UPDATES IN PEDIATRIC DIABETES MELLITUS

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DISCLOSURES

Nothing to disclose

GOALS

▪ Review the types of diabetes mellitus commonly encountered in children
▪ Highlight the latest understanding of the causes of these types of diabetes mellitus
▪ Update on the latest advances being utilized in the pediatric population of type 1 diabetes
▪ Overview of type 2 diabetes in the pediatric population and strategies to prevent progression in early diagnosis
Prevalence of Diabetes per 100,000 US children

<table>
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<th>Type of Diabetes</th>
<th>Prevalence per 100,000 US children</th>
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<tr>
<td>Type 1 diabetes</td>
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<td>Type 2 diabetes</td>
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<td>MODY</td>
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**Neonatal diabetes mellitus (NDM)**

- Defined as insulin-dependent persistent hyperglycemia occurring in first 6 months of life
- Estimated to affect one in 300,000 to 400,000 newborns
- Monogenic form of diabetes with insulin deficiency
  - abnormal pancreatic islet development
  - decreased B-cell mass
  - B-cell dysfunction
- **Transient NDM (TNDM)**
  - accounting for 50% to 60% of all cases
  - requires initial insulin therapy
  - resolves spontaneously by average 2 weeks of age
  - Relapses later in life (teens)
- **Permanent NDM (PNDM)**
  - less common
  - has no period of remission

**SEARCH STUDY FOR DIABETES IN YOUTH**

- Funding by Division of Diabetes Translation of the Centers for Disease Control and Prevention and the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health

- Why? Gaps are present in the understanding of diabetes in youth
  - Limited data on the burden of diabetes and trends in incidence and prevalence by type, age, sex, and race/ethnicity,
  - the natural history and etiologic classification of childhood diabetes,
SEARCH STUDY FOR DIABETES IN YOUTH

- Six recruitment centers: Ohio, Colorado, Washington, South Carolina, Hawaii, California; American Indian reservation-based populations in Arizona and New Mexico.
- Each site identified prevalent (in 2001 and 2009) and incident cases (ongoing since 2002) of diagnosed diabetes (excluding gestational diabetes) in youth <20 years of age.
- Phase 3: 2010 initiated

Overall, between 2001 and 2009:
- Prevalence of type 1 diabetes in youth increased by 21.1% (95% CI 15.6–27.0)
- Prevalence of type 2 diabetes increased 30.5% (95% CI 17.3–43.1)

Two main etiologic markers: autoimmunity and insulin sensitivity
- 54.5% of SEARCH cases were classified as typical type 1 (autoimmune, insulin-sensitive) diabetes
- 15.9% were classified as typical type 2 (non-autoimmune, insulin-resistant) diabetes.
- 10% no evidence of either autoimmunity or insulin resistance
- Additional testing (additional measurements of diabetes-related autoantibodies; only two antibodies were measured in SEARCH testing for monogenic forms of diabetes)
- 8% of those tested had a mutation in one or more of the hepatocyte nuclear factor-1α (HNF-1α), glucokinase, and HNF-4α genes,
- Estimated monogenic diabetes population prevalence of at least 1.2%
SEARCH STUDY FOR DIABETES IN YOUTH:

COMPLICATIONS

- 17% of youth with type 1 diabetes and 27% of youth with type 2 diabetes had A1C levels ≥9.5% (≥80 mmol/mol)
- Minority youth were significantly more likely to have higher A1C levels compared with non-Hispanic white youth, regardless of diabetes type
- Cardiovascular disease risk factors were also elevated, including high blood pressure and dyslipidemia, elevated apolipoprotein B (apoB) levels and small, dense LDL particles
- Early signs of kidney disease, retinopathy, neuropathy, as well as increased arterial stiffness

SEARCH STUDY FOR DIABETES IN YOUTH

- Proposal for algorithm for classification of diabetes in youth

Incidence Among Children and Adolescents

Data from the SEARCH for Diabetes in Youth Study indicated that:

