Advances in Prevention of T1D Complications

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Conflicts of Interest

- Adam Wolfe, DO
  - No financial disclosures

- Jose Jimenez-Vega, MD
  - Honoraria (consultant): Dexcom
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  - Educational activities: Medtronic, Omnipod
Objectives

- Understand the natural progression of T1D on the body
- Consider the historical data on complications of T1D
- Understand the limitations of HbA1C measurement and new targets
- What can we do today to prevent bad things from happening?
- Have a better understanding of the progress made in the last 30 years
- What does the future hold for prevention of complications?
Current Thinking: YOUR RISK of complications is often thought of reactively.

We need to change the dialogue, focusing on early and aggressive prevention of complications! Let’s understand a little more about complications themselves first!!

- Pre-insulin era – 50% of patients died within the first 20 months of diagnosis
- 1922 – insulin discovered, patients lived longer! 20-year reduction in life expectancy
- 20th century – survival gap decreased to < 4 years and shrinking quickly!! Why...?
What we know (fear)...

- Management should not be motivated by fear...
- Proactive approach to prevention!
- Look how far we’ve come!!
Microvascular vs Macrovascular

Major Complications of Diabetes

**Microvascular**

- **Eye**
  High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma.

- **Kidney**
  High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

- **Neuropathy**
  Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.

**Macrovascular**

- **Brain**
  Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

- **Heart**
  High blood pressure and insulin resistance increase risk of coronary heart disease.

- **Extremities**
  Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.
We are moving in the right direction!

- Drops in heart attack (-67.8%), stroke (-52.7%), amputation (-51.4%), kidney failure (-28.3%) are dramatic!!!
It starts with thinking differently!
What does the data tell us?

- DCCT – Diabetes Control and Complications Trial (DCCT) : conducted from 1983 to 1993
  - Conducted 3 decades ago – patients aged 13-39 studied over time – there have been a number of advances in technology since then...
  - Still showed that early aggressive treatment prevents progression of eye, kidney, and nerve damage caused by diabetes

  - Followed patients through 2012 (total of 27 years follow-up of T1D patients)
  - Persistent effects of earlier, more intensive glucose lowering population!! Both women and men. “Metabolic Memory”
  - Higher A1C levels and albuminuria were associated with all-cause mortality increase!
  - Hypoglycemia increased risk of mortality in intensively treated group!

JAMA 2003. 290;2159-67
JAMA 2015. 313;45-53
Relationship of HbA1c to Risk of Microvascular Complications

Diabetes Control and Complications Trial (DCCT)

So what’s new in testing?

A1C is so last week!
Hemoglobin A1c (HbA1c)

- > 30 years:
  - clinical and research benchmark for assessing control of diabetes

- But.... Should we consider other tools to assess control?
Glucose naturally binds to hemoglobin

This binding creates glycated hemoglobin (HbA1c)

- A red blood cell lives for approx 120 days
- Hemoglobin is contained in the red blood cell
- Glucose (sugar) enters in the bloodstream and the red blood cell
Average Hba1c By Age

*≤2 years old and ≥80 years old are pooled
Association between Frequency of SMBG per Day and HbA1c

- 1-<13 year old
- 13-<26 year old
- 26-<50 years old
- ≥50 years old

Mean HbA1c

SMBG per Day

- 0-2
- 3-4
- 5-6
- 7-8
- 9-10
- 11-12
- ≥13

JDRF
TypeOneNationSummit
Improving Lives. Curing Type 1 Diabetes.
Role of insulin therapy and glycemic control

Figure 1—Declining retinopathy in parallel with greater use of MDI/CSII and improving glycemic control in 1,604 adolescents with type 1 diabetes.
Average Glucose vs HbA1c

Limitations of HbA1c as a Biomarker

- Issues with the hemoglobin molecule
  - Sickle cell disease, thalassemia, anemia

- Liver or kidney disease, iron deficiency anemia, menopause, female sex

- Heart murmur

- Certain drugs (alcohol, opioids, vitamin C, E, aspirin, dapsone, EPO)

- Does not reflect variations in glucose
  - Fails to capture glucose variability GV
  - Risks associated with the extremes of hypo- and hyperglycemia

- Results can be over-interpreted

- Patients have different glycation rates

What Happens To A1C When Rx’ing Fe-Deficiency Anemia*

A1C%

12
10
8
6
4
2
0

10.6
10.3
8.3
7.7
6.4
5.9

T1D w/anemia
T1D w/o anemia
C w/anemia
C w/o anemia

*no difference in glucose control

Before Fe

Pediatrics International (1999) 41, 357-362
Racial differences of HbA1c

- Mean glucose concentration were significantly lower in AA persons than in white persons.

- Values in AA persons being 0.4 percentage points higher than those in white persons for a given mean glucose concentration.

Glucose is our enemy, not the HbA1c!
Changing dialogue require changes in terminology and targets.

That moment when he finds out his HbA1c is lowered.

Full of win!
Assess glucose fluctuations

Glucose Control

Glucose variability

Risk for hypoglycemia

Speed
Magnitude

Diabetes Care 2016 Apr; 39(4): 502-510
Glycemic variability (GV)

- Risks of hypo and hyperglycemia:
  - Contributed by amplitude and the timing of blood glucose
- Increased GV consistently associated with mortality in the intensive care unit
- Consistent predictor of hypoglycemia
Not all HbA1c’s are created equal...

