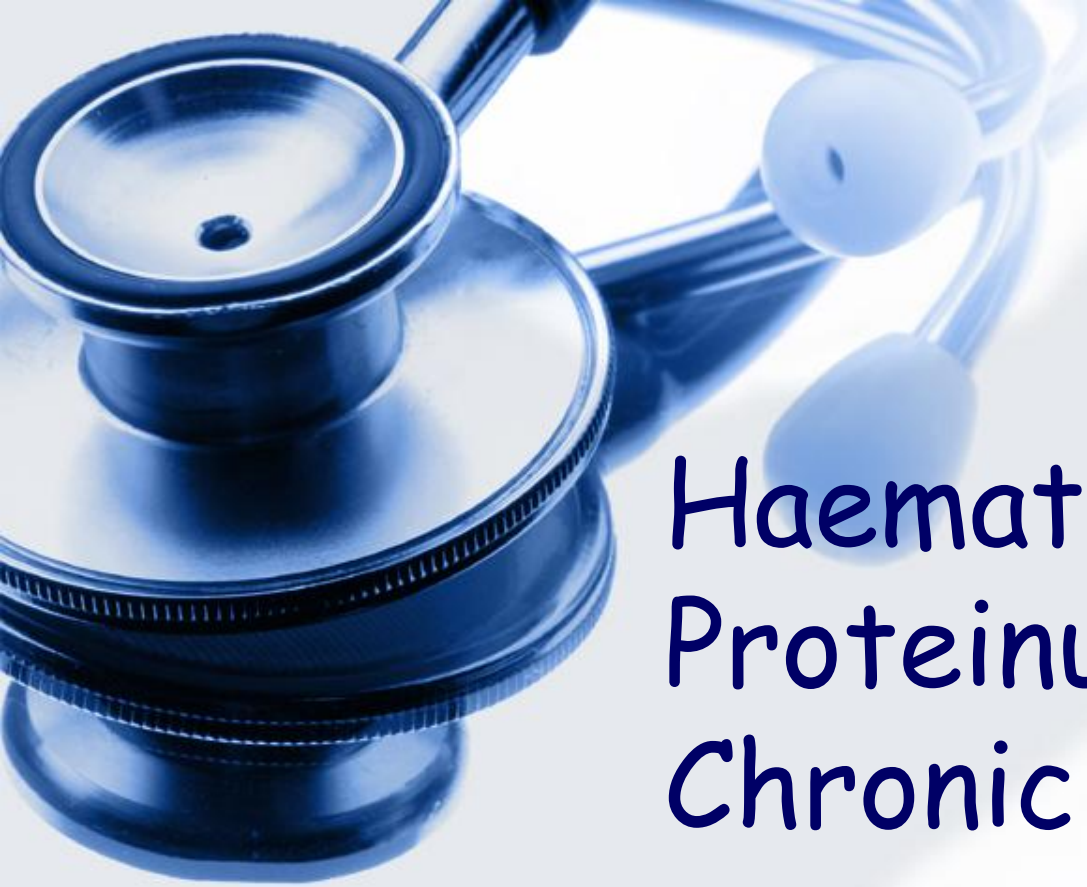

Haematuria, Proteinuria and Chronic Renal Failure

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Procare Group: Wednesday 12 October 2011 @ 19:00

St Heliers Presbyterian Church Community Centre

Haematuria

Haematuria - macroscopic

- Clots => lower urinary tract origin
- Trauma and UT stones
- Tumour
- Glomerulonephritis
- UTI
- Meatal or perineum irritation
- Contamination from menstrual periods
- Structural: stricture; VUR; RN
- Drugs
  - cyclophosphamide

Haemoglobinuria

- Haemoglobulinuria
  - Dimer – M. Wt = 34,000
    - Protein bound (haptoglobin)
  - From intravascular lysis
    - Occurs once haptoglobin saturated
  - Met-haemoglobulinuria (“Coke colour”)
    - Slow nephron transit time
    - Acid urine

