Prevention of Cardio-Renal Complications in Pediatric Type 1 Diabetes

Keystone Conference
July 20, 2013

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Financial Disclosures

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Outline

- Why are Cardio-Renal Complications Important in Pediatric T1D?
- Epidemiology
  - Early T1D Kidney Disease
  - Do Youth with T1D have Atherosclerosis?
  - Risk Factors
- Rationale for Treatment
- Challenges
- Summary/Conclusions
Case Presentation

• 16 year old ♂ with T1D for 2 years with:
  • A1c=6.8%
  • BP=123/77 mm/Hg
  • BMI=22 kg/m²
  • LDL=117 mg/dl
  • ACR=4 µg/mg

• What next???
  – Diet, exercise, repeat evaluation, consider medication?
  – Ignore until you can transfer care at 18y?
Why are Cardio-Renal Complications Important in Pediatric T1D?

- Persistent MA is any early stage of Diabetic Nephropathy (DN)
  - established CVD risk factor
- DN occurs in 20-40% of patients
  - Single leading cause of ESRD
- CVD leading cause of death in T1D
- PREVENTABLE with risk factor control
  - Metabolic memory → start in youth!
"The cracks can be fixed--it's your cholesterol level that worries me."
**Historic Data**

- **Microalbuminuria predicts clinical Nephropathy**  
  (Viberti, Lancet, ’82)

- **Proteinuria increases relative mortality in T1D**  
  (Borch-Johnsen, Diabetologia, ‘85)

![Graph showing cumulative incidence of persistent proteinuria over diabetes duration]

Marshall, Diabetologia, ‘12
Scottish Registry, n=21,789

Total Mortality*
males IRR 2.58 (2.23-2.98)
females IRR 2.71 (2.18-3.38)

Livingstone, PLOS Medicine, '12
Scottish Registry

Livingstone, PLOS Medicine, ‘12
Renal but not CAD Outcomes Improved in T1D

A: Renal failure

B: Total CAD (events and procedures)

C: CAD events (MI and CAD deaths only)


P values adjusted for age at onset of diabetes. Pambianco, Diabetes 55:1463-9, ‘06
Combined effects of albuminuria and eGFR levels at baseline on the risk for adverse outcomes

Ninomiya T et al. JASN 2009;20:1813-1821
Epidemiology
Early Diabetic Kidney Disease
Cumulative prevalence of MA (110/527) in childhood onset T1D after 10 years, by year of onset

Amin R et al. Arch Dis Child 2009; 94:258-262
Change in retinopathy and microalbuminuria

Mohsin F et al.
Diabetes Care
Higher Prevalence of Elevated Albumin Excretion in Youth With Type 2 Than Type 1 Diabetes

The SEARCH for Diabetes in Youth Study

OBJECTIVE — To determine the prevalence of elevated albumin-to-creatinine ratio (ACR) in youth with type 1 (T1D) and type 2 (T2D) diabetes.

RESULTS — Elevated ACR was detected in 9.2% of T1D and 22.2% of T2D youth.

CONCLUSIONS — Youth with type 2 diabetes have a higher prevalence of elevated ACR than youth with type 1 diabetes, in an association that apparently does not completely depend on age, duration of diabetes, race/ethnicity, sex, level of glycemic control, or features of insulin resistance.

Elevated ACR in 9.2% of T1D and 22.2% of T2D Youth

Diabetes Care 30:2593–2598, 2007
FinnDiane: T1D Mortality Risk by albuminuria and ESKD

Impaired Renal Function Increases Coronary Artery Calcification With Type 1 Diabetes

The CACTI Study

David M. Maahs, MD, PhD
Diana Jalal, MD
Michel Chonchol, MD

OR for CAC Progression

ACR

T1D < 10
T1D 10-30
T1D > 30

eGFR

CKD EPI serum creatinine
CKD EPI cystatin C
CKD EPI combined
Do youth really have atherosclerosis?
Landmark Studies of CVD Risk Factors in Youth

• Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY)

• CVD risk factors:
  – 1) exist in childhood
  – 2) track into adulthood
  – 3) associated with atherosclerosis in autopsies
Natural History of Atherosclerosis

