Kidney Disease due to Diabetes
Alessia Fornoni, MD PhD
Professor of Medicine
Chief, Katz Family Division of Nephrology and Hypertension
Director, Peggy and Harold Katz Family Drug Discovery Center
University of Miami School of Medicine

Case
JD is a 30 year old male with a 15 year history of type 1 DM and established retinopathy. A urine dipstick is negative for protein, but spot urine for albumin shows a concentration of 10 mg/dl (“normal” values 0-15 mg/dl) in two of three urine collections. Urine creatinine is 40 mg/dl: ratio is 0.25 = 250 mg/24 hours.

Is JD affected by DKD?

Objectives
• Definition and screening for DKD
• 2017 Treatment guidelines

Disclosures
I am vice President and CSO of L&F Health LLC
L&F Health LLC and affiliated companies have a patent estate covering some of the topics being presented
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Variant Pharmaceuticals, Inc. has licensed worldwide rights to develop and commercialize hydroxypropyl beta cyclodextrin for treatment of kidney disease from L&F Research

DKD yearly updates
Page 88: Microvascular complications

Diabetes Care, 2017, Supplement 1
DKD remains the most common cause of ESRD

Prevalence of Diabetic Kidney Disease (DKD)

Kidney disease is among the top causes of death

Screening for DKD

Natural progression of DKD in T1D

Early biomarkers are missing
Definition of DKD
DIABETES with:
Abnormal urine albumin excretion
>30 mg/24 hours
>30 mg/g creatinine (preferred)
>20 \( \mu \)g/min
and/or diabetically glomerular lesions
and/or loss of glomerular filtration rate (CKD-EPI preferred)

Proteinuria and GFR: risk factors for ESRD

Risk stratification

Normoalbuminuric DKD

Natural history of albuminuria

Nephrology referral and biopsy
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 |

Objectives
- Definition and screening for DKD
- 2017 Treatment guidelines

Prevention and treatment of DKD
American Diabetes Association recommendations 2017

Level of evidence A:
- control BP with appropriate agents (goal <140/90mmHg, <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 mg/kg/day (more if dialysis)

Role of BP in DKD

Prevention and treatment of DKD
American Diabetes Association recommendations 2017

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Metabolic and hemodynamic factors in DKD

Role of BP in DKD

Fig. 5. Relationship between sustained blood pressure control and reduced GFR in clinical trials of diabetic and nondiabetic renal disease. In the trials, the differences in GFR are those in nondiabetic renal disease patients.
Recommendations for the treatment of hypertension in DKD

Role of ACEi to treat DKD

Role of ARB to treat DKD

ACEi vs CCB in primary prevention of DKD with mild hypertension

ARB vs placebo in primary prevention of DKD with normal BP

ACEI or ARB?

Table 1. Secondary renal end points at 5 years of treatment, stratified according to baseline diastolic blood pressure (DBP).

- Primary and secondary prevention of DKD.
- Secondary change in eGFR.
- 4.7 years follow-up.

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

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


Combination not supported

Aldosterone antagonism in DN

Randomized trial
- 50 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

ARTS-DN Japan

Prevention and treatment of DKD

American Diabetes Association recommendations 2017

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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
- DCCT: 1441 patients with type 1 DM
  - 6.5 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)

Standard treatment
With A1C 9.1

- NEJM 1993; 329:977

Role of glycemia in type 2 DM and DKD

Treatment with A1C 7.0
- Any Diabetes Related Endpoint
  - -12
- Microvascular Endpoint
  - -25
- Laser Rx
  - -29
- Cataract
  - -24
- Albuminuria
  - -34

Diet with A1C 7.9

Role of glycemia in advanced DKD

Intensive treatment
- Target HbA1c for Dialysis Patients?
  - 6-8% vs. 7.9%
- Diabetics without CKD

Role of glycemia in type 1 DM

Regression of MA in type 1 DM

<table>
<thead>
<tr>
<th>% Risk Reduction</th>
<th>Perkin, NEJM, 2003;348:2285</th>
</tr>
</thead>
<tbody>
<tr>
<td>386 patients with persistent albuminuria</td>
<td>Total f/u of 6 periods of 2 years each</td>
</tr>
<tr>
<td>Regression defined as &gt;50% reduction in UAE from one period to the other</td>
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Role of glycemia in type 2 DM

