Comprehensive education course for Asian diabetes educators
- Title: Seeking for the united collaboration in Asia through education

Chronic complications other than DM foot/neuropathy

Mi Kyung Kim
Keimyung University
Complications of Diabetes

- Acute
  - Macrovascular complications
    - Coronary heart disease
    - Cerebrovascular disease
    - Peripheral vascular disease
  - Microvascular complications
    - Retino-pathy
    - Nephro-pathy
    - Neuropathy

- Chronic
  - Stroke
  - Blindness
  - Heart attack
  - Kidney failure
  - Amputation
## Impact of Intensive Therapy for Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UKPDS</strong></td>
<td>![Down]</td>
<td>![Double Arrow]</td>
<td>![Down]</td>
</tr>
<tr>
<td>*<em>DCCT / EDIC</em></td>
<td>![Down]</td>
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<tr>
<td><strong>ACCORD</strong></td>
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<td>![Red Arrow]</td>
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<td><strong>ADVANCE</strong></td>
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<td>![Double Arrow]</td>
</tr>
<tr>
<td><strong>VADT</strong></td>
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<td>![Double Arrow]</td>
<td>![Double Arrow]</td>
</tr>
</tbody>
</table>

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

Microvascular Complications
Microvascular complications

• Newly diagnosed T2DM patients
  – Above 50% : more than one complications
    • Retinopathy : 21%
    • Nephropathy : 7%
    • S-Cr ≥ 1.4 mg/dL : 3%
    • Erectile dysfunction : 20%

Microvascular complications

- Diabetic Retinopathy
- Diabetic Kidney Disease
- Diabetic Neuropathy
• The most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries.

• Risk factors
  – Duration of diabetes
  – Chronic hyperglycemia
  – Diabetic kidney disease
  – Hypertension
  – Dyslipidemia
Diabetic Retinopathy

Normal

Nonproliferative

Proliferative

Retinal Hemorrhage

Diabetes Care 2018;41(Suppl. 1):S105–S118
2015 Treatment Guidelines for Diabetes
Diabetic Retinopathy

Screening

Initial dilated and comprehensive eye examination

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Within 5 years after the onset of diabetes</td>
<td>• At the time of the diagnosis</td>
</tr>
</tbody>
</table>
Diabetic Retinopathy

Screening of pregnant women

- Pregnancy is associated with a rapid progression of diabetic retinopathy.
- Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy.
- Eye examinations should occur
  - before pregnancy or
  - in the first trimester in patients
- Monitoring
  - Every trimester and for 1 year postpartum as indicated by the degree of retinopathy
Diabetic Retinopathy

General Recommendation

- Optimize glycemic control
- Optimize blood pressure
- Optimize serum lipid control

Reduce the risk or slow the progression
Diabetic Retinopathy

With no retinopathy

- Repeat the examination every 2 years

With retinopathy

- Refer to ophthalmologist
- Promptly refer to ophthalmologist
  - Any level of macular edema
  - Severe nonproliferative diabetic retinopathy
  - Proliferative diabetic retinopathy
- Examinations will be required more frequently depending on the severity
Diabetic Retinopathy

Treatment

- Laser photocoagulation therapy (A)
  - in patients with high-risk proliferative diabetic retinopathy
  - in some cases, severe nonproliferative diabetic retinopathy

- Intravitreal injections of anti–vascular endothelial growth factor (A)
  - for central-involved diabetic macular edema

- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. (A)
Microvascular complications

- Diabetic Retinopathy
- Diabetic Kidney Disease
- Diabetic Neuropathy
The single most common cause of End stage Renal Disease in the world

Geographic variations in the incidence rate of treated ESRD (per million population/year), by country, 2015
Nephropathy in Diabetes

The prevalence of diabetic nephropathy (albuminuria or decreased eGFR) is 30.3%.

“Three among 10 persons with diabetes have albuminuria or decreased renal function”

The definition of nephropathy is increased albuminuria determined by albumin-creatinine ratio > 30 ug/mg of creatinine and/or estimated glomerular filtration rate (estimated GFR, eGFR) < 60 mL/min/1.73 m². GFR (mL/min/1.73 m²) by MDRD equation = $175 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female).
• Urinary albumin
  - e.g., spot urinary albumin–to–creatinine ratio (UACR)

<table>
<thead>
<tr>
<th>Category</th>
<th>Spot Collection (µg/mg creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Increased urinary albumin*</td>
<td>≥ 30</td>
</tr>
</tbody>
</table>

*Historically, ratios between 30 and 299 have been called microalbuminuria and those 300 or greater have been called macroalbuminuria (or clinical albuminuria).