Myoglobinuria

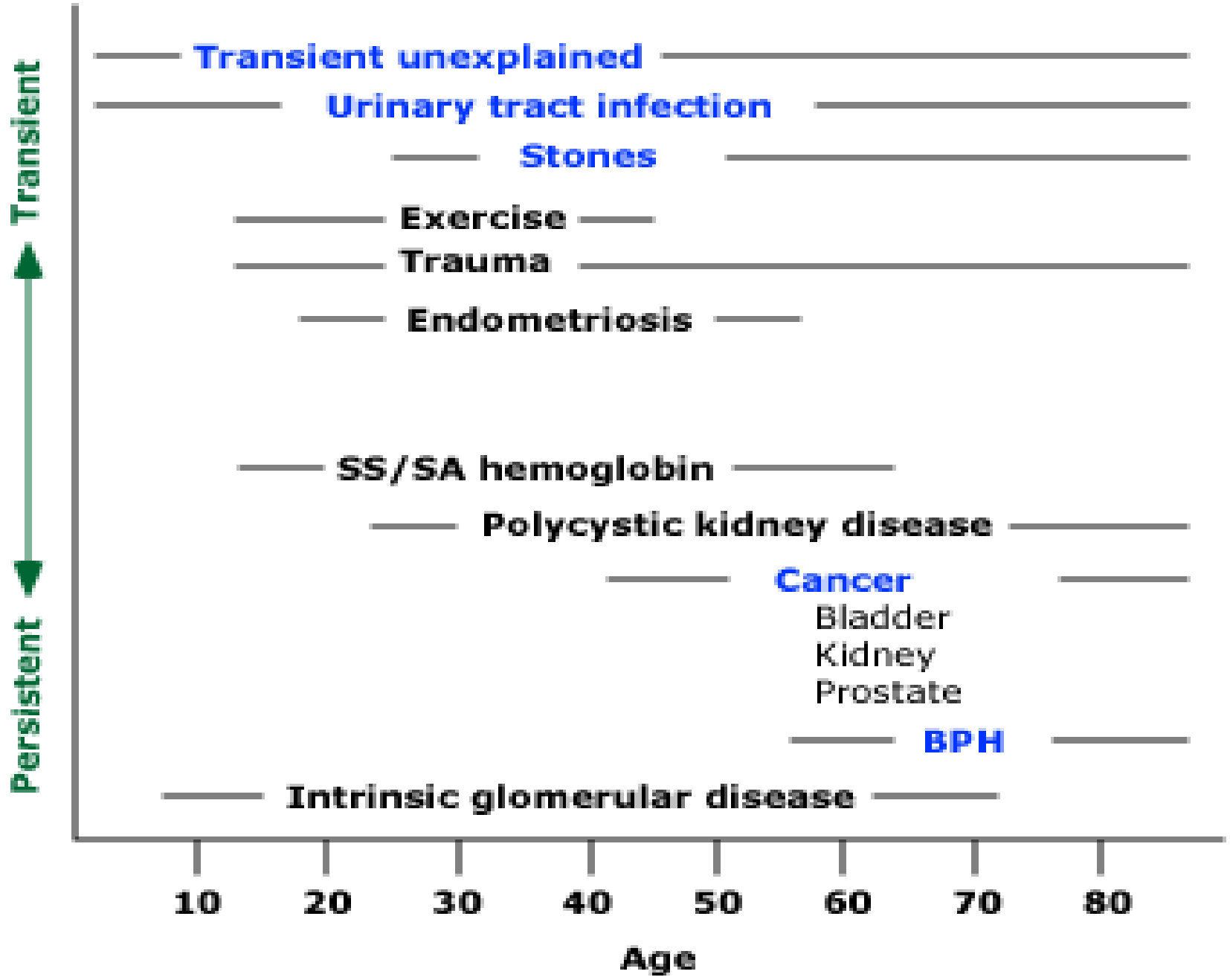
- Myoglobinuria
  - Monomer – M. Wt = 17,000
  - Not protein bound
  - Readily filtered in glomerulus
    - Therefore clears serum rapidly
    - Discolours urine
- Rhabdomyolysis
  - CK (creatine phosphokinase) levels

Other red urine (1)

- Beet – beta(al)nin (14% of population)
  - Not seen in ileostomy patients
  - ?colonic absorption
  - Worse in:
    - Fe deficiency
    - Oxalaturia (rhubarb, oysters, chocolate, tea, spinach)
    - Pernicious anaemia induced achlorhydria
- Food dyes
- Porphyria

