Diabetes and Kidney Disease
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Disclosures
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Objectives
• Definition and screening for DKD
• 2018 Treatment guidelines
• New approaches to patients risk stratification
DKD yearly updates

Prevalence of Diabetic Kidney Disease (DKD) in the US Population

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Prevalence of ESRD by cause</th>
<th>Prevalence of ESRD by cause by cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>0.2 (0.1-0.4)</td>
<td>0.2 (0.1-0.4)</td>
</tr>
</tbody>
</table>

DKD remains the most common cause of ESRD

CVD risk protection needs early implementation

No Nephropathy 1.4% 
Microalbuminuria 2.6% 
Albuminuria 2.8% 
Elevated Creatinine or Renal Replacement Rx 2.3% 
Death 3.0% 
CVD risk protection needs early implementation

> 50% Type 2 Diabetes patients

Yearly risk associated
Kidney disease is among the top causes of death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Deaths (N = 2644)</th>
<th>Years of Life Lost (N = 45,140)</th>
<th>Years Lived with Diabetes (N = 34,454)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rank No. (%)</td>
<td>Rank No. (%)</td>
<td>Rank No. (%)</td>
</tr>
<tr>
<td>IHD</td>
<td>1</td>
<td>543 (21.1)</td>
<td>1</td>
</tr>
<tr>
<td>Renal and pulmonary disease</td>
<td>2</td>
<td>1785 (71.8)</td>
<td>16</td>
</tr>
<tr>
<td>Cancer of the lung, breast, ovary</td>
<td>3</td>
<td>143 (5.4)</td>
<td>4</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>4</td>
<td>258 (10)</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5</td>
<td>29 (1.1)</td>
<td>1</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>6</td>
<td>3 (0.1)</td>
<td>1</td>
</tr>
</tbody>
</table>

Type 1 DM

Natural progression of DKD in T1D

- Microalbuminuria
- Macroalbuminuria

277 patients
Type 1 DM
f/u 18 yrs

75% ESRD at 20 years

Early Detection and Treatment are Essential

Early biomarkers are missing

Natural progression of DKD in T2D

Screening for DKD

10,290 members of a managed care organization with HTN and T2D (Kayser Permanente)
ACR at baseline and with at least 2 additional determinations over time, 7 1/2 years follow up

Now diagnosis of type 2 diabetes
History of type 1 diabetes for 5 years

At diagnosis if HTN

Check A/C ratio on spot urine (3 times in 6 months)
Check eGFR and repeat in 3 months if abnormal

yearly follow up, Level of evidence B

Vupputuri S et al, Diabetes Care, January 2017

ADA recommendations, Diabetes Care, January 2017
Definition of DKD

DIABETES with:

- Abnormal urine albumin excretion
  - >30 mg/24 hours
  - >30 mg/g creatinine (preferred)
  - >20 µg/min
- and/or
- diabetic glomerular lesions
- and/or
- loss of glomerular filtration rate (CKD-EPI preferred)

ADA recommendations, Diabetes Care, January 2018

ACR & Progression to ESKD

White: F
Black: M

Proteinuria and GFR: risk factors for ESRD

Shahinfar S et al, Kidney Int: S48-S51, RENAAL Baseline Characteristics

Albuminuria and kidney failure risk

Risk calculator: kidneyfailurerisk.com

Chronic Kidney Disease Prognosis Consortium
721357 participants
30 countries
Risk stratification

Prognosis of CKD by GFR and albuminuria category

Prognosis of DKD by GFR and Albuminuric Categories: KDIGO 2012

<table>
<thead>
<tr>
<th>GFR category</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mildly decreased</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Moderately to severely decreased</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Severe</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Is testing for albuminuria enough?

