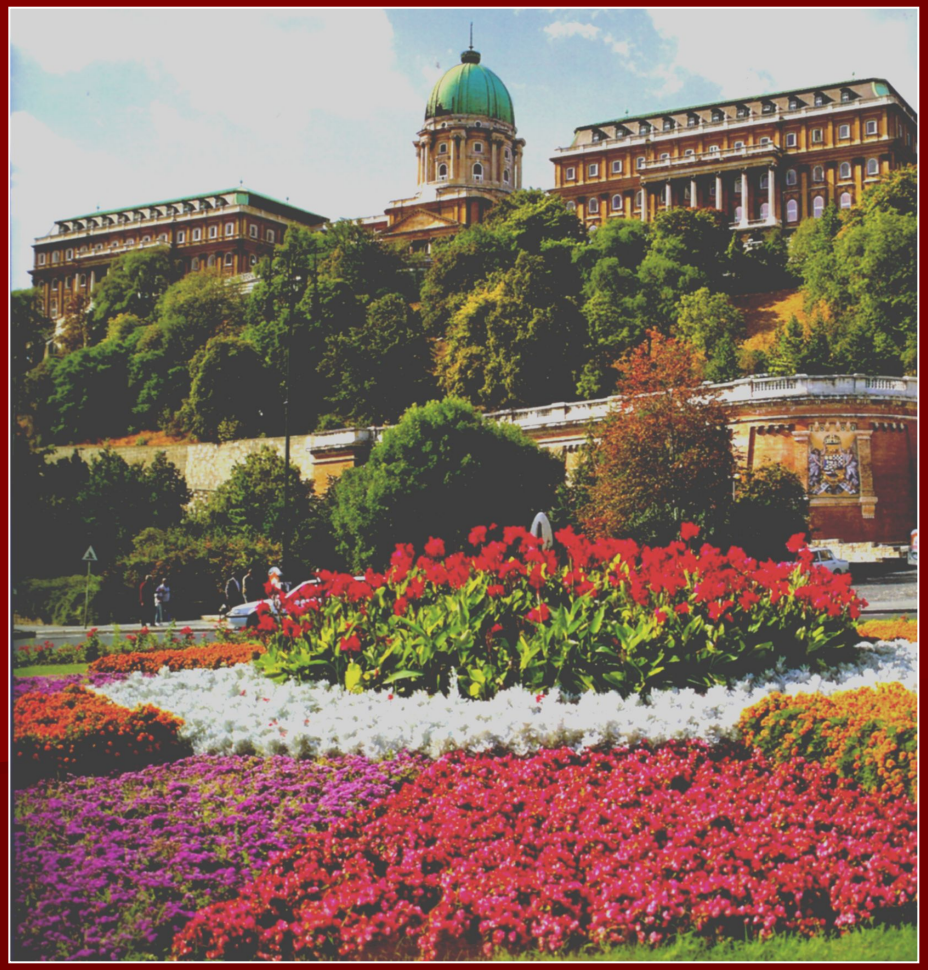
Chronic Renal Failure

Chronic Kidney Disease 2004

“*Mutatis mutandis*”



Chronic Kidney Disease: Another Epidemic

Third National Health and Nutrition Examination Survey:

-19.2 million have Chronic Kidney Disease (11%)
-7.6 million have Stage III Chronic Kidney Disease (4.3%)
-0.7 million have Stage IV and End Stage Renal Disease (0.4%)

Definition of:

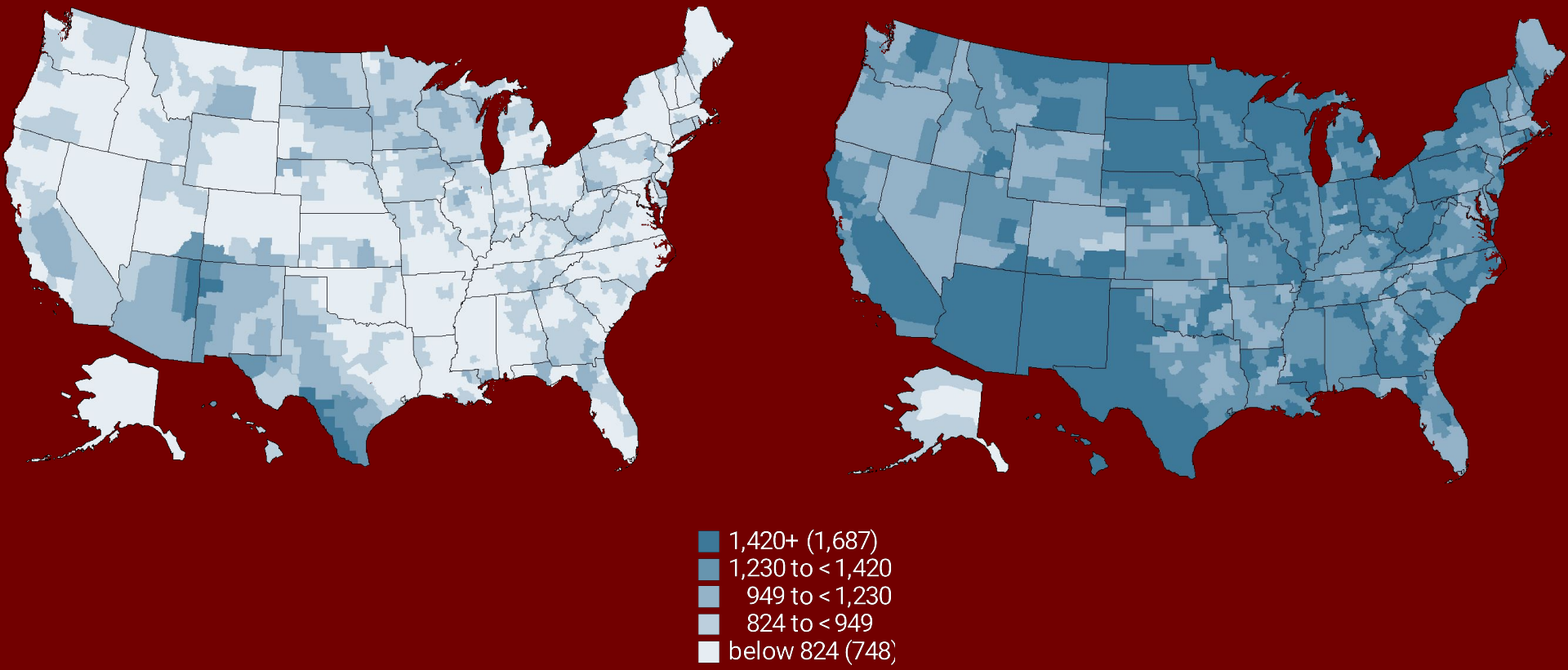
-Chronic Kidney Disease =**GFR<60 ml/min/1.73 m^2 or persistent albuminuria**

-Stage III Chronic Kidney Disease=GFR 20-39 ml/min/1.73 m^2

American Journal of Kidney Diseases Vol 41, No 1, 2003: pp1-12

Prevalence of ESRD: 1991 versus 2001

(per million population)