Myocardial infarct
Cerebral infarct
Gangrene of extremities
Abdominal aortic aneurysm

Clinical Horizon

Calcification: Complicated lesion – hemorrhage, ulceration
Fibrous plaque
Fatty streak

Age in Years

Slides courtesy of Aspen Preventive Pediatric Cardiology Conference 2007 and Drs Berenson and McGill
Pathobiological Determinants of Atherosclerosis in Youth

- Study of atherosclerosis in 15-34 year olds autopsied in forensic laboratories
- Organized in 1985 by 14 centers
- Collected 3,000 cases (arteries and risk factor data), 1987-1994
- Grading and analyses in central labs
Prevalence Map of Raised Lesions of Right Coronary Artery by Age and Non-HDL Cholesterol

<table>
<thead>
<tr>
<th>Age</th>
<th>Non-HDL-C &lt; 160mg/dL</th>
<th>Non-HDL-C &gt; 160 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>n=531</td>
<td>n=159</td>
</tr>
<tr>
<td>25-34</td>
<td>n=523</td>
<td>n=277</td>
</tr>
</tbody>
</table>
IMT is significantly thicker in high-risk children

**T1D**
- A1c=8.8%
- Age=11±2 y
- LDL=2.3±0.7 mmol/L

**HC**
- Age=11±3 y
- LDL=5.1±1.2 mmol/L

Atherosclerosis in Youth

• Atherosclerosis is present in childhood:
  – atherosclerotic pathology lesions
  – surrogate markers of CVD (carotid IMT)

• CVD risk factors track from childhood to adulthood

Pathologic Determinants of Atherosclerosis in Youth
Bogalusa Heart Study, Young Finns
Risk Factors
ADA Guidelines, Standards of Medical Care, 2013
A, B, Cs

• **ADULTS**
  - **A1c**: <7%
  - **BP**: 140/80 mm/Hg
  - **LDL**: <100 mg/dl
    - 160 mg/dl = 4.1 mmol/L
    - 130 mg/dl = 3.4 mmol/L
    - 100 mg/dl = 2.6 mmol/L

• **ADOLESCENTS**
  - **A1c**: <7.5%
  - **BP**: <95th% age, sex
  - **LDL**: <160 mg/dl or <130 mg/dl or <100 mg/dl?

*Obesity, Insulin Resistance, Kidney Disease*
HbA1c by Age

- 1-<6: 8.2%
- 6-<13: 8.2%
- 13-<18: 8.7%
- 18-<25: 8.5%
- 25-<50: 7.7%
- 50-<65: 7.6%
- ≥65: 7.4%
Trends of metabolic control

Average absolute decrease per year: 0.038%  
95% CI: 0.032% - 0.043%  
p < 0.001

Rosenbauer J et al.  
DC 2012;35:80-86

DPV Study, N=30,021
Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

Richard M. Bergenstal, M.D., David C. Klonoff, M.D., Satish K. Garg, M.D., Bruce W. Bode, M.D., Melissa Meredith, M.D., Robert H. Slover, M.D., Andrew J. Ahmann, M.D., John B. Welsh, M.D., Ph.D., Scott W. Lee, M.D., and Francine R. Kaufman, M.D., for the ASPIRE In-Home Study Group*
Meeting Goals in T1D Youth

C  BMI

<table>
<thead>
<tr>
<th>Age, years</th>
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<th>6&lt;13</th>
<th>13&lt;20</th>
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<tr>
<td></td>
<td>63%</td>
<td>67%</td>
<td>51%</td>
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D  LDL

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<th>6&lt;13</th>
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<td>69%</td>
<td>62%</td>
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E  HDL

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<td></td>
<td>97%</td>
<td>94%</td>
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F  TG

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<th>6&lt;13</th>
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<tr>
<td></td>
<td>94%</td>
<td>89%</td>
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</table>

Wood, DC, ‘13
Insulin Sensitivity

Glucose Disposal Rate (mg/kg.min)

Control  Type 1  Obese  Type 2

^p<0.01 vs. controls, #p<0.001 vs controls, *p<0.02 vs obese

Nadeau, JCEM 2010
Development, validation and use of an insulin sensitivity score in youths with diabetes: the SEARCH for Diabetes in Youth study

