# Diabetes Nephropathy

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# Introduction

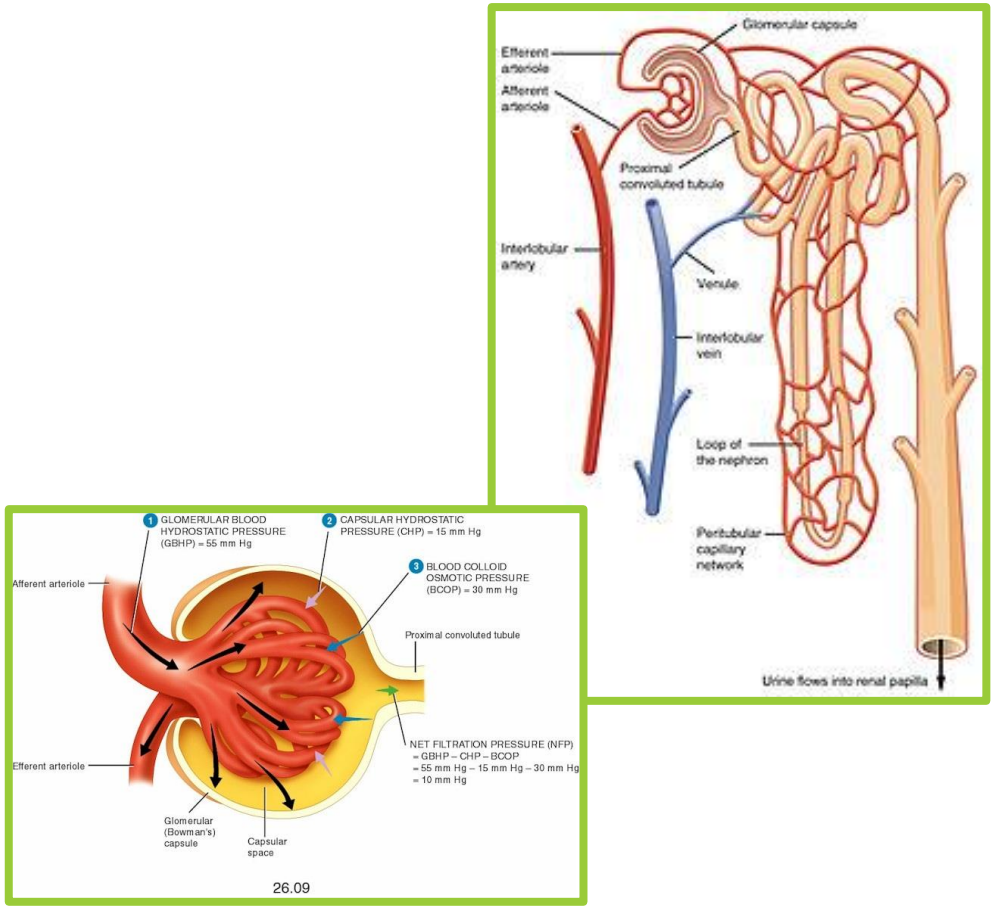
- Occurs in DM I & DM II or other types of DM.
- Depends on duration of DM and level of glycemia.
- In clinical practice; usually seen in DM II.
- Might lead to Chronic kidney Disease (CKD) and dialysis.

# Clinical features

- Diabetic kidney disease is a **glomerulopathy** defined by characteristic structural and functional changes.

- Glomerular basement membrane thickening; and glomerular sclerosis.

- Major clinical manifestations : **albuminuria, hematuria& progressive chronic kidney disease**



# Clinical features

- **Albuminuria:**

**- Increased urinary protein excretion.**

- Functional characteristics include hyperfiltration, microalbuminuria & macroalbuminuria.

→ Microalbuminuria : urinary albumin excretion 30 -300 mg/day

→ Macroalbuminuria : urinary albumin excretion above 300 mg/day

# Clinical features

- **Albuminuria:**

- Microalbuminuria precedes the development of macroalbuminuria

- Predicts high risk for future nephropathy.

