The Many Faces of Diabetes in the Young

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Objectives

- Learn how to detect and diagnose diabetes early.
- Recognize the different types of diabetes in the young, including monogenic diabetes.
- Discuss strategies to prevent Type 2 DM in high risk patients and the general population.
Diabetes in the young

- Type 1 is the most common chronic disease in children. (5-10% of adult diabetes). 17,900 new cases 2011 - 2012 in USA.

- Type 2 incidence was 5,300 in 2011-2012.
  - Prevalence of Type 2 increased 33 percent in 15 years mirroring increasing rate of overweight and obesity in youth.
  - Type 2 accounts now for 45% new onset diabetes in adolescents.

- Monogenic diabetes: 2-4% of diabetes in age < 25 years. It is often misdiagnosed.
Clinical Presentation

Mild
Incidental
Urine or Plasma glucose, ketones
Impaired fasting glucose,
Impaired glucose tolerance

Severe
Symptoms
Polyuria, Polydipsia,
Fatigue, Headaches,
Weight loss **
Signs of DKA
Coma
It can be missed!

- URI and respiratory illness (fatigue, Kussmaul breathing)
- UTI
- Appendicitis
- Gastritis

Parents, providers, school nurses think about it+++ 
Risk of death by DKA especially if cerebral edema. 
Look at family history and risk factors: Obesity, race and ethnicity, medications taken.
Criteria for the diagnosis of diabetes

- FPG $\geq 126$ mg/dl. Fasting = No caloric intake for 8H.
  - OR

- 2 H PG $\geq 200$ mg/dl during an OGGT. WHO 1.75 g/Kg to a max of 1.75g/kg up to a maximum of 75 g of anhydrous glucose dissolved in water.
  - OR

- A1c $\geq 6.5\%$. Lab method NGSP certified and standardized to the DCCT assay.
  - OR

- In a patient with classic symptoms of hyperglycemia, a random PG $\geq 200$ mg/dl.

In the absence of signs of hyperglycemia, the first 3 criteria should be confirmed by repeated testing.
Incidence of Type 1 and Type 2 in the young.

Ref. National diabetes report 2017
The Different Types of Diabetes Mellitus
## Characteristics of primary diabetes in the young

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>MODY</th>
<th>Atypical diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>85 % child and adolescent</td>
<td>12 % Puberty, rare before 10</td>
<td>1-4 %</td>
<td>&gt;10% AA, Asians</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Acute, severe</td>
<td>Insidious to severe</td>
<td>Gradual</td>
<td>Acute severe</td>
</tr>
<tr>
<td><strong>Age at onset</strong></td>
<td>Childhood to adolescence</td>
<td>Puberty. Rare before 10 Y</td>
<td>&lt;25 years</td>
<td>Puberty</td>
</tr>
<tr>
<td><strong>DKA at onset</strong></td>
<td>30 %</td>
<td>6 %</td>
<td>Not typical</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Affected relative</strong></td>
<td>5-10 %</td>
<td>60-90 %</td>
<td>50-90 %</td>
<td>75 %</td>
</tr>
<tr>
<td><strong>HLA-DR 3/4</strong></td>
<td>Association</td>
<td>No association</td>
<td>None</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>All but Caucasians higher risk</td>
<td>All: AA, Hispanics, Natives, Canadians first nation</td>
<td>All</td>
<td>AA/Asian</td>
</tr>
</tbody>
</table>
Characteristics of prevalent forms of primary diabetes in the young

- Diabetes associated autoantibodies to insulin, islet cell cytoplasmic, glutamic acid decarboxylase, or tyrosine phosphatase antibody (IA-2, ICA5C12, ZnT8 antibodies) in 85-95% at diagnosis Type 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1</th>
<th>Type 2</th>
<th>MODY</th>
<th>Atypical diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin secretion (C peptide)</td>
<td>Decreased or absent</td>
<td>Variable</td>
<td>Decreased variably</td>
<td>Variably decreased</td>
</tr>
<tr>
<td>Insulin dependence</td>
<td>Permanent</td>
<td>Variable</td>
<td>Variable</td>
<td>Intermittent</td>
</tr>
<tr>
<td>Obesity</td>
<td>Mirror the rate in GP so there can be obesity</td>
<td>&gt; 90 %</td>
<td>Uncommon</td>
<td>Varies with population</td>
</tr>
<tr>
<td>Acanthosis Nigricans</td>
<td>NO ***</td>
<td>Common</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Islet auto-AB</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Normal if controlled</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Diabetes associated autoantibodies include:
- ICA5C12
- ZnT8
- IA-2

