The Role of Dual Incretin Agonists in the Management of Type 2 Diabetes

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Objectives:

1. Describe the incretin effect
2. Explain the mechanism of action of a dual incretin agonist
3. Summarize the primary outcome and safety outcomes of the SURPASS-2 Trial
4. Identify place in therapy of dual incretin agonists for patients with type 2 diabetes

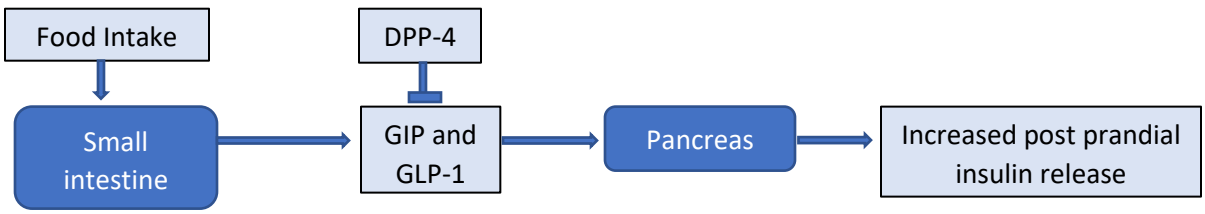
Knowledge Check Questions:

1. What are the incretin(s) involved in the incretin effect and when are they released?
    a) GIP; released post-prandially
    b) GLP-1; released pre-prandially
    c) GIP and GLP-1; released pre-prandially
    d) GIP and GLP-1; released post-prandially
2. What is the mechanism of action of tirzepatide?
    a) GLP-1 agonist
    b) GLP-1 and GIP agonist
    c) GIP agonist
    d) DPP4 inhibitor
3. Which explains the results of the SURPASS 2 trial?
    a) Tirzepatide showed a significant reduction in A1C compared to semaglutide
    b) Tirzepatide showed a significant reduction weight compared to semaglutide
    c) Semaglutide showed a significant reduction in A1C compared to tirzepatide
    d) Tirzepatide showed a significant reduction in A1C and weight compared to semaglutide
4. Which one of the following patients with type 2 diabetes should tirzepatide be avoided in?
    a) 58 yo Hispanic female with proliferative retinopathy and a BMI of 18 kg/m^2
    b) 42 yo Black male with cholelithiasis and a BMI of 42 kg/m^2
    c) 70 yo White male with a BMI of 18 kg/m^2 and history of multiple episodes of pancreatitis
    d) All of the above

Dual Incretin Agonists

Pathophysiology:

- The "ominous octet" depicts 8 of the ways diabetes manifests in the body
    - Decreased insulin production in the pancreatic beta cells*
    - Increased insulin resistance and glucose production in the liver
    - Increased dysfunctional neurotransmitters via the nervous system*
    - Increased reabsorption of glucose in the kidneys
    - Increased production of glucagon in pancreatic alpha cells*
    - Enhanced lipolysis in adipose tissue
    - Deficiency in the incretin effect in the small intestine*
- Dual incretin agonists act on half of these pathways to treat diabetes
    - marked with a "*" above
- A hallmark characteristic of dial incretin agonists are their role in the incretin effect depicted below:



- GIP: glucose-dependent insulinotropic polypeptide
- GLP-1: glucagon-like peptide-1
- DPP-4: dipeptidyl peptidase-4

Mechanism of Action:

- Endogenously, GLP-1 acts on many areas of the body but most notably on the stomach to decrease gastric emptying, on the heart to increase cardioprotection, on the pancreas to increase post prandial insulin secretion and increase beta cell proliferation and decrease glucagon secretion, and on the brain to decrease appetite.
- Endogenously GIP acts in many areas but most notable in the pancreas to increase post prandial insulin secretion and increase beta cell proliferation; however, one key difference between GIP and GLP-1 is that GIP increases glucagon whereas GLP-1 decreases glucagon.
- When in combination as a dual incretin agonist, like tirzepatide, the overall mechanism of action is decreased food intake, decreased gastric emptying, increased cardioprotection, and increased post prandial insulin release and increase beta cell proliferation

