Complications and comorbidities in children with Type 1 and Type 2 diabetes

Evangelia Kalaitzoglou, MD
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Disclosures

No relevant financial relationships to disclose
Learning Objectives

• At the conclusion of this activity, participants will be able to identify the complications and comorbidities associated with Type 1 (T1D) and Type 2 (T2D) diabetes in children.

• At the conclusion of this activity, participants will be able to describe the recommendations for screening for complications and comorbidities associated with Type 1 and Type 2 diabetes in children.
Acute complications/ adverse events (T1D and T2D)

• Hyperglycemia and diabetic ketoacidosis (DKA)
• Hypoglycemia (due to treatment with insulin)
Hyperglycemia and DKA

- Insulin levels inadequate for metabolic needs (Insulin omission, concurrent illness/infection)
- Shift from glucose to lipid metabolism (ketoacids)
- Risk for recurrent DKA increases with older age, female sex, higher HbA1c, higher reported insulin dose, lack or partial insurance and presence of psychiatric disorder (JAMA. 2002;287;2511-2518)

- Signs and Symptoms
  - Polyuria, polydipsia
  - Enuresis
  - Dehydration
    - Tachycardia
    - Orthostasis
  - Abdominal pain
  - Nausea
  - Vomiting
  - Fruity breath
  - Acetone
  - Kussmaul breathing
  - Mental status changes
    - Combative
    - Drunk
    - Coma

- Prevention
  - Frequent BG monitoring
  - Urine/serum ketone monitoring
  - Education of patient and their family on treatment adherence and sick day management

http://www.international-diabetes-association.com/dka-ketoacidosis-ketones/
Hypoglycemia

- Most common acute complication in T1DM
- Usually defined as BG< 70 mg/dl in a child with DM (with or without symptoms)
- Risk factors include young age, lower HbA1c, disease duration, underinsurance and psychiatric disorders (JAMA. 2002;287;2511-2518) as well as exercise, prior hypoglycemic episodes and acute illness

Symptoms

<table>
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<th>Prevention</th>
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<tr>
<td>✓ Inquire about frequency of hypoglycemia</td>
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<tr>
<td>✓ Hypoglycemia unawareness</td>
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<tr>
<td>✓ Reassess BG monitoring, BG targets and insulin regimen</td>
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<tr>
<td>✓ Education of patient and family on recognition of symptoms and treatment (oral glucose load, glucagon etc.)</td>
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</table>
Chronic complications and comorbidities in children with diabetes (T1D and T2D)

• Macrovascular
  • Cardiovascular disease (CVD), cerebrovascular disease, peripheral vascular disease (hypertension, dyslipidemia)

• Microvascular
  • Nephropathy
  • Retinopathy
  • Neuropathy

• Psychosocial (depression, anxiety)

• Specifically for T1D
  • Celiac disease
  • Autoimmune thyroid disease
Macrovascular disease in children with T1D

- The process of atherosclerosis can start soon after diagnosis of T1D
- Patients diagnosed with T1D during childhood are at higher risk of developing premature cardiovascular disease (CVD)
- **Risk factors**
  - poor glycemic control
  - diabetes duration
  - hypertension
  - hyperlipidemia
  - obesity
  - smoking
- **Hypertension and dyslipidemia are more common in diabetic children** compared to healthy children, especially in the presence of poor diabetic control
- Addressing these risk factors in the pediatric population with T1D can decrease premature CVD

- **Screening recommendations for hypertension**
  - Blood pressure should be measured at each routine visit. Children found to have high-normal blood pressure (systolic blood pressure or diastolic blood pressure ≥ 90th percentile for age, sex, and height) or hypertension (systolic blood pressure or diastolic blood pressure ≥ 95th percentile for age, sex, and height) should have blood pressure confirmed on 3 separate days.
Diabetic nephropathy in children with T1D

- Earliest sign of diabetic nephropathy is **microalbuminuria** (urine albumin/creatinine between 30 and 300 mg/g in spot urine)
- Persistent microalbuminuria predicts progression to gross proteinuria within 6–14 years
- Structural changes by biopsy as early as 1.5–5 years after diabetes onset in children
- **Risk factors**
  - diabetes duration
  - poor glycemic control
  - female sex
  - higher diastolic BP
  - smoking
  - positive family hx of parent with HTN or family hx of CVD

**Screening recommendations:**
- Annual screening for albuminuria with a random spot urine sample for albumin–to–creatinine ratio should be considered once the child has had diabetes for 5 years
- Estimate glomerular filtration rate at initial evaluation and then based on age, diabetes duration and treatment
- Exercise, smoking, and menstruation can affect the results and albumin excretion can vary from day to day; an abnormal value should be repeated.
- The diagnosis of persistent abnormal microalbumin excretion requires documentation of two of three consecutive abnormal values obtained on different days