Mirror the rate in GP so there can be obesity > 90%
15 Y old obese African American transfer of care for type 2
Diagnosed 1 year ago, placed on metformin 2000 mg/D and in good diabetes control.
2 weeks prior, asthma flare and placed on prednisone
Blood glucoses 350 mg/dl, no acidosis in ER. Received a fluid bolus and discharged on Lantus 30 units SQ with metformin.
A1c at diagnosis was 7.5 %. BMI 35 kg/m2. Based on family history/race + obesity T2 diagnosed.
A1c remained 6% for 1 year until now
At visit BMI 34.5 kg/m2, BP 140/72, A1c 7.8%
Case 1

- Because of history and doing well off steroids and also because of presumptive diagnosis, the dose of Lantus decreased by ½. Sent home to monitor BG until his Antibody tests returns.

- After 1 months, A1c 8.3%. His control has worsened. Gad 65 and IA2 antibodies were positive in high titers consistent with Type 1.

- Started Intensive insulin therapy with multiple daily injections of short acting insulin and one long acting at night.

- At visit 2 months later A1c=6.8%.
What is your diagnosis in this case?
This 15-year-old H obese young man was transferred from ER comatose with Initial BG 900 mg/dl and in acute renal failure. He was found unconscious on the couch and taken to the nearest ER.

Bicarbonate was 13 and he had some ketones but mild compared to the severity of his coma.

He has a history of **hypertension for the past 2 years** which was briefly treated then no follow up.

He lost 30 lb. this summer and parents thought related to playing football. Has significant acanthosis nigricans .

Father has type 2 with retinopathy, neuropathy, amputated toes etc..
Case 2= Type 2

- He was intubated for a week on a ventilator, an insulin drip and he also received hemodialysis, antihypertensive medications and Lasix. Eventually his kidney functions recovered.

- His antibody tests; islet cell antibodies and Gad 65, IA2, ZnT8 were negative.

- He has developed neuropathy at Age 15. Can hardly walk and prognosis is dire.
Case 3 & 4

- N is a now 5-year-old female diagnosed at another institution shortly after birth. She has cortical blindness and she is severely delayed and does not talk or walk. She came to me at 3Y. Parents are Palestinians and first cousins. They have 2 normal girls 10 and 11 and lost another baby at 6 months from neonatal diabetes prior to N.

- Despite my recommendations, the mother became pregnant again and had a son, A. The baby was found to have elevated BG from day 2 and transferred to my hospital for management on an insulin drip and then on flexible insulin and a small dose of long acting.
Case 3 and 4

- He followed the same path as his sister with delayed development and only partial blindness but was able to walk by age 3. He cannot talk and has little vision.

- Both children DNA samples were sent to a lab in Exeter, U.K.

- Dr. Andrew Hattersley and his team studied the samples against a large data base of DNA from their data bank and determine a new mutation for these 2 children and another child. NKX2-2 mutation.

- This research was done free of charge on a grant and was published in the peer reviewed Journal, Cell Metabolism:19:146,2014.
Other specific types of diabetes

- **Genetic defect in insulin action**: Type A1 insulin resistance, Leprechaunism, Rabson–Medenhall sd, Lipoatrophic diabetes, etc...

- **Diseases of exocrine pancreas**: Pancreatitis, pancreatectomy, cystic fibrosis, hemochromatosis, etc...

- **Endocrinopathies**: Acromegaly, Cushing’s sd, Glucagonoma, Pheochromocytoma, hyperthyroidism etc..

- **Drugs and chemicals**: Vacor, Glucocorticoids, Diazoxide, beta-adrenergic agonists, thiazides, Dilantin, Alpha interferon.
Other specific types of diabetes

**Infections**: Congenital Rubella, CMV, etc...

**Uncommon forms of immune mediated diabetes**: Stiff-man syndrome, Anti-insulin receptor antibodies, etc...

**Genetic syndromes associated with diabetes**: Down, Kleinefelter, Turner, Wolfram, Friederich’s ataxia, Prader Willi etc...
Type 1 DM in the young

- SEARCH study found a 21.1% rise in prevalence between 2001 and 2009 in youth 0-19 years across all ages, sex, race and ethnicity.
- 40% cases can occur after 30 years of age.
- Non-Hispanic whites are the most commonly affected.
- Association with other autoimmune disease is possible: Auto immune thyroiditis, celiac disease, Addison's disease...
- The rate of destruction of beta cell is variable and tends to be faster in younger individuals. Kids often present in DKA.
Type 1 DM