Landmark Trials:

- The SURPASS trials examine the use of tirzepatide in patients with type 2 diabetes (T2DM)
  - SURPASS 1: tirzepatide vs placebo[1]
    - Showed tirzepatide significantly lowered A1C vs placebo
    - Tirzepatide showed more incidence of gastrointestinal (GI) side effects
  - SURPASS 2: tirzepatide vs semaglutide 1 mg[2]
    - Tirzepatide showed significant A1C lowering vs semaglutide
    - Tirzepatide was found to have significantly more weight loss than semaglutide
    - Comparable GI side effects among groups
  - SURPASS 3: tirzepatide vs insulin degludec[3]
    - Tirzepatide showed significant decrease in A1C vs insulin degludec
    - Weight loss with tirzepatide vs weight gain with insulin degludec
  - SURPASS 4: tirzepatide vs insulin glargine in patients with high cardiovascular (CV) risk[4]
    - Tirzepatide showed significant A1C lowering compared to insulin glargine
    - Revealed safety of tirzepatide in patients with CV risk
  - SURPASS 5: tirzepatide vs placebo in patients on insulin glargine[5]
    - Tirzepatide significantly lowered A1C compared to placebo
    - Decreased insulin requirement with tirzepatide vs increased requirement with placebo
  - SURPASS 6: tirzepatide vs insulin lispro[6]
    - Results yet to be published
- Overall, tirzepatide showed significant reduction in A1C from baseline in each SURPASS trial (table 1)

Table 1: Summary of the Primary Outcome of Each SURPASS Trial- Change in A1C from Baseline

Trial	Tirzepatide vs	Δ A1C % baseline to follow up				P value
		Tirzeptatide			Comparator	
		5 mg	10 mg	15 mg		
SURPASS 1	Placebo	-1.87	-1.89	-2.07	0.04	P < 0.0001
SURPASS 2	Semaglutide 1 mg	-2.01	-2.24	-2.30	-1.86	P = 0.02 (tirzepatide 5 mg) P < 0.001 (tirzepatide 10 & 15 mg)
SURPASS 3	Insulin degludec	-1.93	-2.20	-2.37	-1.34	P < 0.0001
SURPASS 4	Insulin glargine in pts w/ high CV risk	-2.24	-2.43	-2.58	-1.44	P < 0.0001
SURPASS 5	Placebo in pts on insulin glargine	-2.11	-2.40	-2.34	-0.86	P < 0.001
SURPASS 6	Insulin lispro	To be determined…				

Summary:

- Tirzepatide is a dual incretin agonist that is a novel and emerging treatment for T2DM
- Tirzepatide increases post prandial insulin secretion as a result of agonizing GIP and GLP-1 receptors
- Tirzepatide may be used an alternative to GLP-1s for the treatment of T2DM for further A1C lowering
- Tirzepatide carries many of the same contraindications as GLP-1s given their similarity in mechanism of action

Clinical Takeaways:

- Place in clinical guidelines is to be determined
  - Awaiting 2023 guideline updates from American Diabetes Association (ADA)
- Factors to consider:
  - Cost to the patient
  - CV safety established but still awaiting further CV data
  - Contraindications
- May consider for treatment intensification in:
  - Those who have trialed semaglutide but need more glycemic and weight control

Upcoming Trials:

- SURMOUNT Trials (1-4) → tirzepatide's effects on weight loss[7-10]
  - SURMOUNT 1 published, SURMOUNT 3-4 in clinical trials
- SUMMIT Trial → tirzepatide in patients with heart failure with preserved ejection fraction (HFpEF)[11]
- SURPASS-CVOT Trial → effect of tirzepatide on major adverse cardiovascular events in type 2 diabetes[12]

<u>References:</u>

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12) A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT). Clinicaltrials.gov. NCT04255433.