DM Nephropathy

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Definitions

Albuminuria

Increased excretion of albumin in the urine

Proteinuria

Increased excretion of albumin, other specific proteins, or total protein in the urine

National Kidney Foundation. NKF KDOQI Guidelines. Available at: www.kidney.org
# How NOT to Measure Microalbuminuria

Dipsticks only measure urinary concentration of protein. They can overestimate proteinuria in a concentrated urine, underestimate proteinuria in a dilute urine, and are typically insensitive to microalbuminuria. Do not do 24 hour urine collections for MAU.

<table>
<thead>
<tr>
<th>Dipstick</th>
<th>Concentration (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEG</td>
<td>0.3</td>
</tr>
<tr>
<td>TRACE</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>

- Dipsticks only measure urinary concentration of protein.
- They can overestimate proteinuria in a concentrated urine.
- They can underestimate proteinuria in a dilute urine.
- They are typically insensitive to microalbuminuria.
- Do not do 24 hour urine collections for MAU.
UACR

\[ UACR = \frac{\text{mg}}{\text{mmol}} \]

Normal values

- UACR < 2.2 for men
- UACR < 3.0 for women

- Use of the UACR removes the effect of urinary dilution/concentration
- Creatinine and albumin are equally concentrated
- Therefore volume is irrelevant

UACR = urine albumin:creatinine ratio; NB = nota bene
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference Range</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALBUMIN (R U)</td>
<td>439 HI</td>
<td>0 - 30</td>
<td>mg/L</td>
</tr>
<tr>
<td>Test repeated and results confirmed.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREATININE (U)</td>
<td>7.5 HI</td>
<td>2.7 - 27.5</td>
<td>mmol/L</td>
</tr>
<tr>
<td>ALBUMIN CREATININE RATIO U</td>
<td>58.5 HI</td>
<td>&lt; 2.0</td>
<td>mg/mmol</td>
</tr>
</tbody>
</table>

UACR = urine albumin:creatinine ratio
Stage of Diabetic Nephropathy by Level of Urinary Albumin by Various Test Methods

<table>
<thead>
<tr>
<th>Urine test</th>
<th>Stage of nephropathy</th>
<th>Urinary Albumin Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Reversible</td>
<td>24-hour</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Reversible</td>
<td>Negative</td>
</tr>
<tr>
<td>0</td>
<td>Positive</td>
<td>30 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0 mg/mmol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.8 mg/mmol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACR (female)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACR (male)</td>
</tr>
<tr>
<td>Overt nephropathy (macroalbuminuria)</td>
<td>Irreversible</td>
<td>1000 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66.7 mg/mmol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93.3 mg/mmol</td>
</tr>
</tbody>
</table>

ACR: albumin-creatinine ratio

Adapted from:
Natural History of Diabetic Nephropathy

Duration of diabetes (years)

(stage)

STAGE I
STAGE II
STAGE III
STAGE IV
STAGE V

Glomerular filtration rate (mL/min)

0
20
40
60
80
100
120
140
160

Microalbuminuria
Proteinuria

Urinary protein excretion (g/24 h)

0
2
4
6
8

Adapted from Pylypchuk GB, Beaubien E. Can Fam Physician 2000;46:636-42.
UKPDS: Annual Transition Rates through the Stages of Nephropathy in Patients with Type 2 Diabetes

No Nephropathy: 1.4%
Microalbuminuria: 3.0%
Macroalbuminuria: 4.6%
CRI or RRT: 19.2%

CRI = chronic renal insufficiency
RRT = renal replacement therapy

Why Screen for Proteinuria?

- The presence of protein in the urine is usually a marker of kidney damage
- To delay or prevent loss of renal function through early detection and initiation of effective therapies
- To manage complications in those identified with renal disease
- Screening may also identify people with increased vascular risk

Impact of Microalbuminuria

MAU = Microalbuminuria
NML = Normal

Ref: Neil, A. A prospective population-based study of MAU as a predictor of mortality in NIDDM. *Diabetes Care* 1993;16:996-1003
CHD Mortality in Diabetes: Odds Ratios for Selected Risk Factors

- Microalbuminuria: 10.02
- Smoking: 6.52
- Diastolic BP: 3.20
- Cholesterol: 2.32