**A**

**High GV**

Subject 1: HbA1c = 8.0%

**B**

**Low GV**

Subject 2: HbA1c = 8.0%

Diabetes Care 2016 Apr; 39(4): 502-510
And to make it more complicated...

### 42 Factors That Affect BG

**Food**
- 1. Carbohydrate quantity
- 2. Carbohydrate type
- 3. Fat
- 4. Protein
- 5. Caffeine
- 6. Alcohol
- 7. Meal timing
- 8. Dehydration
- 9. Personal microbiome

**Medication**
- 10. Medication dose
- 11. Medication timing
- 12. Medication interactions
- 13. Steroid administration
- 14. Niacin (Vitamin B3)

**Activity**
- 15. Light exercise
- 16. High-intensity and moderate exercise
- 17. Level of fitness/training
- 18. Time of day
- 19. Food and insulin timing

**Biological**
- 20. Insufficient sleep
- 21. Stress and illness
- 22. Recent hypoglycemia
- 23. During-sleep blood sugars
- 24. Dawn phenomenon
- 25. Infusion set issues
- 26. Scar tissue and lipodystrophy
- 27. Intramuscular insulin delivery
- 28. Allergies
- 29. A higher glucose level
- 30. Periods (menstruation)
- 31. Puberty
- 32. Celiac disease
- 33. Smoking

**Environmental**
- 34. Expired insulin
- 35. Inaccurate BG reading
- 36. Outside temperature
- 37. Sunburn
- 38. Attitude

**Behavioral & Decision Making**
- 39. Frequency of glucose checks
- 40. Default options and choices
- 41. Decision-making biases
- 42. Family relationships and social pressures

[https://diatrib.org/42factors](https://diatrib.org/42factors)
Continuous Glucose Monitoring

Real-time use (rtCGM)  Intermittently viewed (iCGM)

Diabetes Care 2017;40:1631–1640
Benefits of rtCGM

- Improves glycemic control and quality of life in both children and adults with type 1 diabetes
- Improving HbA1c
- Shortening time spent in hypoglycemia and hyperglycemia
- Reducing moderate-to-severe hypoglycemia
- Reduced overall diabetes related complications
Time in range (TIR)

- No current guides
- Should be individualized

If you ask us:

- Normal range (70-180 mg/dL):
  - Goal of 70% of the time (80% closed loop)
  - More realistic 40 – 60%
  - (JDRF CGM study, DiaMonD, and REPLACE-BG) 50% = HbA1c 7.7%
- Hypoglycemia: < 3-5% (<1% below 54 mg/dL)
Asking the right questions

Things that you can do today that will affect your future...

WCIDT?
So what can I do today? WCIDT

- Check regularly for infections
  - Skin / soft tissue
  - Urinary tract
  - Sinus infections

- Vaccinations important!!
  - Influenza annually
  - Pneumonia (pneumovax) once before 65 years
  - Pneumonia (prevnar and pneumovax) over 65 years

- When was my last eye examination?
  - Annual eye examinations with an ophthalmologist
  - Immediate referral if there is any concern for bleeding
  - See us immediately if you are noticing any changes (floaters, pain, blurriness, etc.)
When did I have my urine last checked for protein?
- ADA guidelines recommend annual checks for protein
  - If you are +, this can be reversible!
- Also checks for kidney function generally
- Ask my care team if I am going to take any medications over the counter – some may be harmful for the kidneys
- Caution if I am having any radiology testing done

What was my blood pressure at my last office visit?
- Goal is less than 130/80 mm Hg
- Elevated blood pressures is an important risk for both macrovascular and microvascular complications
- Certain medications can be very helpful to protect the body from DM and BP changes
- Low salt diet can help significantly with BP (less than 2000 mg daily sodium)
So what can I do today? WCIDT

- **When is the last time I had my feet checked?**
  - Remove your socks and shoes at every visit!
  - If you are noticing anything feeling different, let us know – even if there isn’t anything visible.
  - Any sore or skin breakdown is critical that we look at ASAP – even small blisters!
  - Changes to nails count too.

- **How’s my cholesterol looking?**
  - ADA recommends statin-based therapy for almost every patient with T1D, regardless of their numbers.
    - Less than 40 years, no statin if T1D is your only risk.
    - 40-75+ years, moderate to high-intensity statin therapy depending on overall risk.
Key Take-Home Points

Adam and Jose
Summary – Think proactive approach!

- Treat the glucose, not the HbA1c
- Use meal time insulin with pumps or multiple daily injections
- Avoid excessive hypoglycemia
- HbA1c fully tested vs outcomes
  - Not to be thrown away
- TIR makes clinical sense, specially if NON concordant with HbA1c
  - Can be a much better quality measure of glucose management than HbA1c
- There is room for both TIR and HbA1c – more research needed on TIR
- Prepare yourself for your visits – know what needs to be done and your expected goals for care
Summary

- Perfection is not required!
  - This is not a pass/fail grade
  - Don’t’ be OCD about TIR!
  - Collaborate with your DM Care Team!!