Diabetic Nephropathy
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Diabetic Nephropathy
Clinical Stages

Hyperfunction / Renal Enlargement
- 0-15 years after onset of DM
- GFR normal or increased

Microalbuminuria (Protein: 30-300 mg/d)
- 10-15 years after onset of DM
- GFR normal

Macroalbuminuria (Protein: > 300 mg/d)
- 11-20 years after onset of DM
- GFR decreasing

Progressive CRF / ESRD
- 15-25 years after onset of DM
- GFR < 30 ml/min
Diabetic Nephropathy

Clinical Stages

Hyperfunction / Renal Enlargement

- ~50% if DM < 5 years

Microalbuminuria (Protein: 30-300 mg/d)

- 20-30% at 15 years

Macroalbuminuria (Protein: > 300 mg/d)

- 25-45% at 15-20 years

Progressive CRF / ESRD

- 4-17% at > 20 years
Diabetic Nephropathy
Pathological Changes

Mesangial Expansion
- Glycosylation of matrix proteins (AGEs)
- Increased production of matrix proteins

Glomerular Basement Membrane Thickening
- Glycosylation of GBM proteins (AGEs)
- Intraglomerular hypertension (vasodilation)

Glomerular Sclerosis (+/- Nodules)
- Intraglomerular hypertension (vasodilation)
- Ischemic injury (hyaline vascular narrowing)
Diabetic Nephropathy

**Light Microscopy**
Diffuse and nodular glomerulosclerosis. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis.
Advanced Diabetic Glomerulosclerosis

**Light Microscopy**
Diffuse and nodular mesangial expansion and characteristic hyaline thickening of the arteriole at the glomerular hilum (arrow). Diabetes typically affects both the afferent and efferent arterioles, whereas hypertension typically affects only the afferent arterioles.
Diabetic Nephropathy

Pathogenesis

Renal Hemodynamic Changes
- Vasodilation / Increased Renal Blood Flow
- Glomerular Hypertension and Hyperfiltration
- Systemic Hypertension

Metabolic Alterations
- Activation of Aldose Reductase pathway
- Activation of Protein Kinase C pathway
- Glycosylation of Renal Proteins (AGEs)

Growth Factor and Cytokine Changes
- AII, TGF-β, IGF-1, PDGF, CTGF, Eicosanoids

Oxidative Stress

Genetic Susceptibility
Aldose Reductase Pathway

Advanced Glycosylation End Products

Adapted from: Bucala R, Drug Development Research 1994; 32:77
Diabetic Nephropathy
Genetic Susceptibility

Candidate genes

- ACE gene (DD polymorphisms)
- AII gene (AA haplotype)
- Aldose Reductase gene (Z-2 allele)
Clinical Practice Recommendations: ADA 2009

Nephropathy Screening

Type 1 DM: ≥ 5 years duration of DM, test urine albumin excretion (UAE) annually (E).

Type 2 DM: test UAE annually (E).

Measure Albumin/Creatinine Ratio (preferred method): random spot urine sample (E).

Measure Serum Creatinine: at least annually in adults with DM regardless of UAE and use to estimate GFR and stage of chronic kidney disease, if present (E).

Diabetes Care 2009; 32 (Suppl 1):S1-S98 (S9, S33-34)
# Urine Protein Measurement

## Significance of Findings

<table>
<thead>
<tr>
<th>Urinary Protein Measurement</th>
<th>Spot Urine (ug/mg Cr)</th>
<th>24 Hr Urine (mg/24 h)</th>
<th>Timed Urine (ug/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>Macroalbuminuria</td>
<td>&gt; 300</td>
<td>&gt; 300</td>
<td>&gt; 200</td>
</tr>
</tbody>
</table>
Evidence that Proteinuria is Not Due to Diabetes

- Acute onset of renal disease
- Onset of proteinuria < 5 years after onset of DM
- Active urine sediment with RBCs or cellular casts
- Absence of retinopathy or neuropathy
Diabetic Nephropathy
Treatment Strategies

Glucose Control
- All patients

Blood Pressure Control
- Patients with BP > 130/80

Proteinuria Reduction
- Patients with microalbuminuria

Lipid Reduction
- Patients who exceed lipid goals

Investigational
- Aldose Reductase inhibition
- Protein Kinase C inhibition
- Advanced Glycosylation End-product inhibition
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Glucose Control in Type 1 DM
Effect on Microalbuminurinuria Development

