Diabetes Mellitus in Children and Adolescents

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Learning objectives

- Discuss initial screening and diagnostic criteria for Type 1 and Type 2 Diabetes
- Discuss treatment strategies for Type 1 and Type 2 Diabetes
- Review the management of Diabetic Ketoacidosis (DKA)
- Discuss the pharmacist role in the care of the pediatric diabetic patient
Prevalence

- Diabetes is one of the most common chronic diseases of childhood.

- Based on 2002–2003 data rate of new cases:
  - type 1 diabetes: 19 per 100,000 children
  - type 2 diabetes: 5.3 per 100,000
  - About 2 million adolescents aged 12-19 have pre-diabetes

- Incidence is increasing for both Type 1 and Type 2
- Increasing rates, especially Type 2, correlates with increased obesity rates

Some Hong Kong statistics

- Type I DM
  - Wide variation of incidence within Chinese children
  - Highest rate in Hong Kong: 2 per 100,000

- The incidence rates of both type 1 and type 2 diabetes mellitus in Chinese children are increasing.
- 10% to 15% of cases of childhood diabetes in Hong Kong are type 2
- High prevalence of childhood obesity is 10% to 14% in Hong Kong children,
- Incidence of type 2 diabetes mellitus in adolescents and young adults is expected to increase

Chan, J. Heterogeneity of diabetes mellitus in the Hong Kong Chinese population. The Chinese University of Hong Kong—Prince of Wales Hospital Diabetes Research and Care Group *HKMJ* 2000;6:77-84
ADA Classification (2010)

- **Type 1**: β-cell destruction, absolute insulin deficiency
- **Type 2**: insulin resistance with progressive insulin secretory defect
- **Other**:
  - Genetic defect in β-cell function
    - MODY (Maturity Onset Diabetes of Youth)
  - Genetic defect in insulin action
  - Diseases of the exocrine pancreas (Cystic Fibrosis, Pancreatitis etc.)
  - Endocrinopathies (acromegaly, Cushing’s, etc.)
  - Drug or chemical induced (Glucocorticoids, Immunosuppressants, thyroid hormones, thiazides etc.)
- **Gestational diabetes**: diagnosed during pregnancy
Criteria do diagnosis diabetes (ADA 2010)

- A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
- OR
- FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*
- OR
- 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
- OR
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).
Microvascular complications

- **Retinopathy**
  - Faster rate of progression in adolescents with poor glycemic control

- **Nepropathy**
  - Major cause of morbidity and mortality in young adults with Type 1 DM
  - Early detection nephropathy and BP control important to prevent ESRD
  - Hypertension and/or albuminuria: consider ACEIs

- **Neuropathy**
  - Incidence 9 to 58% of T1DM
Macrovascular complications

- Atherosclerosis changes have been observed in young adults with childhood onset diabetes
- Early onset DM increase risk of MI later in life by 4 fold
- Risk factors:
  - Poor glycemic control
  - Hypertension
  - Lipid abnormalities
  - High BMI
  - Smoking
## Screening and follow up management

<table>
<thead>
<tr>
<th>Disease</th>
<th>Screening</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic control</td>
<td>Hg A1C every three months</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>TSH at dx and q 1 – 2 years</td>
<td>Thyroid replacement</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Start at 10 y.o and 5 years after diagnosis. Annually</td>
<td>Improve glycemic control, stop smoking, optimize BP control, ACEI</td>
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<tr>
<td>Hypertension</td>
<td>Every visit R/o other causes</td>
<td>Life style modification ACEI</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Start at age 2 y if + family hx</td>
<td>Keep LDL &lt; 100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Start at 12 y if – family hx and repeat every 5 years</td>
<td>Optimize glycemic control</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>At age of 10 and 3-5 years after dx. Annually</td>
<td>Improve glycemic control</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>If sub optimal wt gain. Every other year.</td>
<td>Gluten free diet</td>
</tr>
<tr>
<td>Mental health</td>
<td>Screen for depression start &gt; 10 y.o.</td>
<td></td>
</tr>
<tr>
<td>Growth assessment</td>
<td>Every visit</td>
<td>Ensure proper wt/ht growth</td>
</tr>
<tr>
<td>Immunizations</td>
<td>Follow AAP schedule</td>
<td>Flu vaccine in all children &gt; 6 months</td>
</tr>
</tbody>
</table>
Acute complication: Diabetic Ketoacidosis (DKA)

