The Changing World of Pediatric Diabetes

…or "wait, what Type do they have?"

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2023 EXPLORE Healthcare Summit

Relevant Disclosure and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

David P Sparling, MD, PhD

I have no relevant financial relationships or affiliations with commercial interests to disclose.

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Learning Objectives

Upon completion of this session, participants will improve their competence and performance by being able to:

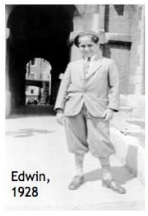
1) Recognize and properly initiate workup for diagnosis of diabetes mellitus in children

2) Understand the basics of new goals of treatment in children, such as Time in Range, and

3) Understand the evolving nature of Type 2 diabetes in youth

A quick history lesson…we've come a long way

- Edwin: Dx age 6, 1918, placed on starvation diet
- 1922: age 10, 27 lbs, admitted and started on insulin
- Lived to age 50, but became blind as a young adult
- 90 years later, great-granddaughter diagnosed with T1DM



http://www.nbdiabetes.org/news/diagnosis-type-1-diabetes

Jack

- A 7 year old Caucasian male presents to the emergency room with a 1 day history of nausea and vomiting, in the setting of a 3 week history of decreased energy, poor sleep, new nocturnal enuresis, polyuria, and polydipsia.
- FHx: autoimmune thyroid disease in his mother, grandmother, and a maternal aunt.
- Vital signs: BMI 15%ile, HR 95, RR 27, BP 109/79.
- PE: thin appearing, tired, deep rapid breathing, cap refill 3 seconds

Question for Jack

What leads your differential?

A: UTI

B: Pneumonia

C: Type 1 diabetes

D: Type 2 diabetes

Daniel

- A 19 year old African-American male presents to his PMD for a school physical. His family notes recent increased thirst
- FHx: diabetes controlled with oral medications in mom, dad, and 2 maternal uncles.
- Vital signs: BMI: 99%ile, HR 80, RR 18, BP 121/82.
- PE: obese habitus, darkened skin on back of neck and in axillae bilaterally

Question for Daniel

What leads your differential?

A: fungal skin infection

B: psychogenic polydipsia

C: Type 1 diabetes

D: Type 2 diabetes

Victoria

- A 10 year old Hispanic female presents to the ED due to a 1 day history of increased frequency of urination and some nausea. Her family notes a recent asthma exacerbation (currently on prednisone) and she has been more tired recently.
- FHx: gestational diabetes controlled with insulin in mom, and type 2 diabetes in maternal grandparents.
- Vital signs: BMI: 95%ile, HR 92, RR 26, BP 119/81.
- PE: obese habitus, Tanner 2, ill appearing, faint darkened skin on back of neck

Question for Victoria

What leads your differential?

A: gastroenteritis

B: pneumonia in setting of asthma

C: Type 1 diabetes

D: Type 2 diabetes

Diagnosis?

- Initial impressions for Jack, Daniel, and Victoria?
- Initial labs:
  - All 3: A1c 13%
  - All 3: 4+ glucose in urine
  - Jack and Victoria (in the ED): Na 129, glucose 670, bicarbonate 8, and elevated β-hydroxybutyrate in serum

Diabetes mellitus?

Type 1:
- Juvenile onset diabetes
- Insulin dependent diabetes mellitus (IDDM)
- Young child/skinny teenager

Type 2:
- Adult onset
- Non-insulin dependent diabetes mellitus (NIDDM)
- Obese adult, frequently minority ethnicity

Blurred lines?

- 39 year old Caucasian male presents for an annual physical. More tired recently. Occasional polyuria. BMI 40%ile. Family history of Type 1 diabetes in father and sister
- UA: 3+ glucose.
- OGTT: fasting glucose of 105 and a 2 hr glucose of 230.
- Fasting labs at the beginning of the OGTT significant for detectable insulin and c-peptide.
- 25 years later his son becomes a pediatric endocrinologist.

Blurred lines?

