Where we’re at and where we’re headed

Type 1 Diabetes: Barriers, Resources, and Research Updates

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Disclosure Statement

- I do not have any conflict of interest, nor will I be discussing any off-label product use.

- This class has no commercial support or sponsorship, nor is it co-sponsored.
Who are we?
What is Type 1 Diabetes?
Objectives

- Identify **BARRIERS** to management and the **EFFECT** on individuals and communities
- Recognize the impact of diabetes **RESEARCH** on the community
- List current and anticipated **UPDATES**: technology and immunology
- Appreciate your **ROLE**: tools to discuss research and technology

Photo by Jeremy Bishop

SURF THROUGH DIABETES AS A TEAM
American Diabetes Association Glycemic Targets

• HbA1c target should be INDIVIDUALIZED and target should be REASSESSED

• 4 Critical times to re-evaluate:
  – Diagnosis
  – Annually
  – When complicating factors arise
  – Transitions in care

• Time In Range (TIR): 70%

• HbA1c at least 2x/year
American Diabetes Association Glycemic Targets

Appropriate for many children (this is suggested for adults)

6.5%  7.0%  7.5%  8.0%  8.5%  9.0%  9.5%
American Diabetes Association Glycemic Targets

Appropriate for some children

6.5%  7.0%  7.5%  8.0%  8.5%  9.0%  9.5%
American Diabetes Association Glycemic Targets

UNABLE TO ARTICULATE SYMPTOMS, LACK ACCESS TO INSULIN OR TECHNOLOGY, UNABLE TO CHECK BG, BLOOD DISORDERS

6.5% 7.0% 7.5% 8.0% 8.5% 9.0% 9.5%
History of severe hypoglycemia, limited life expectancy, extensive co morbidities

6.5%  7.0%  7.5%  8.0%  8.5%  9.0%  9.5%
Where we are:

**Average at 5 years old**
- 6.5%
- 7.0%
- 7.5%
- 8.1%

**Average 15-18 years old**
- 9.0%
- 9.3%

Diabetes Care 2020 Jan; 43
Rodbard D, 2019; 21
Where we are:

CGM use between 2011-2018

Mean HbA1c in USA by age

Foster et al. Diab Tech Ther 2019
Where we are:

- Average at 5 years old: 8.1% vs. 9.3%
- Average at 15-18 years old
A goal is not always meant to be reached, it often serves simply as something to aim at.

- Bruce Lee
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**SURF THROUGH DIABETES AS A TEAM**
The “Hang 5” Barriers

SYSTEMIC

Photo by Espen Bierud

Photo by Jeremy Bishop

Photo by Max Rovensky
The “Hang 5” Barriers

1. Developmental
2. Psychological
3. Family/Cultural
4. Socioeconomic
5. Transition
Five Barriers to Glycemic Targets

1. Developmental

   Physical

   Neurological
Five Barriers to Glycemic Targets

2. Psychological

Depression
Psychopathy
Distress
Sleep
“Lay Expertise”
Three barriers to glycemic targets:

3. Family

   Community

   Marital Status/ Family Structure

   Parent-child conflict
Five Barriers to Glycemic Targets

4. Socioeconomic

Race

Family income

Medicaid

Snyder LL, Diabetic Medicine, 2019
Hassan KL, J Pediatr, 2006
Patel MR, NH Interview Survey, 2016
Five Barriers to Glycemic Targets

4. Socioeconomic
   - Race
   - Family income
   - Medicaid

**Mean HbA1c according to race/ethnicity and insulin regimen**

- **Pump use:**
  - 61% Non Hispanic White
  - 26% Non Hispanic Black
  - 39% Hispanic

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Snyder LL, Diabetic Medicine, 2019
Hassan KL, J Pediatr, 2006
Patel MR, NH Interview Survey, 2016
Willi, S. M. et al. (2015)
Five Barriers to Glycemic Targets

4. Socioeconomic
   Race
   Family income
   Medicaid

Utilization of Pump (CSII) and CGM in relation to family income by race/ethnicity