- During 2011–2013, the estimated annual number of newly diagnosed cases in the United States included:
  - 1,900 children and adolescents younger than age 13 years with type 1 diabetes.
  - 3,200 children and adolescents age 13 to 19 years with type 2 diabetes.
  - Among children and adolescents younger than age 20 years, non-Hispanic whites had the highest rate of new cases of type 1 diabetes compared to members of other U.S. racial and ethnic groups (Figure 4).
  - Among children and adolescents aged 10 to 19 years, U.S. minority populations had higher rates of new cases of type 2 diabetes compared to non-Hispanic whites (Figure 4).
Type 1 Diabetes

Type 2 Diabetes
CSII IN PEDIATRICS: STUDIES

<table>
<thead>
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<th>Author(s)</th>
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<th>Study Design</th>
<th>Participants</th>
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<th>Mean Duration (weeks)</th>
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*Note: Data is based on a subset of studies presented in the text.*
Continuous Glucose Monitor

- 3 currently on market
- DEXCOM and Medtronic pediatric approved
- Freestyle Libre - 18 and older

CGM AND PEDIATRICS: STUDIES

- 2014: T1D exchange: survey on CGM use
  - Associated with higher education, higher income, longer duration of diabetes, pump use, lower A1c
- Studies show longer duration of wear associated with lower HbA1c
- Less clean pediatric studies for hypoglycemia unawareness
- Overall improvement in hypoglycemia and counter regulatory response
- Pump and CGM
  - Support improvement of HbA1c

**PUMP AND CGM**

- Medtronic 630G (threshold-suspend-pump stops infusion with hypoglycemia) and 670G (hybrid closed loop-control basal settings)

- DEXCOM (G5) and T-Slim X2 – communicate; open loop

**CLOSED LOOP**

- Hybrid: Medtronic 670G
  - Approved ages 14 and older
  - Basal rates adjusted with sensor data (auto mode)

- On the horizon
  - Omnipod Dash – use locked down Android device instead of PDM
  - Omnipod Horizon – use DEXCOM sensor for hybrid closed loop (basal rates)

- T-Slim
  - Integration with DEXCOM G5 sensor into hybrid closed loop
  - Integration with new DEXCOM G6 sensor for closed loop

- The Bionic Pancreas
  - Insulin and glucagon
  - DEXCOM integrated inside pump

**BEYOND PUMP AND SENSOR**

- Encapsulated beta cell replacement therapies
- Glucose-responsive insulin
- Research into prevention of Type 1
- Targeted immune therapies
CHILDHOOD OBESITY

▪ Incidence
▪ Increasing worldwide
▪ Region specific
▪ Classification of pediatric obesity (CDC)
  ▪ Over age 2–18
  ▪ Overweight: 85–95th percentile BMI
  ▪ Obese: >95th percentile BMI
▪ Proposed class I (BMI 95th percentile to 120% of the 95th percentile)
▪ Class II (BMI 120–140% of the 95th percentile)
▪ Class III (BMI >140% of the 95th percentile)
INSULIN RESISTANCE AND PEDIATRICS

- Obesity to insulin resistance to type 2 diabetes
- Rates of prediabetes in adolescents aged 12–19 years
  - HbA1c threshold 5.7% - 6%
  - Fasting glucose 100 mg/dL - 125 mg/dL
  - 2-h glucose threshold of 140 mg/dL - up to 21% of obese youth could be classified as having prediabetes.

- Glucose intolerant adolescents
  - Progression to diabetes at rate of 10–15% per year
  - Highest rates in African-American youth with severe obesity

<table>
<thead>
<tr>
<th>Table 1: Cardiovascular risk factors associated with prediabetes or abnormal glucose status</th>
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<tbody>
<tr>
<td>Cardiovascular risk factors</td>
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<tr>
<td>Risk factors</td>
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<tr>
<td>- Genetic factors:</td>
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<td>- Lifestyle factors:</td>
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<tr>
<td>- Medication use:</td>
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<tr>
<td>- Family history:</td>
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<tr>
<td>- Environmental factors:</td>
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</table>

Note: Factors should be reviewed in the context of overall cardiovascular risk.
Insulin Resistance

THE TREATMENT OPTIONS FOR TYPE 2 DIABETES IN ADOLESCENTS AND YOUTH (TODAY) STUDY

- Multicenter randomized clinical trial
- Question: would combination therapy early in type 2 diagnosis maintain adequate glycemic control vs metformin alone?