Other red urine (2)

- Food dyes
- Porphyria
- B12
  - In treatment of cyanide poisoning


Transient
Persistent
Transient unexplained
Urinary tract infection
Stones
Exercise
Trauma
Endometriosis
SS/SA hemoglobin
Polycystic kidney disease
Cancer
Bladder
Kidney
Prostate
BPH
Intrinsic glomerular disease
10
20
30
40
50
60
70
80
Age

Detection/diagnosis

- Dipstick
  - More sensitive than microscopy
    - False positives
      - Semen (positive haem reaction)
      - Alkaline urine
      - Myoglobinuria
    - Very dilute urine can haemolyse RBCs
  - False negatives
    - Excessive vitamin C
  - Factitious (rare)

Clues from history

- Vigorous exercise or trauma
- Dysuria and pyuria
- Family history
- Unilateral flank pain
- Prostatic obstructive symptoms
- Bleeding disorders
  - The case of anti-coagulants
- Travel
- Sterile pyuria (e.g. Tb; analgesics; IN)

Site/level of haematuria

- Glomerular
  - RBC casts
  - Proteinuria > 500mg/24 hours
  - Dysmorphic RBCs
    - Especially acanthocytes
  - “Coke” coloured urine
- Non-glomerular
  - Lower UT symptoms
  - clots

Investigations

- Cytology
  - 90% sensitivity for CA bladder
  - < 35% for upper UT tumours
- Imaging
  - USS
  - IVP / IVU
  - CT
  - MR
  - pyelography

Imaging

- CT urogram (radiation dose is high)
  - Replaced IVU / IVP
- USS
  - Not so good for small urothelial lesions
- MR urography
  - Misses smaller lesions and non-obstructing stones
- Retrograde pyelography
  - Similar detection to CT urography

The 40 year-old cut off age

- < 40 year old
  - Non-tumour
  - Renal origin
  - USS
    - CT if high risk
- >40 (maybe 45 year old)
  - CT urography

Cystoscopy

- In combination with CT urogram
  - Excellent screening in combination
- Only method to visualise prostate and urethra
- Source of bleeding
  - And treatment

“No cause found”

- Intermittent?
  - How far do we investigate?
- 5-10% of cases
- Hypercalciuria and hyperuricosuria
  - Family history
- Rare:
  - Schistosomiasis
  - Radiation
  - AV malformations/fistulae
  - Haemorrhagic telangiectasia
  - Loin pain syndrome
  - Nutcracker syndrome

Follow-up / treatment

- Treat the cause
- No specific treatment for haematuria *per se*

- No cause found
  - 3 to 6 monthly monitoring
  - ?duration
    - 3-5 years

Summary – haematuria investigation

- Renal function, MSU, urine microscopy
  - Urine RBC morphology
- Quantify proteinuria
  - 24 hr; protein-creatinine ratio (PCR); random
- Urinary cytology
- Others: Ca and PO_4; SPE; BJ proteinuria; LFT; ANA, dsDNA; ANCA; Ig; PTH; complements.
- If < 40 year old renal USS
  - otherwise CT urogram

Summary – haematuria referral

- Isolated microscopic
  - With symptoms -> urologist
  - Painless
    - < 40 year old -> renal physician
    - > 40 year old => cancer (urologist)
- With proteinuria and/or impaired renal function

  -> Renal physician / nephrologist

Proteinuria

Proteinuria

- Marker of urinary tract inflammation
  - Primarily renal in origin
    - Glomerulonephritis
    - Tubulo-interstitial nephritis
- “Transient contamination”
  - Prostatitis
  - UTI
    - Minor
  - Seminal fluid

Proteinuria types or origins

- Isolated
  - Glomerular
  - Tubular
  - Overflow
  - Mixed
    - Any combination of above (e.g. myeloma)
- Other
  - Concurrent haematuria

Glomerular proteinuria

- Serum macromolecular proteins
  - Albumin
  - Glomerular diseases
  - Diabetic nephropathy
  - “Benign” causes
    - Usually < 2 gram/24 hours proteinuria
    - Orthostatic
    - Exercise induced