- Potentially life threatening complication of DM
- Severe insulin deficiency along with high levels of counter regulatory hormones (glucagon, cortisol, growth hormone), induce a catabolic state with gluconeogenesis and decrease glucose uptake which will result in hyperglycemia and osmotic diuresis.
- Lyposis is stimulated leading to ketogenesis which resultant metabolic acidosis
Figure 43-10 Mechanisms of diabetic ketoacidosis. Diabetic ketoacidosis is associated with very low insulin levels and extremely high levels of glucagon, catecholamines, and other counterregulatory hormones. Increased levels of glucagon and the catecholamines lead to mobilization of substrates for gluconeogenesis and ketogenesis by the liver. Gluconeogenesis in excess of that needed to supply glucose for the brain and other glucose-dependent tissues produces a rise in blood glucose levels. Mobilization of free fatty acids (FFA) from triglyceride stores in adipose tissue leads to accelerated ketone production and ketosis.
DKA: clinical manifestations

- Dehydration
- Rapid, deep sighing respirations (Kussmaul)
- Nausea, vomiting, abdominal pain
- Increased leukocyte count
- Fever when infection is present
- Progressive obtundation and loss of consciousness
- It may progress to cerebral edema and death
- Stress, trauma, infections can lead to DKA

Precipitant factors:
- New presentation
- Non compliance with insulin
Risk factors

- Poor metabolic control
- Adolescent girls
- Limit access to medical services
- Insulin pump therapy
- Unstable family situation
DKA: lab abnormalities

- Hyperglycemia (blood glucose > 11 mmol/L (200 mg/dL))
- Venous pH < 7.3 or bicarbonate < 15 mmol/L
- Blood positive for ketones
- Urine positive for ketones (Ketonuria)
- Hypokalemia
- Hypophosphatemia
Assessing severity

- Based on degree of acidosis
  - Mild: venous pH < 7.3 or bicarbonate < 15 mmol/L
  - Moderate: pH < 7.2 or bicarbonate < 10 mmol/L
  - Severe: pH < 7.1 or bicarbonate < 5 mmol/L
Hyperglycemic hyperosmolar state (HHS)

• Rare in T1DM

• Characterized by:
  ○ Blood sugar > 33.3 mmol/L (600 mg/dL)
  ○ Arterial pH > 7.3
  ○ Serum bicarbonate > 15 mmol/L
  ○ Mild ketonuria, mild or absent ketonemia
  ○ Serum osmolality > 320 mOsm/kg
  ○ Stupor or coma
DKA management goals

1) Correct dehydration
2) Correct acidosis and reverse ketosis
3) Restore blood glucose to close to normal
4) Avoid complications of therapy
5) Identify and treat precipitating event
Fluid replacement

- Restore circulatory volume
  - 0.9% NaCl or Lactate Ringers
  - 20 mL/kg given as quickly as possible
  - 10 mL/kg if necessary

- Subsequent IV therapy
  - 10% deficit correction + maintenance - bolus
  - Isotonic fluids (0.45% or higher), add potassium when patient has voided
Insulin treatment

- 0.1 unit/kg/hour as continuous infusion, may be decreased if blood glucose dropping too fast
- Do not give bolus as it increases risk of cerebral edema
- Rate of plasma glucose concentration no faster than 2 – 5 mmol/L/hour
- Add dextrose to IV fluids (5% dextrose) when blood sugar reaches 14 – 17 mmol/L (250 – 300 mg/dL)
- Insulin therapy continues until metabolic acidosis is resolved (pH > 7.3 and bicarbonate > 15 mmol/L)
Electrolyte abnormalities