D. Dabelea · R. B. D’Agostino Jr · C. C. Mason · N. West · R. F. Hamman · E. J. Mayer-Davis · D. Maahs · G. Klingensmith · W. C. Knowler · K. Nadeau

Received: 13 April 2010 / Accepted: 20 August 2010 / Published online: 1 October 2010 © Springer-Verlag 2010
Albinunuria According to Status of Autoimmunity and Insulin Sensitivity Among Youth With Type 1 and Type 2 Diabetes

1) DAA-/IR group had highest UACR (Mottl, DC, ’13)
2) ISI OR=0.69 (0.51-0.93) for incident MA,
OR=0.80 (0.67-0.97) for rapid GFR decline
(Bjornstad, DC, in press ‘13, CACTI data)
NEWS ITEM: U.S. OBESITY GROWING.
Rationale for Treatment of Cardio-Renal Complications in Youth with T1D
Microalbuminuria by Duration & A1c

4.4% Clinical Dx of MA
36% ACE/ARB Tx

HbA1c, %
- <6.5%
- 5.5-<7.5%
- 7.5-<8.5%
- 8.5-<9.5%
- ≥9.5%

Duration
- <5 yrs N=2209
- 5-<10 yrs N=3550
- ≥10 yrs N=2593

M Daniels, DC, ‘13
“Stages” in Development of Diabetic Nephropathy

- Genetic Predisposition
- Hyperglycemia
- Progressive loss of nephrons + GFR
- Microalbuminuria
  - HTN, Dyslipidemia, IR, other risk factors
  - ACE/ARB TX

Maahs, DTT, 2012
Lipid Abnormalities in The SEARCH for Diabetes in Youth Study

Kershner, JPeds '06

1% on lipid-lowering medications
Hypothetical Relationship of LDL, LDL-lowering and Future CVD in Youth with DM

Figure 2A
Background increased risk of CVD in youth with diabetes due to elevated HbA1c and increased risk of other CVD risk factors in addition to dyslipidemia, HTN, albuminuria, etc.

160 mg/dl
130 mg/dl
100 mg/dl

Increasing Age

Figure 2B

160 mg/dl
130 mg/dl
100 mg/dl

Increasing Age

Maahs, et al
JPeds ‘08
# Pros and Cons of Rx Treatment

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids track into adulthood</td>
<td>Wait until adults</td>
</tr>
<tr>
<td>Lipids associated with atherosclerosis in childhood</td>
<td>- 10 yr risk of CVD event very low</td>
</tr>
<tr>
<td>Lipids important microvascular and macrovascular risk factor</td>
<td>- Send patient to Adult Endo once 18 yrs</td>
</tr>
<tr>
<td>DM considered a CVD risk factor equivalent in adults</td>
<td>- data to suggest regression of atherosclerosis possible with adult treatment</td>
</tr>
<tr>
<td>Earlier DM onset → longer DM disease burden, potential adverse “vasculo-metabolic memory” and increased area under the curve for CVD risk factors</td>
<td>No data that treatment in youth will reduce long-term CVD complications</td>
</tr>
<tr>
<td>Long-term elevated risk of CVD (PDAY, Young Finns, Bogalusa) Preponderance of data on lowering CHD risk in adults, why wait?</td>
<td>Primum non nocere</td>
</tr>
<tr>
<td></td>
<td>Potential adverse events from dyslipidemia medications</td>
</tr>
<tr>
<td></td>
<td>Potential teratogenicity for adolescent females</td>
</tr>
<tr>
<td></td>
<td>Cost: 1) number needed to treat to prevent CVD event unable to be calculated, but undoubtedly high; 2) many years of treatment required with potential for life-time treatment</td>
</tr>
<tr>
<td></td>
<td>Variability, regression to mean of lipids</td>
</tr>
</tbody>
</table>

No outcome data, no safety data in youth with diabetes

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Maahs, etal
JPeds ‘08
Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