Regression of MA in type 2 DM

<table>
<thead>
<tr>
<th>% Risk Reduction</th>
<th>Araki, Diabetes, 2005;54:2983</th>
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</thead>
<tbody>
<tr>
<td>216 Japanese patients with type 2 DM</td>
<td>Total f/u of 6 periods of 2 years each</td>
</tr>
<tr>
<td>Regression defined as &gt;50% reduction in MA</td>
<td>Regression: back to NA</td>
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Intensive treatment
- 216 Japanese patients with type 2 DM
- 6-8% vs. 7.9%
- Regression: >50% reduction in MA
- Regression: back to NA
SGLT2 inhibitors and TG feedback

Cherney D et al, CirculationAHA 2013

No difference in incident albuminuria!

Other effects?

K–Meier Analysis of Two Key Renal Outcomes.

Liraglutide and DKD: LEADER trial

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

Prevention and treatment of DKD

American Diabetes Association recommendations 2017

Level of evidence A:
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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

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education

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

Statins and DKD progression

American Diabetes Association recommendations 2017

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counsel about smoking cessation
education

Level of evidence B:
protein intake to 0.8 mg/kg/day (more if dialysis)
Cigarette smoking and DKD (T1D)


Prevention and treatment of DKD

American Diabetes Association recommendations 2017

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- 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

Multifactorial intervention in type 2 DM

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

Prevention and treatment of DKD

American Diabetes Association recommendations 2017

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- protein intake to 0.8 mg/kg/day (more if dialysis)
Dietary protein intake in DKD


Case

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

- Smoker: Non smoker
- Obese: Exercise TW
- BP 150/90: BP 130/80
- A1c 11%: A1c 6.9%
- LDL 150: LDL 70
- High protein diet: Low protein diet
- GFR loss 20 cc/min/year: GFR loss 2 cc/min/year

IT’S UP TO MR JD AND TO YOU!

Acknowledgments

Questions?

Objectives

- Definition and screening for DKD
- 2017 Treatment guidelines
- Novel biomarkers

DKD: Ongoing trials on new targets

Is hyperuricemia a predictor of outcome?

355 patients with DM and MA
Baseline uric acid determination
6 years f/u
End points: GFR, Cystatin decline, albuminuria


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 (23 with macroalbuminuria at f/u)

Hovind P et al, Diabetes, 2009 Jul;58(7):1668-71

DKD: role of Vitamin D

168 consecutive patients in a CKD clinic (28% with DM)
6 years follow-up
Baseline Vitamin D adjusted for age, sex, smoking, CRP inflames, ACE/ARB usage, eGFR


DKD: role of Vitamin D

Role of dyslipidemia in DKD

Sacks F M et al. Circulation. 2014;126:999-1008

TNF Receptors: new biomarkers

T1DM  T2DM

Plasma metabolomic analysis of patients with type 2 DM and DKD

Mr BN is a 38 yo male with a 15 years history of type 1 diabetes. His A1C is 7% and his blood pressure is 130/80. He comes to you for an upper respiratory infection that started 10 days prior. His Strep throat test is positive. You screen for DKD and find no albuminuria and normal eGFR. His complement is normal. He has microhematuria. A renal US demonstrates a complex mass that is confirmed by biopsy to be a renal cell carcinoma. When the patient undergoes nephrectomy, the pathologist reports thickening of the glomerular basement membrane in the non-tumoral portion of the parenchima and no deposits.

The likely diagnosis is:
- IgA nephropathy
- Post-infectious GN
- Diabetic kidney disease
- Alport syndrome

Ms AF is a 48 yo female comes to you with uncontrolled type 1 diabetes, heart failure and new onset of severe albuminuria despite maximal dose of ramipril. She does not have diabetic retinopathy. Her urinary sediment is unremarkable and her urine ACR is 1600 mg/g. She has a normocytic anemia and normal platelet count. Her PCP send the patient to you for evaluation of DKD. Her lab work demonstrated a creatinine of 1.3 mg/dl. Which test is most likely to reveal the appropriate diagnosis?
- HbA1C
- A peripheral blood smear
- A Congo red staining on a kidney biopsy
- the presence of 2/3 urine collections with an ACR>30 mg/g

