ADA Type 1 Diabetes Guidelines
Pediatric and Adult Patients with T1D:
Glycemic Targets
and more

AADE
New Orleans, LA
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Lori Laffel MD MPH
Chief, Pediatric, Adolescent & Young Adult Section
Senior Investigator, Genetics and Epidemiology Section
Professor of Pediatrics
Boston, USA

2014 CDC June Report

Estimates of Diabetes and Its Burden in the United States
"
This document is intended to provide up-to-date scientific data and statistics on diabetes and its burdens in the United States. Formerly referred to as the National Diabetes Fact Sheet, this consensus document is written for a scientific audience."

FAST FACTS ON DIABETES
29.1 million people or 9.3% of the U.S. population have diabetes.
Diagnosed 21.9 million people
Undiagnosed 7.2 million people


Prevalence of Type 1 and Type 2 Diabetes Among Children and Adolescents From 2001 to 2009
JAMA. 2014;312(17):1778-1796

- Prevalence estimates of T1D in youth 0-19 and T2D in youth 10-19 in 2001 and 2009 in 5 representative US areas in the SEARCH Study
- T1D prevalence: 1.48/1000 in 2001 (1/676)
1.93/1000 in 2009 (1/518)
- T2D prevalence: 0.34/1000 in 2001 (1/2941)
0.46/1000 in 2009 (1/2174)
- T1D increased 21.1% (95% CI, 15.6-27.0%)*
- T2D increased 30.5% (95% CI, 17.3-45.1%)*

* After adjustment for case ascertainment

2014 CDC June Report

T1D in Adults
- No precise estimates of T1D in adults >20 y/o
- Greatest number of patients with T1D are adults:
  - Increasing numbers of patients diagnosed with T1D at all ages
  - Patients w/ childhood onset T1D survive to adulthood
- Estimated that 50-75% of T1D diagnosed in childhood (25-50% diagnosed in adulthood)
- LADA: latent autoimmune diabetes in adults
  - ~9% of adults with diabetes ages 30-70 have +GAD ab
  - Prolonged period of residual beta cell function (T1DX)
  - Additional peak age of onset of T1D in 6th to 7th decades of life

Residual C-peptide present in 1/3 persons
with T1D of 3+ years duration

Diabetes Care. 2015 Mar;38(3):476-81
**Agenda**

- Glycemic targets – definitions, A1c
- Evidence for glycemic targets: DCCT
- National and Society guidelines
  - Changes in A1c targets: ADA
- Recent shift in A1c outcomes, changing complications rates, and mortality
- More opportunities for improvement

- Cases

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**T1D: Cases - 1**

- **Case 1**: DOB 1976, T1D Dx 1981 @ 5 y/o
  - A1c’s: 9.5-15.2%
  - Complications: PDR, vision loss, CKD, stroke, autonomic neuropathy by age 30
- **Case 2**: DOB 1976, T1D Dx 1989 @ 13 y/o
  - A1c’s: 7.5-9.5% 1st 4 years, then 10.0-15.0%
  - Complications: PDR, neuropathy, gastroparesis, death from DKA age 28
- **Case 3**: DOB 1985, T1D Dx 1991 @ age 6 y/o
  - A1c’s: 8.0-9.0% 1st 5 years, then 5.5-7.5%
  - Complications: NONE

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**T1D: Cases - 2**

- **Case 4**: DOB 1985, T1D Dx 1991 @ 6 y/o
  - A1c’s: 6.7–7.7% 1st 5 years, then 9.0-15.0%
  - Complications: HTN, MA, PDR, ME by early 20’s
- **Case 5**: DOB 1970, T1D Dx 1982 @ 12 y/o
  - A1c’s: 9.3-14.5% until late 20’s, then <8%
  - Complications: NONE