Challenges
## Pros and Cons

### Albuminuria
- **PROS**
  - Predictive
  - Extensive data
- **CONS**
  - Progress/Regress
  - False +
  - Collection

### eGFR
- **PROS**
  - Predictive
  - Easy to collect
  - SCr standardized
- **CONS**
  - Less reliable >60 ml/min/1.73m²
  - Limited Pediatric data

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### Complementary Data
Estimating Glomerular Filtration Rate

Inker et al. NEJM 2012; 367-20-29
Diabetic Kidney Disease
Variability in Clinical Course

- Increased or Normal GFR
- Normoalbuminuria
- Microalbuminuria
- Overt Nephropathy
- Decreased GFR
- ESRD

Diabetes onset
~5 years
~10 years
~15-20 years

Time

Courtesy A. Mottl, UNC
Hyperfiltration in type 1 diabetes: does it exist and does it matter for nephropathy?

M. C. Thomas · J. L. Moran · V. Harjutsalo · L. Thorn · J. Wadén · M. Saraheimo · N. Tolonen · J. Leiviskä · A. Jula · C. Forsblom · P. H. Groop · on behalf of the FinnDiane Study Group

Received: 10 September 2011 / Accepted: 16 January 2012 / Published online: 10 February 2012
© Springer-Verlag 2012
Priorities?

• Prevention of diabetic kidney disease and cardiovascular disease may not be priority?
  – See talks by Wysocki, Schatz, Klingensmith, etc
• Asymptomatic
• Hard to imagine future
Summary

• Make case that management of cardio-renal complications in adolescents with diabetes is:
  – an unmet need
  – an opportunity to improve outcomes
  – progressing since initial guidelines in past decade
  • Pharmacologic treatment is rare
Questions to address for Cardio-Renal Disease in Youth with T1D

Should we treat cardio-renal risk factors to prevent future disease?

At what age to start?

How aggressively should cardio-renal risk be treated in adolescents

Adult goals or less stringent?

Pharmacologic or TLC?
Conclusions:
on Cardio-Renal Disease in T1D Youth

• Risk factors and early disease common in T1D youth
• Atherosclerosis begins in childhood
• Treatment goals infrequently met
• ACE/ARB & dyslipidemia meds rarely used
• CVD and kidney disease increased in T1D
• Data on treatment and long-term outcomes are needed

How early and how aggressively do we need to treat Cardio-Renal risk in T1D adolescents?
Life Expectancy Improvement in T1D

• Pittsburgh Epidemiology of Diabetes Complications study (Miller, Diabetes, ‘12)
  – Life expectancy for cohort diagnosed 1965-1980 was 15 years greater than for participants diagnosed 1950-1964!
  • 68.8 (64.7-72.8 years) vs. 53.4 (50.8-56.0 years)
Further Improvements in T1D Care Needed!

- Glucose control → artificial pancreas
- AdDIT Trial:
  - Factorial design (ACE/Statin) in T1D adolescents with ACR and cIMT as outcomes in UK
- Obesity and IR
- Behavioral
- Quality of Life
ADA Guidelines for T1D Youth

• Annual screening >10y + T1D >5y
  – More frequent if values increasing

• Methods
  – Spot, timed, 24 hour

• Repeat if abnormal, 2/3 required for diagnosis of persistent abnormal microalbumin excretion (exercise, smoking, menstruation all effect results)

Silverstein, Klingensmith et al, *Diabetes Care*, January 2005
“Stages” in Development of Diabetic Nephropathy

- Genetic Predisposition
- Hyperglycemia
- Progressive loss of nephrons + GFR
- Normal GFR
- Microalbuminuria
- HTN,
  Dyslipidemia,
  IR,
  other risk factors
- ACE/ARB TX

Maahs, DTT, 2012
GFR in T1D

• Good methods to estimate GFR if < 60 ml/min/1.73m²
  – CKD-EPI, serum creatinine based
  – Cystatin C based

• Options for Adolescents?
  – eGFR less reliable > 60 ml/min/1.73m²
  – Regression and Progression with albuminuria
    • Can be difficult to collect
Early RASS blockade in T1D did not slow nephropathy progression, but did slow progression of retinopathy.
SEARCH  A1c by DM type