- …said pediatric endocrinologist sees a 12 yo Native American male in the clinic. Initial A1c 7.1, fasting glucose 132, no acanthosis nigricans, all markers of type 1 diabetes negative
  - mother had GDM, maternal grandfather, maternal uncles all with similar presentations of DM
  - all treated in different methods (insulin versus oral agents), all with A1c's in the low 7's…
  - Child taken off insulin due to hypoglycemia, A1c still 7 after 1 year (and he's still drinking soda/juice)

Definitions

Type 1 diabetes: due to β-cell destruction, usually leading to absolute insulin deficiency

Type 2 diabetes: due to a progressive loss of b-cell insulin secretion frequently on the background of insulin resistance

Gestational diabetes mellitus (GDM): diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes prior to gestation)

Specific types of diabetes due to other causes (neonatal, monogenic diabetes, cystic-fibrosis related DM, drug/chemical induced)

American Diabetes Association, *Diabetes Care* 2018; 40(Suppl. 1): S11-S24

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Definitions

Type 1 diabetes: due to β-cell destruction, usually leading to absolute insulin deficiency

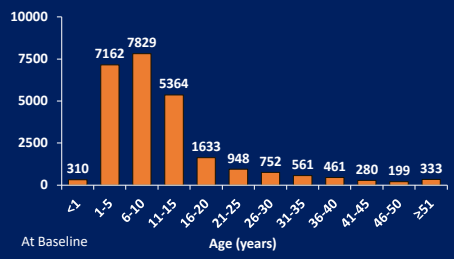
- ❖ Not age based
- ❖ Not insulin-use based

T1D Exchange Clinic Registry

A Snapshot of Type 1 Diabetes in the United States

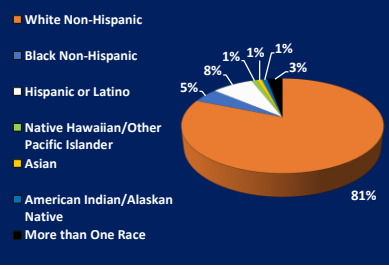
A Helmsley Charitable Trust Initiative

Age at Diagnosis of T1D

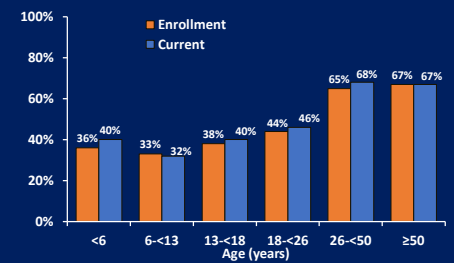


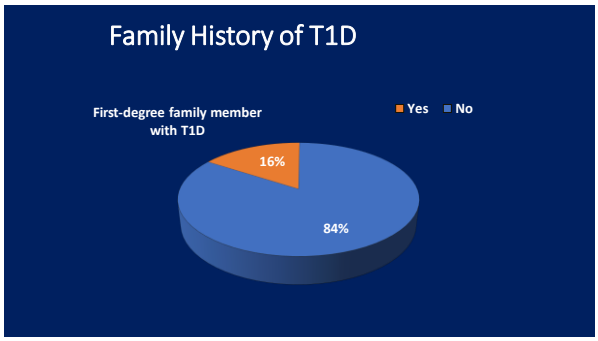
At Baseline

Race/Ethnicity



Many with T1D Are Overweight /Obese





Initial diagnosis

- The hope is to prevent diagnosis BEFORE diabetic ketoacidosis, BUT…
  - DKA at diagnosis: 15% to 70% of new-onset T1DM (US: ~25%)
  - Higher rates: <5 years of age, less access to care
- DKA in T2DM: Overall 5% of new onset T2DM, up to 25%
  - More likely in obese African Americans
- What do we look for? What do we draw? Why?