- The onset of macroalbuminuria is usually followed by a slowly progressive decline in glomerular filtration rate (GFR) and might lead to end-stage renal disease

# Clinical features

➢ **Detection of Microalbuminuria:**

- Establishing the diagnosis requires an elevation in albumin excretion over a 3-6 month period.
- Fever, exercise, heart failure, and poor glycemic control can cause transient microalbuminuria.
- **Urine albumin concentration** — 24-hour urine collection was a gold standard.
- **Urine albumin-to-creatinine ratio -** 30 to 300 mg/g of creatinine (2-3 specimens)

# Clinical features

- **Progressive disease with little or no albuminuria:**

- For reasons that are not understood, the degree of albuminuria is not necessarily linked to disease progression.

- The factors responsible for are not fully known.

- One possibility is intrarenal vascular disease.

- Nonproteinuric progression occurs in type 1 diabetes

# Clinical features

- **Hematuria :**

- Not a major feature of nephropathy.

- Usually present in nondiabetic renal disease, either alone or with diabetic nephropathy.

- Might indicate  more severe diabetic nephropathy

# Epidemiology

- **Type I DM:**

- Around 20 -30 % will have microalbuminuria after a mean duration of diabetes of 15 years.
- Less than half of these patients will progress to overt nephropathy.
- Microalbuminuria may regress or remain stable in a substantial proportion, probably related to glycemic and blood pressure control.
- Previously : 4-17 % at 20 years from time of initial diagnosis and 16% at 30 years.
- **Nowadays → rate decreased (Why ?)**

# Epidemiology

- **Type II DM:**

- In Caucasians, the prevalence of progressive renal disease was lower in DM II than in DM I.

- **Might be due to; "**later-onset disease and shorter-duration "

- Modern therapies lowers the incidence of ESRD, even in high risk groups.

-**Renal risk is currently equivalent in the two types of diabetes.**

- Some patients with microalbuminuria , particularly those with good glycemic control, experience regression of microalbuminuria

# Pathogenesis

1. **Glomerular hyperfiltration:**

- A 25 - 50% elevation in the glomerular filtration rate (GFR) is seen early in the course in up to ½ DM I patients & in DM II.
- Accompanied by Glomerular hypertrophy and increased renal size.
- The role of glomerular hypertension and hyperfiltration in diabetic nephropathy is reinforced by the apparent benefits of blockade of the renin-angiotensin system.
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# Pathogenesis

1. **Glomerular hyperfiltration:**

-**Hormones** might play a role, such as**;** insulin-like growth factor I (IGF-1) and sex hormones.

- **Sorbitol :** Intracellular accumulation and the formation of glycosylated proteins; the enzyme aldose reductase converts intracellular glucose to sorbitol, which then accumulates within the cells which increases GFR.

# Pathogenesis

**2. Hyperglycemia and AGEs:**

- Hyperglycemia may directly induce renal injury
- Tissue accumulation of AGEs, in part by crosslinking with collagen, which can contribute to renal and other microvascular complications.
- Hyperglycemia lead to activation of protein kinase C → increase albumin permeability.

# Pathogenesis

3. **Cytokines :**

- Activation of cytokines, profibrotic elements, inflammation, and vascular growth factors may be involved in diabetic nephropathy.

# Risk factors

1. **Genetic susceptibility** → incidence and severity.
2. **Age** — Among patients with DM II, increasing age, along with increasing duration of DM, has been associated with an increased risk for developing albuminuria in Australia
3. **Blood pressure.**
4. **Glomerular filtration rate**→ Glomerular hyperfiltration.
5. **Glycemic control**→ higher HbA1c levels

# Risk factors

6. **Race** — The incidence and severity are increased in blacks, Mexican-Americans, and Pima Indians with DM II.
7. **Obesity** — A high body mass index (BMI) has been associated with an increased risk of chronic kidney disease among DM patients.
8. **Smoking.**
9. **Oral contraceptives**