Mr RN is a 35 yo male with type 1 diabetes and established DKD. He comes to you with concerns about his DKD progression. He does have established diabetic retinopathy. He is not a smoker and blood pressure and HbA1C are at target. His urinary sediment is unremarkable and his urine ACR is 400 mg/g. You test for uric acid and the value is 8 mg/dl. At this point you tell the patient that:
- he should absolutely start allopurinol now
- high uric acid is not a biomarker for DKD progression
- the benefits of treating patients with DKD and high uric acid with allopurinol is being studied
- he is at high risk to develop gout

Which one of the following statements is true?
1. Nodular glomerulosclerosis is pathognomonic for DKD
2. Interstitial fibrosis and tubular atrophy is an early finding and starts before diabetic glomerulopathy becomes established
3. DKD lesions are more homogeneous in type 2 compared to type 1 diabetic patients
4. Podocytopenia correlates with albuminuria

Mr BN is 53yo male with type 2 DM and CKD 4A2 who comes to your clinic to discuss how best to slow the progression of DKD. His BP is controlled, he exercises, he quit smoking, his Vitamin D is being replaced, his metabolic acidosis is corrected. However, his HbA1C is still 8.5% and he was advised to discontinue metformin. He is asking if there is any advantage to be on one hypoglycemic agent versus another.

You suggest the following:
A. There is no advantage of one hypoglycemic agent versus another
B. He should definitely be on a SGLT2 inhibitor given the results of the EMPA-REG trial
C. At an earlier stage of CKD, either liraglutide or empagliflozin may have additional benefits on DKD progression
D. He should stay on metformin
Mr. PG is a 62 yo male who is receiving chronic hemodialysis because of kidney failure attributed to type 2 diabetes. He is new to your practice. His blood pressure is 150/82 mmHg, Hgb is 11.5 g/dl, and HbA1c is 9.5%. He is not being treated with any hypoglycemic medicines. The patient previously took metformin and never experienced a severe hypoglycemic episode, but his PCP took him off this medicine when his eGFR dropped below 45 ml/min/1.73 m² because of the increased risk of lactic acidosis. When Mr. PG went on dialysis, his nephrologist did not start any hypoglycemic medicines. The patient takes a statin daily and erythropoietin to maintain his Hgb within the recommended range. He has good nutritional status. Which of the following statements is true?
A. The apparent hyperglycemia should not be treated because HbA1c is not a reliable indicator of ambient glucose in the setting of kidney failure and the patient is otherwise in good condition.
B. The use of erythropoietin and the reduced RBC lifespan seen in kidney failure causes the HbA1c to overestimate ambient glucose, so the patient is in good glycemic control and should not be treated with a hypoglycemic drug because it would increase the risk of severe hypoglycemia.
C. Treatment with insulin should be considered to achieve a modest reduction in HbA1c and reduce mortality risk.
D. Measure glycated albumin instead of HbA1c to assess glycemic control, as it provides a measure of intermediate-term glycemic control and is not confounded by anemia and shortened red cell survival, and decide how to treat the patient after results of this test become available.

Ms. AF is a 28 yo female with T1D and severe albuminuria and an eGFR >60 cc/min/1.73 m² who comes to see you for uncontrolled hypertension (160/95 mmHg). Her A1C is currently at target and she exercise regularly. She is also on a low salt diet. She recently got married and is planning to have a baby before her disease progresses. She has not been taking any blood pressure medication. You discuss with her the risk of experiencing progressive DKD should she become pregnant. Which of the following advise is correct
A. She should immediately start RAS blockade
B. Blood pressure targeting will affect the chance to develop major cardiovascular events but will not affect DKD progression
C. Blood pressure should be targeted at 130/80 with appropriate safe agents
D. A combination of ACEi and ARB would be most beneficial

Ms. OL is a 46 yo male with T1D that comes to you with a 30 years history of diabetes. He is normoalbuminuric and normotensive. He is concerned that one day he may develop DKD. Which one of this is the correct advise?
A. He should be placed on RAS blockade to prevent DKD development
B. You advise the patient to undergo a kidney biopsy
C. You tell the patient that his chance to develop DKD after so many years from the diagnosis of diabetes is unlikely
D. you tell the patient that insulin treatment is protecting his kidneys