Rodbard D, 2019; 21
Five Barriers to Glycemic Targets

5. Transition

Complex time-Exploration

Pediatric to Adult Care
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SURF THROUGH DIABETES AS A TEAM
When targets aren’t met:

**INDIVIDUAL**
- Physical complications
- Developmental impact
- Diabetes burnout
- Financial burden/lost income
- Family conflict
- Provider conflict

**COMMUNITY**
- Cost
- Felt as a burden for friends, supporters, and schools
- Care Team Burnout

Giannopoulou EZ, Pediatric Diabetes 2019
Now the fun stuff: OVERCOMING the barriers

- Improvements within pediatric Endocrinology practice
- Mental health focus
- Social Media and community
- Healthcare reform
- Transition clinic
- TECHNOLOGY
- CLINICAL RESEARCH

Photo by Michael Longmire
Now the fun stuff: OVERCOMING the barriers

- Improvements within pediatric Endocrinology practice
- Mental health focus
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- TECHNOLOGY
- CLINICAL RESEARCH

Photo by Michael Longmire
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SURF THROUGH DIABETES AS A TEAM
For now….TECHNOLOGY!
Blood Sugar Monitoring

Glucometers: Not much has changed…

- Bluetooth

Continuous Glucose Monitors (CGM)

- Standard of Care
- SENSOR glucose vs BLOOD glucose
Blood Sugar Monitoring

Continuous Glucose Monitors (CGM)

• Standard of Care
• SENSOR glucose vs BLOOD glucose
• Awesome tools, not perfect
• Constant information
• Endpoints for RESEARCH!
Insulin Delivery

Smart Pens

– Bluetooth enabled insulin pen
– Smartphone capable
– Age 12 and older
Insulin Delivery

Automated Insulin Delivery

– vs “artificial pancreas”

– FDA approved systems

– DIY “Looping”
Insulin Delivery
Automated Insulin Delivery
Insulin Delivery

Automated Insulin Delivery
Automated Insulin Delivery (AID)

Considerations

• Active engagement
• Highs and Lows still happen
• Trusting the algorithm
• Treatment may change
• Have a backup plan
• Diabetes is still WORK
The Tech Pipeline

- Improved CGMs
- Tighter targets
- Improved software
- More, improved automation
- More data
- More collaboration
- Smart Phone Integration

Contact companies with questions 😊
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**SURF THROUGH DIABETES AS A TEAM**
Clinical Research: A community RESOURCE

Frankenstein, 1931
- Patients have QUESTIONS about their diagnosis

- Promotes autonomy and gives some control back to the patient

- Encouraging to know that work is being done to understand, treat, and prevent T1D

- Normalizing the term

- Treatment vs Research

- Public access
Most Therapies Interrupt Immune Cell Signaling
Immunotherapy in Juvenile Rheumatoid Arthritis
Juvenile Rheumatoid Arthritis
Type 1 Diabetes
Type 1 Diabetes

Where we were

THE Breakthrough

Realizing tomorrow’s reality
Your child has type 1 diabetes
What did we do wrong?
INSULIN
Islet
Pancreas
GLUCOSE
Beta-cell
INSULIN
T cells protect us against infections and foreign organisms
In T1D, T cells mistakenly attack beta-cells as if they are foreign.
What did we do wrong?

It is an autoimmune disease. You did nothing wrong.
Can we **FIX** it and eventually stop having to inject insulin?
At birth

Healthy Pancreas
Many years before diagnosis
A period of time before diagnosis
At diagnosis

<20% functioning islets
The disease started years ago. The damage is largely done. Can we FIX it and eventually stop the insulin?
Could we have detected disease earlier?
The only window we currently have into the attack on the pancreas is through a blood test.
Too few circulating islet-attacking T cells to detect easily on a blood test.
B cells help direct T cells to where they are needed
In T1D, B cells send wrong messages and direct T cells to the islets.
Evidence of these wrong messages can be found in the bloodstream.
95% of children who develop T1D before puberty have autoantibodies by age 5.

