Apollo BRAMWELL HOSPITAL

COMMITTED TO HEALING,
DEVOTED TO CARING

CHRONIC KIDNEY DISEASE
-AN OVERVIEW-

Dr.Asit Mehta

Consultant Nephrologist & Transplant Physician

WHY ARE WE DISCUSSING CHRONIC KIDNEY DISEASE (CKD)

- Kidney failure is a worldwide public health problem.
- Consequences of CKD are many and complex and include hypertension ,anemia, acidosis ,the interrelated phenomena of renal malnutrition and inflammation and varied consequences of aberrant bone mineral metabolism.
- Responsible for high morbidity and mortality.
- Incurs great financial burden on government and society

DEFINATION OF CKD

1. Kidney damage for more than or equal to 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest

   by either:

- Pathological abnormalities; or
- Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests.

2. GFR < 60 mL/min/1.73 m2 for > 3 months, with or without kidney damage.

CKD : ESSENTIALS OF DIAGNOSIS

- Progressive azotemia over months to years.
- Signs and symptoms of uremia when nearing end stage.
- Hypertension in majority
- isosthenuria and broad cast in urinary sediment are common.
- B/L small kidneys on ultrasound examination.

Stages of CKD

GFR (ml/min)	With Kidney Damage		Without Kidney Damage*	
	With HBP	Without HBP	With HBP	Without HBP
≥90	1	1	HBP	Normal
60-89	2	2	HBP with ↓ GFR	↓ GFR
30-59	3	3	3	3
15-29	4	4	4	4
< 15	5	5	5	5

ESTIMATION OF GFR

(1) Cockroft & Gault Formula :-

$$\text{Crcl (ml /min.)} = \frac{(140 - \text{Age}) \times \text{wt.} \times (0.85 \text{ if female})}{72 \times \text{S.creatinine}}$$

(2) MDRD Formula

(3) Schwartz Formula

$$\text{Crcl (ml /min.)} = \frac{0.55 \times \text{length}}{\text{S.Cr.}}$$

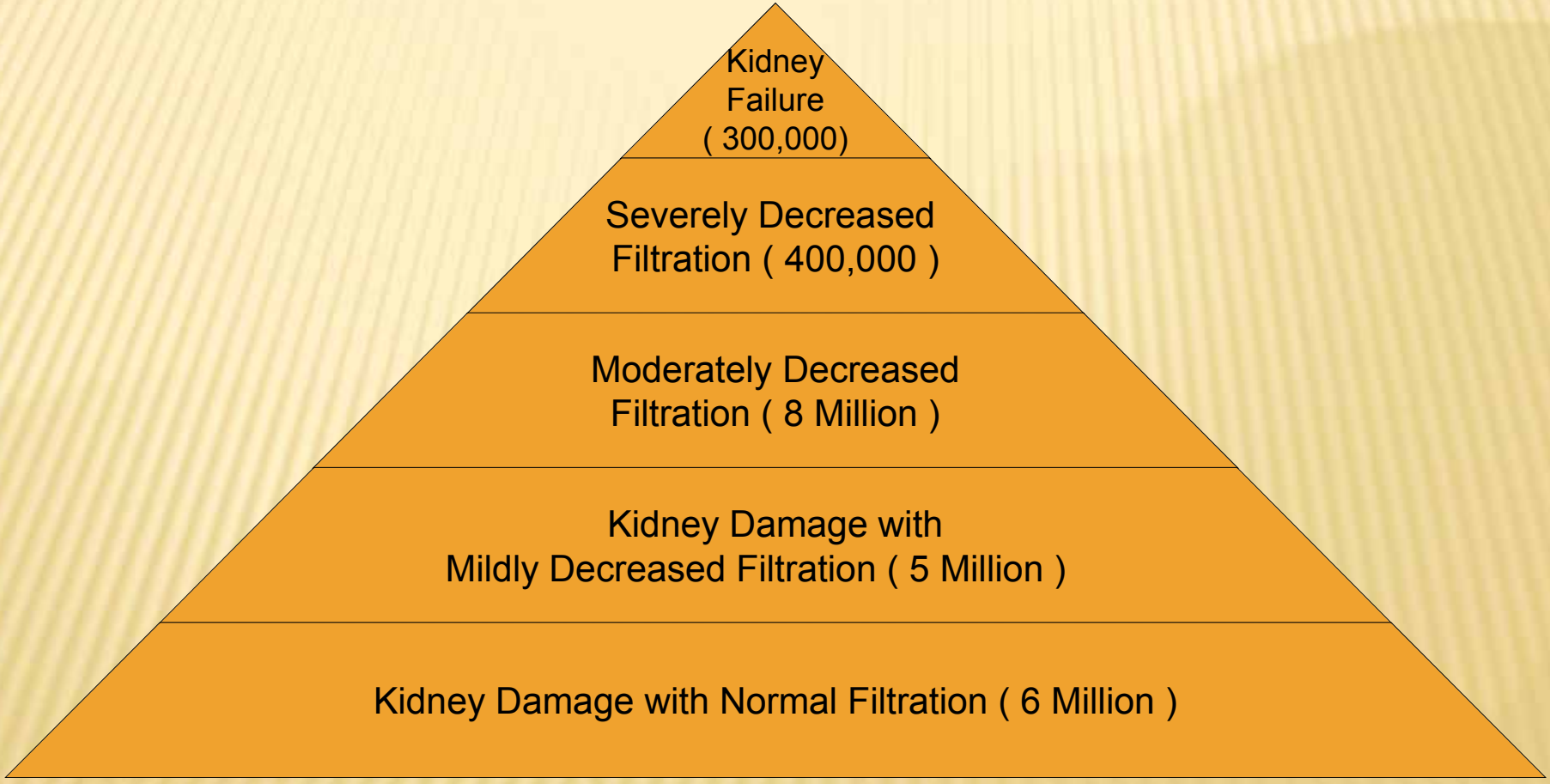
CAUSES OF CKD

- Diabetes
- Glomerulonephritis
- Chronic Interstitial nephrits
- Hypertension
- Others…
  - ADPKD
  - Renal calculus disease
  - Analgesic Abuse
  - Alport’s syndrome

INCIDENCE AND PREVALANCE OF CKD

- Increasing worldwide.
- The NHANES DATA - 2007 in a population based survey in USA estimated that 16.8% of adult population aged >20 years may have some stage of CKD.
- USA data also suggest that for every patient with ESRD there are more than 200 pts. with overt CKD in stage III & stage IV and almost 5000 patients with covert renal disease (stage I & Stage II)

SPECTRUM OF CKD IN USA



Incidence of ESRD (End Stage Renal Disease) -

- European average ~ 130pmp/year
- United States ~ 333pmp/year

Rise in ESRD patients worldwide most likely reflects :

