Prevention And Treatment of Diabetic Nephropathy

MOH Clinical Practice Guidelines
3/2006
Dr Stephen Chew Tec Huan
GFR in Diabetes

- Hyperfiltration and/or microalbuminuria
- Proteinuria
- Azotemia
- ESRD

Years of Hyperglycemia

GFR ml/min
Diabetic Nephropathy: Natural History

Microalbuminuria
albumin >30 mg/day or 20 μg/min

Overt Nephropathy
albumin ≥300 mg/day or ~200 μg/min

ESRD

Type 1
~80% progress
~10-20%/year
>75% by 20 years

Type 2
~20-40% progress
>20% by 20 years

Diabetes Care 2000;23Suppl1:S69-S72
Prevention

- Tight glucose control reduces the development of diabetic nephropathy
Progression Of Complications In Type 1 Diabetics With Intensive And Conventional Treatment (DCCT) - Primary Prevention

<table>
<thead>
<tr>
<th>Complications</th>
<th>Conventional Therapy</th>
<th>Intensive Therapy</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate/100 patient-year</td>
<td></td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Urinary Alb (mg/24hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>3.4</td>
<td>2.2</td>
<td>34 (2-56)</td>
</tr>
<tr>
<td>&gt;300</td>
<td>0.3</td>
<td>0.2</td>
<td>44 (-124-86)</td>
</tr>
<tr>
<td>Clinical Nephropathy at 5 years</td>
<td>9.8</td>
<td>3.1</td>
<td>69 (24-87)</td>
</tr>
</tbody>
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The Diabetes Control And Complications Trial Research Group, NEJM 1993
Progression Of Complications In Type 1 Diabetics With Intensive And Conventional Treatment (DCCT) -Secondary Prevention

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<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>5.7</td>
<td>3.6</td>
<td>43 (21-58)</td>
</tr>
<tr>
<td>&gt;300</td>
<td>1.4</td>
<td>0.6</td>
<td>56 (18-76)</td>
</tr>
<tr>
<td>Clinical Nephropathy at 5 years</td>
<td>16.1</td>
<td>7.0</td>
<td>57 (29-73)</td>
</tr>
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</table>

The Diabetes Control And Complications Trial Research Group, NEJM 1993
UKPDS

• Prospective randomized trial in type II diabetics
• Selected newly diagnosed Type II DM with little or no preexisting renal complications
• Compared the effect of intensive therapy and conventional therapy on development of complications.
UKPDS

- Patients on the intensive therapy arm were treated with a sulphonylurea, or if needed insulin was added, to keep fasting blood glucose <7mmol/l.
- Conventional therapy was started with diet, and a sulphonylurea added to keep fasting blood glucose <15mmol/l.
- Patients followed up 10 years.
Effect of Intensive Therapy And Conventional Therapy On Renal End Points At Nine Years In Type 2 DM with Normoalbuminuria

<table>
<thead>
<tr>
<th></th>
<th>Intensive (FG &lt;7)</th>
<th>Conventional (FG&lt;15)</th>
<th>p</th>
<th>RR for intensive (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria</td>
<td>19.2</td>
<td>25.4</td>
<td>&lt;0.001</td>
<td>0.76 (0.62-0.91)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>4.4</td>
<td>6.5</td>
<td>0.02</td>
<td>0.67 (0.42-1.07)</td>
</tr>
<tr>
<td>Doubling of serum creatinine</td>
<td>0.91</td>
<td>3.52</td>
<td>&lt;0.01</td>
<td>0.26 (0.07-0.91)</td>
</tr>
</tbody>
</table>

UK Prospective Diabetes Study Group, Lancet 1998
Prevention

- Blood pressure control reduces the development of microvascular disease in diabetics
Tight BP control reduces microvascular events

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group, BMJ 1998;317:703-713
Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38.

UK Prospective Diabetes Study Group
Tight Blood Pressure Control Confers CV Benefits in Diabetic Patients

The benefits of lowering BP in the UKPDS were greater than those achieved through glycemic control.

- Stroke: -20%
- Any DM endpoint: -10%
- DM death: -20%
- Microvascular complications: -30%

DM=diabetes mellitus
FPG=fasting plasma glucose
*P<0.05.

