Type 2 Diabetes as Clinical Endpoint in Pediatric NASH

Liver Forum 10
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Objectives/Outline

1. Overlap between T2D and NAFLD in youth
2. Differences between youth vs. adult-onset T2D
3. Relevance to pediatric clinical trials in NASH and T2DM
4. Considerations/Recommendations
Type 2 Diabetes (T2D) in Adolescents

A growing proportion of diabetes in youth

![Pie chart showing the percentage of T2D, T1D, and Other cases in 1994 and 2008-09.]

1994
- T1D (91%)
- T2D (4%)
- Other (5%)

2008-09
- T1D (62%)
- T2D (33%)
- Other (5%)

Modified from CDC.gov
Youth Onset T2D Prevalence rose 30%

2001 vs 2009

p<0.05 from 2001 to 2009 in
• Both sexes
• All ages 10-19
• Hispanic
• Non-Hispanic white
• Black youth

Dabelea. JAMA. 2014 May 7;311(17):1778-86
Racial differences in Type 2DM

African-American Youth:
High risk of Type 2 Diabetes, but low risk of NAFLD

Diabetes Care 2014;37:402
Global increase in T2D

Age < 40 years

Among children with Type 2 Diabetes, Nonalcoholic Fatty Liver Disease is Common

- N=115 children with T2DM
- 42% had liver enzymes (Similar age, sex, BMI, A1C)

48% had ALT ≥ ULN for lab ref range (approximately 40 IU/L)

Majority > biologically normal ALT threshold (<26 IU/L males, <22 IU/L for females)

Nadeau KP. JPGN 2005;41:94-98
Normal ALT does not exclude NAFLD or NASH
50% prevalence in 103 adults with T2DM & normal ALT

56% prevalence of NASH

Portillo-Sanchez. JCEM 2015; 100(6):2231
Among children with NAFLD, T2DM carries increased risk of NASH

- 675 children with biopsy-confirmed NAFLD, mean age 12.6, mean BMI 32.5
  - 23.4% had prediabetes
  - 6.5% had diabetes

Newton KP et al. JAMA Pediatrics

![Bar chart showing risk of NASH with different glucose levels and diabetes statuses.]

- 3X higher risk (OR 3) for definite NASH
- 2X higher risk for definite NASH

% with NASH

- Normal Glucose
- Pre-T2D
- T2D
Diabetes risk factor for NASH in adolescents undergoing bariatric surgery

- **ALT elevation**
  - Mild (22-39 females, 26-39 males) \(^{\text{OR 3.41}}\)
  - High (>40 U/L) \(^{\text{OR 6.66}}\)

- **Fasting glucose elevation**
  - 100-125 mg/dL \(^{\text{OR 1.48}}\)
  - ≥126 mg/dL \(^{\text{OR 8.10}}\)

*Xanthakos et al.. Gastroenterology 2015*
Diabetes and ALT only significant predictors of fibrosis in bariatric cohort

- Diabetes  OR 2.56 (1.10, 5.96)  p=0.03
- ALT>40 U/L  OR 2.41 (0.84, 6.98)  p=0.08

Xanthakos et al.. Gastroenterology 2015
T2DM risk factor for NASH progression?

• In 122 (88%) of children receiving standard lifestyle counseling and placebo over 1 or 2 years in the NASH CRN,
  – Half showed improvement in NASH or fibrosis
  – But over 1/3 experienced worsening in NASH or fibrosis,

• Disease progression related to worsening HbA1C
  – Progression to NASH (RO 3.4)
  – Progression to fibrosis (RO 2.3)
Does NAFLD increase risk of T2DM?