CHD: coronary heart disease
Albuminuria: Factor Predicting Renal Events


Primary endpoint
ESRD/Death
ESRD

Hazard ratio by baseline proteinuria subgroup

< 1000 mg/g
1000-2000 mg/g
2000-4000 mg/g
> 4000 mg/g

n=1513
ESRD = end-stage renal disease
Proteinuria and Renal End Points

- The key point is not how much proteinuria you start with, it's how much you finish with.
- For each halving of proteinuria, the relative risk of a renal endpoint was reduced during follow-up.
- There was an 18 percent decrease in risk of a cardiovascular event for every 50 percent decrease in the rate of albumin excretion.
Blood Pressure Targets

- General: < 140/90 mmHg
- Diabetes mellitus: < 130/80 mmHg
- Chronic kidney disease: < 130/80 mmHg

CHEP 2009 Recommendations.
Association of Systolic BP and Cardiovascular Death in Type 2 Diabetes

Priorities for Treatment in Diabetes: The Three Pillars of Protection

Optimal Treatment of Diabetes

#1 Vascular Protection

#2 BP Control

#3 Nephroprotection

Two Goals in Protecting a Diabetic Kidney

- Lower BP to target
- Decrease proteinuria
Treatment of Hypertension in Association with Diabetes Mellitus

THRESHOLD EQUAL OR OVER 130/80 mmHg
AND TARGET BELOW 130/80 mmHg

Diabetes

with Nephropathy

ACE Inhibitor or ARB

1. ACE Inhibitor or ARB
2. Thiazide diuretic or DHP-CCB

≥ 2-drug combinations

without Nephropathy

More than 3 drugs may be needed to reach target values for patients with diabetes.

If Creatinine over 150 µmol/L or creatinine clearance below 30 ml/min (0.5 ml/sec), a loop diuretic should be substituted for a thiazide diuretic if control of volume is desired.

CHEP 2010 Recommendations
Natural History of Diabetic Nephropathy

**STAGE I**

**STAGE II**

**STAGE III**

**STAGE IV**

**STAGE V**

Duration of diabetes (years)

- Glomerular filtration rate (mL/min)
- Urinary protein excretion (g/24 h)

0 2 4 6 8

0 2 4 6 8

60 80 100 120 160

Primary prevention Secondary prevention Life support

Duration of diabetes (years)

Microalbuminuria

Proteinuria

Adapted from Pylypchuk GB, Beaubien E. Can Fam Physician 2000;46:636-42.
1,209 patients with type 2 DM, normoalbuminuria, serum creatinine <133 µmol/L, and BP >130/85 mmHg

Screening/enrollment

Washout period

6 weeks ACEI
3 weeks NDP-CCB

Verapamil SR 240 mg/day (n=303)
Trandolapril 2 mg/day (n=301)
Trandolapril + Verapamil SR (n=300)
Placebo (n=300)

3.6 years

Target BP <120/80 mmHg and target A1C <7.0%
Primary endpoint: development of persistent MAU

Bergamo Nephrologic Diabetes Complications Trial (BENEDICT)

**MEAN ARTERIAL PRESSURE**

<table>
<thead>
<tr>
<th>mmHg</th>
<th>Combo</th>
<th>ACEI</th>
<th>Non-DHP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>97</td>
<td>101</td>
<td>105</td>
<td>102</td>
</tr>
<tr>
<td>96</td>
<td>98</td>
<td>102</td>
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<td>103</td>
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<tr>
<td>105</td>
<td>107</td>
<td>111</td>
<td>113</td>
<td>112</td>
</tr>
</tbody>
</table>

* Significant vs. placebo

**DEVELOPMENT OF PERSISTENT MICROALBUMINURIA (%)**

<table>
<thead>
<tr>
<th>% of patients</th>
<th>Combo</th>
<th>ACEI</th>
<th>Non-DHP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>12</td>
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<td>10</td>
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</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Natural History of Diabetic Nephropathy

- STAGE I
- STAGE II
- STAGE III
- STAGE IV
- STAGE V

Duration of diabetes (years)

Glomerular filtration rate (mL/min)

Urinary protein excretion (g/24 h)

Microalbuminuria
Proteinuria

Primary prevention
Secondary prevention
Life support

Adapted from Pylypchuk GB, Beaubien E. Can Fam Physician 2000;46:636-42.
IRMA 2: Study Design

590 patients with type 2 diabetes, microalbuminuria (albumin excretion rate: 20-200 µg/min), normal renal function, and hypertension

SCREENING/ENROLLMENT

DOUBLE-BLIND TREATMENT

Usual care/Placebo (n=201)