Albuminuria and DKD progression in T1D: DCCT/EDIC >20 years follow up

Severe albuminuria was a strong predictor of risk of developing sustained eGFR <60 ml/min/1.73 m²

Screening with AER alone would have missed 24% of cases of sustained impaired eGFR

Normoalbuminuric DKD progression in T2D

5102 UKPDS patients with T2D

Normal albuminuria and creatinine at baseline
**Normoalbuminuric DKD**

**Prevalence of low GFR and normoalbuminuria**

<table>
<thead>
<tr>
<th>Diabetes type</th>
<th>Study</th>
<th>Year</th>
<th>Number with GFR &lt; 60 cc/min/1.73m²</th>
<th>Number with albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td>ITN</td>
<td>2002</td>
<td>928</td>
<td>92</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>ITN</td>
<td>2002</td>
<td>121</td>
<td>33</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>ITN</td>
<td>2004</td>
<td>928</td>
<td>92</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>ITN</td>
<td>2004</td>
<td>121</td>
<td>33</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>ITN</td>
<td>2006</td>
<td>928</td>
<td>92</td>
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<tr>
<td>Type 2 Diabetes</td>
<td>ITN</td>
<td>2006</td>
<td>121</td>
<td>33</td>
</tr>
</tbody>
</table>

**Natural history of albuminuria**

- Progression to macroalbuminuria
- Remission to normoalbuminuria
- Remission related to RAS blockades

**Nephrology referral and biopsy**

- eGFR < 30 cc/min/1.73m² at diagnosis
- CKD care and referral for renal replacement strategies
  - Worsening proteinuria despite treatment
  - Loss of eGFR > 1 cc/min/1.73m²/month
  - Active urine sediment
  - Absence of retinopathy

**ADA**

- biopsy
  - >30% reduction in eGFR after initiation of ACEi/ARB
  - Refractory hypertension

**QDOQI**

**Limitation of clinically indicated kidney biopsies**

- Often the diagnosis in clinically indicated kidney biopsies differs from DKD
- Protocol kidney biopsies are needed to understand the disease

ADA recommendations. Diabetes Care, January 2010
NKF QDOQI guidelines for diabetes. AHD 2014
TYPICAL DIABETIC NEPHROPATHY (C2) – 30 %

(a) Both normal and totally destroyed glomeruli

(b) Severe arteriolohyalinosis

(c) Tubulointerstitial fibrosis

Albuminuria and T2D: pathologic heterogeneity

GBM thickening can predict decline in kidney function in T1D with NA

Podocytopathy in early DKD in T2D

Change in GFR (%) in patients with T2D and albuminuria

(n=33, 4 year follow-up)

* p<0.05, C2 vs C1 ja C3

GBM thickening can predict decline in kidney function in T1D with NA

Podocytopathy in early DKD in T2D

Table III: Quantitation of Epithelial and Nonpapillary Cells in the Glomerular Tapp

Podocytopathy in early DKD in T2D

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GBM thickening can predict decline in kidney function in T1D with NA

Podocytopathy in early DKD in T2D

Table III: Quantitation of Epithelial and Nonpapillary Cells in the Glomerular Tapp
Podocytopathy in DKD in T1D

Podocyte detachment occurs in T1D correlates with AER and loss of GFR

Objectives

- Definition and screening for DKD
- 2017 Treatment guidelines
- New approaches to patients risk stratification

Prevention and treatment of DKD

American Diabetes Association recommendations 2018

Level of evidence A:
- control BP with appropriate agents (goal <140/90mmHg, <130/80 if high risk for CVD)
- control glycermia (A1C about 7%, personalized)
- control dyslipidemia (LDL goal <70-100 mg/dl)
- counsel about smoking cessation education

Level of evidence B:
- protein intake to 0.8 mg/kg/day (more if dialysis)
Prevention and treatment of DKD

American Diabetes Association recommendations 2018

**Level of evidence A:**
- control BP with appropriate agents (goal <140/90 mmHg, <130/80 if high risk for CVD)
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- counsel about smoking cessation
- education