- More common in Winter but can occur all year long.
- May be precipitated by viral infection, environmental changes and stressors.
- Will always require insulin
- Flexible insulin therapy (Long acting and rapid acting) versus insulin pumps (new hybrid closed loops)
- One must adapt treatment for each individual and family circumstances. Family and patient centered care.
- Use CGMS when possible.
Type 1 DM: Always insulin
<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Onset of action (h)</th>
<th>Peak of action (h)</th>
<th>Duration of action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting analogs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart (Novolog)</td>
<td>0.25–0.5</td>
<td>1–3 1.5–2</td>
<td>3–5 3–5</td>
</tr>
<tr>
<td>Aspart Niacinamide (Fiasp)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro (Humalog, Admelog)</td>
<td>0.25–0.5</td>
<td>1–3</td>
<td>3–5</td>
</tr>
<tr>
<td>Glulisine (Apidra)</td>
<td>0.25–0.5</td>
<td>1–3</td>
<td>3–5</td>
</tr>
<tr>
<td>Regular insulin</td>
<td>0.5–1</td>
<td>2–4</td>
<td>5–8</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>2–4</td>
<td>4–8</td>
<td>12–18</td>
</tr>
<tr>
<td><strong>Long-acting analogs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir (Levemir)</td>
<td>2–4</td>
<td>none</td>
<td>12–24</td>
</tr>
<tr>
<td>Glargine (Lantus, Basaglar, Toujeo)</td>
<td>2–4</td>
<td>none</td>
<td>up to 24</td>
</tr>
<tr>
<td>Degludec (Tresiba)</td>
<td>2–4</td>
<td>none</td>
<td>&gt;24</td>
</tr>
</tbody>
</table>

*Table 5* Ref. Diabetes Care, 2018: September: 41(9)2026-2044

Types of insulin preparations and approximate insulin action profiles
What is this?
Type 2 DM in the young

- From Peripheral insulin Resistance with relative insulin deficiency to secretory defect with insulin resistance.
- Increased incidence in children linked to obesity epidemic.
- 5,000 new cases in children per year.
- Some children already have complications at diagnosis: Renal, Cardiac…
- More common in minority ethnic groups: Native Americans, Non-Hispanic blacks, Hispanics, Asians/ Pacific islands.

Pediatric onset type 2 differs from adult onset regarding durability of glycemic control.
Type 2 DM of the young

- **Metformin** is an insulin sensitizer with few side effects.
- **Pioglitazone can be used** in addition to metformin but has more side effects and is not FDA approved. (Today study group: N Engl J Med 2012;366;2247-56.
- **Lifestyle modifications:**
  1. Moderate to vigorous exercise 60 min a day
  2. Low sugar and low carbohydrate (no sugary drinks )
  3. Increase vegetables consumption 3-5 serving a day
  4. Decrease screen time to less than 2 hr. a day.
  5. Decrease processed foods.

Some will require insulin at the start or after a few years.
There is a phenotypic overlap between the different types of diabetes

T1D exchange registry 2015 included 11,000 US kids: 24% were overweight and 15% were obese.

Type 2 DM phenotypically, 10-17 years in 2010: 10% had some evidence of islet autoimmunity.

In such cases, a detailed family history, measurements of islet autoantibodies and plasma C peptide measurement may be helpful.

The Treatment with Insulin if needed.+++

Determining the type of diabetes should not delay

+++

The Treatment with Insulin if needed
What tests might help to differentiate them?

- Fasting C peptide. Below 0.85 ng/ml, it has a 83% sensitivity in distinguishing type 1 and 2.
- Autoantibody tests pancreatic islet cell, GAD 65, IA2, ZnT8 antibodies.
- IGFBP1 an indirect measure of insulin resistance. IGFBP1 less than 3.6 ng/dl distinguished T2DM with 93% sensitivity.

IF acceptable BG cannot be maintained with lifestyle changes and Metformin, you must use Insulin.

Also if BG over 250 mg/dl, + ketones, symptoms or A1c over 8.5 % start Insulin while waiting for lab results and for Metformin to work. Educate the patient and family.
Monogenic diabetes

- Caused by one gene, autosomal dominant.
  1. Neonatal diabetes *before 6 months of age*
  2. MODY

- This diagnosis has **profound implications** for treatment of the patient and diagnosis of other family members.
Monogenic Diabetes

1.2 to 4% of pediatric diabetes.