Diabetes Care 36:2639–2645, 2013
DIABETES CARE, VOLUME 28, NUMBER 1, JANUARY 2005,
Diabetic retinopathy in children with T1D

• Retinopathy has been detected in up to 23% of pediatric patients with T1D (J Pediatr Endocrinol Metab. 1997 Nov-Dec;10(6):587-92)

• Risk factors
  • longer disease duration
  • poor glycemic control
  • hypertension
  • microalbuminuria
  • smoking
  • dyslipidemia

• Screening recommendations
  • An initial dilated and comprehensive eye examination is recommended at age ≥10 years or after puberty has started, whichever is earlier, once the youth has had type 1 diabetes for 3–5 years
  • After the initial examination, annual routine follow-up is generally recommended. Less frequent examinations, every 2 years, may be acceptable on the advice of an eye care professional
Diabetic neuropathy in children with T1D

- Divided in peripheral and autonomic neuropathy
- Subclinical impairment of neurologic function has been reported in up to 68% of children with T1D (Pediatr Neurol. 1999;20(3):204)
- Prevalence of cardiovascular autonomic neuropathy reported 28% of children with T1D

**Risk factors**
- longer diabetes duration
- poor glycemic control
- older age
- smoking
- increased diastolic blood pressure
- obesity
- increased LDL and triglycerides, and lower HDL cholesterol

**Screening recommendations**
- Consider an annual comprehensive foot exam for the child at the start of puberty or at age ≥10 years, whichever is earlier, once the youth has had type 1 diabetes for 5 years
Youth with T1D are at increased risk of

- Anxiety
- Depression
- Eating disorders
- Diabetes-related stress

**Screening recommendations**

- At diagnosis and during routine follow-up care, assess psychosocial issues and family stresses that could impact adherence to diabetes management and provide appropriate referrals to trained mental health professionals, preferably experienced in childhood diabetes.
- Consider mental health professionals as integral members of the pediatric diabetes multidisciplinary team.
Other autoimmune disease in children with T1D

- **Celiac disease** - 1.6-16.4%
- **Screening recommendations**
  - Consider screening children with type 1 diabetes for celiac disease by measuring either tissue transglutaminase or deamidated gliadin antibodies, with documentation of normal total serum IgA levels, soon after the diagnosis of diabetes.
  - Consider screening in children who have a first-degree relative with celiac disease, growth failure, weight loss, failure to gain weight, diarrhea, flatulence, abdominal pain, or signs of malabsorption or in children with frequent unexplained hypoglycemia or deterioration in glycemic control.

- **Autoimmune thyroid disease** - 17-30%
- **Screening recommendations**
  - Consider testing children with type 1 diabetes for antithyroid peroxidase and antithyroglobulin antibodies soon after the diagnosis.
  - Measure thyroid-stimulating hormone concentrations soon after the diagnosis of type 1 diabetes and after glucose control has been established. If normal, consider rechecking every 1–2 years or sooner if the patient develops symptoms suggestive of thyroid dysfunction, thyromegaly, an abnormal growth rate, or an unexplained glycemic variation.
  - Consider other autoimmune diagnoses, such as Addison’s disease, autoimmune hepatitis, dermatomyositis etc. depending on symptomatology.
Additional considerations for children with T1D

• Smoking
  • Elicit a smoking history at initial and follow-up diabetes visits and discourage smoking in youth who do not smoke and encourage smoking cessation in those who do smoke

• Alterations in cognitive function and brain structure of youth with T1D, especially if diagnosed at <5 years

• Menstrual irregularities and vaginal yeast infections (poor glycemic control- Hba1c>10%)
• Bone disease (lower bone mineral accrual and bone mineral content, higher risk for fracture compared to healthy children)
## Screening recommendations for children with T2D