# Nephropathy & Retinopathy

- The retinopathy is easy to detect clinically, and typically precedes the onset of overt nephropathy.
- Mostly predictable in DM I.
- DM II patients with marked proteinuria and retinopathy most likely have diabetic nephropathy, while those without retinopathy have a high frequency of non-diabetic glomerular disease

# Screening

- **At least once a year, assess urinary albumin and estimated glomerular filtration rate (eGFR):**
  - In patients with type 1 diabetes duration of ≥5 years
  - In all patients with type 2 diabetes
  - In all patients with comorbid hypertension

American Diabetes Association Standards of Medical Care in Diabetes.
Microvascular complications and foot care. Diabetes Care 2017; 40 (Suppl. 1): S88-S98

# Stages of CKD

| Stage | Description | eGFR (mL/min/1.73 $m^2$) |
|---|---|---|
| 1 | Kidney damage* with normal or increased eGFR | ≥ 90 |
| 2 | Kidney damage* with mildly decreased eGFR | 60–89 |
| 3 | Moderately decreased eGFR | 30–59 |
| 4 | Severely decreased eGFR | 15–29 |
| 5 | Kidney failure | <15 or dialysis |

E GFR = estimated glomerular filtration rate

* Kidney damage defined as abnormalities on pathologic, urine, blood, or imaging tests.

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# Screening/ Important notes

- Decreased eGFR might occur **without** increased urine albumin excretion in high percentage of adults with DM.
  - → Thus screening with albumin excretion rate alone would miss >20% of progressive disease.

- **Serum creatinine with estimated GFR** should be assessed at least annually, **regardless of the degree of urine albumin.**
- **Serum creatinine should be used to estimate GFR and to stage the level of CKD, if present.**

# Treatment of Nephropathy

# Glycemic control

- The efficacy depends in part upon the stage at which it is begun and the degree of normalization of glucose metabolism.

- Intensive insulin therapy:

- Partially reverse the glomerular hypertrophy and hyperfiltration.
- Delay the development of elevated albumin excretion.
- Stabilize or decrease protein excretion after onset.

# Blood pressure control

- Angiotensin Converting Enzyme (ACE) inhibitors:

- For management of HTN.
- The renal goal of ACE inhibitor is a modest reduction in urine albumin excretion.
- In one trial ; albumin excretion fell by 9.6 % per year in patients receiving captopril compared to an increase of 14.2% per year with placebo.

# Blood pressure control

- In non-pregnant patients with DM & HTN, an ACE inhibitor is recommended for modestly elevated urinary albumin excretion (30–299 mg/g creatinine).

- Strongly recommended for patients with urinary albumin excretion ≥300 mg/g creatinine and/or eGFR <60.
- Consider monitoring serum creatinine & K+ levels for increased creatinine or changes in K+.