HbA1c Mean 8.33% SD (1.56)

- type 1
  - N=2999
- type 2
  - N=369

HbA1c Mean 8.24% SD (1.56)

- <=8%
- 8.1-9.4%
- 9.5+%}

C Pihoker, et al
JPeds, ‘09
Mean HbA1c by Age Group

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>8.3%</td>
</tr>
<tr>
<td>6-12</td>
<td>8.3%</td>
</tr>
<tr>
<td>13-17</td>
<td>8.7%</td>
</tr>
<tr>
<td>18-25</td>
<td>8.5%</td>
</tr>
<tr>
<td>26-49</td>
<td>7.7%</td>
</tr>
<tr>
<td>≥ 50</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

N=20,110
Declining retinopathy in parallel with increased MDI/CSII and lower A1c  N=1,604 T1D adolescents

Downie E et al. DC 2011;34:2368-2373
Start slides for Keystone

• Confirm title & time limit (20-30 slides?)
• Update data on scope of DKD in DM (T1D emphasis, some T2D, see Chip’s email)
• Emphasis then on early DKD detection
• Rick for advice and other slides
• See AJKD & R21
• Give screening recs: Peds v Adult
• Find Cartoon bank
Early GFR markers

- Cjasn---cystatin C assay issues + Krolewski correction
- 6y Cacti renal, if corrected for scentat
- DC Peds cyst C + search abstract
- See R21----
Data on Peds/early DKD

- Search ACR; T1D&T2D; implications for future
- Donaghue
- Daneman/Gorman
- Oxford
- Perkins and regression
- Uric acid data/proteomics data/Krolewski tnf-a/Johnson data
- RASS data
Kidneys

Nephropathy: persistent macroalbuminuria associated with changes in the kidney leading to abnormal ability to filter and HTN
• Treatable with medications
• Earliest sign is microalbuminuria
• Failure to detect/treat can lead to macroalbuminuria, renal failure
Treatment

• Angiotensin-converting enzyme inhibitors (ACE)
• Glycemic control
• Smoking cessation
• Treat Hypertension if it exists
• LDL treatment may be of benefit
• Consider Nephrology referral
Orchard, Diabetologia, ‘11
Microalbuminuria According to Duration

- <5 yrs (N=2209): 2.5%
- 5-<10 yrs (N=3550): 3.4%
- 10-<15 yrs (N=1951): 6.0%
- ≥ 15 yrs (N=642): 7.0%
Figure Legend:

Person-years at risk were counted from the first diabetic examination or the 25th birthday, whichever occurred later.
For any duration category, participants with youth-onset type 2 diabetes have a lower risk of diabetic end-stage renal disease ($P = .007$) and natural mortality ($P < .001$) than those with older-onset diabetes mellitus. Participants were observed from onset of diabetes mellitus to outcome or December 2002. Natural mortality panel has 5 more participants than the end-stage renal disease panel because 5 participants diagnosed with diabetes mellitus in the course of routine medical care were excluded because they had no research examination between date of diagnosis and onset of dialysis.
Figure 3. Sensor Glucose Values during Threshold-Suspend Events.
Shown are mean (±SD) sensor glucose values during 1438 nocturnal threshold-suspend events lasting for 2 hours. Time 0 indicates the time that the pump suspension started, and 120 minutes indicates the resumption of insulin delivery. The dotted line is at 70 mg per deciliter. See Figure S3 in the Supplementary Appendix for the percentages of sensor glucose values in various ranges at 2 and 4 hours after the beginning of nocturnal 2-hour threshold-suspend events.
Figure 1. GBM width in normoalbuminuric T1D patients who remained normoalbuminuric (nonprogressors) or progressed to proteinuria and/or ESRD (progressors) during follow-up. The shaded area represents the normal range (mean ±2 SD) of GBM width.
Course of Albuminuria in Type 1 Diabetes

Regression More Common than Progression

Course of Albuminuria and Risk of GFR Loss in T1D

Normoalbuminuric CKD

Normoalbuminuric diabetic CKD and rate of eGFR decline

Molitch et al. Diabetes Care 2010; 33(7):1536-43
Heterogeneity in Pathology of Type 2 Diabetic Kidney Disease