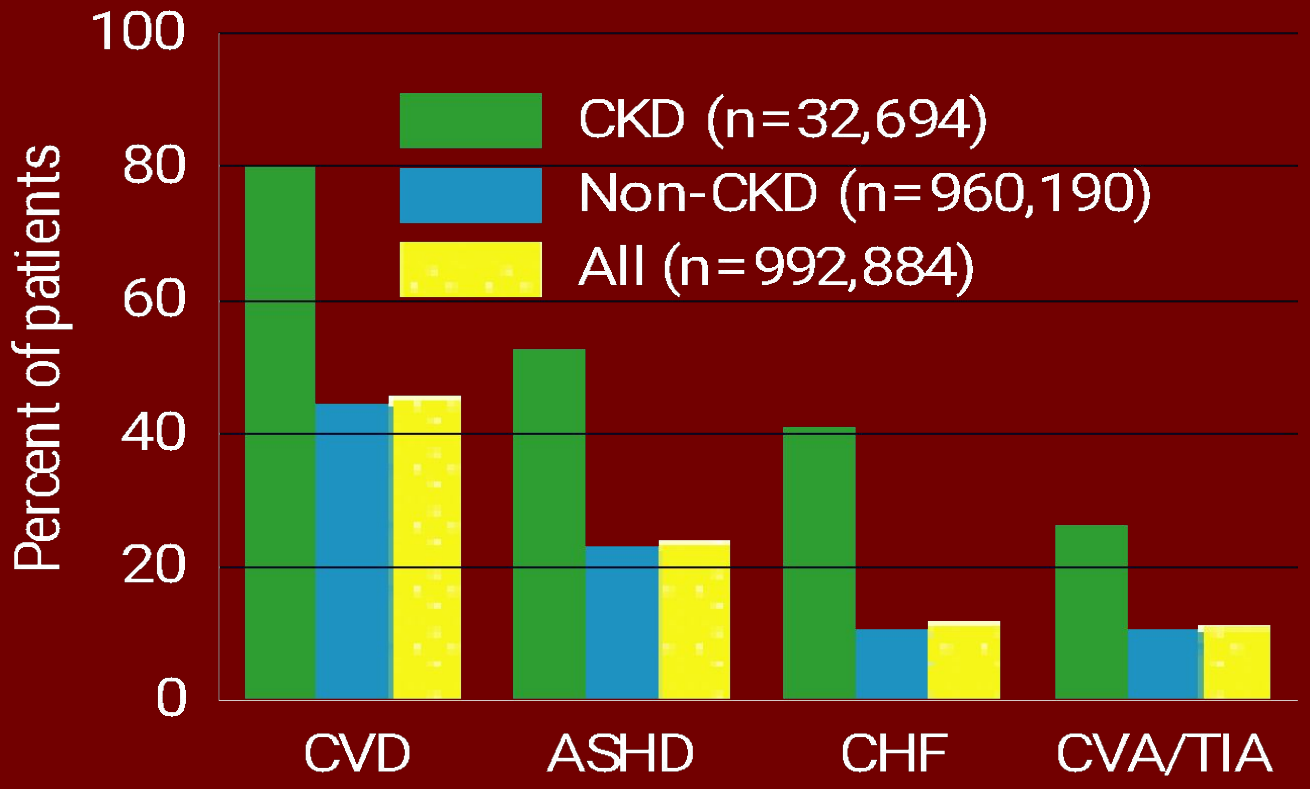
CKD: Problem for the Internist

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII)

Major Cardiovascular Risk Factors:

- -Hypertension
- -Cigarette Smoking
- -Obesity (BMI>30)
- -Physical Inactivity
- -Dyslipidemia
- -Diabetes Mellitus
- -**Microalbuminemia or Estimated GFR<60**
- -Age (>55 for men, >65 for women)
- -Family history of premature coronary artery disease (men<55, women<65)

Heart Disease is Highly Prevalent in the CKD Population



More Than Catches the Eye….

- **CKD is associated with**:

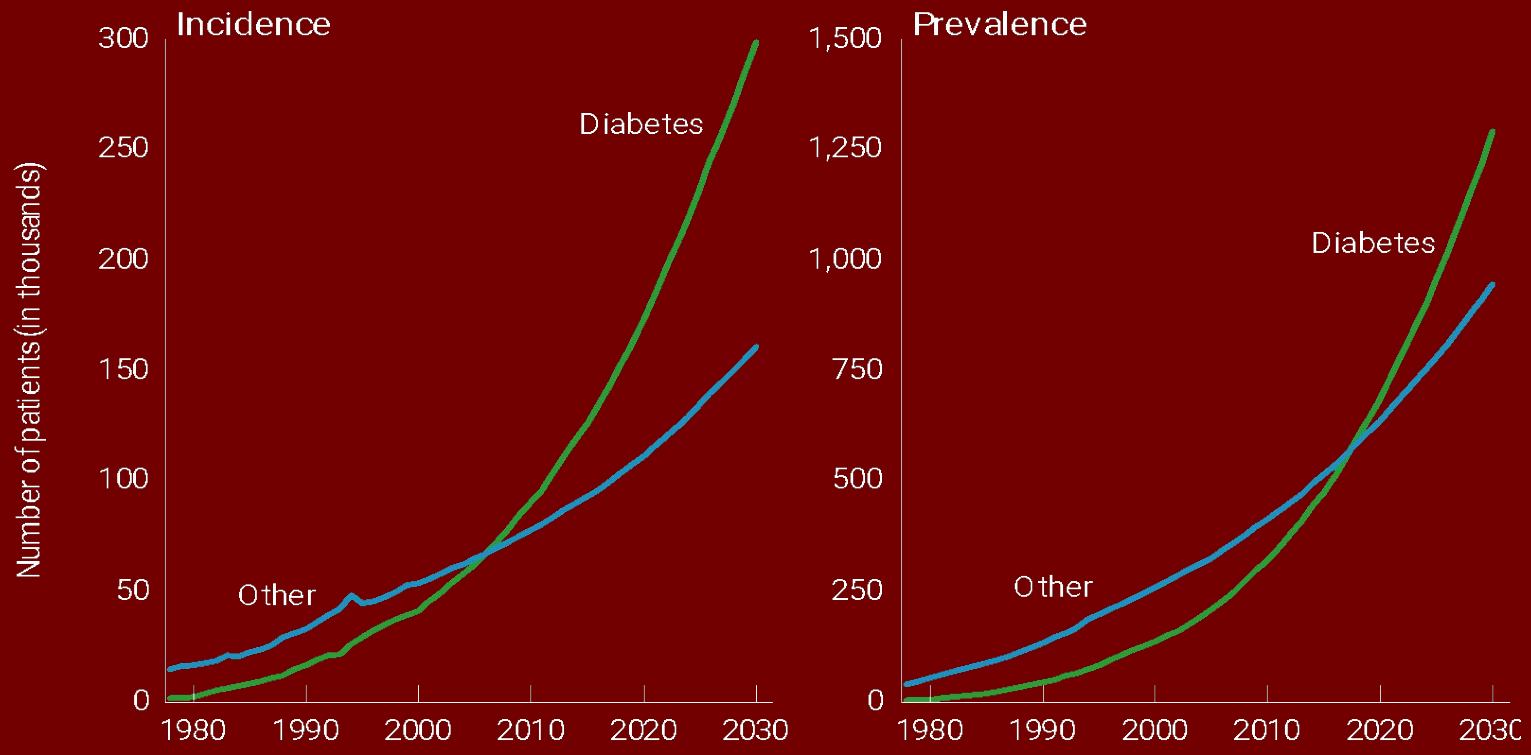
-Hypertension
-Cigarette Smoking
-Obesity (BMI>30)
-Physical Inactivity
-Dyslipidemia
-Diabetes Mellitus
--Age (>55 for men, >65 for women)
-Family history of premature coronary artery disease (men<55, women<65)