# Blood pressure control

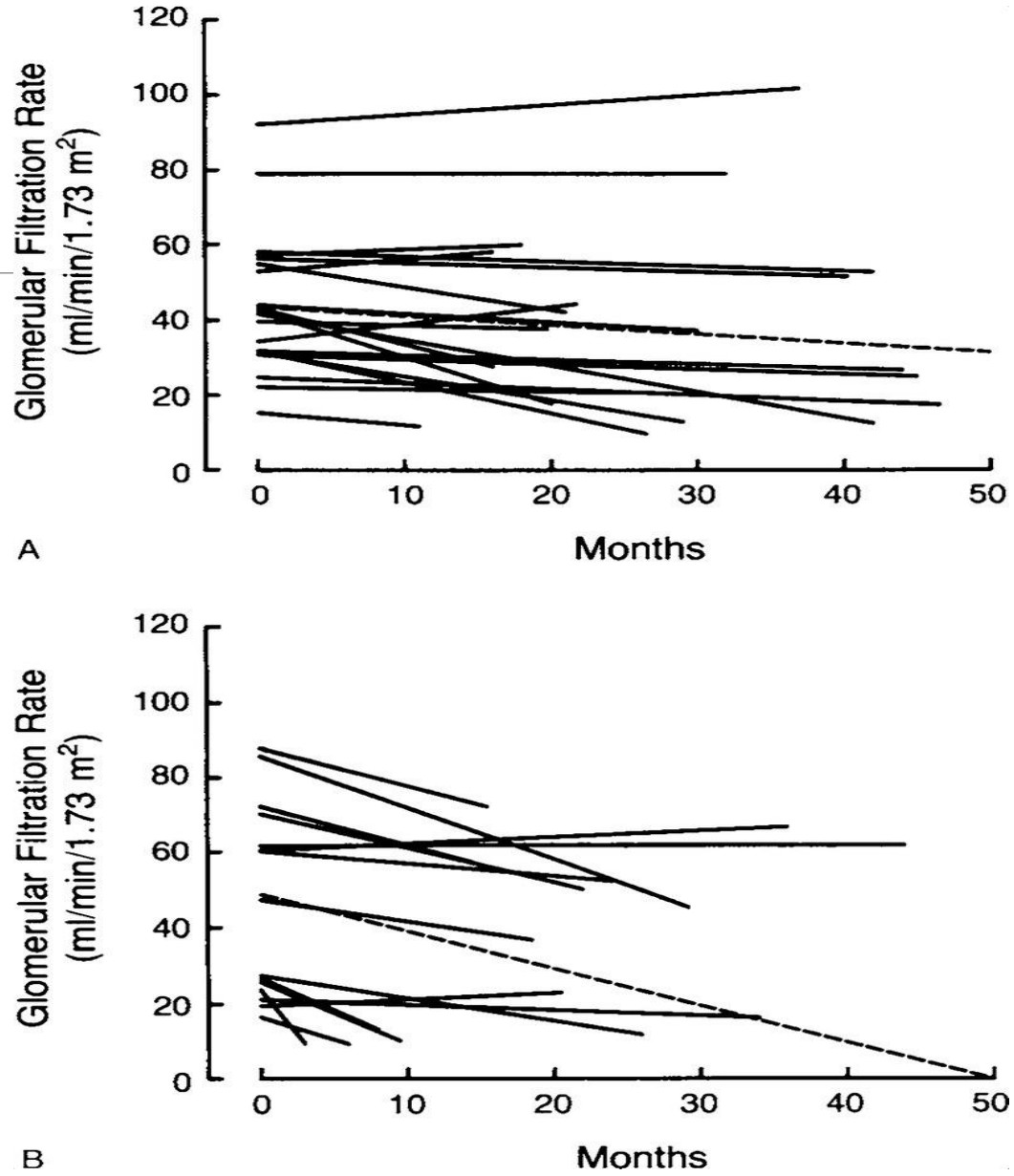
- An ACE inhibitor isn't recommended for primary prevention of diabetic kidney disease in patients with diabetes with normal BP, normal UACR (<30 mg/g creatinine) & normal eGFR

# Nutrition and dietary factors/Protein intake

- Non-dialysis dependent diabetic kidney disease, dietary protein intake should be ~0.8 g/kg body weight per day.
- Controlling protein intake → can minimize progression of or even prevent glomerular disease in the absence of glycemic control ?
- For patients on dialysis, higher levels of dietary protein intake should be considered.

# Nutrition and dietary factors

Figure 1. Progression of Renal Failure in 20 Patients with Diabetic Nephropathy **Who Were Following a Low-Protein, Low Phosphorus Diet (Panel A) and in 15 Patients Following a Diet with Normal Intake of Protein and Phosphorus (Panel B·)**.




Zeller K, Whittaker E, Sullivan L, et al. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 1991; 324:78.

# Nutrition and dietary factors/Salt intake

- A high salt intake can blunt (decrease) the antiproteinuric effects of ACE inhibitors in patients with non-diabetic kidney disease.
- **Salt restriction** and/or diuretics enhance the effect of renin-angiotensin blockade on proteinuria in these patients.

- Thus, patients on ACE inhibitors who do not have sufficient reduction in proteinuria despite appropriate blood pressure goals should follow a low sodium diet.