- **Potassium**
  - Deficit of 3 – 6 mmol/kg.
  - Start replacement at time of volume expansion. If hyperkalemic wait until patient voids
  - Start with 40 mmol/L, adjust based on serum electrolytes
  - May combine KCL 20mmol/L + Kphosphate 20 mmol/L
  - Potassium infusion rate not to exceed 0.5mmol/kg/hr

- **Phosphate**
  - Secondary to diuresis
  - Watch for hypocalcemia
  - Combine with KCL as above
Acidosis

- Reversible by fluid and insulin replacement
- No benefit from bicarbonate administration.
- It can lead to paradoxical CNS acidosis and worsen hypokalemia
- Cases where bicarbonate may be considered:
  - Severe acidemia (arterial pH < 6.9) with decreased cardiac contractility
  - Severe hyperkalemia
DKA management

- Therapy complications
  - Hypoglycemia
  - Hypokalemia
  - Hyperchloremic acidosis
  - Cerebral edema
  - Inadequate hydration

- Monitoring
  - At least hourly Input/Output measurements
  - Hourly blood glucose
  - At least hourly vital signs
  - At least hourly neurological exam for signs of cerebral edema
Cerebral edema

- Incidence 0.5% - 0.9%  Mortality: 21% to 24%

- Signs
  - Headache and bradycardia
  - Change in neuro status
  - Rising BP
  - Decrease O2 saturations
  - Neuro signs (cranial nerve palsies)

- Treatment
  - Decrease IV fluids by 30%
  - Mannitol 0.5 to 1 g/kg over 20 minutes
  - Hypertonic 3% saline 50-10 mL/kg over 30 minutes
  - Elevate head of bed
  - Endotracheal intubation if necessary
Type 1 Diabetes
T1DM: epidemiology

- More than 75% of T1DM is found in children
- Girls and boys equally affected
- Peak presentation
  - 5 – 7 years
  - Puberty
- Tends to run in families
T1DM: pathogenesis

- Insulin deficiency secondary to autoimmune destruction of the pancreatic β-cells.
- Genetic predisposition and environmental factors initiate the autoimmune process against pancreatic beta cells.
- The autoimmune attack to pancreatic islets cells leads to progressive destruction of beta cells and decrease of insulin secretion.
- At the time of onset up to 90% of pancreatic cells have been destroyed.
T1DM: pathogenesis

- Multiple autoantibodies may be present at time of onset:
  - Islet cell autoantibodies.
  - Glutamic acid decarboxylase autoantibodies (65K GAD isoform).
  - IA2 (also known as ICA512 or tyrosine phosphatase) autoantibodies.
  - Insulin autoantibodies.

- Associated with other autoimmune disorders: thyroiditis (17%), celiac disease, multiple sclerosis, Addison’s disease.
T1DM: clinical manifestations

- Severe hyperglycemia (typically > 200 mg/dL)
- Several weeks history of:
  - Polyuria
  - Polydipsia
  - Polyphagia
  - Weight loss
- 20%-30% present in diabetic ketoacidosis (DKA)
- Progression of symptoms may be accelerated in infants and young children. Most weight loss is acute water loss leading to potentially severe dehydration.
- “Flu-like” symptoms often present and susceptibility to infections
T1DM: Treatment goals

- Insulin replacement
- Glycemic goals vary depending on age, and ability to recognize hypoglycemic symptoms
- Prevent DKA
- Prevent hypoglycemia
- Promote adequate growth and development
- Prevent long term complications
Children are at a higher risk of developing hypoglycemia.