1) Aging of the population –

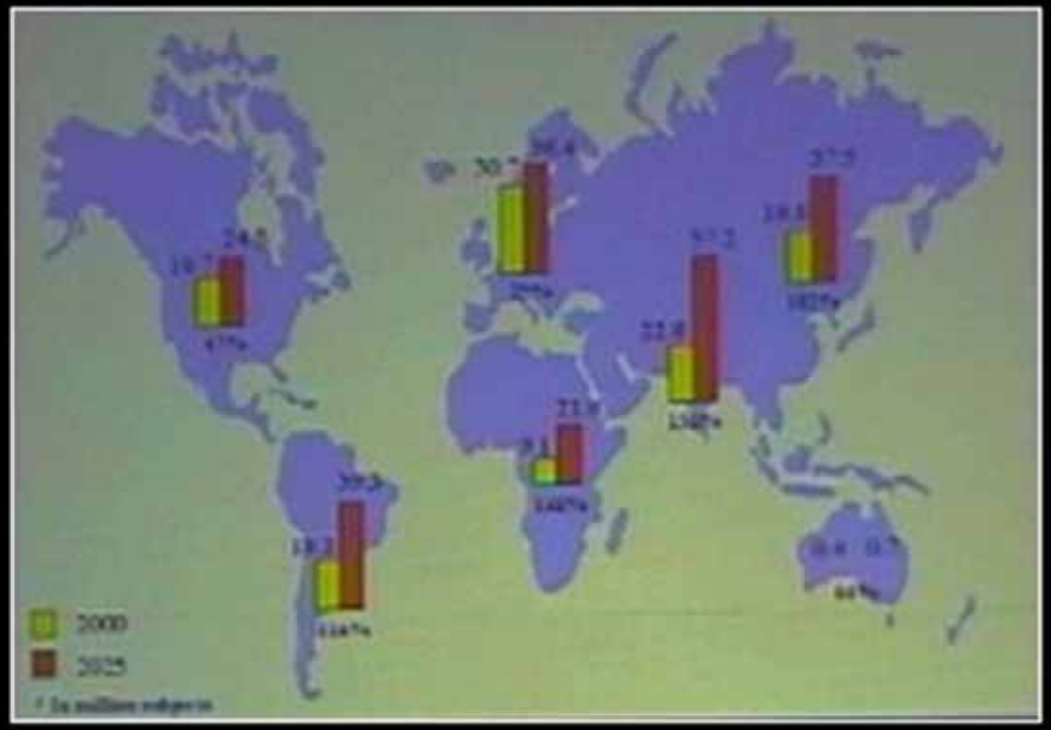
Annual incidence of ESRD in population older than 65 years –

UK ~ 350pmp/year

US ~ 1200pmp/year.

2) Global epidemic of type 2 diabetes mellitus

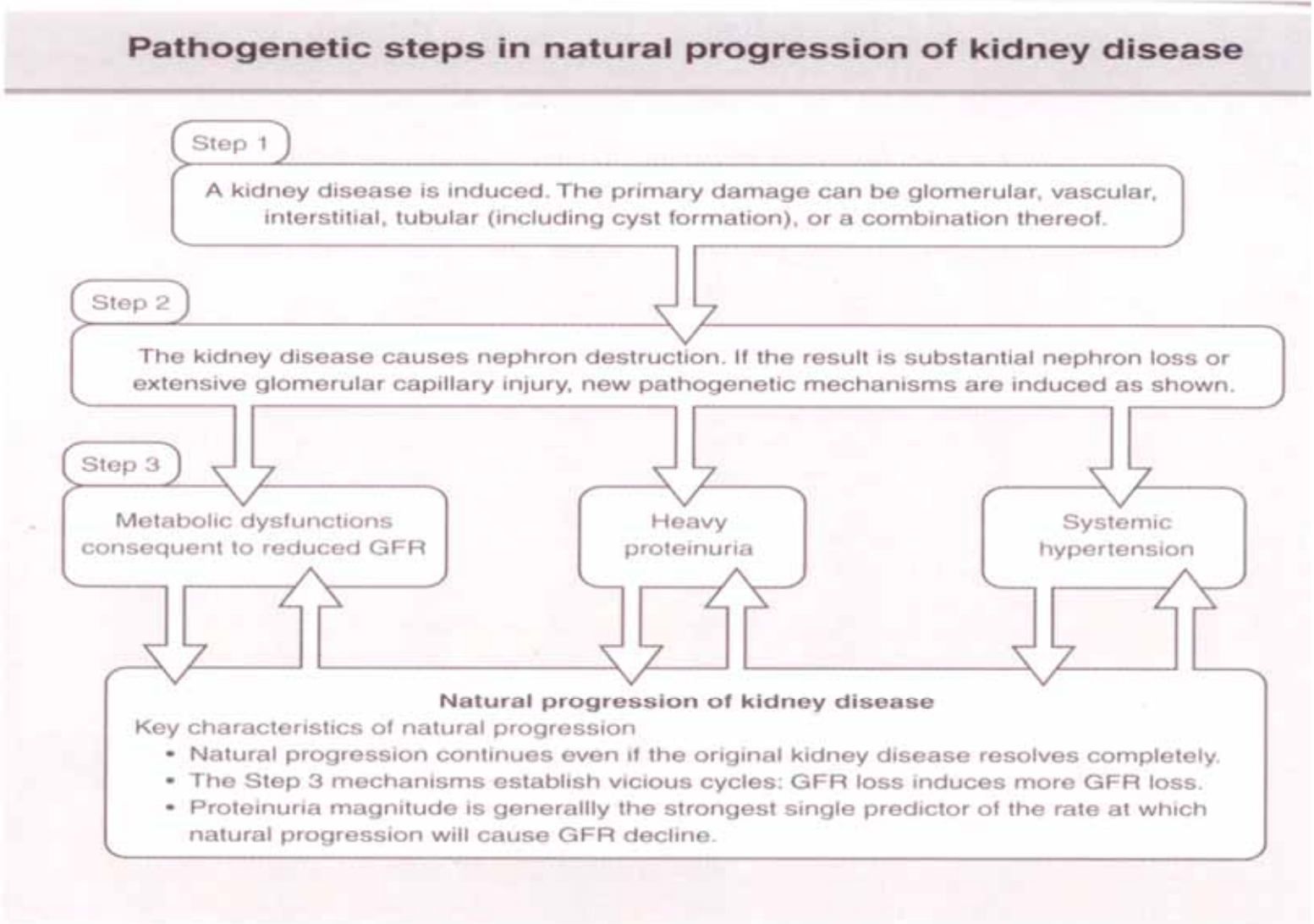
The Global Burden of Diabetes (2000 – 2025)



	World	Developed	Developing
2000	154 m	55 m	99 m
2025	300 m	72 m	218 m

The Global Burden of Chronic Diseases: The Way Forward

Chronic non-communicable conditions (including diabetes, high blood pressure, and chronic renal diseases) are expected to become the main cause of death and disability in the world by 2020, contributing around the two thirds of global burden of disease, with enormous healthcare costs for societies and governments



ure 69.1 Pathogenetic steps in natural progression of kidney disease. The mechanisms of natural progression are arbitra decreased glomerular filtration rate (GFR), proteinuria, and systemic hypertension.