(A) normal/ near normal structure
(B) typical diabetes histopathology
- Nodular mesangial expansion
- Thickened GBM
- Arteriolar hyalinosis
(C) atypical patterns of renal injury
- Tubular atrophy
- Thickened tubular BM
- Interstitial fibrosis
- Advanced arteriolar hyalinosis

Fioretto P et al. Diabetologia 2008; 51: 1347-1355
## Table 1. Clinical Characteristics of the DCCT/EDIC and EDC Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Conventional</th>
<th>Intensive</th>
<th>DCCT</th>
<th>EDIC</th>
<th>EDC</th>
<th>DCCT</th>
<th>EDIC</th>
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<td>20 (4)</td>
<td>27 (7)</td>
<td>20 (4)</td>
<td>27 (7)</td>
<td>20 (4)</td>
<td>27 (7)</td>
<td>20 (4)</td>
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<td>Duration, mean (SD), y</td>
<td>5 (4)</td>
<td>5 (2)</td>
<td>6 (4)</td>
<td>5 (2)</td>
<td>6 (4)</td>
<td>5 (2)</td>
<td>6 (4)</td>
<td>5 (2)</td>
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<tr>
<td>BMI, mean (SD)</td>
<td>24 (3)</td>
<td>24 (3)</td>
<td>24 (3)</td>
<td>24 (3)</td>
<td>24 (3)</td>
<td>24 (3)</td>
<td>24 (3)</td>
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<tr>
<td>BMI &gt;=30, %</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Current smoker, %</td>
<td>18</td>
<td>20</td>
<td>18</td>
<td>20</td>
<td>18</td>
<td>20</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>HbA1c, % (SD)</td>
<td>8.9 (1.6)</td>
<td>9.1 (1.5)</td>
<td>7.7 (1.2)</td>
<td>9.0 (1.7)</td>
<td>8.5 (1.4)</td>
<td>8.3 (1.8)</td>
<td>8.9 (1.6)</td>
<td>7.4 (1.1)</td>
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<td>Proliferative retinopathy, %</td>
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<td>0</td>
<td>12.7</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td>40</td>
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<td>Renal</td>
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<td>AER, mg/24 h c</td>
<td>12 (7-19)</td>
<td>12 (7-17)</td>
<td>10 (6-20)</td>
<td>10 (6-20)</td>
<td>14 (9-26)</td>
<td>11 (7-34)</td>
<td>12 (7-17)</td>
<td>9 (6-14)</td>
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<td>≥40 mg/24 h, %</td>
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<td>≥300 mg/24 h, %</td>
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<td>Serum creatinine ≥2 mg/dL, %</td>
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<td>1</td>
<td>1</td>
<td>0</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors or ARBs</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>45</td>
<td>15</td>
<td>42</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;14 Aspirin per mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4</td>
<td>0</td>
<td>25</td>
<td>NA</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Statin</td>
<td>NA</td>
<td>NA</td>
<td>36</td>
<td>1</td>
<td>2</td>
<td>32</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Uric acid in predicting worsening DKD

Pathophysiology
DKD Pathophysiology
GFR in T1D

• Good methods to estimate GFR if < 60 ml/min/1.73m²
  – CKD-EPI, serum creatinine based
  – Cystatin C based