Irbesartan 150 mg (n=195)

Irbesartan 300 mg (n=194)

Follow-up: 2 years

IRMA 2:
Development of Overt Proteinuria

<table>
<thead>
<tr>
<th>Subjects (%)</th>
<th>Usual care (n=201)</th>
<th>150 mg (n=195)</th>
<th>300 mg (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.9</td>
<td>RRR=39% p=0.08</td>
<td>9.7</td>
<td>RRR=70% p&lt;0.001</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>5.2</td>
<td></td>
</tr>
</tbody>
</table>

Natural History of Diabetic Nephropathy

![Graph showing the natural history of diabetic nephropathy](image)

- **Stage I**: Microalbuminuria
- **Stage II**: Proteinuria
- **Stage III**: Proteinuria
- **Stage IV**: Proteinuria
- **Stage V**: Proteinuria

Duration of diabetes (years)

Glomerular filtration rate (mL/min)

Urinary protein excretion (g/24 h)

| **Population** | n = 1,715  
| NIDDM with albuminuria and HTN  
| (900 mg/24 hrs) |

| **Treatment** | Irbesartan vs. Amlodipine vs. Placebo  
| (+non-ACEI, non-CCB agents)  
| 2.6 years average |

| **Primary Endpoints** | Doubling sCr/ESRD/death |

| **Secondary Endpoints** | CV morbidity/mortality  
| Proteinuria |

| **Population** | n = 1,513  
| NIDDM with albuminuria and HTN  
| (300 mg/g creatinine)  
| Serum creatinine ≥115-265 μmol/L |

| **Treatment** | Losartan vs. Placebo  
| (+ non-ACEI agents)  
| 3.4 years average |

| **Primary Endpoints** | Doubling sCr/ESRD/death |

| **Secondary Endpoints** | CV morbidity/mortality  
| Proteinuria |

IDNT Primary Endpoint
Time to Doubling of Serum Creatinine, ESRD, or Death

For diabetic patients at risk over a 3.5 year period, it is estimated:
- one case of ESRD can be prevented for every 16 treated
- losartan reduces days with ESRD by 32%

Extrapolating these results to the 595,000 Type 2 diabetic patients with proteinuria in the US:
- 37,500 fewer new ESRD patients
- $3.1 billion reduction in the cost of ESRD alone
  (savings increase $4.4 billion at 4 years)
- Delay the need for dialysis in a diabetic by 2 years
ONTARGET: results

- no significant difference in primary or secondary outcomes
- combination showed no additional benefit

ONTARGET: results

- no significant difference in primary or secondary outcomes
- combination showed no additional benefit

ONTARGET Investigators et al. NEJM 2008;358:1547-59.
“Combinations of an ACEI with an ARB are specifically not recommended except in patients who have CHF”

- CHEP 2010 Guidelines
## Aliskiren in the EVAluation of PrOteinuria In Diabetes AVOID study – Design

<table>
<thead>
<tr>
<th>Study design:</th>
<th>Double-blind, randomized, placebo-controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population:</td>
<td>496 patients</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>Mild-to-moderate hypertension</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td></td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Treatment period:</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Study status*:</td>
<td>Completed</td>
</tr>
</tbody>
</table>

*Study status as of May 2007

Clinicaltrials.gov 2006; Data on File, Novartis 2007
AVOID study – Design overview

- All patients continue to receive open-label losartan 100 mg and optimal antihypertensive therapy during the double-blind period
- Patients force-titrated after 12 weeks
- All treatments administered once daily

Clinicaltrials.gov 2006; Data on File, Novartis 2007
DRI or Placebo + Optimal Treatment Including ARB (The AVOID study): Mean Change in ACR


*\( p < 0.001 \) vs. optimal care + placebo

20% reduction in ACR vs. placebo

% change from baseline

Optimal treatment + aliskiren 300 mg (n=287)

Optimal treatment + placebo (n=289)
Blockers of the RAAS delay the onset of MAU and slow the progression of diabetic nephropathy to ESRD
Vascular Protection: Summary

Non-pharmacological
- Smoking cessation
- Exercise
- BMI <25 kg/m$^2$
- Alcohol <2 drinks/day
- Low salt diet

Pharmacological
- ASA 81 mg/day
- A1C <7%
- LDL-C ≤2.0 mmol/L
- BP <130/80 mmHg
- Blockers of the RAAS