As well as:

-Anemia
-Left Ventricular Hypertrophy
-Inflammation
-Atherosclerosis
-Resistant hypertension/hypervolemia

CKD is Increasingly Associated with Diabetes Mellitus

(Predicted ESRD Incidence and Prevalence Rates due to Diabetic Nephropathy)



Chronic Kidney Disease: The Extreme Of Metabolic Syndrome?

- Ludovicus Giomus (**IInd Century** Roman physician of Greek origin):

"The prospect for chronic renal malady is rendered optimal by the combination of habitual excess of culinary pleasures and physical inactivity."

(N.B. Historical Note:

The physician after this statement was hunted down by the angry Roman populace and forced to withdraw his remark.)

Risk Shared….alias You get what You Eat

- Many cardiovascular risk factors are also associated with faster deterioration of chronic kidney disease:

-diabetes mellitus
-hypertension
-dyslipidemia
-truncal obesity
-smoking
-proteinuria…….

Benefits of Cibus Rapidus!

- Salt: hypertension
- Protein: glomerular hypertension
- Sugars: diabetes melitus (55%)
- Lipid: dyslipidemia

You only need to add smoking. (The Romans did not have that yet...)

Expected Survival Times General Population versus Dialysis

	All races			White			Black		
	All	M	F	All	M	F	All	M	F
0	76.7	73.9	79.4	77.3	74.6	79.9	71.4	67.8	74.7
1	76.3	73.5	78.9	76.8	74.1	79.3	71.5	67.9	74.7
5	72.4	69.6	75	72.9	70.2	75.4	67.6	64.1	70.9
10	67.4	64.7	70.1	67.9	65.3	70.5	62.7	59.2	66
15	62.5	59.8	65.1	63	60.3	65.5	57.8	54.3	61
20	57.7	55	60.2	58.2	55.6	60.7	53.1	49.6	56.2
25	53	50.4	55.4	53.4	50.9	55.8	48.5	45.2	51.4
30	48.2	45.7	50.5	48.6	46.2	50.9	43.9	40.7	46.6
35	43.5	41.1	45.7	43.9	41.5	46.1	39.3	36.3	41.9
40	38.8	36.5	41	39.2	36.9	41.3	34.8	31.9	37.4
45	34.3	32	36.3	34.6	32.4	36.6	30.6	27.8	33
50	29.8	27.7	31.7	30.1	28	32	26.6	24	28.7
55	25.5	23.5	27.3	25.7	23.8	27.5	22.8	20.4	24.7
60	21.5	19.6	23.1	21.6	19.8	23.2	19.3	17.2	20.9
65	17.7	16.1	19.1	17.8	16.1	19.2	16	14.3	17.3
70	14.3	12.8	15.4	14.4	12.9	15.5	13	11.6	14
75	11.2	10	12.1	11.2	10	12.1	10.4	9.2	11.1
80	8.5	7.5	9.1	8.5	7.5	9.1	8.2	7.3	8.6
85	6.3	5.5	6.6	6.2	5.5	6.6	6.2	5.6	6.5
90	4.6	4.1	4.8	4.5	4	4.7	4.8	4.4	4.8
95	3.4	3	3.5	3.2	2.9	3.3	3.6	3.5	3.6
100	2.6	2.4	2.7	2.3	2.2	2.4	2.8	2.8	2.7