Tubular proteinuria

- Low molecular weight proteins
  - ***Not detected by dipsticks***
  - Freely filtered
    - Usually reabsorbed unless tubular overload or dysfunction
  - β2 microglobulin
  - Immunoglobulin light chains
  - Retinol protein
  - Amino acids

Overflow proteinuria

- Myeloma (most common)
  - Immunoglobulin light chains
- Less common causes:
  - Lysosomal (a. myelomonocytic leukaemia)
  - Myoglobin (rhabdomyolysis)
  - Haemoglobin (haemolysis)

Detection of Proteinuria

- Dipstick
  - Albuminuria
  - Misses tubular proteins
- Laboratory quantification
  - Pros and cons

Detection of Proteinuria

- 24-hour versus timed urine collection
  - Accuracy of 24 hour collection
  - Total urine volume in timed collections

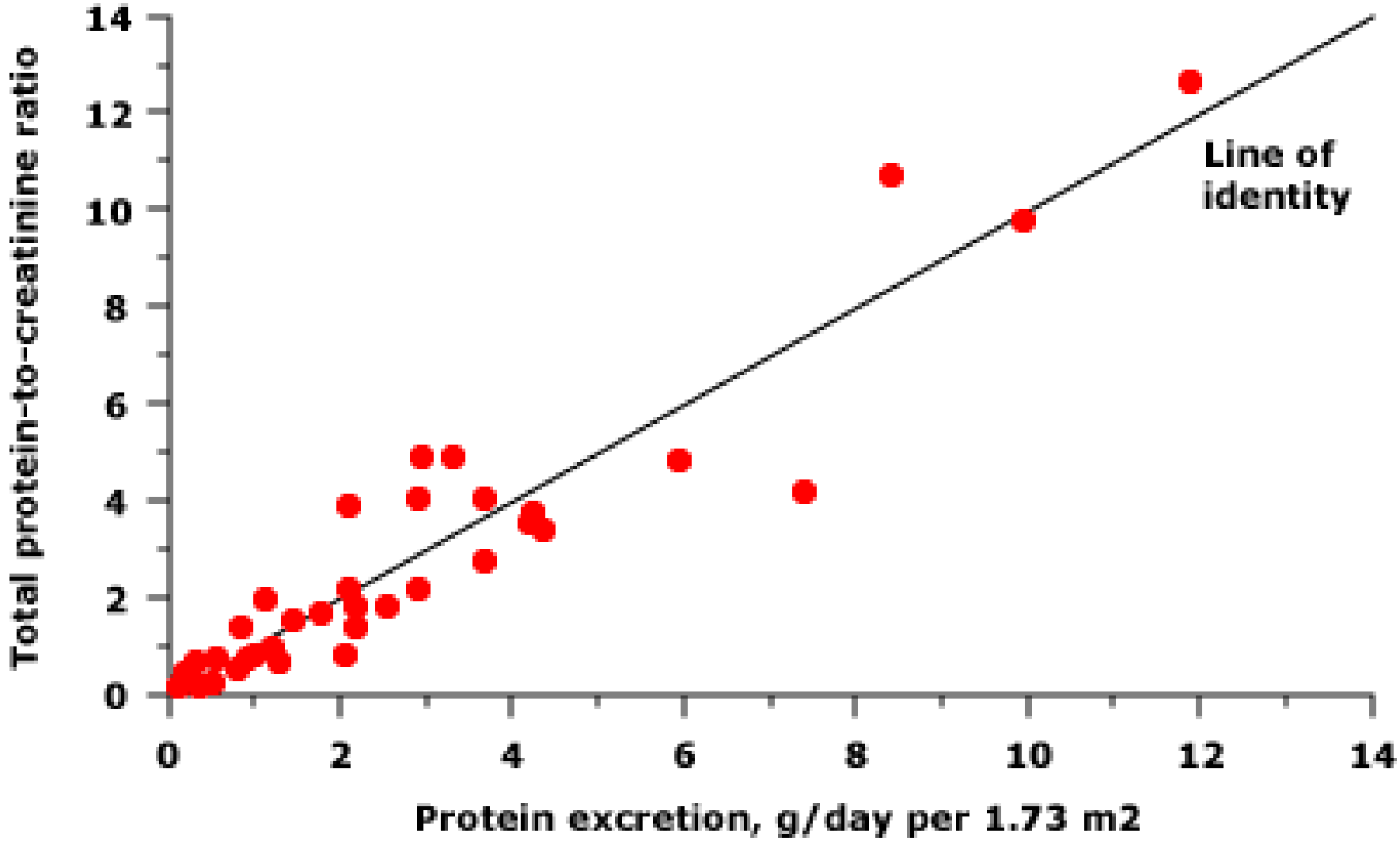
- Untimed urinary protein-creatinine ratio
  - Pragmatic
  - Reproducible
  - Affordable and effective