• Two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have albuminuria.
## Diabetic Kidney Disease

### Diagnosis

- estimated Glomerular Filtration Rate (eGFR)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min per 1.73 m² body surface area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage* with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage* with mildly decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate

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


Diabetes Care 2017;40(Suppl. 1):S88–S98
2015 Treatment Guidelines for Diabetes
Diabetic Kidney Disease

Screening

: Urinary albumin, eGFR

: At least once a year

Type 1

• ≥ 5 years after the onset of diabetes

Type 2

• At the time of the diagnosis.
## Table 10.1—CKD stages and corresponding focus of kidney-related care

| CKD stage† | eGFR (mL/min/1.73 m²) | Evidence of kidney damage* | Diagnose cause of kidney injury | Evaluate and treat risk factors for CKD progression** | Evaluate and treat CKD complications*** | Prepare for renal replacement therapy |
|------------|-----------------------|-----------------------------|================================|==================================================|========================================|======================================|
| No clinical evidence of CKD | ≥60 | — | — | — | — | — |
| 1 | ≥90 | + | √ | √ | — | — |
| 2 | 60–89 | + | √ | √ | — | — |
| 3 | 30–59 | +/- | √ | √ | — | — |
| 4 | 15–29 | +/- | √ | √ | — | — |
| 5 | <15 | +/- | √ | √ | — | — |

†CKD stages 1 and 2 are defined by evidence of kidney damage (+), while CKD stages 3–5 are defined by reduced eGFR with or without evidence of kidney damage (+/−). *Kidney damage is most often manifest as albuminuria (UACR ≥30 mg/g Cr) but can also include glomerular hematuria, other abnormalities of the urinary sediment, radiographic abnormalities, and other presentations. **Risk factors for CKD progression include elevated blood pressure, glycemia, and albuminuria. ***See Table 10.2.

## Table 10.2—Selected complications of CKD

<table>
<thead>
<tr>
<th>Complication</th>
<th>Medical and laboratory evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated blood pressure</td>
<td>Blood pressure, weight</td>
</tr>
<tr>
<td>Volume overload</td>
<td>History, physical examination, weight</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>Serum electrolytes</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Serum electrolytes</td>
</tr>
<tr>
<td>Anemia</td>
<td>Hemoglobin; iron testing if indicated</td>
</tr>
<tr>
<td>Metabolic bone disease</td>
<td>Serum calcium, phosphate, PTH, vitamin 25(OH)D</td>
</tr>
</tbody>
</table>
Optimize glucose control (A)

Optimize blood pressure control (A)
Antidiabetic Therapy in Patients with Chronic Kidney Disease

GFR

Insulin
Liraglutide
Exenatide
Sitagliptin
Glitazones
Miglitol
Acarbose
Repaglinide
Glimepiride
Gliclazide
Metformin

Dose Reduction
Dose Reduction
Dose Reduction
Dose Reduction
Dose Reduction

G. Schernthaner – State of the Art Lecture

Fig. 1. Antidiabetic therapy in patients with chronic kidney disease
Diabetic Kidney Disease

Treatment

- ACE inhibitor or angiotensin receptor blocker

**eGFR**

- Strongly Recommended
- 90<br>60<br>30<br>15 mL/min/1.73 m²

**UACR**

- Not recommended
- Recommended
- Strongly Recommended
- 30<br>300<br>modestly elevated<br>Higher elevated

Periodically monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used.
Nutrition

- For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day (the recommended daily allowance).

- For patients on dialysis, higher levels of dietary protein intake should be considered.
When to refer

• Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate < 30 mL/min/1.73 m².

• Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
Diabetic Kidney Disease

When to refer

• Alternative or additional causes of kidney disease
  – An active urinary sediment (containing red or white blood cells or cellular casts)
  – rapidly increasing albuminuria or nephrotic syndrome,
  – rapidly decreasing eGFR,
  – the absence of retinopathy (in type 1 diabetes)
Microvascular complications

- Diabetic Retinopathy
- Diabetic Kidney Disease
- Diabetic Neuropathy
Macrovascular Complications
Macrovascular complications

= Atherosclerotic Cardiovascular Disease (ASCVD)

- Coronary heart disease
- Cerebrovascular disease
- Peripheral vascular disease
Macrovascular complications

= Atherosclerotic Cardiovascular Disease (ASCVD)

- Coronary heart disease
- Cerebrovascular disease
- Peripheral vascular disease

- Major cause of morbidity and mortality in diabetes
- Underlying abnormality - atherosclerosis
What is atherosclerosis?

