THE ROLE OF GLP-1 RECEPTOR AGONISTS AND GAMMA-LINOLENIC ACID IN WEIGHT MANAGEMENT

ELLEN STEHOUWER, D.O.

360 WEIGHT MANAGEMENT

PALI MOMI, O'AHU

OBJECTIVES:

1. To recognize obesity as a chronic disease
2. Mechanisms of action of GLP-1/GIP receptor agonists
3. Safety and efficacy of GLP-1/GIP receptor agonists
4. Other promising indications for use of GLP-1/GIP receptor agonists
5. Role (?) of gamma-linolenic acid in weight management

DISCLOSURES:

- Neither I, nor my spouse, have any financial relationships to disclose.

OBESITY IS A CHRONIC DISEASE

"OBESITY IS DEFINED AS A CHRONIC, PROGRESSIVE, RELAPSING, AND TREATABLE MULTI-FACTORIAL, NEUROBEHAVIORAL DISEASE, WHEREIN AN INCREASE IN BODY FAT PROMOTES ADIPOSE TISSUE DYSFUNCTION AND ABNORMAL FAT MASS PHYSICAL FORCES, RESULTING IN ADVERSE METABOLIC, BIOMECHANICAL, AND PSYCHOSOCIAL HEALTH CONSEQUENCES."

OBESITY MEDICINE ASSOCIATION(2023 OBESITY ALGORITHM)

GLP-1 RECEPTOR AGONISTS:

MECHANISMS OF ACTION(1)

MECHANISMS OF ACTION IN THE LIVER AND PANCREAS

Liver

- Decreases glucose production
- Decreases liver fat content
- Decreases plasma liver enzyme level
- Decreases hepatic steatosis

Pancreas

- Increases insulin synthesis and secretion
- Decreases blood glucose
- Increases Islet beta cell protection and proliferation

MECHANISMS OF ACTION IN THE GI TRACK

- Slows gastric emptying
- Slows gastrointestinal peristalsis

MECHANISMS OF ACTION IN THE BRAIN AND HEART

Brain

- **Increases signal level of satiety**
- Increases synaptic transmission
- Increases nerve protection
- Decreases neuroinflammation
- Increases memory and motor function

Heart

- Increases CV protection and anti-inflammatory action
- Decreases endothelial dysfunction and myocardial ischemia injury
- Decreases blood lipid levels
- Increases atrial natriuretic peptide

MECHANISMS OF ACTION OF GLUCOSE-DEPENDENT INSULINOTROPIC PEPTIDE (GIP)(2)

- **Stimulation of satiety in the hypothalamus**
- Produced in the small intestine, increasing general insulin sensitivity
- Improves glycemic control
- GIP does **not** appear to effect gastric emptying

SAFETY OF GLP-1 RECEPTOR AGONISTS

ABSOLUTE CONTRAINDICATIONS TO THE USE OF GLP-1 RECEPTOR AGONISTS

- Personal history of pancreatitis
- Personal/family history of medullary thyroid cancer (all thyroid cancers?)

The exposure to a GLP-1RA from 1 to 3 years was associated with a statistically significant increase in the risk of all thyroid carcinomas by 58% (hazard ratio or HR: 1.58; 95% interval confidence or 95% IC: 1.27–1.95), and medullary thyroid cancer by 78% (HR: 1.78; 95% IC: 1.04–3.05). (3)

- Personal/family history of multiple endocrine neoplasia (MEN)syndrome type 2

POTENTIAL SIDE EFFECTS/ADVERSE REACTIONS

Most common are GI symptoms

- loss of appetite
- nausea/vomiting
- constipation/diarrhea
- bloating

Less common:

- acute gallbladder disease
- hypersensitivity reaction
- hypoglycemia
- diabetic retinopathy complications
- acute kidney injury
- gastroparesis
- pancreatitis

EFFICACY OF GLP-1 RECEPTOR AGONISTS AND GLP-1/GIP (4)