# Nutrition and dietary factors/Weight reduction

- Marked decreases in proteinuria may be observed in obese diabetics who lose weight

- 30 overweight patients (BMI >27 kg/m $^2$ ) with proteinuric nephropathy, 14 had DM II.

- **Proteinuria significantly decreased at five months among dieters versus the non-dieters control group.**

# Nutrition and dietary factors/Hyperlipidemia

- In addition to promoting systemic atherosclerosis, Hyperlipidemia may contribute to the development of glomerulosclerosis in CKD.

- lipid lowering (at least with statins) may slow the rate of CKD progression, including diabetic nephropathy.

# Management of CKD- ADA

| eGFR | Recommended |
|---|---|
| All patients | Yearly measurement of creatinine, urinary albumin excretion, potassium |
| 45-60 | • Referral to a nephrologist.<br>• Consider dose adjustment of medications<br>• Monitor eGFR every 6 months<br>• Monitor electrolytes, bicarbonate, HGB, Ca, P, PTH at least yearly<br>• Assure vitamin D sufficiency<br>• Consider bone density testing<br>• Referral for dietary counselling |

# Management of CKD- ADA

| eGFR | Recommended |
|---|---|
| 30-44 | Monitor eGFR every 3 months |
| | • Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin<br>• Weight every 3–6 months<br>• Consider need for dose adjustment of medications |
| <30 | Referral to a nephrologist |

# Renal replacement therapy

- In patients with eGFR <30; End Stage Renal Disease (ESRD).

- Promptly refer to a physician experienced in the care of DKD for:

  - Uncertainty about the etiology of disease
  - Difficult management issues
  - Rapidly progressing kidney disease

# Renal replacement therapy

Clinical management in ESRD is complicated and should consider several issues:

- Anemia.
- Secondary hyperparathyroidism.
- Metabolic bone disease.
- Electrolyte disturbance.