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**Glycemic Targets**

- **Definition of target:**
  - Something that you are trying to do or achieve (reach A1c goal)
  - A place, thing, or person at which an attack is aimed (NEED to avoid blaming the person with diabetes who may NOT be at target)

http://www.merriam-webster.com/dictionary/target

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**T1D: Cases - 3**

- **Case 6**: DOB 1940, T1D Dx 1950 @ 10 y/o; 75 y/o
  - A1c’s: 7.5-8.5% (since measured)
  - Complications: treated HTN, no kidney disease, NPDR, no CVD
- **Case 7**: DOB 1960, T1D Dx 1975 @ 15 y/o; 55 y/o
  - A1c’s: 9-10% (since measured)
  - Complications: CKD Stage 3, PDR, CVD

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**Glycemic Targets**

- **Definition of target:**
  - Something that you are trying to do or achieve (reach A1c goal)
  - A place, thing, or person at which an attack is aimed (rather, blame the diabetes – it is challenging to manage)

http://www.merriam-webster.com/dictionary/target
Why glycemic targets?

• “Blood glucose control reduces the risk of developing the eye, nerve, and kidney complications of diabetes.”
• “Older patients with (type 1/2) diabetes and children with type 1 diabetes are at particularly high risk for adverse outcomes associated with hypoglycemia.”
• “Individual blood glucose targets, with the selection of targets based on the potential risks and benefits to the patient, are encouraged for people with diabetes.”

2014 CDC June Report

Glycemic Targets: A1c

• Hemoglobin A1c is the “gold standard” target for monitoring glucose control in patients with diabetes
• A1c provides an average of BG levels over the previous 2-3 months (weighted towards the last 4 weeks; ~50% formed in the month before the test, 25%/25% in the previous 2 months)
• A1c levels give the best estimate of risk for the development of complications

Sacks DB, John WB. JAMA 2014; 311:2271

Glycated Hemoglobin

• Glycohemoglobin = The total of CHO adducts to N-terminal amino acids and/or ε-amino acid lysine groups of hemoglobin
• HbA1 = Sum of various minor hemoglobin species, including HbA1c
• HbA1c = Glucose adduct to the N-terminal valine of the β-chain of hemoglobin; the major component of glycohemoglobin in blood

Sacks DB, John WB. JAMA 2014; 311:2271

Non-enzymatic Formation of HbA1c

• Glucose freely permeable in RBCs
• Glycated hgb formed in direct proportion to the ambient glucose concentration

2-part glycation reaction for hemoglobin:
• glucose reversibly attaches to the N-terminal valine of the β chain forming Schiff base
• Irreversible Amadori rearrangement forming ketoamine

Sacks DB, John WB. JAMA 2014; 311:2271

NGSP* IFCC** eAG (estimated average glucose)

<table>
<thead>
<tr>
<th>(%)</th>
<th>(mmol/mol)</th>
<th>(mmol/L)</th>
<th>(mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>31</td>
<td>5.4 (4.2–6.7)</td>
<td>97 (76–120)</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>7.0 (5.5–8.5)</td>
<td>126 (100–152)</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>8.6 (6.8–10.3)</td>
<td>154 (123–185)</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>10.2 (8.1–12.1)</td>
<td>183 (147–217)</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>11.8 (9.4–13.9)</td>
<td>212 (170–249)</td>
</tr>
<tr>
<td>10</td>
<td>86</td>
<td>13.4 (10.7–15.7)</td>
<td>240 (193–282)</td>
</tr>
<tr>
<td>11</td>
<td>97</td>
<td>14.9 (12.0–17.5)</td>
<td>269 (217–314)</td>
</tr>
<tr>
<td>12</td>
<td>108</td>
<td>16.5 (13.3–19.3)</td>
<td>296 (240–347)</td>
</tr>
<tr>
<td>13</td>
<td>119</td>
<td>18.1 (15–21)</td>
<td>326 (260–380)</td>
</tr>
<tr>
<td>14</td>
<td>130</td>
<td>19.7 (16–23)</td>
<td>355 (290–410)</td>
</tr>
<tr>
<td>15</td>
<td>140</td>
<td>21.3 (17–25)</td>
<td>384 (310–440)</td>
</tr>
<tr>
<td>16</td>
<td>151</td>
<td>22.9 (19–26)</td>
<td>413 (330–480)</td>
</tr>
<tr>
<td>17</td>
<td>162</td>
<td>24.5 (20–28)</td>
<td>441 (360–510)</td>
</tr>
</tbody>
</table>