PIONEER TRIALS

SEMAGLUTIDE DAILY ORAL FOR DIABETES

PIONEER TRIALS

Pioneer 1: Semaglutide vs placebo in people with diabetes and A1c 7.0-9.5

By week 26 - those on semaglutide 14 mg

A1c reduction of 0.6-1.1

Average weight loss 5 kg

Pioneer 2: People with diabetes and taking metformin. Semaglutide vs empagliflozin

By week 52 – those on semaglutide 14

A1c reduction of 1.3 vs 0.9

Weight loss of 4.7 kg vs 3.8 kg

Pioneer 3: Persons with diabetes on metformin +/- sulfonylurea. Semaglutide 14 mg vs sitagliptin.

A1c reduction of 0.3-0.5 with semaglutide

Weight loss of 1.6-2.5 kg more with semaglutide

Pioneer 4: Persons with diabetes on metformin +/- SGLPT2 inhibitor. Semaglutide vs liraglutide.

Alc reduction of 1.2 with semaglutide vs 1.1 with liraglutide

Weight loss of 1.6-2.5 kg more with semaglutide

Pioneer 8 – Persons with diabetes on basal insulin +/- metformin. Semaglutide 3, 7 and 14 mg vs placebo

A1c reduction in semaglutide 0.6, 0.9, 1.3 respectively compared to 0.1 in placebo group

Weight loss in semaglutide -1.4, -2.4, -3.7kg respectively and 0.4 kg in placebo group

OASIS TRIAL: SEMAGLUTIDE DAILY ORAL 50 MG FOR WEIGHT LOSS

Persons with overweight or obesity with 1 or more comorbidity. Semaglutide vs placebo plus lifestyle intervention. At the end of 68 weeks:

Weight loss in those taking semaglutide 17.4% from start of study vs 1.8% in the placebo group

Participants achieving 5% or more total body weight loss in the semaglutide group was 89.2% vs 24.5% in the placebo group

STEP TRIALS

SEMAGLUTIDE WEEKLY INJECTION FOR WEIGHT MANAGEMENT.

- Step 1: Persons without diabetes given semaglutide 2.4 mg vs placebo. Each group was also given lifestyle intervention.

Weight loss in those taking semaglutide was 14.9% vs 2.4% in placebo group.

In the semaglutide group 86.4% of participants lost 5% or more of their total starting body weight.

Step 2: Persons with diabetes and obesity or overweight.

Semaglutide 1 vs 2.4 mg vs placebo.

At 68 weeks, weight loss seen was 6.99% vs 9.64% vs 3.4% respectively.

Step 3: Persons with diabetes and O/W or obesity. Semaglutide 2.4 mg or placebo and intensive lifestyle intervention.

Weight loss in those taking semaglutide and adhering strictly to lifestyle intervention achieved 16% weight loss from starting weight vs 5.7% in placebo group.

Those achieving 5% or more in total body weight lost was 86% vs 47.6%

Step 4: Persons with O/W or obesity with related comorbidities but without diabetes. All participants received semaglutide 2.4 mg for 20 weeks. Then randomized into semaglutide 2.4 mg vs placebo for 28 weeks.

Those in placebo group regained 6.9% of the weight lost initially. Total body weight lost was 5% at study end.

Those in semaglutide group lost an additional 7.9% of total body weight, with 17.4% total lost at study end.

Step 5: Evaluated durability of weight loss over 2 years in persons with O/W or obesity without diabetes.

Participants lost weight until week 60 and maintained their weight loss until the end of the study at week 104.

There was a placebo-corrected weight loss of 12.6%.

Step 6: Participants were Asians with O/W or obesity with related comorbidities, including diabetes. Groups were divided into those taking semaglutide 2.4 vs 1.7 mg vs placebo.

Weight loss seen was 13.2% vs 9.6% vs 2.1% respectively.

A significant reduction in visceral fat was achieved in those taking semaglutide.

A reduction of 25% in A1c was noted in those taking semaglutide.