Glycemic goals must be balanced against the risk of hypoglycemia.
<table>
<thead>
<tr>
<th>Values by age (years)</th>
<th>Before meals</th>
<th>Bedtime/overnight</th>
<th>A1C (%)</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toddlers and preschoolers</td>
<td>100–180</td>
<td>110–200</td>
<td>≤8.5 (but ≥ 7.5%)</td>
<td>• High risk and vulnerability to hypoglycemia</td>
</tr>
<tr>
<td>(6–12)</td>
<td></td>
<td></td>
<td>&lt;8%</td>
<td>• Risks of hypoglycemia and relatively low risk of complications prior to puberty</td>
</tr>
<tr>
<td>School age (6–12)</td>
<td>90–180</td>
<td>100–180</td>
<td>&lt;7.5%*</td>
<td>• Risk of hypoglycemia</td>
</tr>
<tr>
<td>(13–19)</td>
<td></td>
<td></td>
<td></td>
<td>• Developmental and psychological issues</td>
</tr>
<tr>
<td>Adolescents and young adults</td>
<td>90–130</td>
<td>90–150</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key concepts in setting glycemic goals:
- Goals should be individualized and lower goals may be reasonable based on benefit: risk assessment
- Blood glucose goals should be higher than those listed above in children with frequent hypoglycemia or hypoglycemia unawareness
- Postprandial blood glucose values should be measured when there is a disparity between preprandial blood glucose values and A1C levels

*A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypoglycemia*
Why are the goals different?

• Higher risk of hypoglycemia (BG < 70-80 mg/dL)
• Infants and young children
  o lack of cathecolamine response to hypoglycemia
  o Unable to communicate hypoglycemia symptoms
  o Behavioral changes: low sugar or tantrum?
  o Unpredictability of food intake
  o Unpredictability of physical activity
  o Higher incidence of nocturnal hypoglycemia
• Need to avoid hypoglycemia because:
  o Developing brain is more sensitive to deleterious effects of hypoglycemia
  o Frequency of episodes associated with long term cognitive impairment, especially before 5 years of age
INSULIN TYPES

- **Rapid acting: human insulin analogs**
  - Insulin Lispro (Humalog®, Insulin Aspart (Novolog®), Insulin glulisine (Apidra®).
  - Onset: 15 – 20 minutes
  - Peak: 1 – 3 hours
  - Duration: 3 – 5 hours
  - Works well in young kids who have unpredictable eating habits. May be administered immediately after meals

- **Short-acting insulin**
  - Regular human insulin
  - Rarely used in children anymore
  - May require delay the meal 30 to 60 minutes for optimal effect (hard to do with young child!)
  - More likely to cause prolonged peaks, with higher risk for between meal and nighttime hypoglycemia
  - Onset: 30 – 60 minutes
  - Peak: 2 – 4 hours
  - Duration: 5 – 8 hours
Rapid-acting Insulin Analogs

**INSULIN TYPES**

- **Intermediate acting insulin**
  - Isophane insulin suspension (NPH)
  - Associated with nocturnal hypoglycemia
  - Onset: 2 – 4 hours
  - Peak: 4 – 12 hours
  - Duration: 12 – 24 hours

- **Long acting**
  - Insulin glargine (Lantus®): human
    - Approved for children 6 years and older
  - Insulin detemir (Levemir®)
    - Studied in children with T1DM age 6 to 17 y.o.
    - Often requires twice daily dosing
  - Onset: 1 - 4 hours
  - Peak: None
  - Duration: 20 – 24 hours
T1DM: insulin dosing

- Insulin requirements based on:
  - body weight, age and pubertal status, nutritional intake, exercise, undercurrent illness

- Children with newly diagnosed DM
  - 0.5 to 1 unit/kg/day.

- Younger children may require less insulin.

- Pubertal children:
  - Requirements up to 1.5 to 2 units/kg/day
  - Due to growth hormone and sex steroids induced insulin resistance.
T1DM: insulin regimen

- **Two to three injections daily**
  - Short/rapid insulin analog before meals and/or snacks + intermediate acting insulin twice a day
  - 50%-60% children DOES NOT attain target A1C and blood sugar targets with this regimen
  - Higher incidence of hypoglycemia episodes during the night.
T1DM: intensive insulin regimen

- These are the preferred regimens
- Basal-bolus regimen
  - Rapid acting insulin analog before meals based on CHO intake/activity + long acting insulin once or twice a day

- Continuous subcutaneous insulin infusion (CSII, insulin pump) – Insulin pump
  - Fixed or variable basal dose + bolus doses with meals and snacks
Basal/bolus regimen:

- Have been shown to lower fasting BG with less hypoglycemia than regimens with NPH insulin.
- Allows for greater flexibility for timing and carbohydrate contents.
- Disadvantage: requires multiple injections