Initial diagnosis

- HISTORY: Polyuria/nocturia/enuresis, polydipsia, polyphagia, weight loss, emesis or abdominal pain, preceding or concurrent signs of illness, headache
  - Family history: autoimmunity! (T1DM, Hashimoto's thyroiditis, celiac disease, alopecia)
- EXAM: weight, BP, temp, heart rate, "Kussmaul" respirations, "fruity" breath, mental status, evidence of infection: systemic, urinary, vaginal, dermal, oral
- LABS: Bedside blood glucose by meter, urine dipstick for ketones and glucose, serum electrolytes, ABG/VBG, HgbA1c
- DIAGNOSTIC: anti-GAD65, anti-ZnT8, anti-insulin, anti-islet cell antibodies; celiac screen; TSH, fT4

T1D Disease Progression

The Path to Type 1 Diabetes

Or…

What are all those antibodies???

25

T1D Disease Progression

Scientific Statement from JDRF, Endocrine Society, ADA

Staging Presymptomatic Type 1 Diabetes

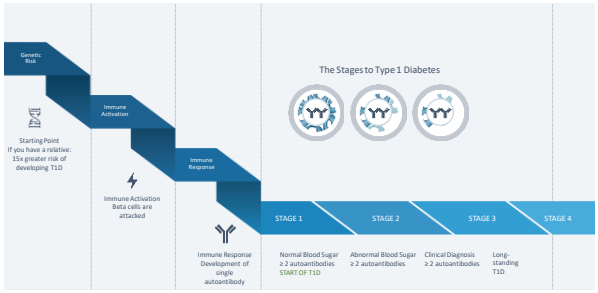
In the January 2016 issue of Diabetes Care, the JDRF, American Diabetes Association (ADA), and Endocrine Society recommend adoption of a new type 1 diabetes staging classification.

The recommendation is largely based on an immense amount of data collected from TrialNet research spanning two decades and involving more than **150,000 relatives of people with type one diabetes**.

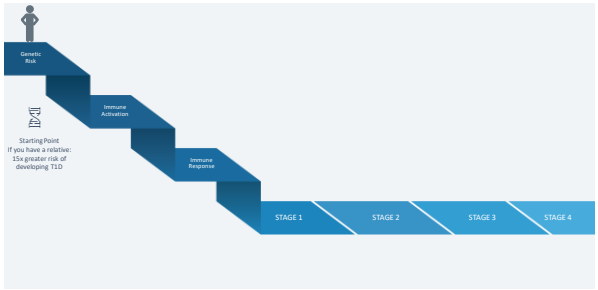
Type one diabetes can now be most accurately understood as a disease that progresses in **three distinct stages**.

Furthermore, the steps to get to T1D are now better defined than ever

T1D Disease Progression



T1D Disease Progression

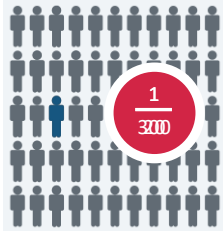


T1D Disease Progression

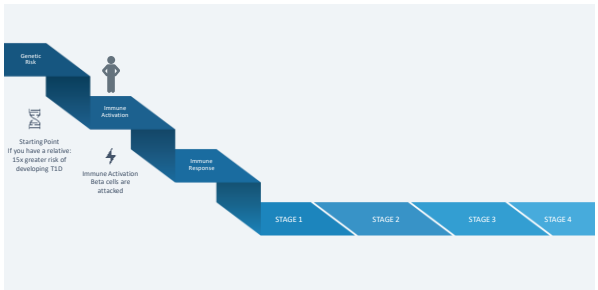
Starting Point
Genetic Risk

The path to T1D starts here

- Everyone who is diagnosed with T1D has the gene(s) associated with T1D
  - General population risk is 1 in 300
- Family members are at 15x greater risk to develop T1D
  - Relative risk is 1 in 20