Screening

- Screening for albuminuria should begin 5 years after the diagnosis of type 1 diabetes.
- It should be done immediately after the diagnosis of type 2 diabetes.
- Screening for albuminuria should be done annually.
# ABNORMAL ALBUMIN EXCRETION

<table>
<thead>
<tr>
<th></th>
<th>Timed (ug/min)</th>
<th>24 hour (mg/day)</th>
<th>Alb/Cr (mg/gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;20</td>
<td>&lt;30</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>20-200</td>
<td>30-300</td>
<td>30-300</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;200</td>
<td>&gt;300</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

Microalbuminuria needs to be persistent over 6 months
Screening

- Serum creatinine should be done annually
- and the GFR estimated
  - Cockcroft – Gault equation (Age/weight/cr)
  - MDRD formula (Age, creatinine)
Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus

- 3rd NHNES; > 40 yrs, T2 DM; Survey
- 13% of type 2 DM with CRI (MDRD)
  - DR 28%
  - Microalbuminuria 45%
  - Macroalbuminuria 19%
- 30% of CRI with neither DR nor albuminuria

Kramer HJ et al; JAMA 2003; 289; 3273-77
Detection of Microalbuminuria
## Impact of Blood Pressure Reduction on Mortality in Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Conventional care</th>
<th>Intensive care</th>
<th>Risk reduction</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>154/87</td>
<td>144/82</td>
<td>32%</td>
<td>0.019</td>
</tr>
<tr>
<td>HOT</td>
<td>144/85</td>
<td>140/81</td>
<td>66%</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Mortality endpoints are:
- **UK Prospective Diabetes Study (UKPDS)** – “diabetes related deaths”
- **Hypertension Optimal Treatment (HOT) Study** – “cardiovascular deaths” in diabetics

Drug choices in the non-albuminuric hypertensive diabetic patient

- Blood pressure control reduces cardiovascular events
- Initial drug choices include
  - Angiotensin converting enzyme inhibitors
  - Angiotensin receptor blockers
  - Beta blockers
  - Diuretics
  - Calcium channel blockers
ABCD: Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes.

- 470 hypertensive diabetics DBP > 90
- 2 x 2;
  - nislodipine vs enalapril;
  - Intensive versus moderate

5 year follow up

Intensive BP 132/78 vs Mod 138/76

Results
- GFR decline no difference
- Normo to Micro: 25% vs 18% (p 0.20 ns)
- Micro to Macro: 16% vs 25% (p 0.28 ns)

Estacio RO et al; Diabetes Care 2000; 23; Suppl 2 B 54-64
Blood Pressure Target

- The blood pressure target in all diabetics should be less than 130/80
- Diabetics with proteinuria in excess of 1 gram should attempt to achieve values of less than 125/75 mm Hg
COURSE OF GFR, ALBUMINURIA, MEAN ARTERIAL BLOOD PRESSURE IN 9 IDDM PATIENTS TREATED WITH ANTIHYPERTENSIVES

MAP (mmHg)  
GFR (ml/min/1.73m²)  
Albuminuria (ug/min)  

Parving HH et al; Am J Kidney Dis. 1993 Jul;22(1):188-95
Meta Analysis: Lower Mean BP Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics


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Mean glomerular filtration rate (GFR) decline and achieved follow-up blood pressure in study B*

* GFR 13-24; n = 255

Mean glomerular filtration rate (GFR) decline and achieved follow-up blood pressure in study A*

* GFR 22-55ml/min; n = 585

Combination Therapy Needed to Achieve Target SBP Goals

**Trial/SBP Achieved**

- **UKPDS** (144 mm Hg)
- **RENAAL** (141 mm Hg)
- **ALLHAT** (138 mm Hg)
- **IDNT** (138 mm Hg)
- **HOT** (138 mm Hg)
- **INVEST** (133 mm Hg)
- **ABCD** (132 mm Hg)
- **MDRD** (132 mm Hg)
- **AASK** (128 mm Hg)

**Number of BP Medications**

Drug choices in early nephropathy

- The initial therapy of choice should include an ACE inhibitor or an ARB
Drug Choices in Type 1 diabetics with overt nephropathy

• In the presence of overt nephropathy in type 1 diabetes, there is evidence that an ACE inhibitor can retard the progression of otherwise progressive renal disease
ACE-I Is More Renoprotective Than Conventional Therapy in Type 1 Diabetes

% with doubling of baseline creatinine

Baseline creatinine $\geq 1.5$ mg/dL & overt proteinuria

Placebo
$\ n=202$
P$<.001$

Captopril
$\ n=207$

Placebo BP achieved 129-136/80-84;
Captopril BP achieved 128/134/77-82

Years of follow-up

Collaborative Study Group Trial

Drug choices in type 2 diabetics with overt nephropathy

- In type 2 diabetes with overt nephropathy, either an ACE inhibitor or an ARB may be used to retard the progression of renal disease.
Long-Term Benefits of ACE Inhibition in Normotensive Type 2 Diabetics With Microalbuminuria