**Level of evidence B:**
- protein intake to 0.8 mg/kg/day (more if dialysis)

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JNC7 versus ACC/AHA 2017

<table>
<thead>
<tr>
<th>SBP/DBP mm Hg</th>
<th>JNC7</th>
<th>2017 ACC/AHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120 and &lt;80</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>120 - 129 and &lt;80</td>
<td>Prehypertension</td>
<td>Elevated BP</td>
</tr>
<tr>
<td>130 - 139 or 80 - 89</td>
<td>Prehypertension</td>
<td>Stage 1 HTN</td>
</tr>
<tr>
<td>140 - 159 or 90 - 99</td>
<td>Stage 1 HTN</td>
<td>Stage 2 HTN</td>
</tr>
<tr>
<td>≥ 160 or ≥100</td>
<td>Stage 2 HTN</td>
<td>Stage 2 HTN</td>
</tr>
</tbody>
</table>

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Metabolic and hemodynamic factors in DKD

![Metabolic and hemodynamic factors in DKD](image)

**Any Diabetic Endpoint**
- DM Death
- Microvascular Complications

- **Tight Glucose Control**
- **Tight BP Control**

*P < 0.05 as compared to tight glucose control*
**Role of BP in DKD**

![Graph showing the relationship between blood pressure (BP) and GFR (glomerular filtration rate) with treatment options.](image)

Summary of studies on nephropathy progression used in figure:
- Viberti GC et al., JAMA, 1990
- Hwang S et al., Kidney Int, 1999
- Lehto K et al., Kidney Int. 1996

**Role of ACEi to treat DKD**

![Graph showing the risk reduction of 51% with Captopril.](image)

- Captopril 25mg x 3
- Placebo

Risk reduction of 51% P=0.006

- Dialysis, transplant, death

**Role of ARB to treat DKD**

![Graph showing incidence of diabetic nephropathy.](image)

- Placebo
- Irbesartan 150 mg
- Irbesartan 300 mg

*P<0.001 vs Placebo

**ACEi vs CCB in primary prevention of DKD with mild hypertension**

![Graph showing BP control with ACEi vs CCB.](image)

- Placebo
- Irbesartan 150 mg
- Irbesartan 300 mg

**IDNT trial, NEJM 345:851, 2001**

1715 pt type 2 DM + HTN
- Irbesartan 300 mg vs amlo 10 mg vs placebo
- End points: doubling creatinine, ESRD, death
- F/u 2.6 years
- -3.3 mmHg mean BP in tx vs placebo

**BENEDICT, NEJM, 251:1941, 2004**

1204 patients, type 2 DM
- Primary end point: persistent MA
ARB vs placebo in primary prevention of DKD with normal BP

Bilius R et al, DIRECT, Annals of Internal Medicine, 2009; 151:11-20

3320/1655 (type 1/type2) patients, nonproteinuric with normal albuminuria. Candesartan versus placebo (significant effect on BP).

4.7 years follow-up
Primary endpoint: development of MA
Secondary: Change in UAE

ACEi or ARB?

ACEi or ARB?

Prospective, multicenter, double-blind study
250 patients with type 2 DM and DN
Telmisartan 80 mg vs enalapril 20 mg
Five year follow-up
Primary endpoint: change in eGFR
Secondary endpoints: creat, UACR, BP

Is there a role for ACEi/ARB combination in DKD in type 2 DM? ON TARGET

Mann J et al, ONTARGET JNC. 2008; 372: 547-562

25620 patients with CV disease or high risk diabetes
Follow up for 5 years
Primary renal outcome: dialysis, x2 creat, death

BP -2.4/1.4 mmHg
BP -0.9/0.6 mmHg

Table 1: Secondary End-Points After Five Years of Treatment.

ACEi or ARB?