T1D Disease Progression



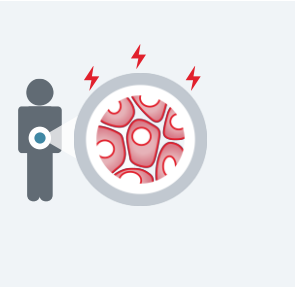
T1D Disease Progression

Immune system is activated

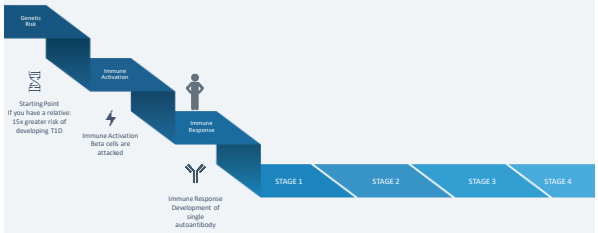
Immune Activation

Immune system attacks beta cells

- Likely a common event
- Research taking place to identify the possible "event" or combination of "events"



T1D Disease Progression



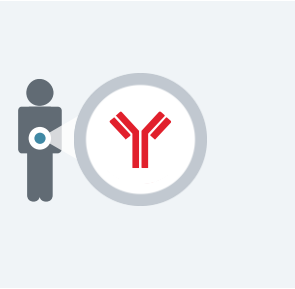
T1D Disease Progression

Development of single autoantibody

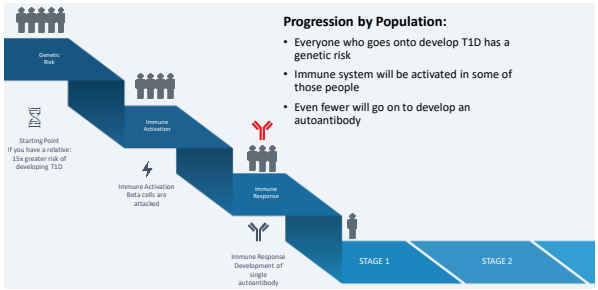
Immune Response

1 autoantibody

- Immune system responds to beta cells being attacked
- Results in the development of autoantibodies
- Autoantibodies are a "visible" signal that the immune system is activated



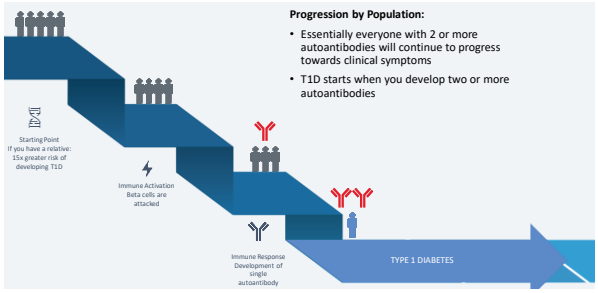
T1D Disease Progression



Progression by Population:

- Everyone who goes onto develop T1D has a genetic risk
- Immune system will be activated in some of those people
- Even fewer will go on to develop an autoantibody

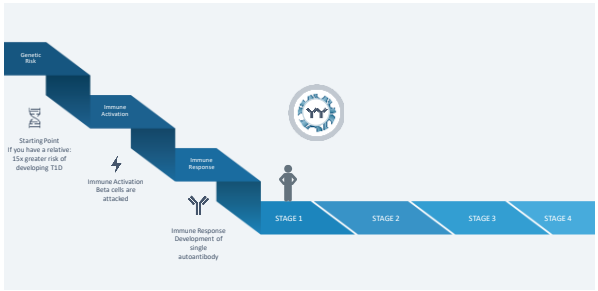
T1D Disease Progression



Progression by Population:

- Essentially everyone with 2 or more autoantibodies will continue to progress towards clinical symptoms
- T1D starts when you develop two or more autoantibodies

T1D Disease Progression

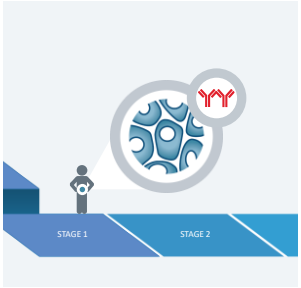


T1D Disease Progression

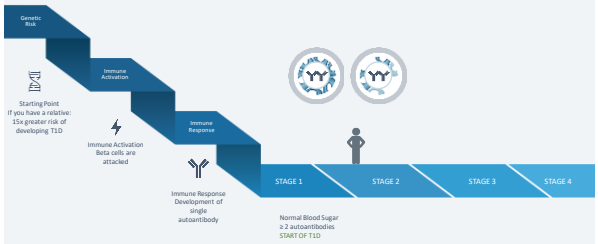
Stage 1 T1D
Normal Blood Sugar

≥ 2 autoantibodies

- START of T1D
- Two or more autoantibodies
- Normal blood sugar
- Lots of beta cells that are able to maintain blood sugar
- No symptoms