Management plan for chronic kidney disease patients, according to stage

K/DOQI Class	GFR (ml/min)	Typical Serum Creatinine in a 65-kg Subject	Consequences	Action
3	30–59	2 mg/dl (170 µmol/l)	Hypertension, secondary hyperparathyroidism	Treat hypertension Start phosphate restriction phosphate binders Start vitamin D analogue Immunize against hepatitis
4	15–29	4 mg/dl (354 µmol/l)	+ Anemia	Restrict dietary potassium 60 mmol/day Advise moderate protein restriction Plan renal replacement the including vascular access
5	<15	8 mg/dl (707 µmol/l)	+ Sodium and water retention, anorexia, vomiting, reduced higher mental function	Plan elective start of dialysi or pre-emptive renal transplantation
5 (uremic emergency)	<5	17 mg/dl (1503 µmol/l)	+ Pulmonary edema coma, fits, metabolic acidosis, hyperkalemia, death	Start dialysis or provide pall care

Figure 70.2 Management plan for patients with chronic kidney disease (CKD), according to stage. The table gives a rough guide to the level c creatinine corresponding to each stage of CKD in a typical 65-kg subject and shows the approximate timing of the anticipated clinical problems and inter required as CKD progresses. At each stage, the action plan for the previous CKD stage should be followed if not already initiated.

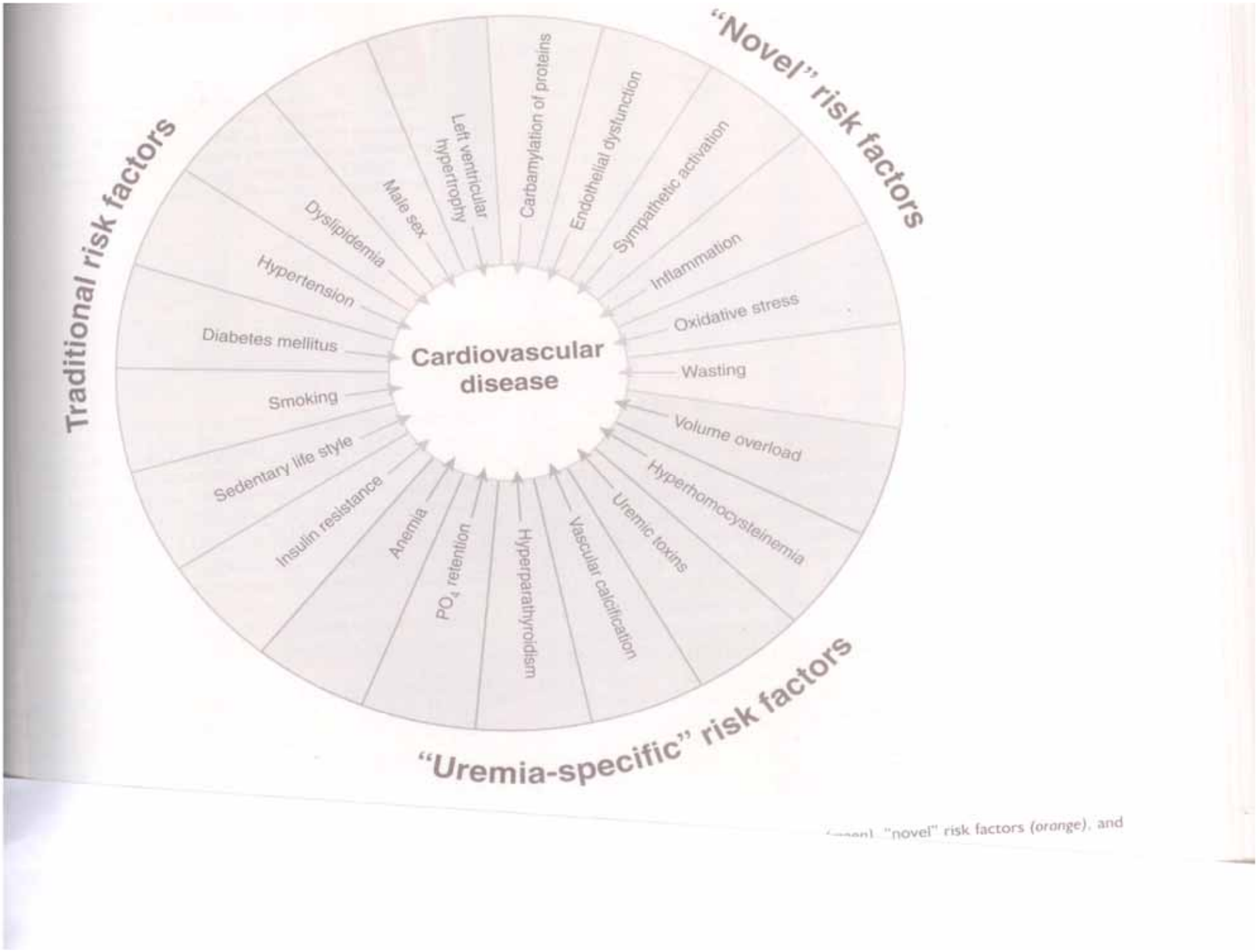
COMPLICATIONS OF CHRONIC KIDNEY DISEASE

- Anemia
- Renal Osteodystrophy
- Cardiovascular complications
- Malnutrition.
- Sleep Disorders.
- Neurological complications
- Gastro-intestinal complications
- Dermatological complications

KIDNEY DISEASE AS A RISK FACTOR FOR DEVELOPMENT OF CARDIOVASCULAR DISEASE

- High risk of CVD in CKD
- Individuals with CKD are more likely to die of CVD than to develop kidney failure
- The Force on Cardiovascular Disease in Chronic Renal Disease report:
  - high prevalence of CVD in CKD
  - mortality due to CVD was 10 to 30 times higher in dialysis patients

Sarnak MJ, et al. Hypertension 2003; 42: 1050 –1065.