ADA 2017:

Type 1 DM with HTN and albuminuria: ACEi
Type 2 DM with HTN and microalbuminuria: either ACEi or ARBs
Type 2 DM with HTN and overt nephropathy: ARBs
When not tolerated, substitute one for the other

Combination not supported

ADA recommendations, Diabetes Care, January 2017
Aldosterone antagonism in DN

Randomized trial
59 patients with type 2 DM
+ macroalbuminuria
On ACEi or ARB
25-50 mg spironolactone x 1 year


Figure 3. Percentage change in median UACR from baseline to week 12, by quartile of baseline estimated glomerular filtration rate (eGFR) and treatment group

Aldosterone antagonism in DKD

Prevention and treatment of DKD

American Diabetes Association recommendations 2017

Level of evidence A:
- control BP with appropriate agents (goal <140/90mmHg,
<130/80 if high risk for CVD)
- control glycemia (A1C about 7%, personalized)
- control dyslipidemia (LDL goal <70-100 mg/dl)
- counsel about smoking cessation

Level of evidence B:
- protein intake to 0.8 mg/kg/day (more if dialysis)
A1C: a real measure in CKD?

Falsely elevated A1C:  
Uremic toxins  
Metabolic acidosis

Falsely decreased A1C:  
Decreased 1/2 life RBCs  
Blood transfusions  
EPO treatment

May need to change to glycated fructosamine, glycated albumin, variation of A1C or glycosylation gap (based on A1C and fructosamine)

Role of glycemia in type 1 DM and DKD

Intensive treatment  
With A1C 7.2

Standard treatment  
With A1C 9.1

DCCT: 1441 patients with type 1 DM  
90.5 years

Insulin 3 x day or pump vs conventional (1 or 2 daily insulin injection)  
Primary prevention/secondary prevention  
Difference maintained after discontinuation of tx (7 yr follow up)

Role of glycemia in type 2 DM and DKD

Treatment with A1C 7.0  
Diet with A1C 7.9

Role of glycemia in advanced DKD

Burnt-Out Diabetes?  
HbA1c<6%

Target HbA1c for Dialysis Patients?  
6.5% vs. 7.9%

Diabetic without CKD

Lancet 1998; 352: 837-853

UKPDS: 3867 type 2 DM  
Median age 54  
Intensive vs (sulpha or insulin) versus diet

Endpoints: any DM related endpoint, diabetes related death and all cause mortality  
F/u 15 years (15 years f/u had no difference in diabetes related death)

NEJM 1993; 329:977
**Regression of MA in type 1 DM**

<table>
<thead>
<tr>
<th>Table 1: Results of the Cox Regression Analysis of Regression of Microalbuminuria with 95% CI</th>
<th>Adjusted Hazard Ratio [95% CI]</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factor</td>
<td>Hazard Ratio [95% CI]</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (1.00-1.00)</td>
<td>0.001</td>
</tr>
<tr>
<td>Incidence cohort (vs. prevalence)</td>
<td>1.00 (1.00-1.00)</td>
<td>0.003</td>
</tr>
<tr>
<td>Male</td>
<td>1.00 (1.00-1.00)</td>
<td>0.000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.00 (1.00-1.00)</td>
<td>0.000</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>1.00 (1.00-1.00)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Regression of MA in type 2 DM**

| Table 2: The HRs of factors associated with the regression and remission of microalbuminuria with the period logistic regression model |
|---------------------------------------------------------------|-----------------------------|
| **Regression** | **Remission** |
| Nonmodifiable factors | 2.0 (1.0-3.9) | 2.0 (1.0-3.9) |
| Modifiable factors | 3.0 (2.0-4.0) | 3.0 (2.0-4.0) |
| Use of ACE inhibitors or ARBs (vs. none) | 3.0 (2.0-4.0) | 3.0 (2.0-4.0) |
| A1C (mmol/L) | 2.0 (1.0-3.9) | 2.0 (1.0-3.9) |
| 6/12/18 (A1C x 175) | 0.9 (0.7-1.0) | 0.9 (0.7-1.0) |
| JCV (mmol/L) | 1.0 (0.9-1.0) | 1.0 (0.9-1.0) |

A1C: how low can we get?

**ADVANCE trial, NEJM, 358:24, 2008**

11,140 patients, standard vs intensive (sulfonamides or other drugs to achieving A1C less than 6.5).