T1D Disease Progression

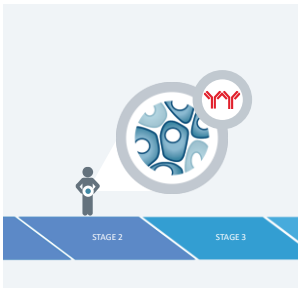


T1D Disease Progression

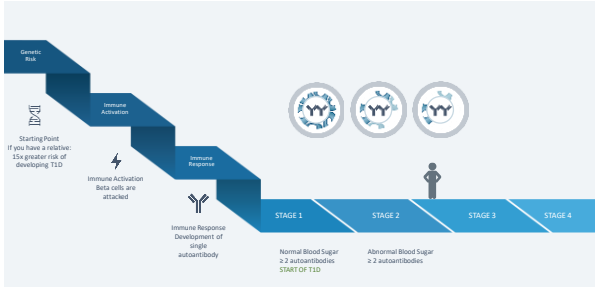
Stage 2 T1D
Abnormal Blood Sugar

≥ 2 autoantibodies

- Two or more autoantibodies
- Fewer beta cells, but not enough to keep blood sugar normal
- No symptoms



T1D Disease Progression

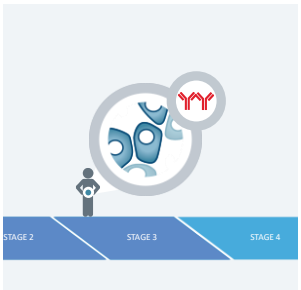


T1D Disease Progression

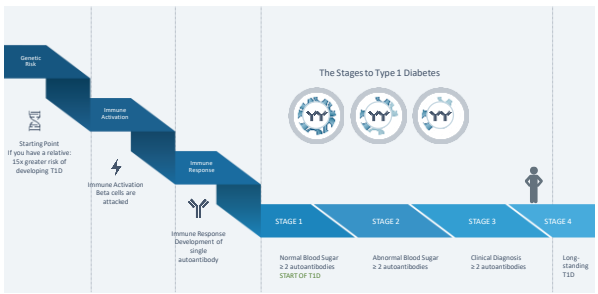
Stage 3 T1D
Clinical Diagnosis

≥ 2 autoantibodies

- Marked by clinical diagnosis (Dx)
- Formerly known as "start of T1D"
- Even fewer beta cells
- Symptoms of high blood sugar



T1D Disease Progression

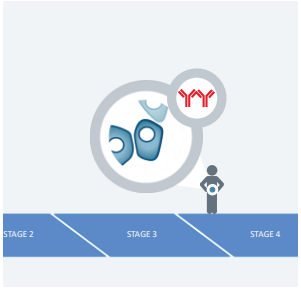


T1D Disease Progression

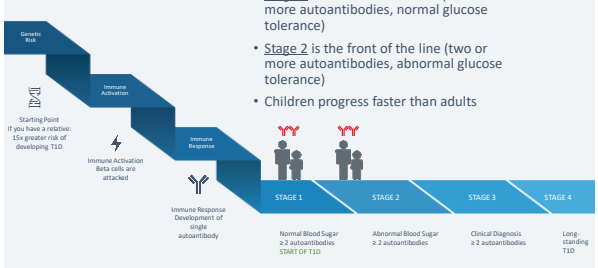
Stage 4 T1D
Long-Standing T1D

Post diagnosis

- Continued loss of beta cells over time
- Research outside of TrialNet is working to replace or replenish beta cells