DCCT Group, N Engl J Med 1993; 329:977
# Glycemic Control

## Microvascular Complications

<table>
<thead>
<tr>
<th>Study</th>
<th>A1C %</th>
<th>Retinopathy</th>
<th>Nephropathy</th>
<th>Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>9 v 7</td>
<td>↓ 76%</td>
<td>↓ 54%</td>
<td>↓ 60%</td>
</tr>
<tr>
<td>UKPDS</td>
<td>8 v 7</td>
<td>↓ 17-21%</td>
<td>↓ 24-33%</td>
<td></td>
</tr>
<tr>
<td>Kumamoto</td>
<td>9 v 7</td>
<td>↓ 69%</td>
<td>↓ 70%</td>
<td>↓ (ss)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>7.3 v 6.5</td>
<td>↓ 21%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lowering A1C to below or around 7% reduces microvascular and neuropathic complications of Type 1 and Type 2 DM. Therefore, for microvascular disease prevention, the A1C goal for nonpregnant adults is < 7% (A).

Diabetes Care 2009; 32 (Suppl 1):S1-S98 (S7, S19-23)
Type 1 Diabetes Mellitus

Pathophysiology

Absolute Insulin Deficiency
Autoimmune Beta Cell Destruction
Type 1 Diabetes Mellitus

Treatment

Physiologic Insulin Therapy

Absolute Insulin Deficiency
Autoimmune Beta Cell Destruction
Basal Bolus Insulin Regimen

- Basal amount ~ 50%
- Bolus amount ~ 50%

Glargine / Detemir / CSII
Lispro / Aspart / Glulisine
## Insulin Therapy
### Chronic Renal Failure

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Insulin Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>None</td>
</tr>
<tr>
<td>10-50</td>
<td>↓ 25%</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>↓ 50%</td>
</tr>
</tbody>
</table>
Type 2 Diabetes Mellitus

Pathophysiology

↓ GLP-1

↓ Insulin

↑ Glucagon

↓ Glucose Utilization

↑ Glucose Production

↓ Glucose Utilization

Hyperglycemia
Type 2 Diabetes Mellitus
Pathophysiology Based Treatment

- Glucose Utilization
- Type 2 Diabetes Mellitus
- Metformin
- Thiazolidinedione
- Sulfonylurea
- Meglitinide
- Exenatide
- DPP4 Inhibitor

- ↑ GLP-1
- ↑ Insulin
- ↓ Glucagon
- ↑ Glucose Utilization

- Thiazolidinedione

- ↓ Glucose Production
- Metformin
Type 2 Diabetes Mellitus

Lifestyle Intervention + Metformin

3 Months: A1C ≥ 7.0

- Basal Insulin
  - Best Efficacy

- Sulfonylurea
  - Low Cost

- Exenatide
  - Weight loss

- Pioglitazone
  - No Hypoglycemia

- DPP4 Inhibitor
  - Weight Neutral

3 Months: A1C ≥ 7.0

- Basal Insulin

3 Months: A1C ≥ 7.0

- Basal Insulin

3 Months: A1C ≥ 7.0

- Basal Insulin

Basal Bolus Insulin

MTM Algorithm
Adapted from ADA 2008
## Oral Diabetes Medications
### Chronic Renal Failure

<table>
<thead>
<tr>
<th>Class</th>
<th>Metabolism</th>
<th>Renal Excretion</th>
<th>Recommend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>None</td>
<td>Active drug</td>
<td>Against</td>
</tr>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>Liver</td>
<td>Inactive metabolites</td>
<td>OK</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Liver</td>
<td>Weak metabolites</td>
<td>Caution</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Liver</td>
<td>Active metabolites</td>
<td>Against</td>
</tr>
<tr>
<td><strong>Meglitinides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Liver</td>
<td>&lt; 10% excreted</td>
<td>OK</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Liver</td>
<td>Active metabolites</td>
<td>Caution</td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Liver</td>
<td>Active metabolites</td>
<td>Against</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Liver</td>
<td>Inactive metabolites</td>
<td>Against</td>
</tr>
<tr>
<td><strong>DPP4 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Liver</td>
<td></td>
<td>OK</td>
</tr>
</tbody>
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Blood Pressure Regulation

