PES 2025 BOARD REVIEW COURSE

Type 2 diabetes

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a. Know the roles of insulin resistance, obesity, and insulin deficiency in the pathophysiology of type 2 diabetes **Slides 4-13**
b. Recognize the clinical and laboratory findings in type 2 diabetes and differentiate from other types of diabetes **Slides 32-36**
c. Recognize the various presentations of type 2 diabetes **Slides 38, 39**
d. Recognize that the co-morbid conditions associated with type 2 diabetes are the same as those associated with metabolic syndrome (eg, hypertension, hyperlipidemia, polycystic ovary syndrome, non- alcoholic fatty liver disease), and their treatment **Slide 63**
e. Understand the treatment of type 2 diabetes, including the mechanisms of action of the medications used **Slides 56-59**

Refer to ISPAD 2022 T2D guidelines (Shah et al., Pediatric Diabetes., 2022) for a table of medications (Table 4)

Biguanides (metformin)

Metformin is currently the most commonly used medication for treatment of T2D

Well studied in adults
- Effective, safe, and inexpensive

Most pediatric experience of oral agents

Metformin activates AMP-activated protein kinase (AMPK)

Predominant effect is suppression of hepatic gluconeogenesis.

Metformin also
- Increases insulin sensitivity
- Enhances peripheral glucose uptake (phosphorylation of Glut-4 enhancer factor)
- Increases fatty acid oxidation
- Decreases GI absorption of glucose.

Desirable properties
- Initial anorexic effect that may promote weight loss
- Mild improvement in lipids
- Improvement in menstrual irregularities/hirsutism in girls with T2D and PCOS
- May improve hepatic steatosis

Initial use is associated with a 1-2% reduction in HbA1c.
- TODAY study results indicate that metformin monotherapy will fail in 50% of adolescents, with median time to failure of 1 year.
- Metformin is least effective in Black youth

Intestinal side effects (transient abdominal pain, diarrhea, nausea) may occur. However, these can be eliminated in most patients with slow dosage titration over 3-4 weeks and instructions to always take the medication with food. The side effects may also be attenuated by the use of extended release formulations.

The risk of lactic acidosis with metformin is extremely low.
- Meta-analyses –no increased lactic acidosis even when used with contraindications
  - Salpeter et al Cochrane Database Syst Rev. 2010
- However, metformin use should be considered carefully in patients with renal impairment, hepatic disease, cardiac or respiratory insufficiency, or who are receiving radiographic contrast materials.
- Metformin should be temporarily discontinued during a gastrointestinal illness or other situations in which dehydration is a risk

- Metformin may normalize ovulatory abnormalities in girls with PCOS and increase pregnancy risk

Sulfonylureas and meglitinides (glipizide, glyburide, glimepiride, nateglinide, repaglinide)

Insulin secretagogue – promote insulin secretion

- most useful when there is residual beta cell function

Bind to receptors on the K+/ATP channel complex causing K+ channels to close, resulting in depolarization, increased intracellular calcium, and increased insulin secretion

Sulfonylurea sites equilibrate slowly and binding persists for prolonged periods; thus, traditional sulfonylureas have prolonged effects

Well studied in adults – effective, safe, inexpensive

- glyburide, glibenclamide, and chlorpropamide no longer recommended due to concerns for increased cardiovascular events in UKPDS

Side effects

- Weight gain
- Hypoglycemia
  - can be prolonged
  - may be more common in adolescents due to robust beta-cell function

No sulfonylurea approved for use in pediatrics

- One published clinical trial of glimeperide
  - Less effective than metformin
  - More hypoglycemia
  - More weight gain

Meglitinides bind to a separate site on the K+/ATP channel complex

Meglitinides have an intermediate equilibration and binding duration

- used for rapid enhancement of insulin secretion, e.g. before meals
- although risk for hypoglycemia less, it still exists

No glitinide agent approved for use in the pediatric population

Adherence a significant problem in adolescents

Thiazolidinediones (**TZDs**: rosiglitazone, pioglitazone)

PPARγ agonists

- bind to nuclear proteins, activating peroxisome proliferator activator receptors (PPARgamma), which are ubiquitous orphan steroid receptors particularly abundant in adipocytes.
- Activation increases formation of proteins involved in the nuclear based actions of insulin, including cell growth, adipose cell differentiation, regulation of insulin receptor activity, and glucose transport into the cell.
- The binding of the thiazolidinediones to PPARgamma receptors is ubiquitous, affecting muscle cell growth and migration in response to growth factors, including arterial walls smooth muscle.

TZDs increase insulin sensitivity in muscle, adipose, and liver tissue, with a greater effect on muscle glucose uptake than biguanides.