T1D Disease Progression



- Stage 1 is the back of the line (two or more autoantibodies, normal glucose tolerance)
- Stage 2 is the front of the line (two or more autoantibodies, abnormal glucose tolerance)
- Children progress faster than adults

T1D Disease Progression

SUMMARY POINTS

1. Type 1 diabetes **starts** with two or more autoantibodies
2. Three defined stages:
   - **Stage 1**: Presence of 2 or more autoantibodies with normal blood sugar
   - **Stage 2**: Presence of 2 or more autoantibodies with abnormal blood sugar
     - NEW TREATMENT!
   - **Stage 3**: Clinical diagnosis (Dx) of type 1 diabetes (symptomatic)
     - Still most kids and adults…but not all!
3. Age matters!
   1. Time from 2 or more autoantibodies to Dx is faster the younger you are
   2. β-cell decline is also faster the younger you are and continues through stage 4

Why this matters…

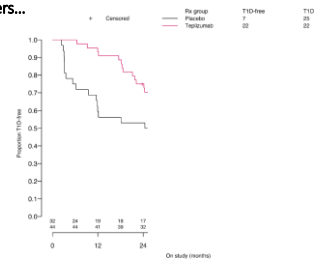
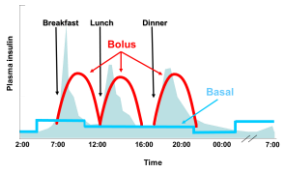


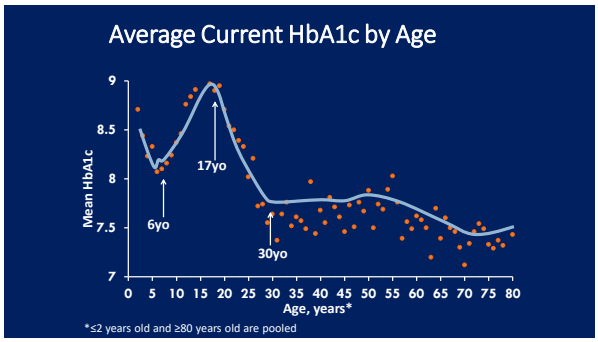
Fig. 1. Teplizumab treatment is associated with a sustained effect on T1D progression over 923 days of follow-up. Updated Kaplan-Meier curve based on 923 days of follow-up (range, 74 to 1119 days). The hazard ratio for development of T1D in teplizumab-treated participants versus placebo was 0.457; $P = 0.01$. The median time to diabetes was 27.1 and 59.6 months in the placebo and teplizumab treatment groups, respectively. At the conclusion of this period, 7 (22%) and 22 (50%) individuals, respectively, were not diagnosed with T1D.

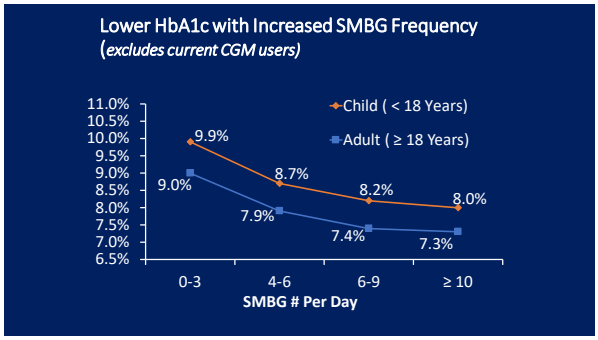
Sims et al *Sci Transl Med* 2021

Eventual treatment: Insulin. Period.

- Multiple daily injections (MDI, "basal-bolus") or insulin pump (continuous subcutaneous insulin infusion, CSII), with a goal HgbA1c of 7.5%







Technology will save us!

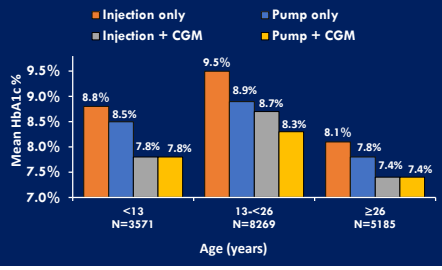
- Insulin pumps!!!
- Continuous glucose monitors!!!
- More rapidly-acting insulins!!!