- Deposits of fatty substances, cholesterol, cellular waste products and calcium build up in the wall of an artery (plaque).

- May grow large enough to reduce the blood flow through an artery.

- An acute event occurs when the plaque ruptures resulting in blood clots or fragments that can block the blood supply to the heart, brain or lungs.
Compared to people without diabetes, people with type 2 diabetes have

- The same risk of heart attack as those who have already had a heart attack
- Two- to three-fold higher risk of heart failure
- Sudden death occurs more commonly in people with diabetes than among peers without diabetes of the same age

Cardiovascular Risk Factors

- Hypertension
- Dyslipidemia
- Smoking
- A family history of premature coronary disease
- Chronic kidney disease
- The presence of albuminuria
Screening

- Cardiovascular risk factors should be systematically assessed at least annually in all patients with diabetes.
Hypertension

- A major risk factor for both ASCVD and microvascular complications.
- Systolic blood pressure and mortality rate in type 2 diabetes

Cardiovascular mortality
(per 10,000 / year)

- DM
- Non-DM

Systolic BP (mmHg)

< 120 120–139 140–159 160–179 180–199 > 200

Diabetes Care 2018:41(Supp1): S86-S 104
Hypertension

Mean systolic blood pressure (mmHg)

Microvascular complications

Myocardial infarction

UKPDS 35. BMJ 2000; 321: 405-12
Hypertension in diabetes (2013-2016)

About half of people with diabetes have hypertension (55.3%). In people 65 years or older with diabetes, Seven out of 10 people have hypertension. 7 out of 10 people with diabetes reached the target goal of blood pressure

Prevalence of hypertension: Systolic blood pressure ≥ 140 mmHg or Diastolic blood pressure ≥ 90 mmHg and/or antihypertensive medications (%)

Control rate of hypertension: Blood pressure <140/85 mmHg according to the KDA Treatment Guideline for Diabetes 2015
• Blood pressure should be measured at every routine clinical visit.

• Patients found to have elevated blood pressure (>140/90) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension.

• All hypertensive patients with diabetes should monitor their blood pressure at home.
Hypertension

**Treatment Goals**
- Sys BP <140mmHg
- Dia BP <90mmHg

**Thiazide-like diuretic;**
- chlorthalidone
- indapamide

***Dihydropyridine CCB**
# Korean Diabetes Association

<table>
<thead>
<tr>
<th>Type of Patients</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>&lt; 140/85 mmHg</td>
</tr>
<tr>
<td>Young, Albuminuria (+), additional risk factors (+)</td>
<td>&lt;130/80 mmHg</td>
</tr>
</tbody>
</table>

Blood pressure targets need to be individualized depending on level of glycemic control, duration of diabetes, level of complications, comorbidities and so on.

KDA clinical practice. 2015.
Main predictors of CVD mortality: LDL and HDL cholesterol

Framingham Heart Study

Castelli WP. Can J Cardiol. 1988;4(suppl A):5A3
Hypercholesterolemia in diabetes (2013-2016)

The prevalence of hypercholesterolemia in people with diabetes is 34.9%.
Only 4 out of 10 people with diabetes reached the target goal of LDL-cholesterol.

Prevalence of hypercholesterolemia: Total cholesterol ≥ 240 mg/dL and/or lipid-lowering medications (%)
Control rate of hypercholesterolemia: LDL-cholesterol < 100 mg/dL according to the KDA Treatment Guideline for Diabetes 2015 (%)

(Unit: %)
Dyslipidemia

- Lipid profile in type 2 diabetes
  - Raised triglycerides
  - Low HDL
  - Raised small dense LDL particles

- In adults with diabetes, it is reasonable to obtain a lipid profile
  - at the time of diagnosis,
  - at the initial medical evaluation,
  - at least every 5 years thereafter in patients under the age of 40 years.

Diabetes Care 2018:41(Supp1): S86-S104
Lipid Goal (KDA 2015)

• Primary target
  – LDL Cholesterol < 100 mg/dL
  – CVD (+) or high risk (+) < 70 mg/dL
※ If maximal dose of statin does not achieve target cholesterol level, 30-40% reduction in baseline LDL-cholesterol may also be a target.