Quantification

dipstick	24 hour
Trace	150 – 300mg
+	300 – 1,000mg
++	1 – 3G
+++	3 – 10G
++++	> 10G

Quantification

24 hour collection	mg/L or g/L (spot urine)	mg/mmol (PCR)
< 300mg	20 – 30 mg/L	20
500mg	40 mg/L	40
1G	0.6 (600mg/L)	60 – 80
3G	2 G/L	180 – 250
10G	6 G/L	600 – 800


Total protein-to-creatinine ratio
0
2
4
6
8
10
12
14
Protein excretion, g/day per 1.73 m2
Line of identity

Albumin / ACR

- ACR problems
  - 24-hour urine and spot urines do not correlate well
    - Orthostatic proteinuria
    - Pragmatically first-am and mid-pm are best times
  - Depends upon serum creatinine (denominator)
    - Muscular people will have a low value
  - Vigorous exercise leads to increased albuminuria
    - Wait 24 hours

The risk of proteinuria…

- Meta-analysis of general population cohort: *n* = 105,872 (ACR) , plus *n* = 1,128,310 (dipstick proteinuria); mean follow-up of 7.9 years (*cf.* a group with mean eGFR of 95ml/min/1.73m^2 BSA)
  - Hazard ratios for all cause mortality
    - eGFR 60 1.18 (CI 1.05-1.32)
    - eGFR 45 1.57 (CI 1.39-1.78)
    - eGFR 15 3.14 (CI 2.30-4.13)

The risk of proteinuria……

- Presence of proteinuria alone -> RR of cardiovascular event = 1.3
- Nat Health and Nutrition Examination Survey cardiovascular death rate (unadjusted):
  - Proteinuria <30 6.2 deaths / 1000 person-yr
  - Proteinuria 30-299 17.9 deaths / 1000 person-yr
  - Proteinuria >300 37.2 deaths / 1000 person-yr
- When adjusted:
  - Relative hazard 1.57 (30-299 cf. <30 cohort)
  - Relative hazard 1.8 (>300 cf. <30 cohort)

Microalbuminuria

- Associated with LV dysfunction; stroke; MI

- Doubles mortality in DM
  - Especially in type I DM
- Indicator of inflammation
  - Within renal tissue
  - Endothelium

Proteinuria

- Concurrent disease
  - Inflammation elsewhere (only → small increase)
    - E.g. ACR < 10mg/mmol
  - Long-standing poorly controlled hypertension
    - Rarely above < 3G per day
  - Diabetes mellitus
    - Usually concurrent diabetic retinopathy
  - Connective tissue diseases
  - Medications

When to refer

- Unexplained proteinuria
- Worrisome concurrent diagnosis
  - Connective tissue diseases
- Nephrotic
- Concurrent impaired renal function
- >1G per 24 hours
  - ~ spot > 600mg/L
  - ~ PCR > 60mg/mmol (60g/mol)

Investigations

- Renal function, uric acid, Ca and PO_4
- FBC; ?LFT
- Serum & urine protein electrophoresis
- Renal ultrasound scan
- Others
  - Serology - CT diseases
- ***Renal biopsy***

Management

- Generic
  - Cease offending agent(s)
    - E.g. Nephrotoxins → interstitial nephritis
  - ACEi and/or ARBs
    - Type I diabetes mellitus
    - Other glomerulonephritides
- Specific
  - Immunosuppressives