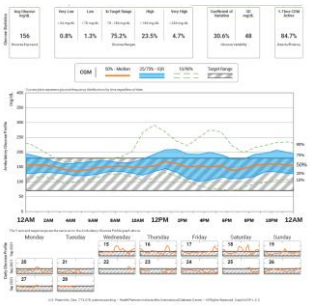
Personal CGM: #1 in our hearts

- ❑ 10-day wear
- ❑ Remote monitoring

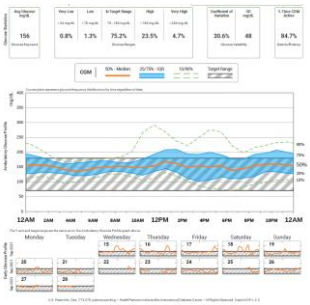
- ❑ 14-day wear
- ❑ Lower cost
- ❑ *No alarms without sensor scan*
- ❑ Remote monitoring
  - ❖ Dependent on user

Lower HbA1c in CGM Users Regardless of Insulin Delivery Method





Key metric: TIME IN RANGE



A quick aside…

16 yo M
Weight: 103 kg

Long Acting Insulin Dose: 16 units
(predicted weight based: 50 units)

Short Acting Insulin:
NO CHO COVERAGE
(predicted 1 unit : 5g)
Correction Factor: 1:45
(predicted 1:20)

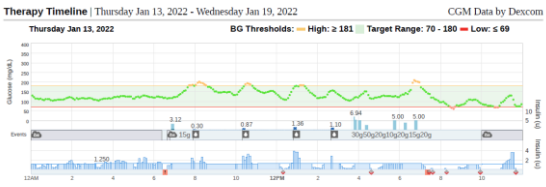
Artificial Pancreas Systems (APS) Available

- **Predictive Low Suspend OR hybrid closed loop**
  - **Using Dexcom G6 sensors**

- **Hybrid Closed Loop *or* manual mode with suspend on low or suspend before low**

- **Other tubeless pump systems (HCL) have recently been approved**

Hybrid Closed Loop



Type 1 diabetes summary

- Type 1 diabetes is an autoimmune disease leading to β-cell destruction and insulin deficiency
- Autoimmunity and exposure are both required
- Only treatment: insulin
- Diagnosis BEFORE DKA is best
- Kids are not little adults; risks of cerebral edema are real

But what about Type 2 diabetes?

- Type 2 diabetes: due to a progressive insulin secretory defect on the background of insulin resistance
  - Still a state of RELATIVE INSULIN DEFICIENCY (β-cell failure)
  - Can present in a similar fashion to T1DM

Diagnosis of T2DM in pediatrics

- Prior debate as to usefulness of the HgbA1c in screening; ADA recommends!
  - OGTT is an option! (more on that in a second)
- If symptomatic, screen!
  - 1 positive value plus symptoms = diabetes
  - A1c progression may be helpful in initial management
- A1c >6.5%, FBG >126 mg/dL, or 2 hour OGTT >200 (all x2, or x1 with symptoms) = diabetes mellitus

American Diabetes Association, Diabetes Care 2017 Jan; 40(Supplement 1)

Diagnosis of T2DM in pediatrics

- Whom to screen (without symptoms)?
  - Overweight (BMI > 85th %ile, weight for height >85%ile, or weight > 120% of ideal), AND
  - Any 1 of the following:
    - FHx in 1st or 2nd degree relative
    - Ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
    - Signs of/conditions associated with insulin resistance (acanthosis, dyslipidemia, hypertension, PCOS, SGA)
    - Maternal history of DM or GDM during gestation
- Start at age 10 or onset of puberty, done every 3 years (or if new/worsening symptoms)

Treatment Options for type 2 Diabetes in Adolescents and Youth

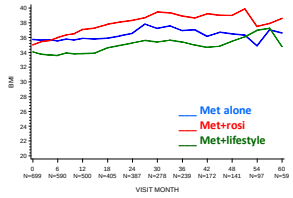
Funded by
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