Frequently misdiagnosed as Type 1 and treated with insulin. Sometimes misdiagnosed as Type 2.

Prevalence in pediatrics = 2.1 per 100,000

Main features
How to work up a young obese diabetic patient?
Neonatal Diabetes

- Rare 1/300,000 - 1/500,000
- Defined by Persistent hyperglycemia at least 2 weeks and requiring insulin.
- Long term sequels: Developmental delay, cardiac anomalies, seizures, poor weight gain.

A) Transient NDM 57 %:
1. May require insulin initially, may spontaneously resolve in less than 18 months to reoccur in later years.
2. Intrauterine growth retardation
3. 68% due to abnormality in 6q24 chromosome. May respond to sulfonylurea.
4. Mutation of hepatocyte nuclear factor 1 Beta (HNF1Beta) can cause MODY 5 and TNDM.
Neonatal Diabetes

B) Permanent NDM in 43%

- Cannot be distinguished from TNDM and has same features with IUGR and FTT.

These babies need genetic analysis right away because it will allow a clinical prognosis, treatment and genetic counseling.

Mutations of 2 genes PDX1/IPF1 and Glucokinase can cause MODY in heterozygous conditions and PNDM in homozygous conditions.
When to suspect diagnosis of type 2 DM is incorrect a young person diagnosed <25 years old:

- No acanthosis nigricans
- Ethnic background has with low prevalence: White non Hispanic
- No evidence of insulin resistance with fasting C peptide in normal range.
- If not markedly obese or diabetic family members who are normal weight.
When to suspect diagnosis of type 1 is incorrect? Pediatric diabetes (2006): 7; 352-361

- Diagnosis before 6 months of age
- Family history with 1 parent affected. (In type 1: only 2-4% of parents are affected).
- Evidence of endogenous insulin production outside of honey moon phase (after 3 Y) with detectable C peptide and mild hyperglycemia.
- Pancreatic islet cell antibodies are absent at diagnosis
<table>
<thead>
<tr>
<th>Common forms monogenic diabetes</th>
<th>Inheritance</th>
<th>Nb of families in UK</th>
<th>Typical age of presentation in pediatrics</th>
<th>Glucose range at presentation</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF-1 alpha MODY3</td>
<td>AD</td>
<td>197</td>
<td>14 (4-18)</td>
<td>198-466 mg/dl</td>
<td>-OGTT increase glucose &gt;90mg/dl -Low renal -Progressive hyperglycemia sulfonylurea</td>
</tr>
<tr>
<td>HNF-4 alpha MODY1</td>
<td>AD</td>
<td>22</td>
<td>17 (5-18)</td>
<td>162-360</td>
<td>-Normal renal threshold -Macrosomia -Prolonged NN hypoglycemia in 20%. Sulfonylurea</td>
</tr>
<tr>
<td>Glucokinase MODY 2</td>
<td>AD</td>
<td>152</td>
<td>10 (0-18)</td>
<td>99-288</td>
<td>-Incidental -FBG 99-144 OGTT:63mg/dl No RX treatment</td>
</tr>
</tbody>
</table>
Preventing Type 2 DM

- WHY?
- WHO?
- HOW?
Why?

- Type 2 DM **is not** a milder disease for kids.
  1. We see them at a younger age each year
  2. They may already have complications and comorbidity when they come to attention.
  3. They will have the disease for a long time or the propensity for the disease.
  4. **Their parents may outlive them+++**
  5. They may require Insulin treatment

- Type 2 is very costly. May not be covered by insurance when the kids start working.

- **IT IS PREVENTABLE!**
Who?

- At risk groups: Native Americans, African, Hispanics, Pacific Islanders.
- Caucasians if there is strong family history of diabetes and/or:
  - Overweight or Obese children
  - Physical signs of insulin resistance: AN, abdominal obesity.
- Comorbidities: Polycystic ovarian syndrome, hypertriglyceridemia, hypercholesterolemia, hypertension.
- Complications: Microalbuminuria, retinopathy, myocardial infarction, neuropathy...
What to look for?


- **EXAMINE THE PATIENT:**
  1. Acanthosis Nigricans, abdominal obesity.
  2. Hirsutism and acne in adolescent females.

- **If LABS SHOW:**
  - Random Blood glucose > 140-160 mg/dl
  - Fasting blood glucose > 106mg/dl
  - A1c > 5.7% for girls, > 6.2% for boys
How to prevent it?
The Million-dollar question.

