Diabetic Nephropathy
Outline

- Introduction of diabetic nephropathy
- Manifestations of diabetic nephropathy
- Staging of diabetic nephropathy
- Microalbuminuria
- Diagnosis of diabetic nephropathy
- Treatment of diabetic nephropathy
Introduction of Diabetic nephropathy

- The leading cause of end-stage renal disease
  - Diabetic nephropathy - 30~40% type 1 DM vs. 20% type 2 DM after years
  
- Majority of diabetic p’ts with ESRD → Type 2 DM
  
- Prevalence of type 2 DM >> type 1DM (10~15x)
Manifestations of Diabetic nephropathy

→ 5 stages

- Clinical and morphologic features

→ Similar in type 1 DM and type 2 DM

- Glomerular hypertension and hyperfiltration are the earliest renal abnormalities
- Course of GFR change: more variable in type 2 DM

→ GFR decline: 5~10cc/min/year
  (1~20 cc/min/year in type 2 DM)
DM nephropathy stages

- Stage 1: hyperfiltration phase
- Stage 2: silent phase
- Stage 3: microalbuminuria phase
- Stage 4: macroalbuminuria phase
- Stage 5: ESRD
Stage of Diabetic nephropathy

Stage 1 - Hyperfiltration phase

- Describes the renal hypertrophy and hyperfiltration that present at the time of diagnosis of type 1 DM.

- GFR and UAER - elevated by 20-40% (UAER: urine albumin excretion rate)

→ GFR and UAER↓ while insulin therapy
Stage of Diabetic nephropathy

Stage 2- Silent phase

- Clinically silent (GFR↑)
  - Early histologic change (GBM/Matrix ↑)
  - Hyperfiltration related to
    - Degree of hyperglycemia (up to 250 mg/dL), higher levels of glycemia- GFR↓
    - Better glucose control- hyperfiltration↓

- Typically lasts for 5-15 years
Stage of Diabetic nephropathy

Stage 3- Microalbuminuria phase

- Incipient nephropathy
  - Occurs after 6 -15 years of diabetes
  - UAER: 30-300mg/d
  - Always small but detectable BP↑
  - Impairment of nocturnal BP “dipping”

- GFR is elevated or reduced into normal range

- Initial hyperfiltration → greater subsequent rate of decline in GFR
24Hr BP Profile in Hypertension (Dipper vs non-dipper)

Blood pressure (mm Hg)

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Dipper</th>
<th>Non-dipper</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00</td>
<td>155</td>
<td>175</td>
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<tr>
<td>11:00</td>
<td>135</td>
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<td>3:00</td>
<td>55</td>
<td>75</td>
</tr>
<tr>
<td>7:00</td>
<td>155</td>
<td>175</td>
</tr>
</tbody>
</table>

Sleep
Stage of Diabetic nephropathy

Stage 4- Macroalbuminuria phase

- Established or overt nephropathy
- Characteristics
  - Clear histologic changes
  - HTN- established in most patients
- Proteinuria $\rightarrow$ increase 15~40 % per year
- GFR decline $\rightarrow$ 10(2~20)mL/min per year
  - The rate of decline in GFR is correlated with blood pressure levels
- Microscopic hematuria: 66% of patient
Stage of Diabetic nephropathy

Stage 4- Macroalbuminuria phase

- Macroproteinuric phase
  - a steady decline in renal function
    - GFR↓ (about 1 mL/min↓ per month)
- A plot of the reciprocal of the serum creatinine level against time
  - usually yields a straight line and allows prediction of the rate of deterioration
Stage of Diabetic nephropathy

Stage 5- ESRD

- ESRD developed in
  - 50% of type 1 diabetic patient with overt nephropathy within 10 years
  - Within a median of 7 years from the development of persistent proteinuria
Accurate measurement of UAER
→ Identification of incipient “early” nephropathy
→ Modify the natural history of DMN

Normal urine contains some albumin
  < 30 mg/day
Diagnosis of Microalbuminuria

- Sample: overnight urine
- Microalbuminuria (MicroA):
  - $30\text{mg/day} < \text{UAER} < 300\text{mg/day}$
- Persistent microA:
  - MicroA found in $2/3$ consecutive urine samples within $3-6$ months
  - DM < 6 years: other causes should be suspected
Screening of Microalbuminuria

- **Screening**
  - An early morning urine sample
  - Screening recommendations
    - Type 1 DM: Age >12 y/o, DM Dx >5 years
    - Type 2 DM: At diagnosis
  - Both: Annually until 70 y/o
Microalbuminuria

- The predictive value of overt DMN
  - A marker of overt nephropathy risk in type 1 DM patients.
  - Type 1 DM > 15 years with microA: 28% developed overt DMN within 10 years.