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Screening Purpose</th>
<th>Initiate</th>
<th>Frequency</th>
<th>Result</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Height, weight, BMI %</td>
<td>Growth/obesity</td>
<td>At diagnosis</td>
<td>Every 3 months</td>
<td>BMI ≥95%</td>
<td>Lifestyle changes, MNT</td>
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<td>Blood pressure</td>
<td>Hypertension</td>
<td>At diagnosis</td>
<td>Every 3 months</td>
<td>BP≥95% for age, sex, height x3</td>
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<td>Hypoglycemia/ diabetes self-management assessment</td>
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<td>Psychosocial assessment</td>
<td>Depression Eating disorders</td>
<td>At diagnosis</td>
<td>Every 3 months</td>
<td>Symptoms of depression</td>
<td>Counseling, mental health professional</td>
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<td>Foot exam</td>
<td>Peripheral neuropathy</td>
<td>At 10 yo or puberty and 5 years of DM</td>
<td>Annually</td>
<td>↓ sensation vibration or pressure</td>
<td>Optimize glycemic control</td>
</tr>
<tr>
<td>Urine microalbumin</td>
<td>Nephropathy</td>
<td>5 years of DM</td>
<td>Annually</td>
<td>&gt;30 mg/g (≥ x2)</td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Hyperlipidemia</td>
<td>At 10 yo or puberty</td>
<td>Every 3-5 years, annually if abn</td>
<td>LDL&gt;100 mg/dl</td>
<td>MNT, optimize glycemic control, statin</td>
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<tr>
<td>Dilated eye examination</td>
<td>Retinopathy</td>
<td>At 10 yo or puberty and 3-5 years of DM</td>
<td>Annually</td>
<td>retinopathy</td>
<td>Optimize glycemic control Laser therapy</td>
</tr>
<tr>
<td>TSH, +/- autoantibodies</td>
<td>Autoimmune thyroiditis</td>
<td>At diagnosis</td>
<td>Every 1-2 years</td>
<td>Abnormal TSH or positive Ab</td>
<td>Treatment of hypo/hyperthyroidism</td>
</tr>
<tr>
<td>tTG IgA Ab, total IgA</td>
<td>Celiac disease</td>
<td>At diagnosis</td>
<td>Depending on history/symptoms</td>
<td>Positive tTG Ab</td>
<td>Gluten free diet</td>
</tr>
</tbody>
</table>

Diabetes Care 2014;37:2034–2054
Diabetes Care 2017;40(Suppl. 1):S105–S113
1. Children with T1D are at increased risk of developing autoimmune thyroid disease and celiac disease  
   *True*

2. Children with T1D should be screened for depression at diagnosis and during routine follow-up  
   *True*

3. Children with T1D require screening for hypertension at every visit  
   *True*

4. Children with T1D should start having routine screening for microvascular diabetic complications at diagnosis  
   *False*
Complications/comorbidities in children with T2D

• Data regarding natural history, progression and screening recommendations for comorbidities are scarce in children and adolescents with T2D compared to adults (Pediatrics 2013;131:e648–e664)

• Recent studies (TODAY and SEARCH) have been informative

• Screening recommendations for complications similar to those for children with T1D but start at diagnosis, due to more aggressive nature of disease in children/adolescent with T2D.

• **Macrovascular complications (CVD)**
  • **risk factors:** Obesity, smoking, poor glycemic control, dyslipidemia, family history of early CVD (Pediatrics 2013;131:e648–e664)
  • Hypertension at presentation of T2D reported between 17-32%
  • Increased prevalence of macrovascular disease in youth with T2D compared to T1D, accounting for increase in mortality (2-fold compared to T1D)
Complications/comorbidities in children with T2D (con’d)

- **Nephropathy**
  - **risk factors**: poor glycemic control, insulin resistance, hypertension
  - Present in 6% at presentation in TODAY study, 20-22% in SEARCH study
  - Higher prevalence of microalbuminuria at diagnosis and more than two fold increased risk of microalbuminuria at any time after diagnosis for youth with T2D compared to T1D
  - Higher risk of renal failure for youth with T2D compared to T1D, not entirely explained by glycemic control differences (metabolic syndrome and insulin resistance)

- **Retinopathy**
  - **risk factors**: poor glycemic control, disease duration, hypertension and higher LDL
  - Similar or increased retinopathy risk for youth with T2D vs T1D for similar glycemic control and duration of disease (TODAY study: 13.7%)

- **Neuropathy**
  - **risk factors**: older age, male sex, longer diabetes duration, smoking, and lower HDL
  - Peripheral neuropathy is more prevalent in youth with T2D compared to T1D, especially after 5 years of diabetes duration (SEARCH study)
# Association of Type 1 Diabetes vs Type 2 Diabetes Diagnosed During Childhood and Adolescence With Complications During Teenage Years and Young Adulthood

Dana Dabelea, MD, PhD; Jeanette M. Stafford, MS; Elizabeth J. Mayer-Davis, PhD; Ralph D'Agostino Jr, PhD; Lawrence Dolan, MD; Giuseppina Imperatore, MD, PhD; Barbara Linder, MD, PhD; Jean M. Lawrence, ScD; Santica M. Marcovina, PhD; Amy K. Mottl, MD; Mary Helen Black, PhD; Rodica Pop-Busui, MD, PhD; Sharon Saydah, PhD; Richard F. Hamman, MD, DrPH; Catherine Pihoker, MD; for the SEARCH for Diabetes in Youth Research Group

