

Cystography

Stenosis of the distal penile urethra after renal transplantation of the left iliac fossa, demonstrated by suprapubic cystography

Renal Biopsy - indication

- Unexplained acute or chronic kidney disease with normal renal size, including:
- Nephrotic syndrome
- Non-nephrotic significant proteinuria
- Mild proteinuria associated with haematuria
- Isolated haematuria
- Acute renal failure
- Unexplained chronic renal failure
- Suspected systemic disease with positive dipstick
- Renal transplant dysfunction

Renal Biopsy - preparation

- 2 normal kidneys on imaging
- BP < 140/90 mm Hg
- Hb > 100 g/l
- normal clotting and platelet count
- send group and save
- antiplatelet agents stopped 5 days before
- sterile urine
- informed consent

Renal Biopsy- contraindications

- chronic renal failure with small kidneys
- bleeding tendency
- uncontrolled hypertension

- urinary infection
- solitary kidney
- multiple cysts

- uncooperative patient
- suspected renal tumour
- hydronephrosis

Renal biopsy - technique

- percutaneously under local anaesthesia
- via posterior approach, either kidney
- USS guided, lower pole , 2 cores of tissues
- on bed rest for 24 hours, good fluid intake

Renal Biopsy- evaluation

- Evaluation of clinical and laboratory data
- Study at low-power magnification (adequacy and preliminary examination)

- Analytical study of light microscopy features (glomeruli, tubules, interstitium, vessels)
- Presumptive diagnosis and correlation with clinical data

- Evaluation of immunohistological and electron microscopy findings

- Confirmation of diagnosis,

OR:

- Revision of light microscopy and clinical data
- Final diagnosis, staging of lesions, and evaluation of prognosis

Renal Biopsy - complications

- Pain
- Bleeding – macroscopic haematuria in 5%, large capsular haematoma 1%, small haematoma 85%
- Arteriovenous fistula 10%
- Incorrect tissue – muscle, fat, liver, spleen, colonic perforation
- Death (0,1%)