"novel" risk factors (*orange*), and

ANAEMIA AND CKD

- Anaemia is highly prevalent in patients with CKD, and Hb levels decrease with declining GFR[1]
  - anaemia becomes evident in stage 3 CKD[2]
  - up to 50% of patients with stage 3–5 CKD may have anaemia[3]
- Anaemia is associated with significant mortality and morbidity in patients with CKD[4]
- Anaemia in patients with CKD increases the burden of CVD[5]
- Quality of life (QoL) is negatively affected by anaemia in patients with CKD[6]

1. Astor et al. *Arch Intern Med.* 2002;162:1401-1408
2. Thorp et al. *Dis Manag*. 2006;9:115-121
3. McClellan et al. *Curr Med Res Opin.* 2004;20:1501-1510
3. Locatelli et al. *Nephrol Dial Transplant.* 2004;19:121-132
4. Silverberg. *Nephrol Dial Transplant.* 2003;18(Suppl 2):ii7-12
5. Perlman et al. *Am J Kidney Dis.* 2005; 45:658-666

ERYTHROPOIETIN AND THE PATHOPHYSIOLOGY OF RENAL ANAEMIA

- Renal disease in progressive renal failure is almost always accompanied by a normochromic, normocytic anaemia†
- Severity of anaemia correlates with severity of kidney disease
- Anaemia associated with kidney disease results from multiple factors
  - failure of the erythropoietin response as a result of kidney damage
  - significant reduction in circulating RBC lifespan secondary to uraemia
  - reduced bone marrow response to circulating erythropoietin

†anaemia characterised by RBCs which are normal in morphology and Hb content, but are too few to sustain adequate oxygen transport

ANAEMIA MANAGEMENT: GOALS AND CHALLENGES

- Goals of optimal anaemia management
  - successfully achieving target Hb levels as recommended by current guidelines[1-4]
  - successfully maintaining stable Hb levels within target ranges
- Challenges in achieving these goals
  - forecast rise in prevalence of CKD
  - difficultly in achieving Hb targets
  - difficulty in maintaining target Hb levels once achieved

1. CSN 1999; 2. EPBG 2004; 3. CARI 2006; 4. KDOQI 2007

GUIDELINES FOR ANEMIA MANAGEMENT

- Exclude causes other than EPO deficiency i.e iron, B12, folate deficiency, occult GI bleed.
- If ferritin< 100 mcg /litre consider trial of IV iron alone - 200-500 mg.
- If ferritin >100 or no response to I/V iron start EPO
- Monitor and maintain iron status

ERYTHROPOEITIN THERAPY

- Conventional EPO: Needs to be given twice/thrice weekly
- 2nd generation Darbopoetin Alfa(Aranesp)

  -Greater half life

  -Can be given once a week or fortnightly
- CERA –

  MIRCERA (Roche) - Once a month

CAUSES OF A POOR RESPONSE TO ESA THEARAPY

Major : Iron Deficiency

: Infection / Inflammation

: Underdialysis

Minor : Poor Compliance, poor adherence to ESA therapy

- :Blood loss
- :Hyperparathyroidism
- : Vitamin B 12 or Folate deficiency
- : Primary Bone marrow disorders
- : ACE Inhibitors therapy
- : Carnitine deficiency
- : PRCA

HALF LIFE OF VARIOUS EPO

Agent	Population	Mean (± SE) half-life (h)	
		IV	SC
Epoetin alfa	Healthy volunteers[1]	6.8 ± 0.6	19.4 ± 2.5
Epoetin beta	Healthy volunteers[1]	8.8 ± 0.5	24.2 ± 2.6
Darbepoetin alfa	Peritoneal dialysis patients[2]	25.3 ± 2.2	48.8 ± 5.2
	Pre-dialysis patients[3]	-	69.6 (29.8)†
MIRCERA	Healthy volunteers[4]	133 ± 9.8	137 ± 21.9
	Peritoneal dialysis patients[4,5]	134 ± 19	139 ± 20

†Mean (SD)

1. Halstenson et al. *Clin Pharmacol Ther*. 1991:50:702-712
2. Macdougall et al. *J Am Soc Nephrol*. 1999;10:2392-2395
3. Padhi et al. *Clin Pharmacokinet*. 2006;45:503-510
4. Macdougall et al. *Am J Kidney Dis*. 2006;47:A41
5. Macdougall et al. *J Am Soc Nephrol*. 2005; 16:759A

MIRCERA: SUMMARY OF SC CORRECTION
PHASE II

- Phase II data suggest that SC MIRCERA at extended administration intervals
  - can effectively correct Hb levels in ESA-naïve patients
  - can maintain stable Hb levels within target range (11–12 g/dL) in the long term
- SC MIRCERA 0.60 μg/kg Q2W appears to be a suitable starting dose for anaemia correction in both CKD patients on dialysis and not on dialysis

IRON MANAGEMENT

- CKD patients are frequently in negative iron balance.
- Iron absorption capacity in patients with CKD is consistently lower than in nonuremic individuals
- Inadequate supply of iron to bone marrow due to –
  -Absolute iron deficiency-Low whole body iron stores - Ferritin <30

  -Functional iron deficiency-Where there is ample or even increased storage iron but the stores fail to release iron rapidly enough to satisfy demands of bone marrow.

RECOMMENDED RANGE OF MARKERS OF IRON

Status in CKD patients

- S. ferritin 200-500
- Transferrin Sat. 20-40%
- Hypochromic red cells <6%

FACTORS IMPACTING ON HB VARIABILITY

OPTIMAL ESA USAGE MAY IMPROVE STABILITY

Patient-related factors	Intercurrent events	Practice pattern-related
• Vascular access modality • RBC survival • Secondary hyperparathyroidism • Cancer • Haematology disorders • Diabetes	• Hospitalisation • Infection • Inflammation • Bleeding / haemolysis • Nutritional deficiencies • PRCA • Medications • Interdialytic weight gain	• ESA dose changes • Protocol design and lab monitoring • Narrow target Hb range • Iron management • Dialysis adequacy • Payment restrictions • Water purity

Limited capacity for physician influence

Fishbane & Berns. *Kidney Int*. 2005;68:1337-1343;
Gilbertson et al. *Nephrol Dial Transplant*. 2006;21(Suppl 4):iv169

ANAEMIA IN CKD: SUMMARY

- The hormone erythropoietin is the physiological regulator of RBC production and lifespan
- In individuals with CKD, damage to the kidney compromises erythropoietin production
- Anaemia correlates with the severity of CKD
- Strong inter-relationships exist between CKD, anaemia, and CVD