<table>
<thead>
<tr>
<th>Complication</th>
<th>Type 2 Diabetes</th>
<th>Type 1 Diabetes</th>
<th>Absolute Difference, % (95% CI)</th>
<th>P Value</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic kidney disease</td>
<td>19.9</td>
<td>5.8</td>
<td>14.0 (9.1 to 19.9)</td>
<td>&lt;.001</td>
<td>2.58 (1.39-4.81)</td>
<td>.003</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>9.1</td>
<td>5.6</td>
<td>3.5 (0.4 to 7.7)</td>
<td>.02</td>
<td>2.24 (1.11-4.50)</td>
<td>.02</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>17.7</td>
<td>8.5</td>
<td>9.2 (4.8 to 14.4)</td>
<td>&lt;.001</td>
<td>2.52 (1.43-4.43)</td>
<td>.001</td>
</tr>
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<td>Cardiovascular autonomic neuropathy</td>
<td>15.7</td>
<td>14.4</td>
<td>1.2 (~3.1 to 6.5)</td>
<td>.62</td>
<td>0.98 (0.57-1.67)</td>
<td>.93</td>
</tr>
<tr>
<td>Arterial stiffness</td>
<td>47.4</td>
<td>11.6</td>
<td>35.9 (29.0 to 42.9)</td>
<td>&lt;.001</td>
<td>1.07 (0.63-1.84)</td>
<td>.80</td>
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<td>Hypertension</td>
<td>21.6</td>
<td>10.1</td>
<td>11.5 (6.8 to 16.9)</td>
<td>&lt;.001</td>
<td>0.85 (0.50-1.45)</td>
<td>.55</td>
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Percentage of young adults with diabetes developing complications from the disease:

- **Type 2 Diabetes**
- **Type 1 Diabetes**

Source: "Association of type 1 diabetes vs. type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood," Journal of the American Medical Association, Feb. 28, 2017

Credit: NIH/NIDDK
Conclusions

- Overall 72% of patients with Type 2 Diabetes (T2D) and 32% with Type 1 Diabetes (T1D) had evidence of 1 early diabetes-related complication or comorbidity.
- The prevalence of complications and comorbidities was higher among those with T2D compared to T1D.
- No single factor could explain why individuals with T2D developed more complications than counterparts with T1D.
- These findings support early monitoring for children with diabetes, especially those with T2D.
Psychosocial assessment in children with T2D

- Depressive symptomatology was two-fold higher in youth with T2D compared to youth with T1D
- Socioeconomic factors contributing to higher incidence of depression in those with T2D
Additional considerations for children with T2D

• In addition to previously discussed complications, other comorbidities include:
  • Non-alcoholic fatty liver disease (NAFLD)
    • Aminotransferase levels at diagnosis
  • Obstructive sleep apnea
  • Orthopedic problems (SCFE, risk of fracture)
  • Polycystic ovary syndrome (PCOS)
## Screening recommendations for children with T1D

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<td>At diagnosis</td>
<td>Annually, less frequently if normal</td>
<td>Retinopathy</td>
<td>Optimize glycemic control, Laser therapy</td>
</tr>
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<td>Liver function tests (ALT, AST)</td>
<td>NAFLD</td>
<td>At diagnosis</td>
<td>Annually (or less frequently)</td>
<td>Elevated aminotransferases</td>
<td>MNT</td>
</tr>
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Pediatrics 2013;131:e648–e664
Diabetes Care. 2017 Sep;40(9):1226-1232
Puberty as an accelerator for diabetes complications


Conclusions

• Type 1 diabetes during puberty is an accelerator of risk for diabetic complications
• Insulin resistance and GH/IGF-1 axis changes in puberty contribute to increased risk for complications
• Females during puberty have greater risk for complications (retinopathy, nephropathy and cardiovascular events), whereas this risk changes in adults – males have higher risk for complications
True or False

1. The prevalence of microvascular diabetic complications is higher in children with T2D compared to children with T1D  **True**
2. Children with T2D often have NAFLD and should have screening at diagnosis  **True**
3. Children with T2D are not at risk of depression like children with T1D  **False**
4. Children with diabetes tend to be more insulin resistant during puberty  **True**
Important points

- Youth with T1D are at risk of developing chronic complications of diabetes, that can start developing soon after diagnosis
- Youth with T1D are at increased risk of autoimmune thyroid disease, celiac disease and other autoimmune disorders
- Youth with T2D have a higher prevalence of comorbidities and risk factors and a more aggressive natural history compared to youth with T1D and adults with T2D
- Glycemic control appears to be a major risk factor for most complications, although other factors contribute
- Puberty is associated with increased risk of complications in T1D and T2D patients, likely due to insulin resistance and GH/IGF-1 axis changes
- Screening recommendations are essential in preventing or delaying diabetic complications and comorbidities in children
Questions

Thank you