- Systemic hypertension
  - A significant relationship between BP and urine albumin excretion rate (UAE).
Microalbimimuria

- Diabetic retinopathy
  - Type 1 DM patients: strong association between UAE and DMR.
  - Close ophthalmologic monitoring advised.
- Atherosclerosis:
  - DM patients with overt DMN: increased risk of CV mortality.
  - Micro A: potentially atherogenic changes
Screening for microalbuminuria

1) Measurement of albumin:creatinine ratio in random spot collection
2) 24-hour collection with creatinine, allowing the simultaneous measurement of creatinine clearance
3) Timed (e.g., 4-hour or overnight collection).
### Albuminuria thresholds for 3 common tests of diabetic nephropathy

<table>
<thead>
<tr>
<th>Category</th>
<th>Albumin:creatinine ratio, spot collection (μg/mg)</th>
<th>24-h creatinine collection (mg/24h)</th>
<th>Albuminuria, timed collection (μg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;30</td>
<td>&lt;30</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30-299</td>
<td>30-299</td>
<td>20-199</td>
</tr>
<tr>
<td>Clinical albuminuria (macroalbuminuria)</td>
<td>≥300</td>
<td>≥300</td>
<td>≥200</td>
</tr>
</tbody>
</table>
Using a specific assay for albumin is a more sensitive technique. The normal rate of albumin excretion is less than 20 mg/day (15 µg/min); persistent albumin excretion between 30 and 300 mg/day (20 to 200 µg/min) is called microalbuminuria and, in patients with diabetes (particularly type 1 diabetes), is usually indicative of diabetic nephropathy.
Although the 24-hour urine collection was previously the gold standard for the detection of microalbuminuria, it has been suggested that screening can be more simply achieved by a timed urine collection or an early morning specimen to minimize changes in urine volume that occur during the day.
Microalbuminuria is unlikely if the albumin excretion rate is below 20 µg/min in a timed collection or if the urine albumin concentration is less than 20 to 30 mg/L in a random specimen. Higher values (particularly those just above this range) may represent false positive results, and should be confirmed by repeated measurements.
There are also a variety of semiquantitative dipsticks, such as Clinitek Microalbumin Dipsticks and Micral-Test II test strips, which can be used to test for microalbuminuria if the urine albumin excretion cannot be directly measured. The reported sensitivity and specificity of these tests range from 80 to 97 percent and 33 to 80 percent, respectively.
Albumin-to-creatinine ratio — The effect of volume can be avoided entirely by calculation of the albumin-to-creatinine ratio in an untimed urine specimen. A value above 30 mg/g (or 0.03 mg/mg) suggests that albumin excretion is above 30 mg/day and therefore that microalbuminuria is probably present.
Patients who progress from normoalbuminuria to microalbuminuria or microalbuminuria to macroalbuminuria are more likely to have higher hemoglobin A1c (A1C) values and a higher blood pressure than nonprogressors.
Patients with type 1 diabetes almost always have a blood pressure of less than 130/80 mmHg if albumin excretion is normal or only slightly increased [23]. The blood pressure usually begins to rise within the normal range in the third year after the onset of microalbuminuria [36]; the incidence of overt hypertension is approximately 15 to 25 percent in all patients with microalbuminuria and much higher as the patient progresses to overt nephropathy.
Type 2 diabetes — Progression from microalbuminuria to overt nephropathy within a 10 year period occurs in 20 to 40 percent of Caucasian patients with type 2 (non-insulin-dependent) diabetes [3,43,44]. Risk factors contributing to progression include hyperglycemia, hypertension, ethnicity, and cigarette smoking.
Screening can be deferred for five years after the onset of disease in type 1 diabetes because microalbuminuria is uncommon before this time. If not found at the initial screen, yearly screening is recommended for microalbuminuria.
Use of the albumin-to-creatinine ratio in an untimed urinary sample is recommended as the preferred screening strategy for all diabetic patients. An elevated ratio should be confirmed with at least two additional tests performed over the subsequent 3 to 6 months, with confirmation of the diagnosis requiring at least 2 of 3 positive samples.
— We recommend that an albumin-to-creatinine ratio be measured yearly in patients with type 2 diabetes [50]. An elevated ratio should be confirmed with at least two additional tests performed over the subsequent 3 to 6 months, with confirmation of the diagnosis requiring at least 2 of 3 positive samples [50].
Microalbuminuria

- Monitor Creatinine
- Screen for Eye Disease
- Investigate for Other Renal Disease
- Screen for Heart Disease
- Screen for Vascular Disease
- Optimize BP
- Optimize Lipids
- Optimize Glucose
- Discourage Smoking
Diagnosis of Diabetic nephropathy