SPECTRUM OF BONE DISEASE IN CKD

- Osteitis Fibrosa-/hyperparathyroidism
- Osteomalacia-Defective mineralisation of newly formed osteoid most often caused by aluminium deposition
- *Adynamic bone disease-Low bo*ne turnover
- Osteopenia or osteoporosis
- Combination of these abnormalities termed mixed renal osteodystrophy

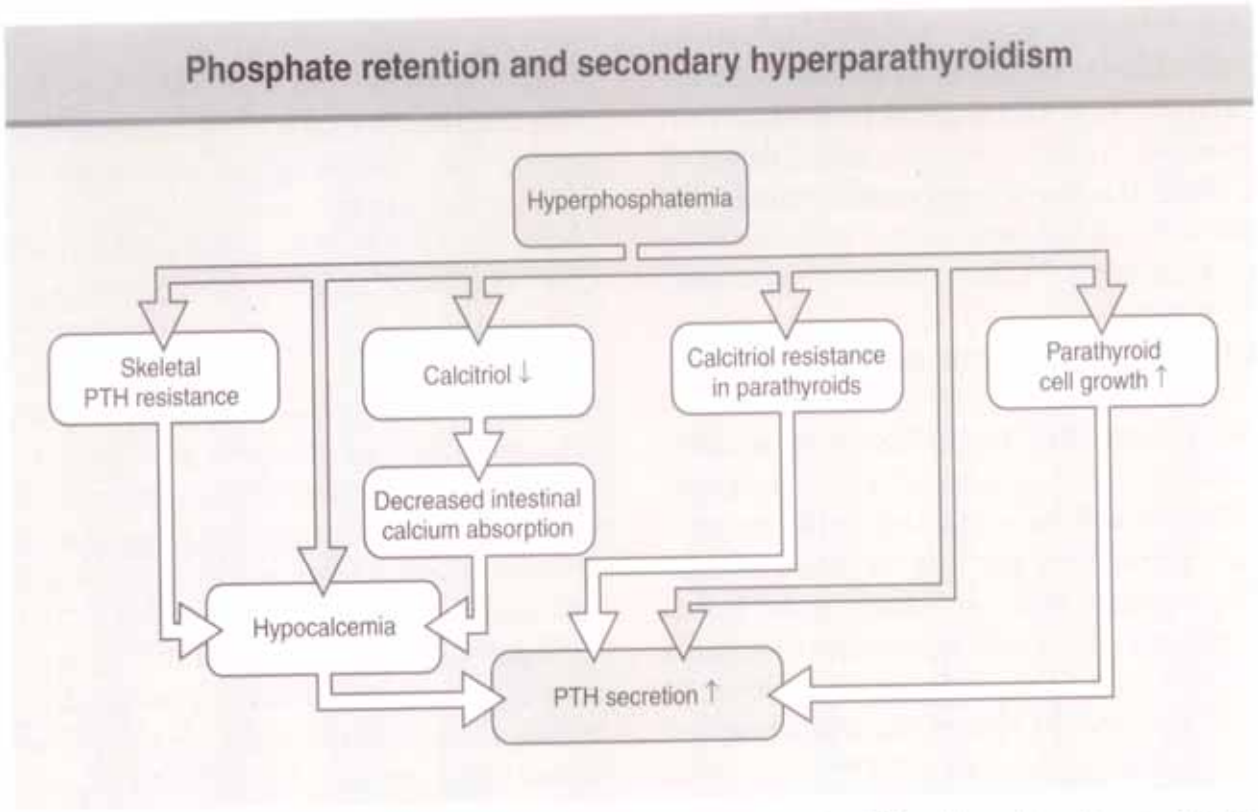


Figure 74.4 Role of phosphate retention in the pathogenesis of secondary hyperparathyroidism. Hyperphosphatemia stimulates parathyroid hormone (PTH) secretion indirectly by inducing hypocalcemia, skeletal resistance to PTH, low levels of calcitriol, and calcitriol resistance. Hyperphosphatemia also has direct effects on the parathyroid gland to increase PTH secretion and parathyroid cell growth.

... skeletal resistance to the calcemic actions of

Calcitriol and secondary hyperparathyroidism

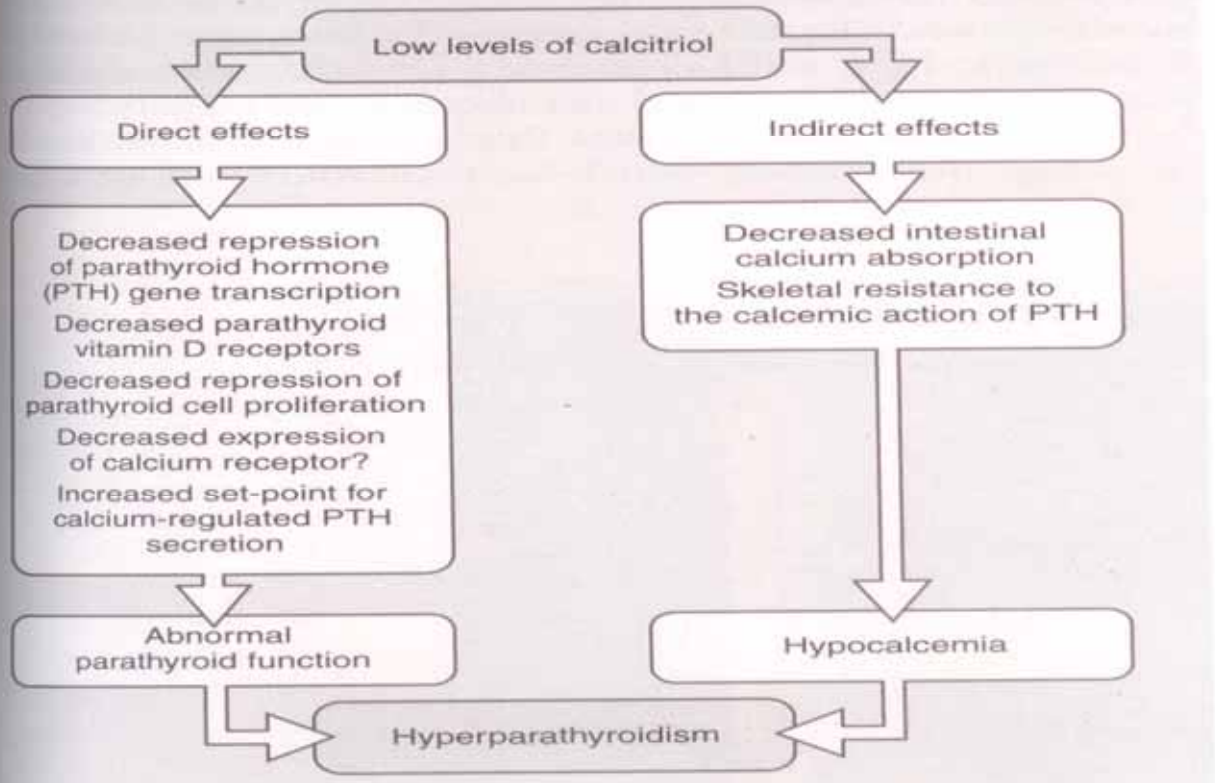


Figure 74.5 Role of low levels of calcitriol in the pathogenesis of secondary hyperparathyroidism.