Management

- Goal is to minimise proteinuria

- General rule:
  - Double ACEi or ARB dose
    → 30-50% reduction in proteinuria
- Limitation of ACEi & ARB
  - hyperkalaemia – when eGFR < 30

Monitoring and follow-up

- Weekly to monthly during initial treatment

- Subsequently 3 monthly ....
  - Takes 3 months, *and up to 2 years* to see maximum benefit of ACEi and ARB dose changes

Dietary salt and proteinuria

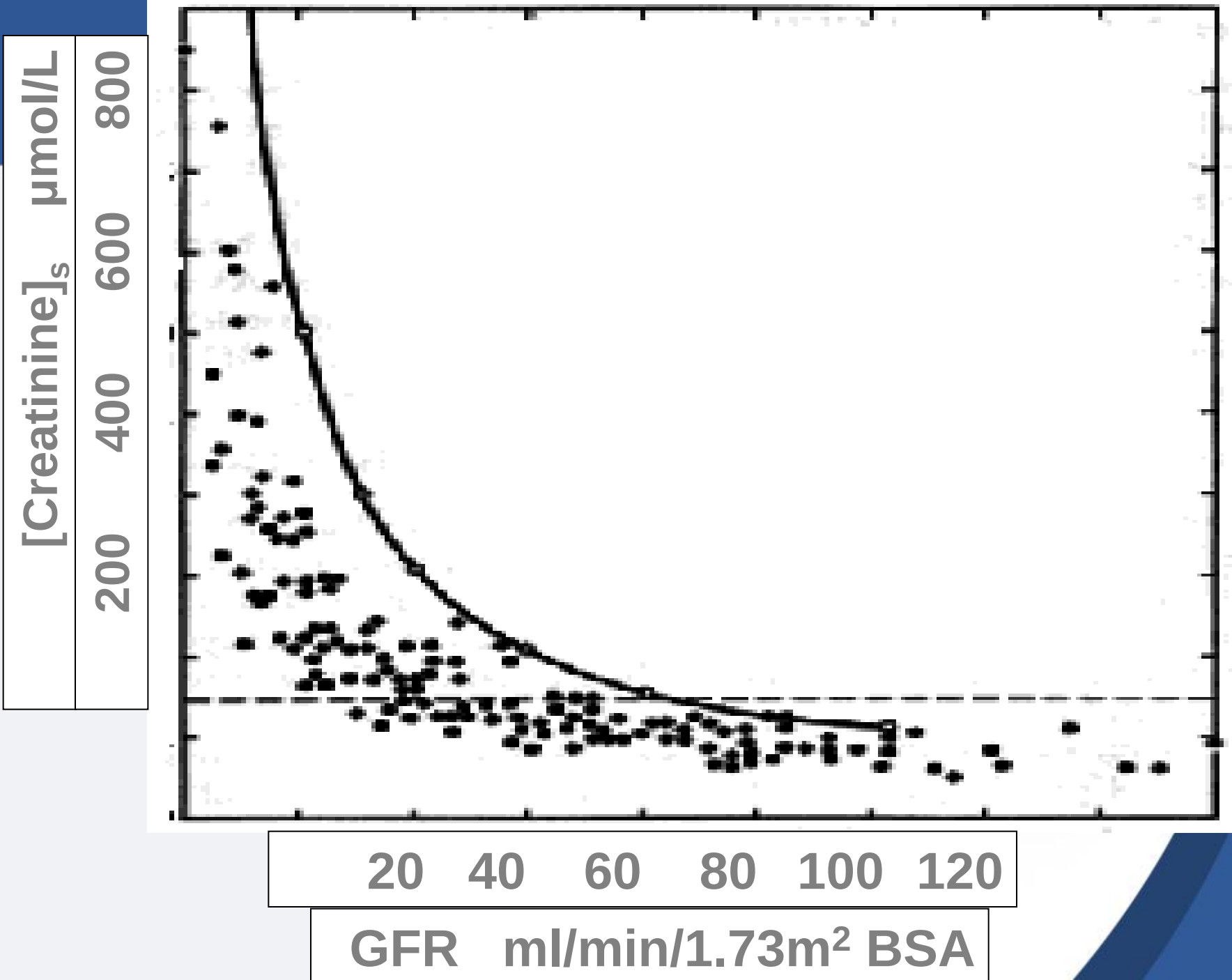
- Anti-proteinuria effects of ACEi and ARB reduced with high salt diet in NON-DIABETICS