There are 5 autoantibodies associated with T1D that we look for:

- Insulin
- GAD
- IA2
- ICA
- ZnT8
Autoantibodies can reliably be detected on a blood test.
More types of islet autoantibodies = greater likelihood of developing clinical diabetes.
Nearly all relatives of people with T1D with $\geq 2$ antibodies will develop clinical diabetes.
### The Impact of AGE on Disease Progression & Beta Cell Decline

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>STAGE 1 (Start of T1D)</th>
<th>STAGE 2</th>
<th>STAGE 3 (Clinical Dx)</th>
<th>STAGE 4 Long-standing T1D</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>≥ 2 autoantibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10-14</td>
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<td>15-19</td>
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<tr>
<td>≥ 20</td>
<td></td>
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</tbody>
</table>
The Stages to Type 1 Diabetes

**STAGE 1**
- Immune Activation: Beta cells are attacked
- Normal Blood Sugar
- Development of single autoantibody

**STAGE 2**
- Immune Activation
- Abnormal Blood Sugar
- ≥ 2 autoantibodies

**STAGE 3**
- Clinical Diagnosis
- ≥ 2 autoantibodies

**STAGE 4**
- Genetic Risk
- Starting Point
- If you have a relative: 15x greater risk of developing T1D

Insel RA et al. Diabetes Care 2015
Your son is a 14 year old boy with type 1 diabetes.
Are your other children also at risk for T1D?

What is a person’s risk of T1D if they have a family member with T1D?

A. 1 in 20
B. 1 in 1000
C. 1 in 300
D. 1 in 100
T1D Risk in Family Members

Starting Point: Genetic Risk

The path to T1D starts here

– General population risk is 1 in 300

– If you have a family member with T1D, your risk is 1 in 20

*Family members are at 15x greater risk to develop T1D*
How do we detect *WHICH* family members will progress to type 1 diabetes?

Test them for diabetes autoantibodies!

ADA Standards of Medical Care in Diabetes 2019:

“…one should consider referring relatives of those with type 1 diabetes for antibody testing for risk assessment…”
Autoantibody Screening through TrialNet

P2P Pathway to Prevention

- No cost
- 1st and 2nd degree relatives
- Screens for autoantibodies
- Based on results
  - Look to enroll in clinical trial to preserve beta cell function
  - Or monitor for disease progression
What do we do when we find that someone is positive for multiple diabetes autoantibodies?

- We monitor them closely for disease progression
  - HbA1c testing Q6mo
  - Glucose tolerance testing Q6mo
  - Observation for symptoms

- We may offer treatment with interventional therapies
  - Attempt to preserve remaining beta cell function
  - Stop or slow the autoimmune disease process
Benefits of Monitoring Those at Increased Risk for T1D

Lower HbA1c at diagnosis

![Graph showing the lower HbA1c at diagnosis in monitoring programs vs. usual care.](image)
Benefits of Monitoring Those at Increased Risk for T1D

Less DKA at diagnosis

Decreased rates of hospitalization

![Graph showing DKA prevalence at diagnosis in monitoring programs vs. usual care. The graph indicates a significant reduction in DKA prevalence from 28.5% to 6.0% with monitoring programs.](image)
Could we have detected disease earlier?

Yes, but there was nothing you could have done to change the course of the disease.
Successful attempts at delaying beta-cell loss in T1D
An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

