Type 2 DM in Adolescents: Use of GLP-1 RA

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Objectives

- Identify patients in the pediatric population with T2DM that would potentially benefit from the use of GLP-1 RA
- Discuss changes in glycemic outcomes of adolescents patients with T2DM after receiving GLP-1 RA
- Develop a plan for patient-centered care coordination and communication in the management of pediatric patients using GLP-1 RA

Background

- T2DM occurs:
  - Youth second decade of life average age 13.5 years
  - All races, but much higher in non-white Europe descent, Black African, native North American, Hispanic Asian, Native Pacific Islanders
  - Role of obesity
  - T2DM complex, chronic metabolic disease associated with many complications.

Scope of Problem: Obesity

- 36% of 6-11year-olds
- More than doubled in children and tripled in adolescents in past 30 years
- 15-40% caloric intake comes from junk food
- Soft drinks # 1 source of added sugar

Scope of Problem: Burden of Diabetes

- Alabama: highest rate of diagnosed diabetes 10.5%
- Diabetes is the 6th leading cause of death in Alabama
- Most common chronic disease among children in US
- The World Health Organization projects that by 2030 approximately 388 million people worldwide will have the disease *(Centers for Disease Control [CDC], 2005)*

Pathophysiology of T2DM

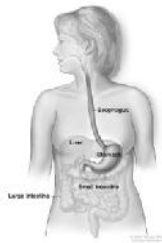
- All T2DM have a relative defect in beta cell dysfunction and mass
- Function: newly diagnosed T2DM had on average about 50% of normal beta cell function at diagnosis *(Diabetes Res Clinical Practice, 2010)*
- Mass: studies comparing volume of beta cells in nondiabetic patients to patients with T2DM found a 41% decrease in beta cell mass in the T2DM patients *(Diabetes Res Clinical Practice, 2010)*

Pathophysiology of T2DM

- Insulin Resistance
- Starts early in course of disease
- Insulin resistance alone will not produce diabetes, beta cell production is normal, patients compensate by increasing insulin secretion

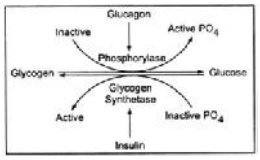
Gastric Emptying Factor

- Many factors can affect the rate of gastric emptying
- Studies suggest that all other factors being equal, most people with type 1 and T2DM have accelerated gastric emptying compared to non-diabetics



Glucagon Factor

- Glucagon secretion in T2DM is increased



- Insulin and Glucagon abnormalities produce an excessive postprandial glucose excursion

Treatment of Problem

- Lifestyle modification is first-line therapy
- Metformin, alone or in combination with insulin, is approved by the FDA to treat T2DM in pediatric patients; many patients remain uncontrolled with these medications
- Rosiglitazone and glimepiride have also been studied in pediatric patients with T2DM
- Limited studies exist; however, studies suggest tight control reduces the risk of microvascular complications

What are Incretins?

- Hormones produced by GI tract in response to incoming nutrients and have important actions that contribute to glucose homeostasis
- Two Hormones:
  - Gastric inhibitory polypeptide(GIP)
  - Glucagon-like peptide-1(GLP-1)

What are Incretins? Glucagon-like Peptide

- 30-amino acid peptide secreted in response to oral ingestion of nutrients by the L-cells in the ileum and colon
- GLP-1 receptors are located in islet cells, CNS among other places
- GLP-1 is metabolized by enzyme DPP-IV(dipeptidyl-peptidase-IV)

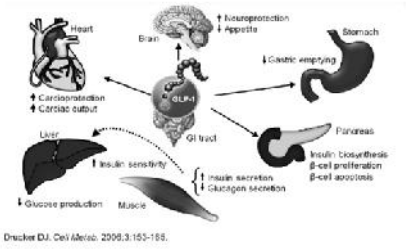
Actions of GLP-1

- In animal studies, it increases beta cell mass by:
  - Decreasing beta cell apoptosis
  - Stimulating the growth of new beta cells *(Diabetes Care, 2003)*

Actions of GLP-1

- Enhances glucose dependent insulin secretion
- Inhibits glucagon secretion and therefore hepatic glucose production
- Slows gastric emptying
- Increases satiety resulting in less food intake
- Stimulates insulin gene transcription and insulin synthesis

Pharmacologic Action: Target Tissues



Drucker DJ. Cell Metab. 2006;3:153-165.

Incretins

- 2005: Byetta - first incretin-related therapy available for patients with T2DM
- 2014: Trulicity approved for treatment of T2DM by FDA

Trulicity Dulaglutide

- GLP-1 available for treatment of T2DM for adult population
- One weekly dose can be administered anytime of day, with or without food

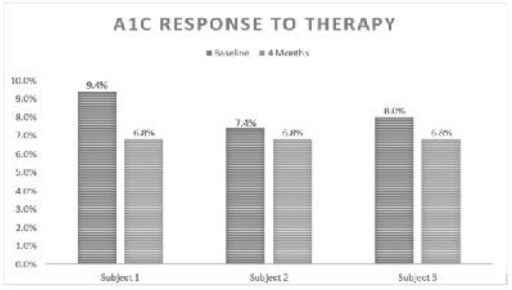
- Recommended dose 0.75mg sq q weekly
- May increase dose 1.5 mg

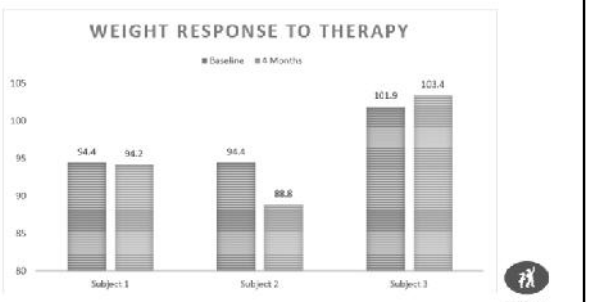
Advantages

- Low rates of hypoglycemia
- Weight loss in some patients
- Effective in controlling PPG
- Once weekly injection
- No PA on Medicaid

Disadvantages

- Nausea, mainly on initiation
- Black Box Warnings
  - Risk of Thyroid C-cell Tumors
  - Contradicted in patients with Multiple Endocrine Neoplasia Syndrome type 2
  - Personal Family History of Medullary Thyroid Carcinoma





Summary

- Insulin resistance and relative insulin secretory defect are key elements in the pathogenesis of T2DM
- GLP-1 deficiency is another key component in diabetic pathophysiology contributing to:
  - Insulin secretory deficit
  - Excess plasma glucagon
  - Postprandial hyperglycemia

Summary

- Incretin mimetics offer a new approach in the management of T2DM
- In addition to improving glycemic control, benefit of weight loss
- Therapies should be undertaken in combination with existing antidiabetic medications and other proven cardiovascular risk reduction strategies

We have to be proactive!

We

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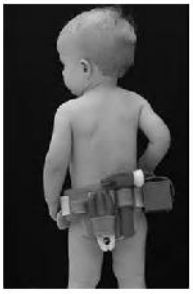
Tools!



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