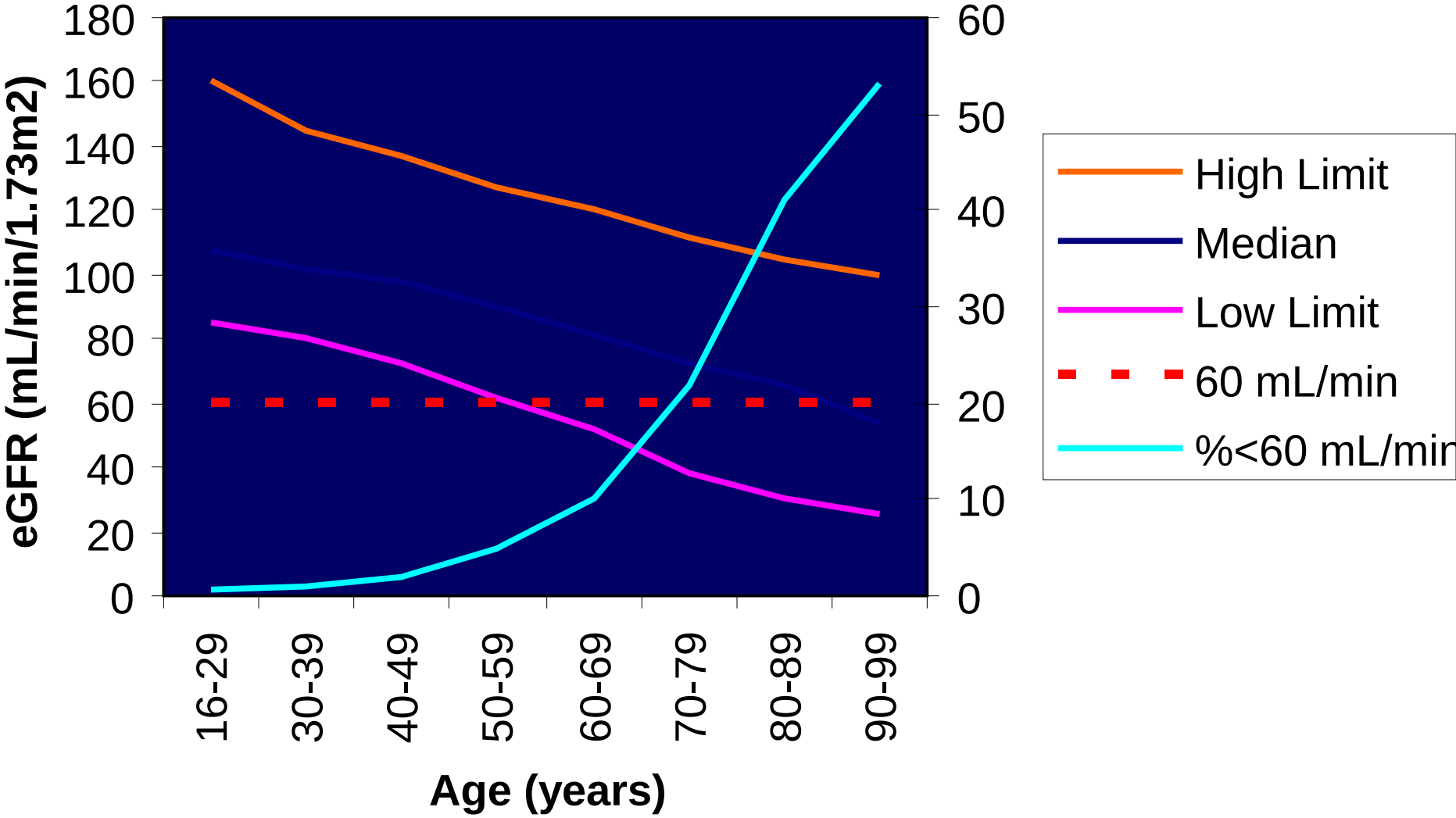
- therefore in the non-diabetic with proteinuria
  - With good BP (systolic < 130mmHg)
  - Should have sodium restricted diet
    - 24 hour urine Na < 100mmol.