Basal insulin (glargine or detemir)
- It usually accounts for 40 to 60% of insulin total daily dose
Basal/Bolus Treatment Program with Rapid-acting and Long-acting Analogs

Breakfast: Aspart Lispro Glulysene
Lunch: Aspart Lispro Glulysine
Dinner: Aspart Lispro Glulysine

Glargine or Detemir

Plasma insulin

4:00 8:00 12:00 16:00 20:00 24:00 4:00 8:00
Basal/bolus regimen
How to determine the bolus dose

Carbohydrate ingestion (carb counting)

On average 1 unit of insulin will cover:
• 20 gm of CH in children (1 – 6 y.o)
• 10 -15 gm of CH in pre-pubertal children
• 8 -10 gm of CH in adolescents
• “500 rule” = 500/TDD = grams of carbohydrate covered by 1 unit short acting insulin
• Adjust according to response:

Correction factor

Rapid acting analog insulin dose (bolus)

Based on blood glucose level
• “1800 rule” = 1800/ insulinTDD = mg/dL that 1 unit of rapid insulin will lower BS
• Commonly 1 unit insulin for each 50mg/dL above BG goal
• Adjust according to response:

Level of activity
T1DM: blood glucose monitoring

- Multiple BG tests should be done daily to determine patterns of low/high BG and adjust insulin regimen.
  - Pre-breakfast, pre-lunch, pre-dinner, bedtime
  - Mid-morning, mid-afternoon and 2a – 3 am may PRN

- Good correlation between frequency of BGM and glycemic control.

- Preprandial BG levels important, but postprandial and overnight also important to adjust insulin regimen.

- Special attention to pre-schoolers that may not be able to identify and report hypoglycemia.
T1DM: exercise

- Exercise is encouraged!
- Hypoglycemia is likely to occur in physical activity lasting > 30 minutes.
- Check BG before and up to 6 hours after activity.
- Activity in late afternoon or evening may cause nocturnal hypoglycemia
- Advise patients not swim alone.
- Coaches/trainers should be aware signs of hypoglycemia, and allow for testing and snacks
T1DM: nutrition

- Consultation with dietitian recommended to develop individualized meal plan that accommodate for food preferences, cultural influences, physical activity and family eating schedule.
- Calories should be adequate for growth and development.
- Caloric mixture: 55% CHO, 30% fat, 15% protein
  - CHO: encourage complex CHO (starches) prolonged digestion and absorption leads to slow increase of BG
  - CHO: restrict intake of sucrose or refined sugars, which leads to wide swings on blood sugar levels.
  - Sugar free carbonated beverages
DM 1: age considerations

- Infants and pre-schoolers
  - Infants have highest risk of severe hypoglycemia with seizures and coma.
  - Nocturnal hypoglycemia more frequent
    - May require lower basal rates during night or lower doses at dinner
  - Unpredictable food intake
    - Give rapid acting insulin after food intake
  - Acute illness have significant impact on BG
DM 1: age considerations

- Children 6 to 12 years old
  - Should start assuming more of daily diabetes management under close adult supervision
  - May require insulin during school hours
  - Able to report hypoglycemia symptoms
DM 1 : age considerations

- Adolescents
  - Hormonal changes lead to insulin resistance and higher insulin requirements
    - Higher insulin requirements during night, when growth hormone secretion peaks
  - Should be able independently perform daily diabetes management tasks.
  - Parents supervision still encouraged.
  - Compliance issues, may skip doses to prevent weight gain
  - Routine annual screening for depression
Education

- Better accomplished by multidisciplinary team
- Essential of diabetes
- Diabetes skills
  - Blood glucose testing
  - Insulin administration
  - Hypoglycemia/Hyperglycemia symptoms
  - Hypoglycemia management
    - Glucagon emergency kit
  - Sick day management
    - Ketones testing
- Nutrition
  - Dietician consult
- School issues
- Psychosocial support
- Follow up
Insulin pens and syringes