ADYNAMIC BONE DISEASE

- Complex pathogenesis-causes
- Characterised by decreased PTH levels in serum
- Use of calcium containing phosphate binders
- Use of active vitamin D sterols-----?
- High calcium dialysate for CAPD fluids
- Diabetes
- Circulating uremic toxins
- Clinically ABD associated with increased fractures and increased mortality

TREATMENT

- Prevention is primary goal
- Therapy should be initiated early in course of CKD(GFR 50-80 ml /min) to prevent parathyroid hyperplasia

1) Prevention of hypocalcemia(potent stimulus for PTH secretion

- Calcium supplements-Calcium carbonate taken between meals
- Measurement of 25 hydroxyvitamin D to assess vit D status if < 30 ng/ml-correction to be done
- Active vitamin D sterols used if hypocalcemia/hyperparathyroidism persists
- Goal is to achieve levels of intake PTH (150-300/ml)

TREATMENT-CONTINUE

2) Control of phosphate
Dietary phosphate restriction
Phosphate binders-calcium carbonate
-Calcium acetate
-Magnesium carbonate
Newer phosphate binders (Non absorbable polymers)
-Sevelemar hydrocholride (Renagel)
-Lanthanum carbonate
3) Use of Vit. D metabolites-calcitriol
Paracalcitol
Problems:Hypercalcemia
Risk of adynamic bone disease
Ca/P product (<55)

ROLE OF CALCIMIMETIC AGENTS

- Recently introduced approach to the treatment of refractory hyperparathyroidism
- Target the calcium sensing receptor and increase its sensitivity to calcium
- Cinacalcet.
- Dose – 30 mg once a day – (max. upto 120 mg)

RETARDING PROGRESSION OF RENAL DISEASE

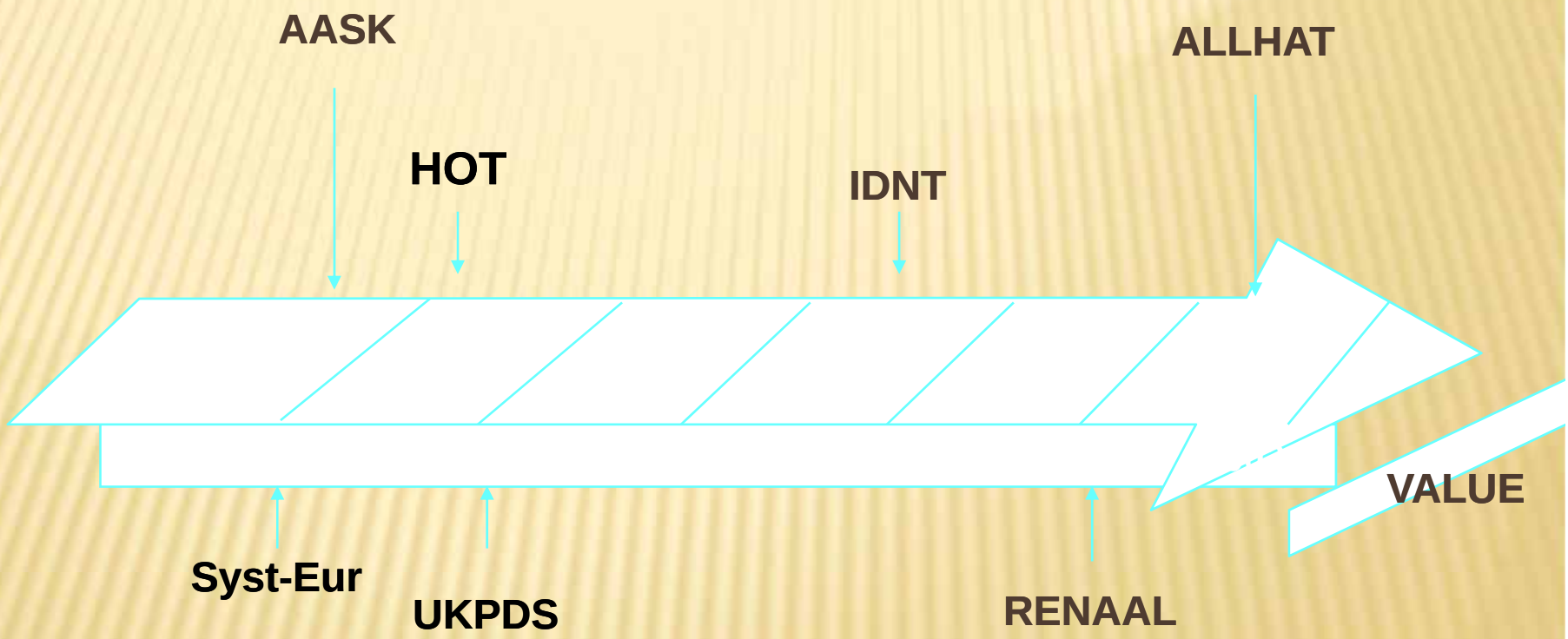
1. Specific renoprotective therapy .
   ACEI or ARB treatment

- Proteinuria < 0.5 g/day
- GFR decline <2ml/min/year

2. Adjunctive cardiorenal protective therapy

- Additional antihypertensive therapy
  BP Goal > 130 / 80
- Dietary protein restriction
  0.6-0.8 g/kg/day

Clinical Trial Update



AASK: African American Study of Kidney Disease and Hypertension

Objective

- **To compare the effects of 2 levels of BP control and 3 different antihypertensive regimens on the progression renal disease in 1094 non-diabetic African American hypertensive patients with chronic renal insufficiency**

Design

- **Prospective, double-blind, randomized, multi-center trial**

BP Levels

- **Usual MAP (102-107 mm Hg) n = 554**
- **Low MAP (≤92 mm Hg) n = 540**

Therapy

- **Calcium antagonist (amlodipine, n = 217), ACE inhibitor (ramipril, n = 436), or β-blocker (metoprolol, n = 441) for 4 to 6 y**

Hall WD et al. Ethn Dis 1997; 7(s

AASK - Conclusions

- The AASK data are consistent with the hypothesis that careful, aggressive BP control is crucial to limiting the progression of renal failure
- The risk of these complications has been shown to be lowered by dihydropyridine calcium channel blockers in a number of clinical endpoint trials, several of which are referenced by the authors of AASK