Dialysis

	White		Black		N Am		Asian	
	Male	Female	Male	Female	Male	Female	Male	Female
0-14	19.8	18.5	20.1	18.1	22.5	23.0	30.6	29.5
15-19	17.0	15.8	18.4	16.5	18.9	18.7	24.5	24.0
20-24	14.5	13.5	16.2	14.3	15.9	16.0	21.5	21.1
25-29	12.3	11.3	14.2	12.6	13.7	13.6	18.6	18.5
30-34	10.1	9.6	12.3	11.0	11.7	11.7	15.7	15.9
35-39	8.6	8.2	10.7	9.7	9.8	10.0	13.1	13.5
40-44	7.4	7.2	9.3	8.4	8.3	8.6	11.0	11.5
45-49	6.3	6.0	7.7	7.3	7.0	7.3	9.0	9.5
50-54	5.3	5.1	6.7	6.3	6.0	6.5	7.6	8.0
55-59	4.6	4.5	5.6	5.5	5.3	5.4	6.4	6.7
60-64	3.9	3.8	4.7	4.8	4.4	4.7	5.3	5.7
65-69	3.2	3.2	4.0	4.0	3.7	4.0	4.5	4.9
70-74	2.8	2.8	3.4	3.3	3.2	3.4	3.7	4.1
75-79	2.4	2.4	2.8	2.8	2.5	2.8	3.1	3.3
80-84	2.0	2.0	2.3	2.3	2.1	2.3	2.6	2.8
85+	1.7	1.7	1.9	1.9	1.7	1.8	2.0	2.2

Expected Survival Times: Dialysis versus Transplantation

Dialysis

	White		Black		N Am		Asian	
	Male	Female	Male	Female	Male	Female	Male	Female
0-14	19.8	18.5	20.1	18.1	22.5	23.0	30.6	29.5
15-19	17.0	15.8	18.4	16.5	18.9	18.7	24.5	24.0
20-24	14.5	13.5	16.2	14.3	15.9	16.0	21.5	21.1
25-29	12.3	11.3	14.2	12.6	13.7	13.6	18.6	18.5
30-34	10.1	9.6	12.3	11.0	11.7	11.7	15.7	15.9
35-39	8.6	8.2	10.7	9.7	9.8	10.0	13.1	13.5
40-44	7.4	7.2	9.3	8.4	8.3	8.6	11.0	11.5
45-49	6.3	6.0	7.7	7.3	7.0	7.3	9.0	9.5
50-54	5.3	5.1	6.7	6.3	6.0	6.5	7.6	8.0
55-59	4.6	4.5	5.6	5.5	5.3	5.4	6.4	6.7
60-64	3.9	3.8	4.7	4.8	4.4	4.7	5.3	5.7
65-69	3.2	3.2	4.0	4.0	3.7	4.0	4.5	4.9
70-74	2.8	2.8	3.4	3.3	3.2	3.4	3.7	4.1
75-79	2.4	2.4	2.8	2.8	2.5	2.8	3.1	3.3
80-84	2.0	2.0	2.3	2.3	2.1	2.3	2.6	2.8
85+	1.7	1.7	1.9	1.9	1.7	1.8	2.0	2.2

Transplant

White		Black		N Am		Asian	
Male	Female	Male	Female	Male	Female	Male	Female
50.4	51.3	45.9	45.4	49.4	46.1	56.6	57.0
39.2	40.3	36.6	36.4	39.2	36.7	45.4	46.3
35.3	36.5	33.1	33.1	35.4	33.2	41.4	42.5
31.5	32.9	29.7	29.9	31.9	30.0	37.6	38.8
27.5	29.0	26.0	26.5	28.0	26.3	33.5	34.8
24.1	25.7	22.7	23.4	24.5	23.1	29.7	31.3
20.9	22.8	19.7	20.6	21.4	20.3	26.0	27.8
17.9	19.9	16.8	17.8	18.4	17.5	22.6	24.4
15.3	17.4	14.1	15.1	15.7	14.7	19.3	21.1
12.8	15.0	11.7	12.9	13.5	12.8	16.4	18.3
10.6	12.8	9.7	11.1	11.5	10.9	13.9	15.7
8.8	10.9	8.1	9.6	9.9	9.8	11.8	13.7
7.1	9.1	6.6	8.1	8.2	8.4	10.0	12.0
6.1	7.7	5.6	7.3	7.1	8.5	8.9	10.5