• Triglyceride < 150 mg/dL
• HDL Cholesterol > 40 mg/dL(M)
  > 50 mg/dL(F)

• Non HDL-cholesterol, Apo B may also be used as treatment goal

KDA clinical practice. 2015.
# Lipids: Treatment

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LDL</th>
<th>TG</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight loss</strong></td>
<td>Maintain Healthy weight</td>
<td>↓</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>
| **Diet** | ↓: saturated fat, trans fat, and cholesterol intake  
↑: dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake | ↓ | ↓↓↓ | ↑ |
| **Exercise** | 30minutes/Day | | ↓↓↓ | ↑ |
| **Alcohol** | ≤2 drinks/day (M)  
≤1 drink/day (F) | | ↓↓ | | |
| **Stop Smoking** | | | | ↑ |

KDA clinical practice. 2015.
Lipids : Treatment

**LDL cholesterol ↓**
- **Statin** (HMG CoA reductase inhibitor): 1st line
- **Ezetimibe, Bile acid binding resin**, or Fenofibrate: 2nd line

**Triglyceride ↓**
- **Glycemic control**
- **Fibric acid derivative** (Fenofibrate)
- **Omega-3**, statin or Ezetimibe

**HDL-cholesterol ↑**
- **Glycemic control, lifestyle modification** (weight loss, exercise, quit smoking)
- **Fenofibrate**

KDA clinical practice. 2015.
**Table 9.2—Recommendations for statin and combination treatment in adults with diabetes**

<table>
<thead>
<tr>
<th>Age</th>
<th>ASCVD</th>
<th>Recommended statin intensity and combination treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>No</td>
<td>None†</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#</td>
</tr>
<tr>
<td>≥40 years</td>
<td>No</td>
<td>Moderate‡</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>High</td>
</tr>
</tbody>
</table>

*In addition to lifestyle therapy. †For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. ‡Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin-based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.
### Table 9.3—High-intensity and moderate-intensity statin therapy*

<table>
<thead>
<tr>
<th>High-intensity statin therapy (lowers LDL cholesterol by ≥50%)</th>
<th>Moderate-intensity statin therapy (lowers LDL cholesterol by 30% to 50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 40–80 mg</td>
<td>Atorvastatin 10–20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20–40 mg</td>
<td>Rosuvastatin 5–10 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40–80 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
</tr>
</tbody>
</table>

*Once-daily dosing. XL, extended release.
Lipids: side effects of statins

- Muscle pain
  (with or without an increase in muscle enzymes)
- Increase of liver enzymes
- Rhabdomyolysis:
  - More common when statins and fibrates are used in combination
Antiplatelet agents

- Meta-analysis of primary prevention effect of aspirin in diabetic patients

Risk of coronary disease ↓ 9%

Risk of cerebral stroke ↓ 15%

10-year CVD risk decreased by 10% overall

Pignone M et al. Diabetes Care 2010;33:1395-402
Antiplatelet agents

• Use aspirin therapy (75–162mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. A

• For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. B
Antiplatelet agents

- **Dual antiplatelet therapy** (with low dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome A and may have benefits beyond this period. B
- Aspirin therapy may be consider primary prevention strategy
  - most men and women with diabetes aged ≥50 years who have at least one additional major risk factor
    - family history of premature atherosclerotic cardiovascular disease,
    - Hypertension
    - Dyslipidemia
    - Smoking
    - Albuminuria
  - not at increased risk of bleeding. C
Take Home Message

Microvascular complications

• General Recommendation: Optimize glucose control

• Screening
  – Type 1: 5 years after the onset of diabetes
  – Type 2: At the time of the diagnosis
Macrovascular disease

• Major cause of early morbidity and mortality
• Cardiovascular risk factors screening
  – at least annually in all patients with diabetes
• Intensive treatment of modifiable risk factors
  – Increase physical activity
  – Choose healthy foods: reduce total and saturated fat,
  – Reduce sodium, increase monounsaturated fat and flavonoids

• Hypertension
  – BP target < 140/90 mmHg ADA (140/85mmHg KDA)
    • Albuminuria (+) : ACE inhibitor or ARB
    • Albuminuria (-) : ACE inhibitor, ARB, CCB, thiazide like diuretics

• Lipid
  – Statin is 1st line treatment for target LDLC <100 (<70)

• Aspirin
  – Secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease
Thank you for your attention