*National Glycohemoglobin Standardization Program
**International Federation of Clinical Chemistry

DCCT: The basis for A1c targets in T1D
**DCCT: A1c by Treatment Group**

![Graph showing A1c by treatment group](image)


**Cumulative Incidence of Retinopathy by Treatment Group**

![Graph showing cumulative incidence of retinopathy](image)

34-76% significant risk reduction for eye, renal, and nerve outcomes across both primary and secondary cohorts

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**Risk of Hypertension**

- Due to intensity of exposure

\[
\text{Intensity} = \text{degree of hyperglycemia} \times \text{duration of hyperglycemia}
\]

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**Risk of Retinopathy Progression According to A1c**

![Graph showing risk of retinopathy progression](image)

JAMA 2002:287

**Cumulative Incidence of Retinopathy Progression - EDIC**

![Graph showing cumulative incidence of retinopathy](image)

JAMA 2002:287

62% Risk Reduction

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**Modern-Day Clinical Course of Type 1 Diabetes Mellitus After 30 Years’ Duration**

*Original Investigation*


*Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group*

Arch Intern Med 2002;162:2111

**Results:** After 30 years of diabetes, the cumulative incidences of proliferative retinopathy, nephropathy, and cardiovascular disease were 50%, 25%, and 14%, respectively, in the DCCT conventional treatment group, and 47%, 17%, and 14%, respectively, in the EDIC cohort. The DCCT intensive therapy group had substantially lower cumulative incidences (21%, 9%, and 9%) and fewer than 1% became blind, required kidney replacement, or had an amputation because of diabetes during that time.
DCCT – Adult & Adolescent Cohorts

- **DCCT: Adolescents Vs Adults**
  - Significantly higher A1c’s:
    - Intensive: 8.1 vs 7.1%
    - Conventional: 9.8 vs 9.0%
  - Significantly more hypoglycemia:
    - Intensive: 86 vs 57/100-pt-yrs
    - Conventional: 28 vs 17/100-pt-yrs
  - Had significantly more DKA than adults:
    - Intensive: 2.8 vs 1.8/100-pt-yrs
    - Conventional: 4.7 vs 1.3/100-pt-yrs

How the DCCT informed A1c targets and reinforces them today

- Restricted to ages 13-39 at entry; no data on young children or older adults
- The adolescent cohort was unable to achieve the same A1c outcomes as the adults
- Loss of the protective effect of metabolic memory on complication risk for the adolescent cohort – due to their higher A1c during the DCCT
- Hypoglycemia risk increased as A1c decreased

DCCT Findings

Lower A1c = Fewer Complications BUT More Hypo

Published A1c Targets

- Tight BG control reduces microvascular complications
- Need to consider risks of severe low BGs
- Patient training needed
- Specific BG targets and treatment goals need to be individualized, considering age, disease progression, CVD risk, & patient lifestyle & capabilities
A1c Targets

- Glycemic targets should be individualized, taking into account disease duration, patient co-morbidities, life expectancy, and risk of severe hypoglycemia
- Also consider A1c target within context of social, emotional, and demographic factors

Published A1c Targets

- AACE (2011): A1c ≤6.5% for adults
- Australian Diabetes Society (2011):
  - A1c <7% for adults
  - A1c <7.5% for youth (APEG 2005)
- Canadian Diabetes (2013):
  - A1c <7% for adults
  - A1c <8% for youth <6 y/o; ≤7.5% for 6-12; ≤7% for 13+
- EASD & ESC (cardiology)(2013): A1c <7%
- ISPAD (2009, 2014); IDF (2011):
  - A1c ≤7.5% (high risk >9%) for youth