- Teach the child to eat better and less.
- Encourage physical activity at home and at school.
- Get off the phone and the computer.
- Spend quality time with your kids.
- ADULTS: PLEASE Show the example everywhere: at home, at school, at work, at places of worship, in hospitals.
Every health care provider, nurse, dietitian, educator, parent, grandparents and guardians must work at preventing it!

- Not enough pediatric endocrinologist to fulfill this role. Primary care providers must start in their office.
- Everyone must start at home, work, schools, places of worship, restaurants and get educated about how to avoid it.
- It can be reversed or prevented by teaching good habits.
- Myths “Bigger is better and healthier”
- There is pressure from various food industries, sodas and juice companies. Advertising++. Get off the TV, the phone and the computer screen.
Nutrition

STOP drinking soft drinks, juices, and sugared beverages (that includes your favorite Starbucks drink), instead Drink water, milk, or equivalents of milk.

- Do not fall in the trap of diet drinks. Your body does not recognize it and you get more hungry.
- Limits sweets and deserts to special occasions. It is not an everyday need. If you want to be nice to your child, rewards with active toys or clothes or time with you.
- Limit portions of carbohydrates and avoid second and third servings.
- Limit animal fats and use leaner proteins; lean meats, fish...
Avoid processed food. They are rich in sugars, salt, colorants and preservatives.

When eating carbs, prefer; whole wheats, brown rice, ancient grains.

Replace carbs with a large portions of vegetables (not potatoes, not corn)

*STOP* Frying foods, instead bake, broil, grill, steam.

- 2 portions of fruits a day, max.
- **Eat out less** and avoid all you can eat buffets.
- Do not buy cereals with colors and added sugars.
Lifestyle

- Limit screen time for you and your children: Phone, TV and computer. No more than 1-2 H a day.
- Eat family dinner together and teach yourself and kids to cook.
- Be physically active on weekends. Family outings. Hiking, biking, camping, tennis, football, soccer, bowling, dancing....
- Be physically active during the week: Walk fast after school or work.
- Sign up for sport activities for your child.
- Show the example!
A Society problem and A cultural problem.

- Be Engaged for the sake of your children; parents, educators, health professionals, business leaders.
Conclusions

- Both type 1 and type 2 incidence continue to increase in young people.
- If poorly controlled, they have similar outcomes and type 2 can present with already severe complications.
- Type 2 DM is preventable and/or can be delayed.
Conclusions

- Some patients are misdiagnosed with Type 1 or 2 diabetes when they have monogenic diabetes. It is important to recognize them because some may be treated without insulin.

- The increase in Type 2 diabetes in children mirrors the increase in obesity rates and can be prevented by starting good habits or reversing bad habits. **START NOW!!!**

- You must be engaged to help prevent diabetes at your children's school, place of work, or worship.

- Don't be afraid to talk to the grandparents and your child.
### Uncommon/common insulin-resistance syndrome

**Table 3. Characteristics of common insulin-resistance syndromes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Onset</th>
<th>Clinical features</th>
<th>Acanthosis Nigricans</th>
<th>Androgen Excess &amp; Hypertrichosis</th>
<th>Insulin levels</th>
<th>Gene Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leprechaunism</td>
<td>Congenital</td>
<td>Abnormal facies, large genitalia, SGA and growth retardation</td>
<td>Yes — marked</td>
<td>💯</td>
<td>💯</td>
<td>Insulin receptor, Usually recessive</td>
</tr>
<tr>
<td>Rabson-Mendenhall</td>
<td>Congenital</td>
<td>Rarely survive infancy, extreme growth retardation</td>
<td>Yes — marked</td>
<td>💯</td>
<td>💯</td>
<td>Insulin receptor</td>
</tr>
<tr>
<td>Type A</td>
<td>Adolescence</td>
<td>Abnormal dentition, IR in absence of obesity</td>
<td>Yes — marked</td>
<td>💯</td>
<td>💯 PCO</td>
<td>Insulin receptor, Usually recessive</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>Congenital or Adolescence</td>
<td>Loss of subcutaneous fat — partial or total</td>
<td>Yes — may be marked</td>
<td>💯 PCO +/-</td>
<td>💯</td>
<td>Total: Seipin &amp; AGPAT2 (recessive), Partial: Lamin AC &amp; PPARG (dominant)</td>
</tr>
</tbody>
</table>

*Source: Pediatric Diabetes 2000: 10 (Suppl. 12): 33–42*