- Usually depend on clinical grounds without a renal biopsy
- Supportive clues are
  - 1. DM hx >10 years
  - 2. Presence of normal or enlarged kidneys
  - 3. Evidence of proliferative diabetic retinopathy
  - 4. A bland urinary sediment.
  - 5. Typical DM nephropathy course

- Retinopathy is found in 90 and 60 percent of patients with type 1 DM and type 2 DDM, respectively, who develop nephropathy
“Typical “ overt nephropathy

- Type 1 DM for > 10 years
- Retinopathy
- Previous microalbuminururia
- No macroscopic hematuria
- No RBC casts
- Normal renal echo

No Biopsy
“Atypical“ proteinuria

- Type 1 DM for <10 years
- No retinopathy
- Nephrotic range proteinuria without previous microalbimurina
- Macroscopic hematuria
- Red cell casts

Renal biopsy
The earliest morphologic abnormalities in diabetic nephropathy:

- Thickening of the glomerular basement membrane (GBM)
- Expansion of the mesangium due to accumulation of extracellular matrix.

With time:
- Matrix accumulation becomes diffuse and is evident as eosinophilic, periodic acid Schiff (+) glomerulosclerosis on biopsy.
Laboratory tests to order at the initial diagnosis of diabetes

**Type 1**
- Fasting plasma glucose OR random plasma glucose
- A1C
- Fasting lipid profile: total cholesterol, HDL, LDL, triglycerides
- Serum creatinine in adults; in children if proteinuria is present*
- Urinalysis: ketones, protein,* sediment
- Thyroid-stimulating hormone (TSH)

**Type 2**
- Fasting plasma glucose OR random plasma glucose
- A1C
- Fasting lipid profile: total cholesterol, HDL, LDL, triglycerides
- Serum creatinine*
- Urinalysis: ketones, glucose, protein,* microalbuminuria,* sediment; culture if abnormal microscopic findings or symptoms of infection are present
Type 2

- Fasting plasma glucose OR random plasma glucose
- A1C
- Fasting lipid profile: total cholesterol, HDL, LDL, triglycerides
- Serum creatinine*
- Urinalysis: ketones, glucose, protein,* microalbuminuria,* sediment; culture if abnormal microscopic findings or symptoms of infection are present
<table>
<thead>
<tr>
<th>Test (specimen or method)</th>
<th>Units</th>
<th>Purpose</th>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis (dipstick)</td>
<td>Varies with component subtest</td>
<td>Screening test for a variety of systemic diseases, renal diseases, and disorders of the urinary tract</td>
<td>Widely available Radiometric and biochemical analysis of urine components</td>
<td>Result may be altered by contaminated reagent strips, reading a strip at the wrong time, exercise Specimen volume &lt;2 mL may limit the number of subtests that can be performed</td>
</tr>
</tbody>
</table>
Microalbuminuria (24 h urine, timed overnight 10 h urine collection, spot AM urine after initial voiding) mg/L or mg/24 h

Spot collections: μg albumin/mg creatinine

Detects small amounts of albumin

Result predicts development of proteinuria (progression of diabetic nephropathy)

Result strongly supports a diagnosis of diabetic nephropathy

Creatinine clearance may be measured from the same urine specimen

Measures lower concentrations of albumin than can be detected by dipstick methods

Creatinine clearance may be assessed from random spot urine

UAE may decline 30-50% at night

Result may be altered by exercise, pregnancy, fever, inflammatory disorders, urinary tract infection, urinary tract bleeding, or benign postural proteinuria

Usually sent to a reference laboratory

Hg albumin/mg creatinine

Hg albumin/proteinuria

Hg albumin/creatinine
<table>
<thead>
<tr>
<th>Proteinuria, quantitative (24 h urine)</th>
<th>mg/24 h</th>
<th>Follow-up assessment of proteinuria and diabetic nephropathy</th>
<th>Readily available</th>
</tr>
</thead>
</table>

Requires vigilant oversight of specimen collection

Check with laboratory regarding need for refrigeration or preservative

Result may be altered by intrinsic variation in proteinuria, x-ray contrast media,* tolbutamine, antibiotics
| Creatinine (serum or plasma) | mg/dL | Result can be used to calculate approximate GFR and should be measured at least annually in all patients with diabetes\(^1\)\(<4 | Readily available; most commonly ordered test of renal function | Moderate changes in GFR may not be detected |
|-------------------------------|-------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|                               |       | Should not be used alone as a measure of kidney function, but to estimate GFR and stage the level of chronic kidney disease 4 |
|                               |       | Result may be altered by meat ingestion, pregnancy, muscular disorders, hyperthyroidism, cephalosporin antibiotics, corticosteroids, cimetidine, other drugs |