Angiotensinogen → Angiotensin I → Angiotensin II

ACE

Angiotensinogen → Renin

Aldosterone

Na retention, K excretion

Norepinephrine +Inotropic +Chronotropism

Vasoconstriction
Blood Pressure Medications

Angiotensinogen → Angiotensin I → Angiotensin II → Aldosterone → Na retention 

ACE → ACE-I

β Blocker + Inotropic + Chronotropism

Calcium Channel Blocker

ARB

Aldosterone → K excretion

Diuretic

Beta Blocker

Calcium Channel Blocker

ARA

Vasoconstriction

Alpha Blocker
ACE-I Therapy in Type 1 DM
Effect on Nephropathy Progression

Type 1 DM, Overt Proteinuria and Creatinine $\geq 1.5$ mg/dl
RCT: Captopril vs Placebo for 4 years

Lewis EJ, N Engl J Med 1993; 329:1456
ARB Therapy in Type 2 DM
Effect on Nephropathy Progression

Median Changes in Proteinuria from Base Line

Placebo
Losartan

ARB Therapy in Type 2 DM
Effect on Nephropathy Progression

ACE-I vs ARB in Type 2 DM
Effect on Nephropathy Progression

ACE-I + NDHP-CCB in Type 2 DM
Effect on Nephropathy Progression
Type 2 DM, Overt Proteinuria and Hypertension
RCT: Trandilopril, Verapamil, or Both for 1 year

ARB vs DHP-CCB Therapy in Type 2 DM
Effect on Nephropathy Progression

Type 2 DM, Overt Proteinuria and Hypertension
RCT: Irbesartan vs Amlodipine vs Placebo for 4 years

Clinical Practice Recommendations: ADA 2009

Nephropathy Treatment: Supporting Evidence

Type 1 DM Patients with Hypertension and Any Degree of Albuminuria: ACE inhibitors have been shown to delay the progression of nephropathy (A).

Type 2 DM Patients with Hypertension and Microalbuminuria: ACE inhibitors and ARBS have been shown to delay progression to macroalbuminuria (A).

Type 2 DM Patients with Hypertension, Macroalbuminuria, and Serum Creatinine $\geq$ 1.5 mg/dl: ARBs have been shown to delay the progression of nephropathy (A).

Diabetes Care 2009; 32 (Suppl 1):S1-S98 (S9, S33-34)
Pharmacological therapy for patients with diabetes and hypertension should include either an ACE Inhibitor or Angiotensin Receptor Blocker (ARB) (C).

**BP Goal: < 130/80**

If needed to achieve BP goal, add a thiazide diuretic if the eGFR ≥ 30 ml/min and a loop diuretic if the eGFR < 30 ml/min (C).

Multiple drug therapy (2 or more agents at maximal doses) is generally required to achieve BP targets (B).

If ACE inhibitors, ARBs, or diuretics are used, kidney function and serum potassium levels should be closely monitored (E).
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Low Protein Diet and DM Nephropathy
Effect on Nephropathy Progression

Patients with Diabetic Nephropathy
Protein Restriction (0.6 mg/kg/day) vs Control for 3 years

Walker J, Lancet 1989; 2:1411
Reduction of protein intake to 0.8-1.0 g/kg/day in those with early stages of CKD and to 0.8 g/kg/day in those with later states of CKD is recommended (B).
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Statin Therapy DM Nephropathy

Articles identified (n = 125)

Excluded studies (n = 110)
- Duplicate study: 64
- Intervention was not a statin: 4
- Control was not placebo: 5
- Not the correct end point: 25
- Not an RCT: 7
- Children: 2
- Urine dipstick only: 1
- Rats: 1
- Outcome not reported: 1

Included studies (n = 15)

Individual and pooled results of 15 RCT’s examining the effect of statins

**Clinical Practice Recommendations: ADA 2009**

**Dyslipidemia Treatment Goals**

**Without Overt CVD:** LDL goal: < 100 mg/dl (A).

**With Overt CVD:** LDL goal: < 70 mg/dl (optional) (B)

**Alternative Goal:** ↓ LDL by 30-40% if unable to reach targets on maximally tolerated statin therapy (A)

TG < 150 mg/dl (C)

HDL > 40 (men) and > 50 (women) (C)

Combination therapy using statins and other lipid agents may be considered but has not been evaluated in outcome studies for CVD outcomes or safety (C)

*Diabetes Care 2009; 32 (Suppl 1):S1-S98 (S8-9, S29-31)*