Macro: CV death, MI, stroke

Micro: development of albuminuria, ESRD

21% relative reduction in nephropathy

**ACCORD, NEJM, 358:24, 2008**

10,251 patients, standard vs intensive (mainly insulin and TZDs).

1/3 patients had prior CV event

End point: CV death, MI, stroke

Discontinued after 3.5 years f/u for high mortality in intensive arm.

A1C: how low can we get?

12,261 patients, standard vs intensive (mainly insulin and TZDs).

1/3 patients had prior CV event

End point: CV death, MI, stroke

Discontinued after 2.5 years f/u for high mortality in intensive arm.
Are all anti-diabetic drugs alike?

Legend:

- MET = Metformin
- GLP1 RA = incretins
- SGLT2i = glycosuric agents
- DPP4-i = incretins
- AGi = alpha-glucosidase inhibitors
- TZD = glytazones
- Su = sulphonylurea
- GLN = glucosaminoglycans
- COLS = bile acids
- BCR = bromocriptin
- PRAM = pramlintide

Glycemia and DKD: drug class effect

SGLT2 inhibition: is sweet urine the solution?

A) In the Absence of an SGLT2 Inhibitor

B) In the Presence of an SGLT2 Inhibitor

SGLT2 inhibitors and DKD: EMPA-REG

Composite outcome: doubling of the serum creatinine, initiation of renal replacement therapy or death from renal disease

SGLT2 inhibitors and DKD: CANVAS trial

Outcome | Canagliflozin (N=3799) | Placebo (N=3827) | Hazard Ratio (95% CI)
---|---|---|---
Death from cardiovascular causes, renal or non-renal, or renal failure | 26.0 | 31.5 | 0.86 (0.75-0.97)
Non-fatal myocardial infarction | 11.6 | 12.8 | 0.91 (0.76-1.09)
Non-fatal stroke | 9.7 | 11.6 | 0.85 (0.71-1.03)
Fistula or non-fistula infection | 11.2 | 12.8 | 0.90 (0.75-1.09)
Fistula or non-fistula infection | 7.0 | 8.6 | 0.82 (0.69-0.99)
Hospitalization for any cause | 118.7 | 131.1 | 0.90 (0.88-0.91)
Hospitalization for heart failure | 3.5 | 8.7 | 0.41 (0.27-0.62)
Death from cardiovascular causes, or hospitalization for heart failure | 16.3 | 20.8 | 0.73 (0.57-0.93)
Death from any cause | 17.2 | 19.5 | 0.87 (0.74-1.03)
Progression of albuminuria | 20.4 | 12.7 | 0.70 (0.55-0.90)
AHR reduction in eGFR, renal replacement therapy or renal death | 5.5 | 9.0 | 0.60 (0.40-0.90)

With better A1C and BP control


Renal Absorption of Glucose and Glucagon Secretion

According to the Presence or Absence of a Sodium-Coupled Glucose Transporter Type 2 (SGLT2) Inhibitor.

Glycemia and DKD: drug class effect


K-Meier Analysis of Two Key Renal Outcomes.

SGLT2 inhibitors and DKD: EMPA-REG

Composite outcome: doubling of the serum creatinine, initiation of renal replacement therapy or death from renal disease


K-Meier Analysis of Two Key Renal Outcomes.

SGLT2 inhibitors and DKD: CANVAS trial

**K–Meier Analysis of Two Key Renal Outcomes.**

**ARB versus SGLT2 inhibitors**

<table>
<thead>
<tr>
<th></th>
<th>IDNT</th>
<th>EMPA-REG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doubling of serum creatinine</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>All cause mortality</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
</tbody>
</table>

**SGLT2 inhibitors and TG feedback**

- **A** normal TG
- **B** impaired TG
- **C** restored TG

No difference in incident albuminuria!

Other effects?