# Renal replacement therapy/Options

1. **Hemodialysis.**
2. **Peritoneal dialysis.**
3. **Kidney transplantation.**

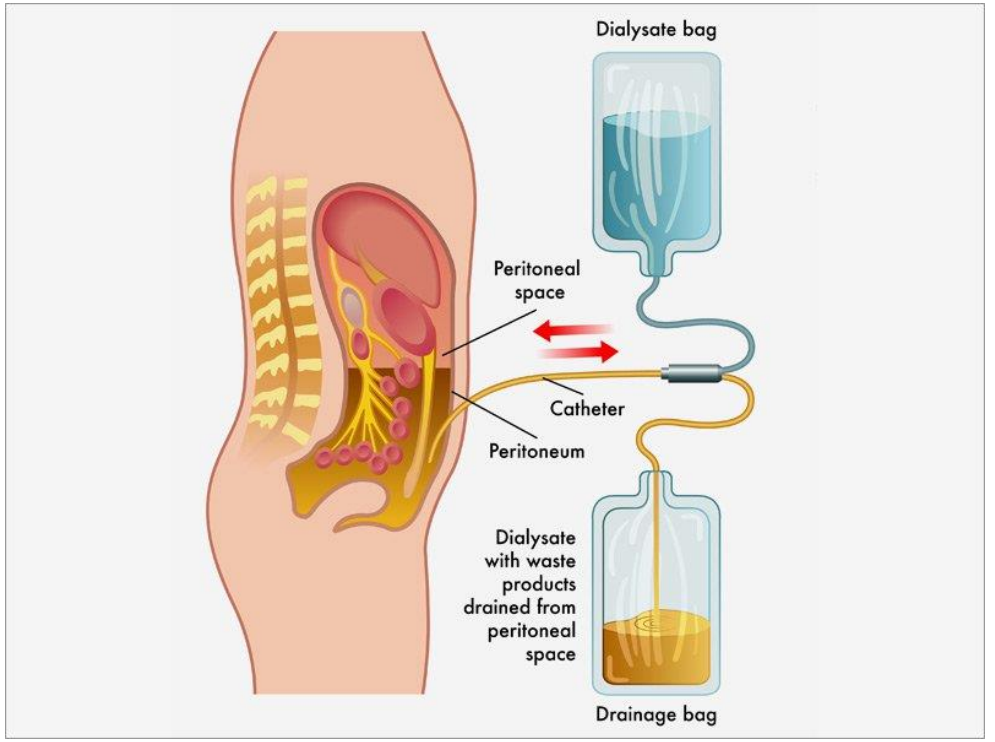
# Dialysis Vs. Transplantation

- Survival → Adjusted patient survival at five years after kidney transplantation in diabetics ranged from 67 to 77% compared to 30% in dialysis.

- Transplantation is associated with a better quality of life and a higher degree of rehabilitation.

- Choice of patients →usually younger and less likely to have DM II or extrarenal vascular disease.

# Hemodialysis Vs. Peritoneal dialysis



# Hemodialysis Vs. Peritoneal dialysis

Choice of a dialysis modality is dependent in part upon the following factors:

- Comorbid conditions
- Home situation
- Independence and motivation of the patient
- Ability to tolerate volume shifts — Diabetic patients with autonomic neuropathy are often more likely to have **hypotensive episodes** during hemodialysis.

→ Fluid removal is more gradual with peritoneal dialysis and therefore hypotension is not a problem unless the patient becomes volume depleted.

# Hemodialysis Vs. Peritoneal dialysis

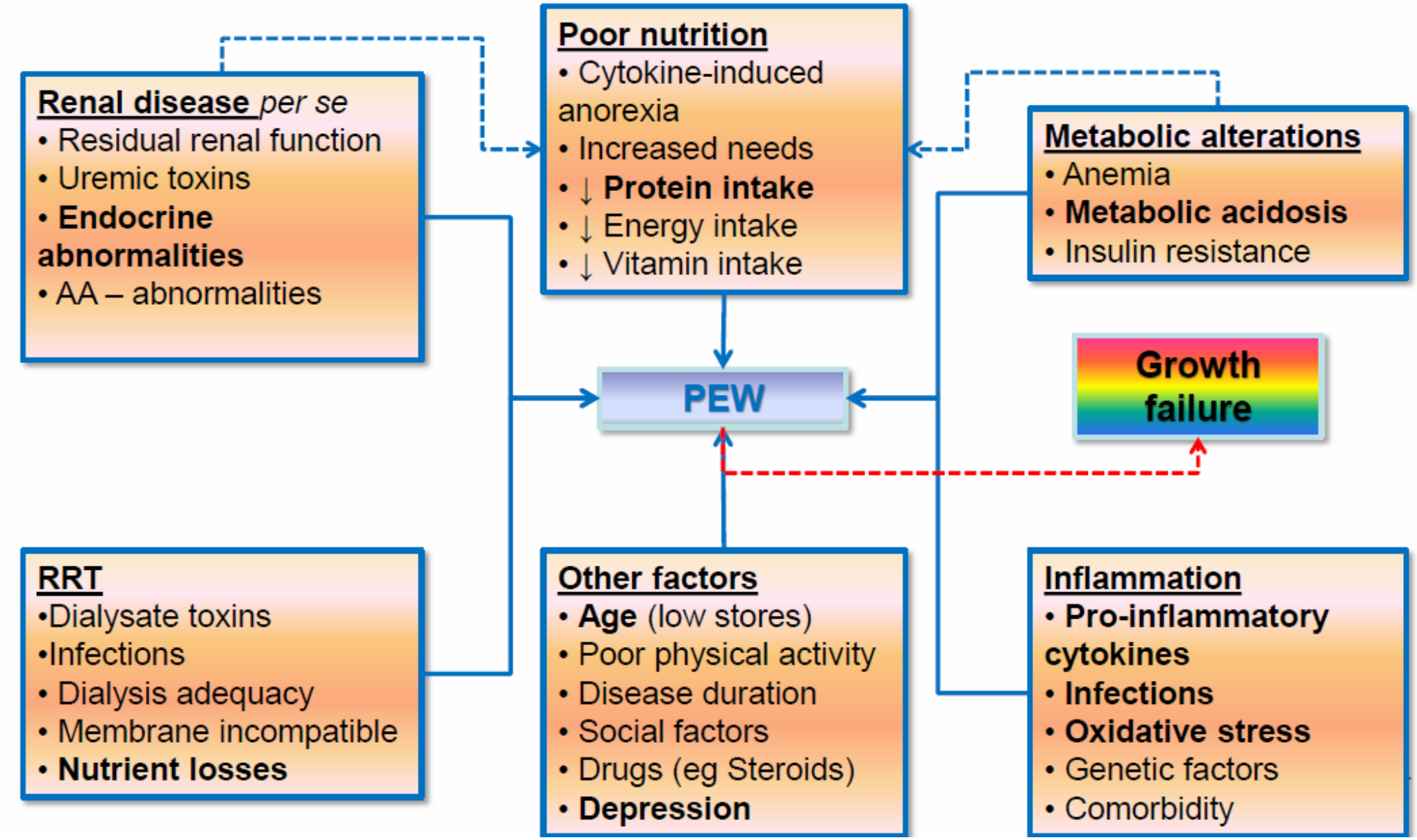
- Status of the vasculature and/or abdomen — Older patients with type 2 diabetes are more likely to have severe peripheral vascular disease that limits the ability to create and sustain **adequate vascular access for hemodialysis.**