Pen Junior allows for 0.5 unit dosing increment

Syringe sizes:
- 30 units (1/3 cc)
- 50 units (0.5 cc)
- 100 units (1 cc)
**Education**

- **Glucagon Kit**
  - Hypoglycemic emergencies

- **Keto-Diastix**
  - √ urine ketones when:
    - BG > 250
    - Sick
Type 2 diabetes (T2DM)
Type 2 Diabetes Mellitus

- Insulin resistance
  - Strongly associated with obesity
  - Genetic predisposition
  - Leads to hyperinsulinemia

- Impaired $\beta$-cell function
  - Insulin secretory defect
T2DM: risk factors

- Obesity/sedentary life
- Race/ethnicity
  - African-American
  - Hispanic
  - Native Americans
- Family history
  - 85% pts have other family members with T2DM
- Puberty
  - augmentation of growth hormone

- Polycystic ovary syndrome
- 15% PCOS have diabetes
- Acanthosis nigricans
- Intrauterine factors
  - Children whose moms had gestational diabetes
  - Low birth infants
Testing for type 2 diabetes in children

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Overweight (BMI &gt;85th percentile for age and sex, weight for height &gt;85th percentile, or weight &gt; 120% of ideal for height)</td>
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<tr>
<td>Plus any of the two risk factors:</td>
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<tr>
<td>Family history of type 2 diabetes in first or second degree relatives</td>
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<tr>
<td>Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)</td>
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<tr>
<td>Signs of insulin resistance or conditions associated with insulin resistance (PCOS, acanthosis nigricans, hypertension, dyslipidemia, or small for gestational age at birth)</td>
</tr>
<tr>
<td>Maternal history of diabetes or GDM</td>
</tr>
<tr>
<td>Initiate at 10 year or at onset of puberty if earlier</td>
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<tr>
<td>Frequency: Repeat every 3 years</td>
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</tbody>
</table>
Onset slow, often asymptomatic
Absence or mild polyuria or polydipsia
Obesity: present in 85% children
Ketonuria (33%), mild DKA (5%-25%)
Acanthosis nigricans (60%-90%)
Positive family history
Ethnicity
Increased C-peptide and insulin levels (although can initially be low due to glucotoxicity and lipotoxicity)
Diabetic autoantibodies should be tested in all pediatric patients
T2DM: treatment goals

- Achieve and maintain normoglycemia (FPG < 126 mg/dL)
- HbA1c < 7%
- Control comorbidities (hypertension, dyslipidemia, nephropathy)
- Lifestyle modification
  - Only 10% of success when used alone
  - Should be used in conjunction with all other tx modalities
  - Increase exercise
  - Weight loss
  - Nutrition plan
  - Family involvement is essential for success
At diagnosis most patients are started on monotherapy either with insulin or metformin.

Evidence in adults suggest: early insulin therapy facilitate glucose control and reverse hyperglycemia damage on β-cells.

Monotherapy is usually insufficient to control glycemia over long term.

Due to progressive loss of β-cell function, partly caused by poor glycemic control, multiple therapeutic agents may be required.
T2DM: treatment

- Asymptomatic
  - Lifestyle changes with diet and exercise

- Mildly symptomatic without ketosis and mild hyperglycemia (BG 126 – 200 mg/dL and HbA1c <8.5%)
  - Lifestyle changes + metformin

- Severe hyperglycemia (>200 mg/dL, HbA1c >8.5%, and/or ketosis)
  - Treat with insulin initially to achieve metabolic control
  - Metformin added when patient non longer ketotic
  - Lifestyle changes
T2DM and Insulin

- If therapy is inadequate after 3 – 6 months
  - Check compliance
  - Consider adding second oral agent or insulin
    - Metformin only agent FDA approved for children
    - Insulin may be added as a once a day injection of long acting analog (insulin glargine)
T2DM and Insulin

- Used more often than in adults
- Likelihood of insulin insufficiency if symptomatic at presentation
- Uncertainty about final diagnosis (type 1 vs. type 2)
- Familiar choice among pediatricians
- Lack of clinical studies on most oral agents
- Efficacy in improving metabolic abnormalities
  - Insulin glargine (Lantus®)
    - adult studies suggest that bedtime dose may improve glycemic control.
Oral antihyperglycemic agents
Metformin (Glucophage®)