**DN: the gut to kidney connection**

- Hyperglycaemia
- Metformin, sulphonylureas, thiazolidinediones, insulin
- Glomerular hypertension
- GFR impairment (GFR-Pi inhibitor)
- Diabetic kidney disease
- Dyslipidaemia
- Metabolic syndrome

**Liraglutide and DKD: LEADER trial**

Time to first renal event: ACR>300, x2 creat, ESRD, renal death

- 9340 T2DM patients
- 3.8 yrs f/u
- CKD1 35%, CKD2 42%, CKD3 20%


DPP4 inhibition and DKD: linagliptin

Prevention and treatment of DKD

American Diabetes Association recommendations 2017

**Level of evidence A:**
- control BP with appropriate agents (goal <140/90mmHg, <130/80 if high risk for CVD)
- control glycemia (A1C about 7%, personalized)
- control dyslipidemia (LDL goal <70-100 mg/dl)
- counsel about smoking cessation
- education

**Level of evidence B:**
- protein intake to 0.8 mg/kg/day (more if dialysis)

Statins do not prevent GFR loss

Prevention and treatment of DKD

American Diabetes Association recommendations 2017

**Level of evidence A:**
- control BP with appropriate agents (goal <140/90mmHg, <130/80 if high risk for CVD)
- control glycemia (A1C about 7%, personalized)
- control dyslipidemia (LDL goal <70-100 mg/dl)
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**Level of evidence B:**
- protein intake to 0.8 mg/kg/day (more if dialysis)
Cigarette smoking and DKD (T1D)

- HR=ns* for current smokers
- HR=2.39* for current smokers
- HR=ns* for current smokers

*Adjusted for duration of diabetes, HbA1c, and hypertension
N=non-smokers, C= current smokers, E=Ex-smokers

Prevention and treatment of DKD

American Diabetes Association recommendations 2017

Level of evidence A:
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- control glycemia (A1C about 7%, personalized)
- control dyslipidemia (LDL goal <70-100 mg/dl)
- counsel about smoking cessation
- education

Level of evidence B:
- protein intake to 0.8 mg/kg/day (more if dialysis)

Multifactorial intervention in type 1 DM

Hovind, P., Diabetes Care, 26: 1258, 2003
600 patients
20 years follow up
**Multifactorial intervention in type 2 DM**


Diabetic Nephropathy Remission and Regression Team Trial (DNETT-Japan)

- 160 patients from Steno2
- 7.8 years tx + 5.5 yrs f/u

**Primary end point:** death

**Secondary end point:** ESRD

**INTENSIVE:**
- Statin
- ASA
- ACEi/ARB
- Exercise
diet

**Prevention and treatment of DKD**

American Diabetes Association recommendations 2018

**Level of evidence A:**
- control BP with appropriate agents (goal <140/90 mmHg, <130/80 only for younger patients)
- control glycemia (A1C about 7%, personalized)
- control dyslipidemia (LDL goal <70-100 mg/dl)
- counsel about smoking cessation
- education

**Level of evidence B:**
- protein intake to 0.8 g/kg/day (more if dialysis)

---

**Dietary protein intake in DKD**


Careful protein restriction in CKD 3 and above

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**Case**

Mr JD comes to you with GFR 50 cc/min/1.73m²

- **Smoker**
  - Non smoker
  - Exercise TIW
  - BP130/80
  - A1c 6.9%
  - LDL 70
- **Obese**
  - Low protein diet
  - GFR loss 2 cc/min/year
- **BP150/90**
  - GFR loss 20 cc/min/year
- **A1c 11%**
  - ESRD in 2 year
- **LDL 150**
  - ESRD in 20 year

IT'S UP TO MR JD AND TO YOU!
Objectives

- Definition and screening for DKD
- 2018 Treatment guidelines
- New approaches to patients risk stratification

Is hyperuricemia a predictor of outcome?