Summary - proteinuria

- Dipsticks test for ALBUMIN
  - Will miss tubular protein and myeloma and light chain disease
- Spot urine for proteinuria is satisfactory
- ACEi and ARBs for proteinuria
- Consider salt restriction if treatment failure
- 3-monthly monitoring of progress
- Refer if proteinuria > 1G/24 hours

CKD – Chronic Renal Failure


[Creatinine]s µmol/L
800
600
400
200
20 40 60 80 100 120
GFR ml/min/1.73m² BSA


eGFR (mL/min/1.73m2)
180
160
140
120
100
80
60
40
20
0
60
50
40
30
20
10
0
16-29
30-39
40-49
50-59
60-69
70-79
80-89
90-99
Age (years)
High Limit
Median
Low Limit
60 mL/min
%<60 mL/min

eGFR deteriorates with age (median eGFR for age – a GUIDE)

AGE (years)	Male	Female
60	80mL/min/1.73 m^2	60mL/min/1.73 m^2
65	75mL/min/1.73 m^2	55mL/min/1.73 m^2
70	70mL/min/1.73 m^2	50mL/min/1.73 m^2
75	65mL/min/1.73 m^2	45mL/min/1.73 m^2
80	60mL/min/1.73 m^2	40mL/min/1.73 m^2
85	55mL/min/1.73 m^2	35mL/min/1.73 m^2
90	50mL/min/1.73 m^2	30mL/min/1.73 m^2

CRF stages

Stage	Description	GFR (ml/min/1.73m^2)
1	Kidney damage with normal or ↑ GFR	>= 90
2	Kidney damage with mild ↓GFR	60 – 89
3	Moderate ↓GFR	30 – 59
4	Severe ↓GFR	15 - 29
5	ESRF	< 15

Chronic Renal Failure

- Deterioration rates
  - >60 yo
    - 0.75 to 1 ml/min per annum
      - Lindeman RD, et al. Kidney Int, 26:861; 1984.

- In CRD - depends upon aetiology

  diabetes > PVD / analgesics > gn / PCK

Avoiding Nephrotoxins

- Common toxins
  - Lithium.
  - Chemotherapeutic agents.
  - NSAIDs; COX-2; allopurinol.
  - H_2 / proton pump blockers - omeprazole.
  - OTC/herbals.
  - Fibrates.

Summary – The Management (1)

- Type 1 and 2 probably the same (renally)
- ACEI or ARB
  - Probably both together (type 1 and 2)
- Good glycaemic control
  - HbA1c < 6.5%; certainly <7%
- Good BP control
  - BP <125/75

Summary – The Management (2)

- Minimise proteinuria
  - ACE and ARB
- Avoid nephrotoxins
  - NSAID
- Exercise
  - Ideal weight or at least weight reduction
  - Glycaemic control
- Statins in CRF
  - ?ezetimbe (SHARP trial)

Summary – The Management (3)

- Aspirin
  - Macrovascular disease; IHD
- Folate
  - >2mg daily (once CRF)
- Refer when eGFR < 30ml/min (MoH)
  - <60ml/min
  - Erythropoietin (GFR at 45ml/min)

Medication Dosing

- Renally cleared medications
  - Needs dose reduction
    - Either dose
    - Or frequency
- Avoid nephrotoxins
  - NSAIDs vs COX2 inhibitors
- Non-prescription OTC & herbals
  - “natural”

Medication Dosing

- Care with combinations
  - E.g. NSAIDs and PPI
- Antibiotics
  - Penicillins and cephalosporins
    - Long courses
  - Aminoglycosides
    - High trough levels
  - Vancomycin
    - Long courses and high trough levels

Avoiding Nephrotoxins

- Commonly prescribed nephrotoxins
  - lithium
  - NSAIDs
  - COX-2 inhibitors
  - Allopurinol
  - Cyclosporine; tacrolimus
  - H_2 / proton pump blockers
  - Fibrates