Agodoa LY, et al. JAMA 2001; 285(2

REDUCTION OF ENDPOINTS IN NIDDM WITH THE ANGIOTENSIN II ANTAGONIST LOSARTAN (RENAAL

Objective:

To compare the effect of losartan *vs* placebo as add-on therapy on the progression of renal disease in type II diabetic patients

Design:

- 1513 NIDDM patients with serum CRTN 1.5-3.0 mg/dl for men and 1.3-3.0 mg/dl for women and albumin/creatinine excretion ratio > 300 mg/g

1° End-points:

- Follow-up 4.5 years
  Doubling of serum creatinine
  End stage renal disease
  Death

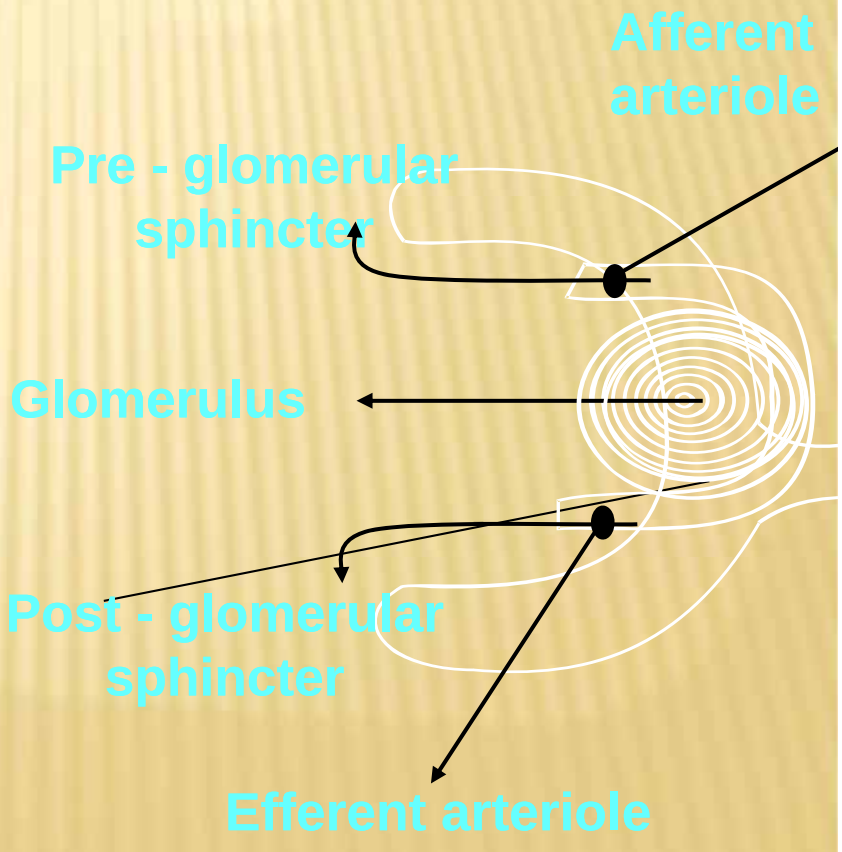
Losartan plus conventional therapy (over 60% in both groups on DHP CCBs) showed significant reduction in risk of progression of kidney disease by 16% ($p < 0.024$)

Brenner BM, et al. NEJM 2001; 345(12): 861-869.

MECHANISMS OF RENOPROTECTION OF ACEI, ARB - DIABETIC NEPHROPATHY

- Lower systemic and intraglomerular blood pressure slows the rate of loss of glomerular filtration
- ACE inhibitors and ARBs slow progression of diabetic nephropathy independent of BP
  - ↓ intraglomerular hypertension
  - Modulate glomerular permselectivity

GBM –ve charge
Hyperglycemia negates -ve charge on GBM



RETARDING PROGRESSION OF RENAL DISEASE

- Dietary salt restriction – 3 – 5g /day
- Tight glycemic control - Hba1c.<6.5 %
- Lipid-lowering - LDL-C < 100mg/dl
- Consider correction of anemia – Hb 11-12
- Smoking cessation
- Weight control