TODAY Study Design

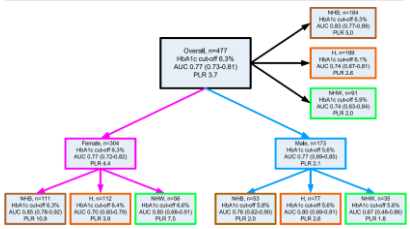
- 2-6 month pre-randomization run-in period
  - Provide standard diabetes education
  - Wean off all other diabetes medications
  - Titrate metformin as tolerated
    - Maximum 1000 mg bid
    - Minimum 500 mg bid
  - Assess ability to adhere to protocol
  - HbA1c < 8.0%
- Eligible and consented participants randomized to one of 3 treatment arms
- 4 year rolling enrollment period
- 2-6 years follow-up with medical visits every 2 months in year 1 and quarterly thereafter

Kids are different than adults…

Mean BMI Over Time (all values prior to failure)

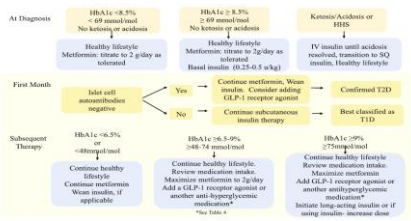


Treatment of T2DM in pediatrics



Zeitler, P, et. al, Diabetes Care 2015; 38:2285-2292

Thankfully, new meds!



Pediatr Diabetes 2022;1-31.

Treatment of T2DM in pediatrics

- Treatment options for T2DM in pediatrics
  - Metformin
  - GLP1-agonists! *(for diabetes…coverage for weight loss is VERY poor)*
  - SGLT2i!
  - Insulin
- Current indications for metformin
  - T2DM (only FDA approved)
  - Impaired fasting glucose / Impaired glucose tolerance
    - A1c has poor PPV for "prediabetes" in obese adolescents (Lee JM, et al, (2011) *J Pediatr* 158(6))
- Start with lifestyle and metformin unless A1c >10; then likely also start alternatives! …*we hope to delay insulin!*

Kids do worse than adults…

	Baseline	End of Study
Elevated LDL	4.5	10.7
Elevated Triglycerides	21	23.3
Elevated hsCRP	41.2	46.3
Hypertension	11.6	33.8
Microalbuminuria	6.3	16.6
Retinopathy		13.7
Depression	14.8	
Binge Eating	6.2	

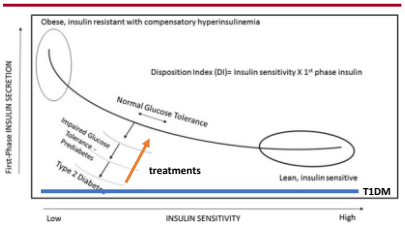
PREVENTION IS KEY!!!

Adapted from: Tryggestad, JB, et al. J Diabetes Complications. 2015 Mar; 29(2): 307–312.

Type 2 diabetes summary

- Type 2 diabetes is a result of β-cell failure
- Children treatment options: metformin, GLP-1a's, SGLT2s, or insulin; send to your local pediatric endocrinologist!
- Prevention is key
- Initial medication (metformin) may not help obesity, but the new ones might!
- Kids are not little adults; progression is common and more rapid, both of disease and complications…so monitor for those complications and treat!!!

Types of diabetes mellitus



Adapted from Current Diabetes Reports 18(8):51 (2018)

Conclusions and Clinical Pearls

- Type 1 diabetes mellitus: autoimmune destruction of β-cells
  - Tech is here to stay!
  - Future therapies will be autoimmune based
- Type 2 diabetes mellitus: β-cell failure
  - Prevention, prevention, prevention
  - Complication? TREAT TREAT TREAT

- If the patient is young (e.g. pre-pubertal), err on the side of Type 1 diabetes
- Call your friendly neighborhood pediatric endocrinologist first!

Questions?