Function of the Normal Kidney-Highlights

- Removal of toxic materials
- Excretion of excess salt and water
- Regulation of electrolyte concentrations
- Regulation of acid-base buffer systems
- Synthesis of erythropoietin
- Synthesis of vitamin D metabolites
- Metabolism of hormones and medications
- Synthesis of renin

Function of the Normal Kidney-the "How"

- Renal function is a continuous function
- Multiple level adaptation: vascular, hormonal,osmotic, tubular
- Renal function is extremely dependent on adequate blood supply
- Cardio-renal axis: close cooperation with multiple feedback systems (ACEI, aldosterone tissue systems)

Chronic Kidney Disease-Pathophysiology: Glomerulus

- Final common pathway of no matter what underlying disease: adaptation to a decreased number of functioning nephrons and consequent decrease of filtration surface
- Hyperfiltration in the remaining nephrons
- Glomerular hypertension: increased mechanical stretch on mesangial and endothelial cells, detachment of podocytes
- Increased production of subclasses of collagen fibers: scarring, fibrosis (glomerulosclerosis)

Chronic Renal Failure-Pathophysiology: Vascular and Tubulointerstitial Systems

- Loss of renal autoregulation
- Vascular hyaline formation
- Tubulointerstitial cells revert to myofibroblast stage: collagen formation
- Tubulointerstitial fibrosis correlates with kidney function
- Loss of tubular regulatory systems-isosthenuria

Chronic Kidney Disease-Histopathology and Gross Anatomy

- Widespread tubulointerstitial scarring means: white, echogenic kidneys on renal ultrasound
- Scarring and loss of parenchyma means small
  (< 10 cm) kidney sizes on renal ultrasound
- If biopsy of the kidney is performed in cases of doubt: fibrosis (focal and segmental or global) in the glomerulus and between renal tubules (especially on trichrome stain:blue)

Main Functional Problems In Chronic Kidney Disease

- Renal dysfunction
- Hypervolemia, Hypertension, Salt retention
- Proteinuria, Metabolic Disturbances
- Anemia and Iron deficiency
- Uremic bone disease, hyperphosphatemia
- Electrolyte problems: hyperkalemia, acidosis
- Cognitive impairment, depression and denial

Renal Dysfunction: What we Do Know and What we Do Not

We know:

Patients with very impaired renal function will go into coma, have painful neuropathy and are very malnourished and susceptible to infections

We do not know:

What exactly causes these fenomena? **We think** that these are due to some mysterious "uremic toxins" because dialysis, a filtering technique improves and prevents **some** of these problems

Renal Dysfunction- More Mystery

- We usually estimate renal dysfunction by markers rather than actual toxins
- On most of the range of these measurements renal dysfunction is asymptomatic
- This situation makes many patients reluctant to believe that there is something wrong until it is very late and renal dysfunction becomes symptomatic
- Therefore patients are often malnourished, develop infections and renal replacement therapy has to be promptly started

Renal Dysfunction: Estimators of GFR

- Creatinine Clearance-measured
- Plasma (serum) creatinine
- Creatinine Clearance-calculated
- Creatinine clearance after cimetidine
- Creatinine and Urea Clearance- arithmetic average
- Most other methods are yet unavailable in everyday clinical practice

Flashback: Theory of Creatinine Clearance

- **Clearance:** volume of body fluid cleared by the kidney in a given amount of time
- Creatinine is largely filtered by the glomerulus and secreted minimally by the tubules (except in advanced CKD) and therefore a reasonable estimator of GFR
- Ideal substance for clearance estimation, inulin, used in research, creatinine is a good compromise

Creatinine Clearance versus GFR: Urine Side Methods

- **CrClx Serum Cr = Urine Cr x Urine Volume**

- **CrCl= Urine Cr / Serum Cr x Urine Volume during elapsed time / Time in minutes**
- **CrCl = Urine Cr / Serum Cr x Urine Volume (cc per 24 hour) / 1440**

Clinical Practice:

"*24 hour urine collection*"

avoid over- or under-collection, these are common sources of error, repeat at least once

Stage III, IV CKD: do the same for urea clearance and

calculate arithmetic average with creatinine clearance

or add cimetidine to block tubular secretion of creatinine!