263 patients with type 1 diabetes, 18.1 years f/u
Uric acid measured 3 years after onset of diabetes
All patients NA at enrollment (22 with macroalbuminuria at f/u)

Awaiting the results of the preventing early renal function loss (PERL) allopurinol study

DKD: role of Vitamin D

168 consecutive patients in a CKD clinic (36% with DKD)
6 years follow up
Baseline Vitamin D adjusted for age, sex, smoking, CRP, albumin, ACE/ARB usage, eGFR

TNF Receptors 1 and 2 in DKD


(Caucasian Americans, 410 patients) Adapted from Niewczas MA et al., JASN, 2012.
(PIMA Native Americans, 193 patients) Adapted from Pavkov ME et al. Kidney Int, 2014.
### Soluble Urokinase Receptor (suPAR)

**2292 patients**
- Q1: eGFR loss of 0.9 cc/min
- Q4: eGFR loss of 4.2 cc/min

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**suPAR levels in patients with T1D and DKD**

#### BASELINE

<table>
<thead>
<tr>
<th></th>
<th>NA = NA</th>
<th>NA = micro</th>
<th>micro = micro</th>
<th>micro = macro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>5 / 5</td>
<td>5 / 6</td>
<td>4 / 6</td>
<td>4 / 6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37 ± 8</td>
<td>34 ± 11</td>
<td>46 ± 7</td>
<td>34 ± 13</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.9 ± 2.6</td>
<td>24.7 ± 4.8</td>
<td>27.0 ± 5.4</td>
<td>26.3 ± 3.9</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>70 (10-110)</td>
<td>60 (72-48)</td>
<td>65 (51-94)</td>
<td>84 (59-103)</td>
</tr>
<tr>
<td>Follow-up time (years)</td>
<td>5.0 ± 1.6</td>
<td>3.0 ± 1.3</td>
<td>5.3 ± 1.4</td>
<td>6.7 ± 2.3</td>
</tr>
</tbody>
</table>

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**Role of dyslipidemia in DKD**

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**Plasma proteome analysis of patients with type 1 DM and DKD**

<table>
<thead>
<tr>
<th>N</th>
<th>MIC</th>
<th>BMN</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>49</td>
<td>49</td>
<td>0.09</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>19 (48)</td>
<td>15 (36)</td>
<td>20 (59)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 11</td>
<td>52 ± 11</td>
<td>46 (29)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>36 (31)</td>
<td>35 (31)</td>
<td>36 (31)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>46.5 (4.9)</td>
<td>42.5 (4.3)</td>
<td>45.5 (4.4)</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>8.6 (3.2)</td>
<td>8.8 (3.5)</td>
<td>8.8 (3.2)</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>83 (274-492)</td>
<td>90 (274-492)</td>
<td>222 (90-274)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.9 (4.4)</td>
<td>7.3 (12.4)</td>
<td>423 (384-590)</td>
</tr>
<tr>
<td>α1-Antitrypsin (ng/mL)</td>
<td>101.3 (71.6)</td>
<td>166.6 (114.4)</td>
<td>168.6 (114.4)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.8 (1.0)</td>
<td>5.1 (1.0)</td>
<td>6.0 (1.0)</td>
</tr>
<tr>
<td>Symmetric IPP (mmol/L)</td>
<td>199 (52)</td>
<td>140 (52)</td>
<td>140 (51)</td>
</tr>
<tr>
<td>Non-symmetric IPP (mmol/L)</td>
<td>7.4 (4.4)</td>
<td>7.2 (4.3)</td>
<td>7.8 (4.4)</td>
</tr>
</tbody>
</table>

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**Transcription factor (n=300)**

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Serum Amyloid A and DKD

135 T2D patients
DKD stage 3a and severe albuminuria
3.5 years of follow up
Outcomes: death and ESRD

Plasma metabolomic analysis of patients with type 2 DM and DKD

DKD: next generation biomarkers

Experimental approaches to the human renal transcriptome

DKD: system biology

1135 T2D patients
DKD stage 3a and severe albuminuria
3.5 years of follow up
Outcomes: death and ESRD
Acknowledgments

Questions?