→ Unfortunately, these are often the same patients who are unable to perform peritoneal dialysis due to concomitant illnesses.

- Risk and history of infection

# ESRD- Nutritional considerations

- 40-70 %of patients with ESRD are malnourished.
- A complication that appears to be associated with increased mortality.
- Periodic assessment of nutritional status should be part of the routine care of dialysis patients.
- Most of the standard methods of assessing nutritional status can be applied to patients with renal failure


Poor nutrition
• Cytokine-induced anorexia
• Increased needs
• ↓ Protein intake
• ↓ Energy intake
• ↓ Vitamin intake
Renal disease per se
• Residual renal function
• Uremic toxins
• Endocrine abnormalities
• AA – abnormalities
Metabolic alterations
• Anemia
• Metabolic acidosis
• Insulin resistance
PEW
Growth failure
RRT
•Dialysate toxins
•Infections
• Dialysis adequacy
• Membrane incompatible
• Nutrient losses
Other factors
• Age (low stores)
• Poor physical activity
• Disease duration
• Social factors
• Drugs (eg Steroids)
• Depression
Inflammation
• Pro-inflammatory cytokines
• Infections
• Oxidative stress
• Genetic factors
• Comorbidity

# Nutritional status assessment

- There is no single measurement that can be used to determine the presence of malnutrition.

- A panel of measurements is recommended, including:

- Measures of body mass (body mass index) and composition.
- A measure of dietary protein and energy intake.
- At least one measure of serum protein status.

# Nutritional status assessment

**History and physical examination :**

- Symptoms such as nausea, vomiting, anorexia.
- Weight loss or gain.

  → Large interdialytic weight gain reflects excessive fluid and Na intake.

- The presence of concomitant problems, such as alcoholism, DM & GI disease.
- Psychosocial issues such as access and affordability of food, ability to prepare meals.
- Signs or symptoms of depression should also be identified; might affect oral intake.

# Nutritional status assessment

**The physical examination** should include an assessment of the patient's volume status, as it is the patient's **"dry weight“.**

→ Which should be compared to the recommended body weight.

→ The percentage change (if any) of the "dry weight" should also be assessed approximately every month

# Nutritional status assessment

**Food intake** — An accurate assessment of the patient's food intake is an important component of the nutritional assessment.

- This should be performed every six months

- Patient recall on a relatively short period of time, such as 3 days, and should include dialysis and non-dialysis days.

- A food diary is very useful.

- Consider calculating protein intake.

# Nutritional status assessment

- **Anthropometric measurements :**

-Provide a rapid, noninvasive, and reproducible method for evaluating body fat and muscle mass.