Metformin +

Rosiglitazone

Metformin

Metformin +

Lifestyle

699

233

234

10-17yrs old
- ADA criteria for type 2 diabetes
- Diabetes diagnosis duration <2 years (avg 7.8 months)
- BMI > 85th percentile
- Negative type 1 autoimmune antibodies
- Measurable c-peptide
- Followed for average 3.86 years
Today

- Good adherence (>80% in the first year)
- Those who failed treatment had higher HbA1c levels at diagnosis
- BMI rose with rosiglitazone and dropped with lifestyle but not significantly different

[Graph and chart images]
Adverse events

- GI disturbances
- LFTs
- Myalgias
- Hypoglycemia (+rosiglitazone)

Treatment failure at higher rates than adults of same period of time.
PROGRESSION OF GLUCOSE TOLERANCE

▪ Patients who transition from normal glucose tolerance to prediabetes
  ▪ Increased BMI/body weight
  ▪ Increased insulin resistance
  ▪ Decreased beta cell release of insulin

▪ Patients who transition from prediabetes to type 2 diabetes
  ▪ Increasing weight gain
  ▪ Worsening insulin resistance
  ▪ Concomitant beta cell failure

▪ Patients who remained normal glucose tolerant
  ▪ Elevated BMI
  ▪ Insulin resistance

ROBUST INSULIN SECRETORY RESPONSE

CAUSES OF METABOLIC SYNDROME — TYPE 2 DIABETES

▪ Genetic factors
▪ Epigenetics
▪ Maternal nutrition and health
▪ Nutrition
▪ Microbiome
▪ Exercise
Figure 3. T2D and genome-wide associated variants. The variants are represented by gene names, which could indicate the location of their effect on gene expression. The number of genes is indicated by the size of the circle. The black circle indicates a gene that is associated with T2D. The remaining genes are depicted with red lines connecting them to their corresponding outcomes. T3D, T2D, and T1D are all associated with T2D and are linked with T2D risk factors. A1C/T2D variant is associated with T2D and is linked with T2D risk factors. T2D risk factors are also linked with T1D, A1C/T2D, and T3D. The figure includes a table showing the association between T2D and other outcomes.

Obesity (Silver Spring) 2008;16:1651-1656
EXERCISE AND METABOLISM

- Insulin sensitivity effects
- Subcutaneous vs visceral fat changes
- Community interventions
TREATMENT OPTIONS FOR PEDIATRIC OBESITY

- Lifestyle modifications
- Nutrition interventions
  - Intensive vs. in-home
- Pharmacologic interventions
- Surgical interventions

AAP POLICY ON PREVENTION OF PEDIATRIC OBESITY

SUMMARY/CONCLUSIONS
1. Prevalence of overweight and its significant co-morbidities in pediatric populations has rapidly increased and reached epidemic proportions.
2. Prevention of overweight is critical, because long-term outcome data for successful treatment approaches are limited.
3. Genetic, environmental, or combinations of risk factors predisposing children to obesity can and should be identified.
4. Early recognition of excessive weight gain relative to linear growth should become routine in pediatric ambulatory care settings. BMI (kg/m²) [see http://www.cdc.gov/growthcharts/]. Should be calculated and plotted periodically.

5. Families should be educated and empowered through anticipatory guidance to recognize the impact they have on their children’s development of lifelong habits of physical activity and nutritional eating.
6. Dietary practices should be fostered that encourage moderation rather than overconsumption, emphasizing healthful choices rather than restrictive eating patterns.
7. Regular physical activity should be consciously promoted, prioritized, and protected within families, schools, and communities.
8. Optimal approaches to prevention need to combine dietary and physical activity interventions.
9. Advocacy is needed in the areas of physical activity and food policy for children; research into pathophysiology, risk factors, and early recognition and management of overweight and obesity; and improved insurance coverage and third-party reimbursement for obesity care.
SUMMARY

Era of transformation in diabetes care

Future looks bright for technology and ease of management of insulin requiring diabetes

Type 2 diabetes and clinical conditions leading up to it will be our future

Start young

- In utero – educate mothers and mothers to be
- Nutrition
- Exercise