• Options for Adolescents?
  – eGFR less reliable > 60 ml/min/1.73m²
  – Regression and Progression with albuminuria
    • Can be difficult to collect
## Table 1 Characteristics of ten studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First author [reference no.]</th>
<th>Year</th>
<th>Country</th>
<th>Hyperfiltration definition (ml min⁻¹ 1.73 m⁻²)ᵃ</th>
<th>Patients included (n)</th>
<th>Mean age at diagnosis (years)</th>
<th>Mean follow-up (years)</th>
<th>Mean baseline diabetes duration (years)</th>
<th>Mean baseline Hba₁c (%)</th>
<th>Mean baseline blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mogensen [22]</td>
<td>1984</td>
<td>Denmark</td>
<td>ND</td>
<td>24</td>
<td>12.3</td>
<td>10.4</td>
<td>12.6</td>
<td>6.9ᵇ</td>
<td>135/89</td>
</tr>
<tr>
<td>Lervang [23]</td>
<td>1988</td>
<td>Denmark</td>
<td>ND</td>
<td>29</td>
<td>18.9</td>
<td>18.5</td>
<td>3.4</td>
<td>9.3ᵇ</td>
<td>118/76</td>
</tr>
<tr>
<td>Lervang [24]</td>
<td>1992</td>
<td>Denmark</td>
<td>ND</td>
<td>34</td>
<td>7.0</td>
<td>12.0</td>
<td>7.0</td>
<td>10.8ᵇ</td>
<td>128/83</td>
</tr>
<tr>
<td>Chiarelli [25]</td>
<td>1995</td>
<td>Italy</td>
<td>140 ᵇ</td>
<td>46</td>
<td>6.2</td>
<td>10.0</td>
<td>9.7</td>
<td>12.2ᵈ</td>
<td>121/74</td>
</tr>
<tr>
<td>Yip [26]</td>
<td>1996</td>
<td>England</td>
<td>135</td>
<td>45</td>
<td>21.5</td>
<td>9.5</td>
<td>8.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Caramori [27]</td>
<td>1999</td>
<td>Brazil</td>
<td>134 ᵇ</td>
<td>33</td>
<td>25.3</td>
<td>8.4</td>
<td>6.5</td>
<td>11.4ᵈ</td>
<td>NA</td>
</tr>
<tr>
<td>Dahlquist [28]</td>
<td>2001</td>
<td>Sweden</td>
<td>ND</td>
<td>43</td>
<td>6.0</td>
<td>18.0</td>
<td>10.9</td>
<td>12.2</td>
<td>114/64</td>
</tr>
<tr>
<td>Amin [29]</td>
<td>2005</td>
<td>England</td>
<td>125</td>
<td>273</td>
<td>9.3</td>
<td>10.9</td>
<td>5.1</td>
<td>10.8</td>
<td>NA</td>
</tr>
<tr>
<td>Steinke [30]</td>
<td>2005</td>
<td>USA</td>
<td>130</td>
<td>107</td>
<td>8.7</td>
<td>5.0</td>
<td>8.0</td>
<td>9.2</td>
<td>119/74</td>
</tr>
<tr>
<td>Zerbini [31]</td>
<td>2006</td>
<td>Italy</td>
<td>ND</td>
<td>146</td>
<td>7.3</td>
<td>9.5</td>
<td>9.5</td>
<td>9.8</td>
<td>119/74</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>780</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ᵃ Where not defined (ND), arbitrarily set at >140 ml min⁻¹ 1.73 m⁻²
ᵇ Hba₁c estimated using reverse estimated average glucose formula (these values omitted when calculating mean)
ᶜ Single compartment GFR estimation technique
ᵈ Hba₁c measurements (these values omitted when calculating mean)
NA, not available
Uric Acid and Cardio-Renal Disease

• Uric Acid
  – Predicts development of micro- or macroalbuminuria over 6 years
  – Predicts CAC progression among people without renal complications (OR 1.25 [95% CI 1.01–1.54], $P = 0.03$).

Jalal, NDT ‘10 and Rodrigues, DC, ‘10
Change in microvascular complications

New Biomarkers

• Cystatin C
• Uric Acid
• TNF Receptors
• Genetics
• Urine Proteomics
Cystatin C: Better Estimate of GFR than current equations

Perkins, NEJM, 2005
A. 100/Cystatin C vs. Iothalamate Clearance (ml/min/1.73m²)

B. 100/Creatinine vs. Iothalamate Clearance (ml/min/1.73m²)

C. GFR Estimated by the Cockcroft-Gault Formula

D. GFR Estimated by the MDRD Equation

Perkins, JASN, 2005
Uric Acid and Cardio-Renal Disease

• Uric Acid
  – Predicts development of micro- or macroalbuminuria over 6 years
  – Predicts CAC progression among people without renal complications (OR 1.25 [95% CI 1.01–1.54], $P = 0.03$).