Estimating GFR: Blood Side Methods

- ***Cockroft-Gault formula:***

$$\frac{140 - \text{age}}{\text{Se Cr}} \times \frac{\text{weight (ideal)}}{72} \quad [\times 0.85 \text{ for females}]$$

Works well for creatinine for stage I or II CKD.

- ***MDRD formula*** : Too complicated but correlates well in more advanced CKD, used very often now

Blood Side Methods versus Urine Side Methods

- Based on plasma creatinine
- Depends not only on renal function but also on muscle mass.
- In the elderly and malnourished low creatinine can be associated with advanced renal failure
- Must use the appropriate corrective formula
- Easy to perform, changes in time can be easily followed up

- Based on urine collection
- Urine collections are rarely accurate as they may be incomplete
- The more advanced the renal failure the more creatinine is secreted by the tubules making this technique less and less precise in estimating glomerular filtration.
- Creatinine based collection must be corrected by cimetidine or urea clearance

Chronic Kidney Disease- A Spectrum of Renal Dysfunction

- Normal Glomerular Filtration Rate (80-120 ml/min) is a relative term and must be adjusted to body surface area
- Women, the elderly and patients with smaller body frame may filter less
- Filtration is only one of the many functions of the kidney, yet only this is measured directly

In a Perfect World……

- Imagine that you have measured GFR accurately-then
- GFR<60 worry about hypertension, proteinuria, hyperlipidemia, hypervolemia, increased cardiac risks
- GFR<40 worry about anemia, iron deficiency and start worrying about bone disease, especially in diabetics
- GFR<20 worry about malnutrition, infections, acidosis, pericarditis, pulmonary edema and hyperkalemia

Additional “Uremic” Symptoms

- Chronic hypervolemia-hidden in the abdomen, causing hypertension, mainly systolic
- Insomnia, disturbed circadian rhythm
- Increased sympathetic activity
- Maintained high blood pressure at night
- Nausea, muscle wasting, weight loss
- Depression, denial, impaired judgment
- Gastrointestinal bleeding

Risk Factors and Predictors of Progression

- CKD is beyond the point of no return- further progression is the rule the only question is its speed
- Speed is determined by risk factors of progression
- Treating risk factors is the primary goal of treatment to slow down progression- so learn them NOW

Risk Factors Associated with Progression

- ***Level of renal impairment***: worse renal function is likely to get worse faster

  Estimators: GFR, renal size
- ***Proteinuria***: more proteinuria means more glomerular hypertension and more subsequent damage

  Estimators: 24 hour collection or spot urine protein/creatinine ratio
- ***Hypertension:*** speeds renal decline dramatically

  Estimator: multiple blood pressure measurements or 24 hour blood pressure monitoring

More Risk Factors

- Hyperlipidemia
- Smoking
- Obesity (especially visceral)
- Sleep apnea
- Excessive protein (meat) intake

Remembering Sun Tzu: the Strategy

- Early on handle renal dysfunction by slowing down renal progression: treat hypertension and proteinuria, lipids, smoking, blood sugars, obesity
- Later you can only fix specific problems: anemia, metabolic acidosis, bone disease
- Gfr<20 ml/min you have to start thinking: renal replacement therapy (we have a whole hour to cover that!)

Specific Problems in CKD: Hypertension

- Hypertension accelerates the progression of CKD
- CKD also produces hypertension by: impaired salt excretion, increased sympathetic activity and often by increased renin activity (renovascular hypertension is common in Americans of European descent)-revascularization may be needed
- Hypertension in CKD is often resistant or difficult to treat
- Hypertension makes proteinuria worse so……

Treat Hypertension!

- Restrict salt intake and give diuretics
- Aim for strict control: if proteinuria present all the way down to 120/75
- Certain classes of blood pressure medicines are more beneficial than others: Angiotensin Converting Enzyme Inhibitors and Angiotensine Receptor Blockers
- Titrate these to urine protein of less than 1 gm, at least

Salt Restriction is Still Important!

- “Perhaps if the value of a salt-restricted intake was rediscovered in the USA, control of hypertension in dialysis patients would improve.” (Sheldon, 2000)
- Patients often eat five times the amount of 2 gm sodium allowed, especially when eating out (memento cibus rapidus)
- Chronic hypervolemia is especially typical in Diabetic Nephropathy
- Edema may be a late sign of volume overload
- Typically, loop diuretics needed but thiazides in combination with loop diuretics may also be useful
- Spironolactone is useful, especially in heart failure, but is limited by hyperkalemia
- Diastolic dysfunction is very prevalent, due to LVH

Proteinuria

- Both a marker of renal progression and subsequent cardiac disease AND a cause of tubular damage
- Hypertension makes proteinuria worse
- Excessive protein intake increases proteinuria
- Proteinuria is a good marker of glomerular hypertension

Treat Proteinuria!