• **Type 2 diabetes mellitus developed in 8%** over period of observation
  – Doubling from baseline (6% to 13%) over 1-2 years

• **Incidence rate of 44.3/1000 person years**

• **>300 fold the estimated population incidence rate** of 0.12/1000 person years in adolescents

Presented at AASLD 2017

¹JAMA. 2007;297:2716-2724
T2DM in youth differs from adults
Adolescent vs. Adult T2D

Youth

Insulin Sensitivity (1/fasting Ipmol/L)

- 50% lower in Youth

Insulin Secretion

- 2-fold higher in Youth

CV risk factor profile worsens rapidly over time in youth

Baseline

3-4 year follow-up

Percent Complications

HTN *

Dyslipidemia *

Microalbuminuria *

*TODAY Study Group

*p<0.05
Carotid Thickness Overtime in
T2D vs. Obese & Lean Youth

Urbina, unpublished data

Slope for obese and T2D vs lean (p<0.05), n=226
Complications in T1D vs T2D Youth-Onset Diabetes

n=342 T2D youth, n=1011 T1D youth
Medical Treatment in Youth with T2D

Failed rates:
- Metformin alone, 51.7%
- Metformin–rosiglitazone, 38.6%
- Metformin–lifestyle, 46.6%

Pairwise tests:
- Metformin–lifestyle vs. metformin–rosiglitazone, P=0.15
- Metformin alone vs. metformin–rosiglitazone, P=0.006
- Metformin alone vs. metformin–lifestyle, P=0.17

N=699
Rapid decline overtime despite treatment

Relevance to pediatric trials for youth with NASH and/or T2DM

• How will having both youth-onset NASH + T2DM affect responses to treatments?
• Unclear as not well phenotyped or represented in prior trials…
  – For most T2DM trials, ALT > 2.5 to 3x ULN is an exclusion, lack of liver imaging
  – For earlier NASH trials, diabetes was an exclusion and/or poorly controlled T2DM an exclusion (A1C >9%)
ALT response after bariatric surgery by liver phenotype

- Most studies short term to date
  - 1-3 years in adults,
  - 1-2 years in teens
  - Remission vs. Cure?

*Bacha F...Xanthakos S. ADA mtg 2018*
Summary

• Strong overlap between T2D and NAFLD in youth
  • Exception: Sub-Saharan African heritage
• T2D in youth more rapidly progressive than Adult T2D
• Will youth with T2DM + NASH have worse outcomes and responses to treatment?
• Finding mutually beneficial treatments important
• Recommendations
  • Important subgroup for NASH and Diabetes clinical trials
  • Correct classification of T2DM at trial entry and follow-up
  • Capture duration of T2DM at trial entry
  • More cross-talk needed in pediatric NASH and T2DM trials
Diagnosis of incident T2D

- **Any** of the following + **Negative islet cell antibodies**
  - Fasting glucose ≥126mg/dL
  - Random glucose >200mg/dL + symptoms
  - **Hemoglobin A1c > 6.5%**
  - 2 hr OGTT blood glucose >200mg/dL
Caveat: Taking metformin can cloud the picture

- If participant has HbA1C < 6.5% could be:
  - Well controlled T2DM
  - PCOS
  - Prediabetes
  - Antipsychotic medication
The Type 2 Diabetes Team!
Email: type2clinic@cchmc.org

**Diabetes Providers**
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- Nancy Morwessel, CNP, Diabetes Nurse Practitioner
- Nancy Crimmins, MD MS, Pediatric Endocrinologist

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**Diabetes Education Team**
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**Bariatrics Team**
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- Susan Sewell, RD, Bariatric Dietician
- Kattyn Wessels, Bariatric Social Worker

**Program Coordinators**
- Kelsey French, T2D Clinic Coordinator
- Penni Taylor, Bariatric Coordinator
- Cassandra McDaniel, Bariatric Coordinator
**Diabetes Auto-antibodies?**

| **Glutamic Acid Decarboxylase (GAD)** | Enzyme in the pancreatic beta cells that produces insulin. |
| **Insulin Autoantibodies (IAA)** | Antibodies targeting insulin itself |
| **Insulinoma-Associated-2 Autoantibodies (IA-2)** | Enzyme in the pancreatic beta cells that produces insulin. |
| **Zinc Transporter 8 (ZnT8)** | Beta cell specific enzyme |

- TODAY study screened n=1,206 youth clinically diagnosed with type 2 diabetes
- 118 (9.8%) were antibody positive
- Antibody + youth tended to be
  - Less obese
  - Fewer features of the metabolic syndrome
  - More likely male
  - More likely Non-hispanic White
- Antibody + youth are “obese type 1”
  - At risk for faster progression to insulin dependence
  - Diabetic ketoacidosis
  - Autoimmune conditions