Well-studied in adults

- Long-term treatment associated with a reduction in HbA1c of 0.5-1.3%

Thiazolidinediones have differing effects on lipid profiles

- Pioglitazone overall effects beneficial
- Rosiglitazone overall effects neutral to slightly deleterious (lower HDL)

Substantial concern for side effects (most studies of rosiglitazone, may be less a problems for pioglitazone, but this is not entirely clear)

- Weight gain
- Edema
- Decreased bone density and increased fractures
- Increased congestive heart failure
  - Implications for youth with "young" hearts but hypertension and dyslipidemia unclear

- Macular edema
- Liver dysfunction
  - May not be a problem with newer TZDs in current use

No TZD approved for use in youth with T2D
- Very limited pediatric experience
- One clinical trial completed – never published
- TODAY trial – rosiglitazone decreased loss of glycemic control by 23%

Glucosidase inhibitors (acarbose)

Reduce the absorption of carbohydrates in the upper small intestine by inhibiting breakdown of oligosaccharides
Delay absorption in the lower small intestine.
Reduce the postprandial rise of plasma glucose.
Long-term therapy is associated with 0.5-1% reduction in HbA1c.
Frequent side effect of flatulence makes these agents unacceptable to most adolescents.

Pramlintide (amylin)

Amylin is co-secreted with insulin from pancreatic beta cells in response to food.
Lowers glucose
- decreasing glucagon release
- slowing gastric emptying
- decreasing food intake

Pramlintide is an injectable drug, given prior to meals.
Long-term therapy associated with 0.5 – 1% reduction in HbA1c
Modest weight loss or weight stabilization is generally seen with treatment.
Side effects are
- Hypoglycemia
  - Recommendation to decrease insulin dose by 50% initially
- nausea,

Pramlintide is not approved in the pediatric population and is only approved for use in the US for patients with T2DM who are taking insulin.

Incretin mimetics

<u>Glucagon-like peptide-1 [GLP-1] receptor agonists</u> (exenatide, liraglutide, dulaglutide, semaglutide)

GLP-1 is rapidly secreted by L-cells from the small intestine into the circulation in response to food
- increased insulin secretion proportionate to BG concentrations
- slowed gastric emptying
- suppression of glucagon release
- decreased appetite

Reduced fasting and post-prandial BG, weight loss, and lower HbA1c.
Adverse effects include nausea (44%), vomiting, diarrhea, and headache. Nausea decreases over time
- Some cases of pancreatitis reported, but association unclear

Black box warning for family history of medullary thyroid carcinoma
Rapidly degraded by dipeptidyl peptidase-IV (DPP-IV)
- both native and injected drug have a half-life of 2 minutes

Liraglutide (daily), exenatide, dulaglutide, semaglutide (once weekly) approved for use in pediatrics (T2D or obesity indications- different doses)

<u>Combined GLP-1 and GIP (gastric inhibitory polypeptide) receptor agonists</u>

Tirzepatide- Increased weight loss compared to GLP-1 receptor agonists
Not approved for use in pediatrics- Trials underway

DPP-IV Inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)
- Inhibit the enzyme that degrades endogenous GLP-1
- Reduce A1c, but have no effect on satiety or weight loss
- Given orally once a day
- Adverse effects limited. Upper respiratory tract infection, nasopharyngitis and headache
- No DPP-IV inhibitor approved for use in pediatrics

SGLT-2 inhibitors (empagliflozin, canagliflozin, dapagliflozin)
- Lower renal glucose threshold
  - Increased glucosuria in glucose dependent fashion
    - Decreased fasting glucose
    - Decreased post-prandial rise in glucose
- Increased vaginal candidiasis, increased UTI in uncircumcised men
- Given orally once a day
- Empaglifozin approved for use in pediatrics

f. Understand the inheritance of type 2 diabetes and its implications for testing and counseling of family members **Slide 27**
g. Recognize the public health implications of type 2 diabetes in youth and possible public health interventions aimed at the prevention of type 2 diabetes **Slide 60**
h. Know the effect of adiponectin, leptin, IL-6, and TNF-alpha on insulin sensitivity and markers of insulin resistance **Slides 15-21**
i. Know the cellular origin of adiponectin, ghrelin, amylin, glucagon- like peptide-1 (GLP-1) and leptin Slides **15-21**
j. Know the effects of exogenous obesity on adiponectin and leptin levels **Slide 23**
k. Know the association between insulin resistance and amylin levels **Slide 25**
l. Understand the actions of glucagon-like peptide-1 (GLP-1) on the GI system, pancreas, and brain **Slide 21**
m. Know when to monitor for lipids, blood pressure, and urine micro- albumin in patients with type 2 diabetes at diagnosis **Slide 63**
n. Know the implications of large, pivotal diabetes trials **Slides 40-52**
o. Understand that a reduced calorie diet and exercise are more effective than metformin in slowing the progression of type 2 diabetes **Slides 53-55 (Not in children!)**
p. Know screening criteria for type 2 diabetes in youth **Slides 28-30**
q. Know the treatment of co-morbid conditions associated with type 2 diabetes and metabolic syndrome **Slides 62-71**