- Treat hypertension!
- Take dietary history- restrict protein intake if excessive (a relative term- we usually aim for 1 gm/kg/day, Italians 0.6-0.8)
- Give ACEI and/or AIIRB and titrate it to minimize proteinuria but at least <1gm/day
- Nephrotic range proteinuria may often be a feature of (chronic) diabetic nephropathy- treat vigorously

Heart Disease

- In a sequel to the Framingham study….even early (serum creatinine <2) renal failure is associated with an up to sevenfold increase of cardiac risk
- Hypervolemia, hypertension, anemia, hyperparathyroidism can all worsen left ventricular hypertrophy- itself associated with cardiac death
- Renal dysfunction and especially advanced renal dysfunction (“uremic state”) is thought to accelerate atherosclerosis

Treat Heart Disease!

- Eliminate risk factors, improve diet
- Control hypertension and hypervolemia
- Give ACEI and AIIRB and (when appropriate) beta blockers
- Treat lipid disorders
- Make the patient stop smoking
- Encourage dieting and exercise
- Increased awareness of cardiovascular risk in patients with either proteinuria or renal dysfunction

Anemia

- Normochromic normocythic anemia is associated with erythropoetin deficiency
- Iron deficiency is common
- Gastrointestinal conditions associated with blood loss and decreased iron absorption are common
- Estimated GFR less than 30-40 ml/min- think about this

Treat Anemia!

- Give erythropoetin
- Give oral iron
- Think about increased risk for gastrointestinal bleeding
- Treating anemia will reduce left ventricular hypertrophy and may reduce cardiac risk
- Treating anemia may slow renal progression and infections, improves LVH and probably decreases cardiovascular mortality

Uremic Bone Disease

- Several histologic forms: osteitis fibrosa cystica, low-turnover bone disease and osteomalatia
- Most common form is caused by rapid bone turnover caused by increased parathyroid hormone secretion (secondary hyperparathyroidism)
- Bone disease presents earlier in diabetics

Secondary Hyperparathyroidism

- Loss of GFR causes decrease of renal ability to secrete phosphorus
- There is also decrease of synthesis of vitamin D3 causing impaired calcium absorption
- Both hyperphosphatemia (more common) and hypocalcemia (less common) induces parathyroid cells to secrete more parathyroid hormones
- Parathyroid hormone increases both osteoclast and osteoblast function causing rapid bone resorption and formation termed: high turnover

Rapid Bone Turnover meaning....

- More bone fractures
- Achy bones- sometimes difficult to differentiate from osteoarthritis (also common in renal disease)
- Hyperphosphatemia commonly causes itching
- Hyperparathyroidism may worsen LVH

Treat Bone Disease!

- Measure and restrict phosphorus!
- Give phosphate binders: ionic resins or complexes that bind phosphorus in the GI tract preventing its absorption-always with meals
- Give calcium and/or vitamin D if calcium is low
- Vitamin D suppresses parathyroid hormone secretion especially if phosphorus is controlled
- Give alkali to correct metabolic acidosis

Dietary Management

- CKD stage I to III: restrict salt, protein, phosphorus, treat lipid abnormalities and hyperglycemia (people tend to eat too much)
- CKD stage IV: restrict salt, potassium, phosphorus (still too much)
- CKD stage IV: replace alkali, check for protein malnutrition, muscle wasting, weight loss, consider diuretics

Chronic Disease also Means….

- Depression and denial- regular follow up visits, talk to your patients
- Simplify medication regimens
- Work closely with dietician and social workers
- Refer to nephrologist early

Common Medications Need-Renal Adjustment!

- Many CKD patients are diabetics- less insulin is needed. Certain medications cannot be used (methformin may cause severe lactic acidosis) certain other medications (sulfonylureas) must be used with caution.
- Higher diuretic dosages are commonly needed
- Many antibiotics need reduction in dosages
- Many common analgesics (non-steroidals) are contraindicated
- Many other medicines need dose adjustmens!
- Consult PDR, pharmacist or a nephrologist

Summary

1. CKD has an increasing incidence
2. Probably part of the Metabolic Syndrome
3. Shares many cardiovascular risk factors
4. Risk factor management is helpful slowing down renal decline
5. Specific problems: salt retention, anemia, bone disease, malnutrition, electrolyte abnormalities have to be addressed one by one
6. Medications need adjustment and often need to change