Kevan C. Herold, M.D., Brian N. Bundy, Ph.D., S. Alice Long, Ph.D., Jeffrey A. Bluestone, Ph.D., Linda A. DiMeglio, M.D., Matthew J. Dufort, Ph.D., Stephen E. Gitelman, M.D., Peter A. Gottlieb, M.D., Jeffrey P. Krischer, Ph.D., Peter S. Linsley, Ph.D., Jennifer B. Marks, M.D., Wayne Moore, M.D., Ph.D., Antoinette Moran, M.D., Henry Rodriguez, M.D., William E. Russell, M.D., Desmond Schatz, M.D., Jay S. Skyler, M.D., Eva Tsalikian, M.D., Diane K. Wherrett, M.D., Anette-Gabriele Ziegler, M.D., and Carla J. Greenbaum, M.D., for the Type 1 Diabetes TrialNet Study Group.*
Teplizumab (anti-CD3) inactivates/depletes T cells
• 76 participants
• Relatives of people with T1D
• 2 or more antibodies AND abnormal glucose tolerance
Majority (nearly $\frac{3}{4}$) were <18 years old
Baseline

Placebo

Randomized Placebo-controlled Blinded Study

Teplizumab
Time to Type 1 Diabetes

Proportion free of T1D

Months from start of study

Rx Group
Placebo
Teplizumab
T1D-Free
9 25
T1D
23 19
Censored

32 44 23 44 18 40 16 36 15 27 11 21 9 15 8 10 4 9

24
Time to Type 1 Diabetes

Proportion free of T1D

Months from start of study

Rx Group
Placebo
Teplizumab
Censored

0 12 24 36 48 60

Teplizumab
Placebo
BREAKTHROUGH

FIRST to DELAY PROGRESSION by two years!

- SAFE and well tolerated
- SCREENING allows for intervention!
<table>
<thead>
<tr>
<th>Risk Screening</th>
<th>Stage 1</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P2P Pathway to Prevention</strong></td>
<td>TN22 Hydroxychloroquine (HCQ)</td>
<td>TN18 Abatacept</td>
<td>TN25 Rituximab followed by Abatacept</td>
<td>TN28 ATG in At-risk</td>
<td>TN10 Teplizumab (Anti-CD3) Results</td>
</tr>
<tr>
<td><strong>Stage 1</strong></td>
<td><strong>Stage 2 Coming soon!</strong></td>
<td><strong>Stage 2 Coming soon!</strong></td>
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</table>

**This study screens relatives of people with T1D to study risk and learn about how the disease occurs.**

- Screens for autoantibodies
- 1st and 2nd degree relatives
- First step to identify eligibility for clinical trial participation

**Can HCQ prevent or slow progression from Stage 1 to Stage 2?**
- Approved for use in treating Lupus and Rheumatoid arthritis

**Can abatacept prevent or slow progression from Stage 1 to Stage 2 or 3?**
- Preserved beta cell function in new onset T1D
- Approved and efficacious for treatment of RA/JIA

**Can Rituximab followed by Abatacept alter disease before dx?**
- First test of sequential therapy
- Both Rituximab and Abatacept have been show to preserve beta cell function in newly diagnosed T1D

**Can ATG prevent or slow progression from Stage 2 to stage 3?**
- Preserved beta cell function in new onset T1D

**This study tests whether teplizumab helps stop or slow down beta-cell decline in people who are at high risk of developing T1D.**
- Results showed for the FIRST TIME EVER, teplizumab delayed the diagnosis of T1D

**This study tests whether ATG used alone or together with GCSF will help people continue to produce their own insulin.**
- Results showed that low dose ATG preserved beta cell function and improved insulin production
Where Are We Headed?

IMMUNOTHERAPY in New Onset and Prevention: preserving beta cell function

Teplizumab

Abatacept

AG019

Rituximab
But, we still have time to preserve the beta-cells. Here is what we’re going to do…
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SURF THROUGH DIABETES AS A TEAM
Finally…YOU!

- Continue to advocate!
- Keep learning
- Say it. “Research”.
  REFER! 1-800-888-4187
- Step back
Sponsors and Supporters

Sponsors

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NIH
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JDRF
American Diabetes Association
The Leona M. and Harry B. Helmsley Charitable Trust
Thank you - participants, researchers & all of YOU!

Refer relatives for screening at: 1-800-888-4187   trialnet.org

Contact BRI: diabetes@benaroyaresearch.org
Thank you Diabetes Clinical Research Program

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