- Body fat is estimated by measuring skin fold thickness , while mid-arm circumference can provide an estimate of the muscle mass.

- However, not as accurate as more sophisticated techniques.

- BIA or DEXA → should be reserved for selected patients.

# Nutritional status assessment

**Plasma protein measurements:**

- **Albumin** — Plasma concentration correlates well with body protein stores.

- Hypoalbuminemia is a late manifestation of malnutrition, has a long half-life.

- Changes in extracellular volume might affect albumin levels.

  → As an example, volume expansion, which is usually present before dialysis, will lower the plasma albumin concentration by dilution.

# Nutritional status assessment

➢ **Transferrin:**

-Plasma transferrin values are frequently reduced in renal failure independent of malnutrition, perhaps due to **fluctuations in iron stores.**

➢ **Prealbumin :**

-Normally excreted and metabolized by the kidney and tends to accumulate in renal failure.

- Serial measurements is needed, one measurement is not accurate.

-Unlike albumin, has a short half-life and changes rapidly in response to alterations in nutritional status.

# Nutritional status assessment

- **Plasma cholesterol concentration** — Reduced in malnourished patients with normal renal function or in ESRD.

- **Blood urea nitrogen** — May be particularly helpful in monitoring protein intake and nutritional status; low BUN indicate malnutrition.

- **Creatinine –** Low values predict malnutrition and higher mortality.

# Nutritional status assessment/Summary

- No one measure alone is accurate to assess the nutritional status.
- Criteria that may be used for the diagnosis of protein-energy wasting include:

- A serum albumin < 3.8 g/L.
- Serum pre-albumin < 30 mg/dL.
- Serum cholesterol <100 mg/dL.
- A number of measures of body mass, such as BMI, anthropometry, and dietary protein and energy intake may also be used to identify the presence of protein-energy wasting.

# Indicators of protein energy wasting for HD Pts/ Summary

- **Body Mass**
  BMI<23
  Total body fat <10%
  Unintentional weight loss over time (5% over 3 months o 10% over 6 months)
- **Serum Chemistries**
  Alb <38mg/dl (care should be taken for factors effecting its levels)
  Cholesterol <100mg/dl
- **Muscle Mass**
  Muscle wasting with reduced mass or 5% over 3 months or 10% over 6 months
  Mid arm muscle circumference area <10%, below the 50th percentile
- **Dietary Intake**
  Unintentional low protein intake <0.8g/kg/d for >2 months
  Unintentional low calorie intake <25kcal/kg for >2 months

# MNT in dialysis / Issues to consider

- **Protein intake→ increase.**
- **K and P intake→ depend on serum levels.**
- **Sodium intake→ decrease.**
- **Fluid intake→ restrict (based on weight values and urine output)**

# MNT in dialysis / Recommendations

| Nutritional Parameter | Stages 1-4 CKD | Stage-5 (Hemodialysis) | Stage-5 (Peritoneal Dialysis) |
|---|---|---|---|
| Calories | 35 (< 60 yrs) | 35 (< 60 yrs) | 35 (< 60 yrs) |
| (kcal/kg/d) | 30-35 (≥ 60 yrs) | 30-35 (≥ 60 yrs) | 30-35 (≥ 60 yrs), include kcals from dialysate |
| Protein (g/kg/day) | 0.6-0.75 | 1.2 | 1.2-1.3 |
| Fat (% total kcal) | For patients at risk for CVD, <10% saturated fat, 250-300 mg cholesterol/day | | |
| Sodium (mg/day) | 2000 | 2000 | 2000 |
| Potassium (mg/day) | Match to lab values | 2000-3000 | 3000-4000 |
| Calcium (mg/day) | 1200 | ≤2000 from diet and meds | ≤2000 from diet and meds |
| Phosphorus (mg/day) | Match to lab values | 800-1000 | 800-1000 |
| Fluid (mL/day) | Unrestricted w/normal urine output | 1000 + urine | Monitor; 1500-2000 |