GFR DECLINE

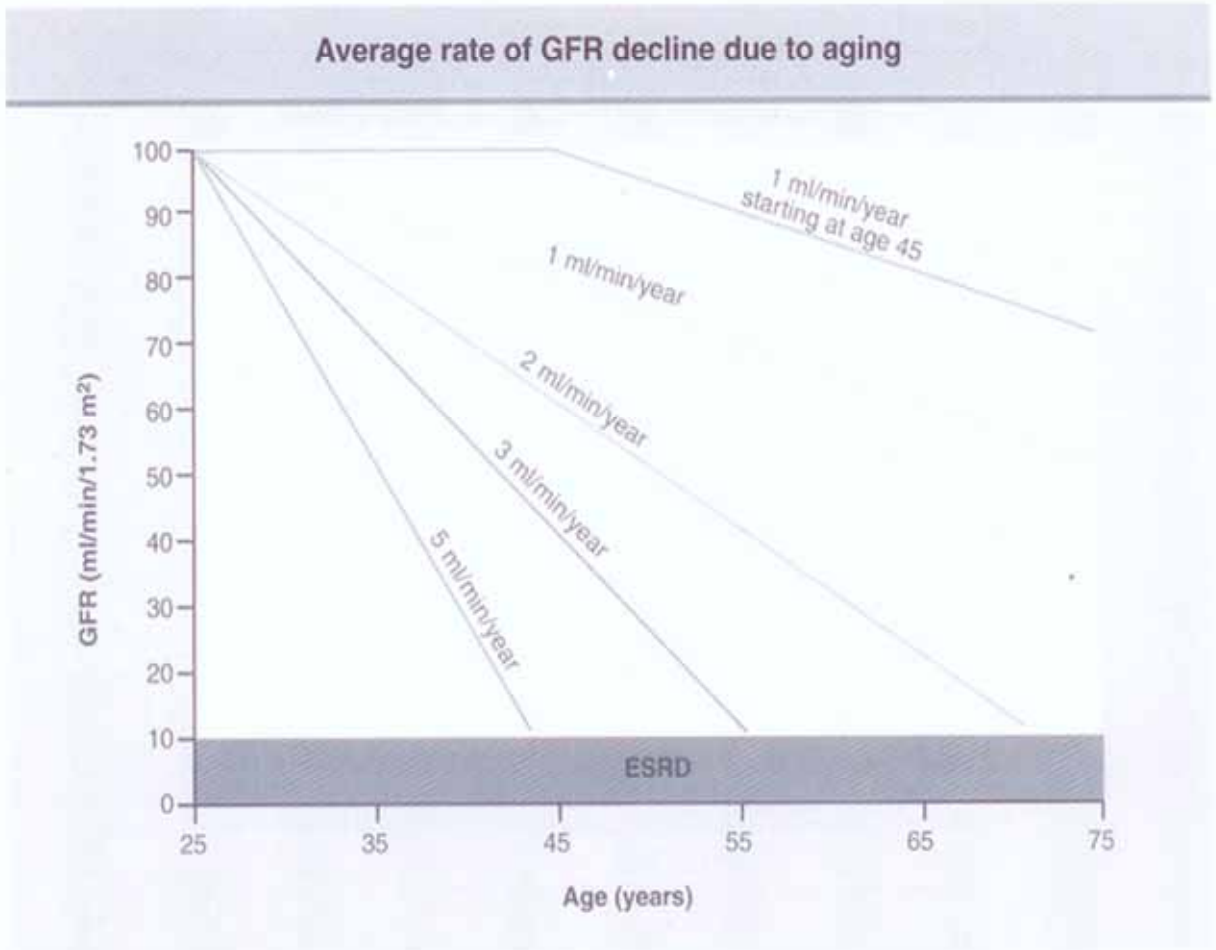


Figure 69.3 Average rate of glomerular filtration rate (GFR) decline due to aging. This average rate *(top curve)* is compared to hypothetical patients each with the onset of a progressive kidney disease at age 25 years but with different rates of GFR decline. Note that small differences in GFR decline can result in large differences in time to onset of end-stage renal disease (ESRD). (From Hebert LA, Wilmer WA, Falkenhain ME, et al: Renoprotection: One or many therapies? Kidney Int 2001;59:1211–1126.)

Recipe for Prevention of Kidney Failure

- Prevent obesity
- Keep physically fit
- Stop your smoking!
- Control blood pressure adequately
- Control diabetes
- Treat proteinuria and early kidney failure
- Treat elevated cholesterol and lipids
- Treat anemia
- Treat calcium and phosphorous abnormality
- Have regular follow-up and treatment as necessary

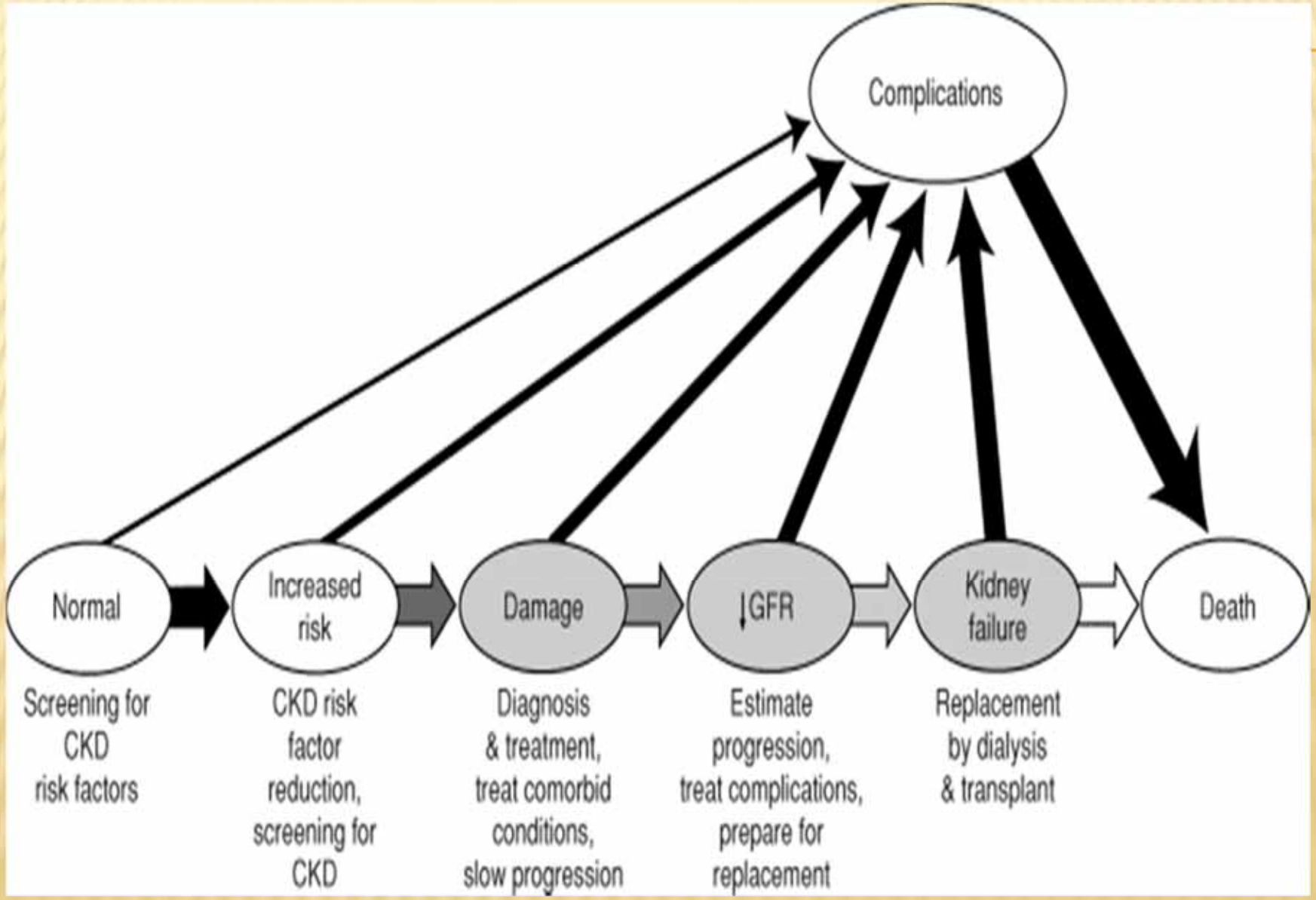
The Polypill for Prevention

One pill containing – at low doses – a statin

- Thiazide diuretic
- Beta blocker
- ACE inhibitor
- Folic acid
- Aspirin

Wald and Law, BMJ, 2003

CONCEPTUAL MODEL OF THE MOURSE OF CKD



SCREENING FOR CKD

- Screening of general population not feasible on account of cost.

- Screening high risk population seems more practical.

- Screening is simple and most cases can be diagnosed by simple laboratory tests like urine R/M & simple blood pressure measurement.

TAKE HOME MESSAGE

- CKD - a silent epidemic
- Prevention and early detection is important .
- Early referral to nephrologists helps in retarding the progression of renal disease and reducing the mortality and morbidity in patients with CKD.