- Biguanide class.
- Decreases hepatic glucose production and increases insulin uptake by tissues
- Only oral agent approved for use in children in the USA
- FDA approved for pediatric use over 10 y.o.
- Oral agent of choice to treat T2DM in children
- Start at 500 mg BID, titrate to 2 gm/day
- Main side effect: abdominal pain, nausea, diarrhea
- May normalize ovulation in PCOS = increase pregnancy risk = counsel appropriately
Metformin

- Shown to improve glycemic control within 2 weeks
- Decreases HbA$_{1c}$ by 1% to 2%
- Can be used as initial therapy for those without symptoms of hyperglycemia
- May be added after glucose levels improve with insulin treatment.

Contraindications:
- Renal impairment, hepatic dysfunction, concomitant use of radiographic contrast agents,
- Wait until ketosis is resolved to avoid lactic acidosis
- Initial anorexic effect may promote weight loss
Oral antihyperglycemic agents
Sulfonylureas

- Glyburide, glipizide, glimepiride
- Increase insulin secretion, useful when there is residual $\beta$-cell function

- In recent study with 285 adolescents glimepiride and metformin equally effective decreasing A1c. But more hypoglycemia

- Prolonged effects may lead to hypoglycemia
- Weight gain: problematic for adolescents
Oral antihyperglycemic agents
Thiazolidinediones (TZD)

- Rosiglitazone (Avandia®), Pioglitazone (Actos®)
- Increase insulin sensitivity in muscle, adipose and liver tissue. May have positive effects on lipids profile
- Side effects, edema, weight gain, possible increased risk of heart disease in adults.
- Limited use of Rosiglitazone in adolescents

TODAY (Treatment Options for Type 2 Diabetes in Youth) study:
- Multicenter study enrolling over 700 adolescents
- Will compare: Metformin alone vs Metformin + rosiglitazone vs. intensive lifestyle modifications
- Schedule to complete in 2011
The U.S. Food and Drug Administration announced that it will significantly restrict the use of the diabetes drug Avandia (rosiglitazone) to patients with Type 2 diabetes who cannot control their diabetes on other medications. These new restrictions are in response to data that suggest an elevated risk of cardiovascular events, such as heart attack and stroke, in patients treated with Avandia.
Oral antihyperglycemic agents

Glucosidase inhibitors

- Acarbose, miglitol
- Reduce absorption of carbohydrates in the upper small intestine, delay absorption in the lower intestine.
- Reduces post-prandial rise of plasma glucose
- The frequent complains of flatulence makes it unacceptable to most adolescents
Newer agents

• Incretin mimetics
  • Glucagon-like peptide 1 receptor agonists (GLP-1). Promote insulin secretion, suppress glucagon release, slow gastric emptying time.
  • Exenatide (BYETTA®)
    • Pharmacokinetic and tolerability study done in T2DM (10 -16 y.o.)
      • 2.5 and 5 mcg doses well tolerated, improved postprandial glucose compared to placebo.
• Amylin
  • Peptide co-secreted with insulin from pancreatic cell in response to food. Lowers BG by decreasing glucagon release, slowing emptying time and food intake.
  • Pramlintide (Symlin) is a synthetic form of the hormone amylin
• DDP-IV inhibitors
  • Inhibit the enzyme that breaks down GLP-1, prolonging its effects
    • Sitagliptin (Januvia) and saxagliptin (Onglyza)

• None are approved for children
• More experience is needed
T2DM: monitoring

- **Glycemic control**
  - FPG = 70 – 100 mg/dL
  - HbA1c < 7% (check every 3 months)

- **Lipid disorders: check annually**
  - LDL < 100 mg/dL, TG < 150 mg/dL, HDL > 35 mg/dL
  - Treat with lifestyle modification first, add statins if fails and child > 10 y.o.

- **Hypertension**
  - BP < 95th % for age, sex, height

- **Annual screening**
  - Microalbumin
  - Retinal exam