Jalal, NDT ‘10 and Rodrigues, DC, ‘10
Circulating TNF Receptors 1 and 2 Predict ESRD in Type 2 Diabetes

Circulating TNF Receptors 1 and 2 Predict Stage 3 CKD in Type 1 Diabetes


*Research Division, Joslin Diabetes Center and †Department of Medicine, Harvard Medical School, Boston, Massachusetts; ‡Division of Nephrology, Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan; §Department of Immunology, Transplantology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland; and ‖Department of Pathology, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts
Genetic Markers

ORIGINAL ARTICLE

Genome-Wide Association Scan for Diabetic Nephropathy Susceptibility Genes in Type 1 Diabetes

Marcus G. Pezzolesi,1 G. David Poznik,1 Josyf C. Mychaleckyj,2 Andrew D. Paterson,3,4 Michelle T. Barati,5 Jon B. Klein,5 Daniel P.K. Ng,1,6 Grzegorz Placha,1,7 Luis H. Canani,1,8 Jacek Bochenski,1 Daryl Waggott,9 Michael L. Merchant,5 Bozena Krolewski,1 Lucia Mirea,4,9 Krzysztof Wanic,1 Pisut Katavenin,1 Masahiko Kure,1 Pawel Wolkow,1,10 Jonathon S. Dunn,1 Adam Smiles,1 William H. Walker,1 Andrew P. Boright,11 Shelley B. Bull,4,9 the DCCT/EDIC Research Group,* Alessandro Doria,1 John J. Rogus,1 Stephen S. Rich,2 James H. Warram,1 and Andrzej S. Krolewski1

OBJECTIVE—Despite extensive evidence for genetic susceptibility to diabetic nephropathy, the identification of susceptibility genes and their variants has had limited success. To search for genes that contribute to diabetic nephropathy, a genome-wide association scan was implemented on the Genetics of Kidneys in Diabetes collection.

RESEARCH DESIGN AND METHODS—We genotyped ~360,000 single nucleotide polymorphisms (SNPs) in 820 case subjects (284 with proteinuria and 536 with end-stage renal disease) and 885 control subjects with type 1 diabetes. Confirmation of implicated SNPs was sought in 1,304 participants of the 0.01, respectively). We demonstrated expression of both FRMD3 and CARS in human kidney.

CONCLUSIONS—We identified genetic associations for susceptibility to diabetic nephropathy at two novel candidate loci near the FRMD3 and CARS genes. Their identification implicates previously unsuspected pathways in the pathogenesis of this important late complication of type 1 diabetes. Diabetes 58: 1403–1410, 2009
Novel urine proteomics biomarkers in CACTI

Schlatzer D et al. Dia Care 2012;35:549-555
Summary: Diabetic Kidney Disease

- Better methods (and treatment) needed for early diagnosis and prediction of who will progress to clinically significant kidney disease.
- Follow current screening and treatment guidelines
- Stay posted for advances
Lancet ‘10
Albuminuria Definitions

• Spot samples:
  – ACR (albumin-to-creatinine ratio)
    • Microalbuminuria: 30-299 mg/g
    • Macroalbuminuria: ≥300 mg/g
• Timed overnight or 24 hour samples:
  – AER (albumin excretion rate)
    • Microalbuminuria: 20-199 μg/min
    • Macroalbuminuria: ≥200 μg/min
## Staging Chronic Kidney Disease

<table>
<thead>
<tr>
<th>GFR stages</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&gt;90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60-89</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3a</td>
<td>45-59</td>
<td>Mild-Moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30-44</td>
<td>Moderately-Severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15-29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>Kidney Failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albuminuria stages</th>
<th>AER (mg/day)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt;30</td>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>A2</td>
<td>30-299</td>
<td>Moderately increased</td>
</tr>
<tr>
<td>A3</td>
<td>≥ 300</td>
<td>Severely increased</td>
</tr>
</tbody>
</table>

DCCT/EDIC: Long-term Renal Outcomes of Patients With T1D and Microalbuminuria

Arch Intern Med. 2011;171(5):412-420
A1c at target per ADA (Black) or ISPAD (Hatched) Goals, N=13,226