ADA A1c Targets Jan 2014
Standards of Medical Care in Diabetes

<table>
<thead>
<tr>
<th>Values by age (years)</th>
<th>Plasma blood glucose goal range (mg/dL)</th>
<th>A1c</th>
<th>Before meals</th>
<th>Bedtime/overnight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toddlers and preschoolers (0-6)</td>
<td>100–180</td>
<td>110–200</td>
<td>&lt;8.5%</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>70–130</td>
<td>&lt;180</td>
<td>&lt;7%</td>
<td></td>
</tr>
<tr>
<td>School age (6–12)</td>
<td>90–180</td>
<td>100–180</td>
<td>&lt;8%</td>
<td></td>
</tr>
<tr>
<td>Adolescents and young adults (13–19)</td>
<td>90–130</td>
<td>90–150</td>
<td>&lt;7.5%</td>
<td></td>
</tr>
</tbody>
</table>

Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association

Type 1 diabetes is characterized by an immune-mediated depletion of β-cells that results in lifelong dependence on exogenous insulin. While both type 1 and type 2 diabetes result in hyperglycemia, the pathophysiology and etiology of the diseases are distinct and require us to consider each type of diabetes independently. As such, this position statement summarizes available data specific to the comprehensive care of individuals with type 1 diabetes. The goal is to enhance our ability to recognize and manage type 1 diabetes, to prevent its associated complications, and to eventually cure and prevent this disease.
Table 7—Summary of A1C recommendations for nonpregnant people with diabetes*

<table>
<thead>
<tr>
<th>Group</th>
<th>A1C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youth (&lt;18 years)</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>Adults</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td>Older adults</td>
<td></td>
</tr>
<tr>
<td>Healthy†</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>Complex/intermediate</td>
<td>&lt;8.0%</td>
</tr>
<tr>
<td>Very complex/poor health</td>
<td>&lt;8.5%</td>
</tr>
</tbody>
</table>

*Targets must be individualized based on a patient’s circumstances. †No comorbidities, long life expectancy.

Changes in A1C Targets

- Separate A1c targets according to age in youth abolished
- ADA A1c targets now harmonized with other international groups (e.g. ISPAD)
- Reduced concerns related to CNS risk of hypoglycemia in young children based upon no observed increased risk of hypoglycemia with lower A1c levels using modern intensive insulin therapies
- Potential CNS risk to young children due to hyperglycemia based upon MRI data

Diabetes management is suboptimal in the majority of patients with T1D

Diabetes Care Volume 37, July 2014

A1c Today

Type 1 Exchange

TEENs Study

DPV

NHANES

Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data From the T1D Exchange Clinic Registry

- Longitudinal data on 16,061 participants
- Baseline collected Sept 2010 - Aug 2012
- Follow-up collected Sept 2013 - Dec 2014
- Baseline mean A1c 8.2% (66 mmol/mol)
- Follow-up mean A1c 8.4% (68 mmol/mol)
- Pump use increased: 58% to 62%
- CGM use did not change: 7%

Proportion of Patients with T1D achieving A1c Targets in T1DX

Proportion of patients with A1c targets of T1DX achieving A1c targets.

Diabetes Care Volume 37, July 2014
Presumably, the text contains graphs and tables related to diabetes control and metabolic improvement in children and adolescents. The graphs show the average current A1c by age, with data from various studies. The tables summarize achievement of A1c targets and changes in A1c levels over time. The text also mentions a significant drop in the frequency of severe hypoglycemia and an increase in the proportion of patients meeting target A1c levels. The data is sourced from multiple studies, including Miller et al., Diab Care 2015, TEENs Study – Glycemic Control, and Laffel et al., ADA 2014, 32-OR.
In the T1D Exchange, for both children and adults, the frequency of severe hypoglycemia was not higher in participants with tight glucose control in contrast to the DCCT.
Table 3. Suggested Glycemic Targets Based on EDCS Score

<table>
<thead>
<tr>
<th>EDCS Score</th>
<th>&lt;5</th>
<th>5-10</th>
<th>11-15</th>
<th>&gt;16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested HbA1c target (%)</td>
<td>&lt;6.5</td>
<td>6.6-7.5</td>
<td>7.6-8.0</td>
<td>&gt;8.0</td>
</tr>
</tbody>
</table>

Consider patient characteristics and disease status when setting goals for glycemic control.