ARBs Can Reduce Diabetic Renal Disease Progression

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**RENAAL**

- Losartan: p = 0.006, rr 25%
- Placebo

**IDNT**

- Irbesartan: p < 0.001, rr 23%
- Amlodipine
- Placebo

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$n = 1513; 3.45$ years

$n = 1715; 2.6$ years

IRMA II Irbesartan vs Placebo Primary Endpoint at 2 Years

<table>
<thead>
<tr>
<th></th>
<th>Total # of Patients</th>
<th>Progression to Nephropathy</th>
<th>Unadjusted Risk Reduction</th>
<th>P Value†</th>
<th>Adjusted* Risk Reduction</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg Irbesartan</td>
<td>194</td>
<td>10</td>
<td>5.2</td>
<td>70%</td>
<td>68%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>150 mg Irbesartan</td>
<td>195</td>
<td>19</td>
<td>9.7</td>
<td>39%</td>
<td>44%</td>
<td>0.05</td>
</tr>
<tr>
<td>Placebo</td>
<td>201</td>
<td>30</td>
<td>14.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

† For irbesartan vs placebo (the significance level for the primary endpoint was 0.025)

*Hazard ratios were adjusted for baseline level of microalbuminuria and blood pressure achieved during the study

IRMA II Change in Urinary Albumin Excretion*

*P<0.001 for difference between both irbesartan groups and placebo

IRMA II Incidence of Progression to Diabetic Nephropathy

P<0.001 for difference between 300 mg irbesartan group and placebo

Drug Choices in type 2 diabetics with early nephropathy

- Both an ARB and ACE inhibitor demonstrate similar benefit in reducing a decline in the GFR
Inclusion criteria

- 250 patients

Inclusion criteria

- Male or female, 35–80 years
- Type 2 diabetes (onset >40 years) on diet ± OHA or insulin
- ACE inhibitor for ≥3 months (ACE inhibitor tolerant)
- Mild-to-moderate hypertension (BP ≤180/95 mmHg)
- Normal gross renal morphology ≤12 months

Outcomes

Primary endpoint

• Change in GFR after 5 years

Secondary endpoints

• Changes in GFR after 1, 2, 3 and 4 years
• Changes in UAER and serum creatinine after 1, 2, 3, 4 and 5 years
• Incidence of clinical events
  – (end-stage renal disease, myocardial infarction, etc.)

ARB vs ACE inhibitors in type 2 diabetes and incipient nephropathy

Total GFR

\( p = \text{NS}^\dagger \)

Change in GFR

<table>
<thead>
<tr>
<th>Telmisartan</th>
<th>Enalapril</th>
</tr>
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<tbody>
<tr>
<td>-17.9</td>
<td>-14.8</td>
</tr>
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\( p = \text{NS}^\dagger \)

*All patients, LOCF; 250 patients; 5 years follow up
\( ^\dagger p = \text{NS}, \text{telmisartan vs enalapril} \)

Drug choices in type 2 diabetics with overt nephropathy

- In type 2 diabetes with overt nephropathy, either an ACE inhibitor or an ARB may be used to retard the progression of renal disease.
Problems of use of ACE inhibitors

- Hyperkalaemia
- Acute renal failure with underlying bilateral renal artery stenosis
Impact of ACE-I on BP and GFR: Acute and Chronic Effects

*P<0.05 compared to baseline

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Recommended Practices

- The serum creatinine and potassium should be checked within 4 weeks of initiation of treatment to detect any rise in the serum creatinine of hyperkalaemia
The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis.

- Jan 1996 to Dec 1994
- 5 studies IDDM; 5 studies non DM CRF
- End points: Death and reduce GFR decline

<table>
<thead>
<tr>
<th></th>
<th>FU (mths)</th>
<th>Study Size</th>
<th>OR</th>
</tr>
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<tbody>
<tr>
<td>IDDM</td>
<td>9 to 35</td>
<td>108</td>
<td>0.56 [0.44 -0.77]</td>
</tr>
<tr>
<td>Non DM</td>
<td>18 to 36</td>
<td>1413</td>
<td>0.67 [0.50-0.89]</td>
</tr>
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</table>

Pedrini MT et al; Ann Intern med 1996; 124: 627-32
Other measures: low protein diet

• Type 1 diabetics with overt nephropathy should be maintained on a low protein diet of 0.8 gram / kg/ day of protein
Clinical Targets

• Therapy should aim to reduce albuminuria as much as possible, and it is reasonable to aim for a urinary protein levels to less than 1 gram per day or at least 50% of the pre-treatment value.
Recommended nephrology consultation

- Decline in renal function
- Difficulties in hyperkalaemia
- Atypical features eg haematuria, casts, renal bruits
- Difficult blood pressure control
- Heavy proteinuria (in excess of 3 gm/day)
- Absence of retinopathy
Summary
Prevention

• Tight glucose control reduces the development of diabetic nephropathy
Prevention

• Blood pressure control reduces the development of microvascular disease in diabetics
Screening

• Screening for albuminuria should begin 5 years after the diagnosis of type 1 diabetes.
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