- Clinical factors: age, duration, A1c Hx, comorbidities, complications, risk of hypoglycemia
- Personal characteristics: attitudes and diabetes knowledge
- Psychosocio-economic factors: resources and supports, psychological status, economic issues

A1c and Mortality
DCCT/EDIC Mortality Data

HR 1.61 (95% CI 1.09-2.39)  p=0.02
HR 0.67 (95% CI 0.46-0.99)  p=0.045

Cause of Death in DCCT/EDIC

Mortality Rates: DCCT/EDIC, Sweden, and Scotland

Mortality in Type 1 Diabetes in the Current Era
Two Steps Forward, One Step Backward

In the penicillin era, survival following the diagnosis of type 1 diabetes was dismal; 50% of patients died within the first 20 months of diagnosis and fewer than 10% survived 5 years. The introduction of insulin therapy in 1922 significantly changed survival as mortality from diabetic ketoacidosis (DKA) decreased substantially. However, in the middle of the 20th century, there was still a 20-year reduction in life expectancy for those diagnosed with type 1 diabetes; 50% of individuals with youth-onset disease died before the age of 50 years. A half-century later, in the current era, intensive insulin therapy has become the standard of care and advances in insulin delivery and glucose monitoring have improved the management of type 1 diabetes. Yet glycemic control remains suboptimal for the majority of patients with type 1 diabetes, and acute and chronic complications persist, reducing life expectancy for many patients.

More is needed to improve the life expectancy in type 1 diabetes. The search for genetic factors and biomarkers related to risk of diabetes complications generally and risk of diabetic nephropathy specifically needs to accelerate. There continues to be inadequate access to advanced diabetes technologies, education and support from health care professionals, and, at times, even family encouragement, which all need to improve. Patients, families, and the health care community await more steps forward. There is some reassurance for the present efforts to improve glycemic control and therapies that provide renal protection and cardiovascular risk reduction can prevent or postpone complications and preserve the futures of persons with type 1 diabetes.
Opportunities for Improvement

The impact of blood glucose and HbA1c goals on glycemic control in children and adolescents with Type 1 diabetes


Youth A1c by A1c Goal Category

<table>
<thead>
<tr>
<th>Goal Category</th>
<th>A1c (%)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤6.0%</td>
<td></td>
<td>8.0±1.4</td>
</tr>
<tr>
<td>6.0-8.0%</td>
<td></td>
<td>8.3±1.2</td>
</tr>
<tr>
<td>8.1-10.0%</td>
<td></td>
<td>9.2±1.7</td>
</tr>
<tr>
<td>&gt;10.0%/Don’t know</td>
<td></td>
<td>9.0±2.0</td>
</tr>
</tbody>
</table>

P=0.02

Conclusions: There was a significant association between lower parent HbA1c goals and lower child/adolescent HbA1c. Future research should assess the relationship between parents’ perceptions of healthcare providers’ goals and healthcare providers’ actual goals and the impact of such family-provider goal-setting on glycemic control.

A1c Targets - 1

- We have new target A1c values for pediatric patients
- We have T1D specific guidelines across the lifespan
- We have opportunities to work as multi-disciplinary teams to implement the new guidelines with the goal of optimizing A1c levels and overall health outcomes for persons with T1D

A1c Targets - 2

- As always, diabetes management requires individualization
- T1D specific guidelines across the lifespan now highlight higher targets for adults, based on co-morbidities and risk of severe hypoglycemia
- Always need to consider socio-cultural, psychosocial, educational, emotional, behavioral issues, etc. in creating treatment targets
Acknowledgments


Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association

Diabetes Care Volume 37, July 2014

The authors also thank Erika Gobel-Berg (American Diabetes Association) for her invaluable editorial contributions.

Bull's eye – hitting the target!
Thank You