STEP TEENS

Included adolescents ages 12-17 with O/W or obesity and related comorbidities. This study looked at semaglutide 2.4 mg vs placebo.

Weight loss seen was 16.1% total body weight from start of study in the semaglutide group vs 0.6% in the placebo group.

Improved lipids, especially triglycerides was also noted.

SURMOUNT TRIALS

TIRZEPATIDE, A GLP-1/GIP RECEPTOR AGONIST WEEKLY INJECTION FOR WEIGHT MANAGEMENT

Surmount 1: Participants with BMI of 27 or greater. Compared tirzepatide 5, 10, and 15 mg vs placebo.

Total body weight % lost at 72 weeks was

15%, 19.5%, 20.9 and 3.1% respectively

Percent of those who lost 5% or more of total body weight was 85%, 89%, 91% and 35% respectively

Surmount 2: Participants with BMI of 27 or greater and diabetes. Compared tirzepatide 10 and 15 mg vs placebo.

Total body weight % lost at 72 weeks was 12.8%, 14.7% and 3.2% respectively

Percent of those who lost 5% or greater of total body weight was 82.7%

Percent of those who lost 15% or more was 48%

OTHER PROMISING OR KNOWN INDICATIONS FOR THE USE OF GLP-1 RECEPTOR AGONISTS

- Heart disease
- Hepatic steatosis
- Diabetic kidney disease (decreasing macroalbuminuria and slowing eGFR decline)
- Parkinson's disease

HAWAI'I ACADEMY OF FAMILY PHYSICIANS

FEBRUARY 16-18 GRAND NANILOA HOTEL

GAMMA-LINOLENIC ACID

WHAT ROLE DOES IT PLAY IN WEIGHT MANAGEMENT?

1. In a meta-analysis of 18 studies in which conjugated linolenic acid was provided to humans in randomized, double-blinded, placebo-controlled trials and in which body composition was assessed, the use of CLA at 3.2 grams daily produced 0.09 kg/week (or 0.2 lbs) compared to placebo. This effect plateaued at 6 months and then began to decrease in effectiveness thereafter. (5)
2. In another study healthy participants with BMI > 28 were put on calorie restricted diets for 8 weeks. Those who lost >8% total body weight were randomized to a 1-year double blinded CLA (3.2 gm/day) vs placebo (olive oil), along with a modest hypocaloric diet. After 1 year, there was no significant difference in body weight or body fat regain between those taking CLA and those taking placebo. (6)
3. In one study done on rats, study results indicated a decrease in white adipose tissue and an up-regulation of brown adipose. This has not been replicated in human studies. (7)

POSSIBLE SIDE EFFECTS OF GAMMA-LINOLENIC ACID SUPPLEMENTATION

- Headache
- Abdominal pain
- Loose stool
- Worsening of lipid profile: decrease in HDL and increase in Lp(a)
- Elevation in CRP
- Elevation of liver enzymes

IN CONCLUSION

GLP-1 Receptor Agonists/GIP

1. There is strong evidence that the newest GLP-1 Receptor Agonists provide significant in the fight against obesity.
2. These medications are generally well tolerated but do come with potential health risks.
3. Although currently approved only for diabetes and weight management, there is evidence that these medications may be beneficial in multiple other disease states.

Gamma-Linolenic Acid

1. There is very little evidence of a beneficial role in weight loss.
2. These supplements do have potential for worsening metabolic health.

REFERENCES

1. Frontiers in Endocrinology, August 23, 2021. Volume 12-2021

2. Diabetes Symposium, June 27, 2021

3. Endocrine Connections, volume 12, 11/21/2023

4. DiabetesMedicineMatters.com

5. American Journal of Clinical Nutrition, May 2007: 85(5), 1203-1211

6. American Journal of Clinical Nutrition, March 2006: 86(3), 606-612

7. Comparative Biochemistry and Physiology. Part B, Biochemistry and Molecular Biology, October 2000; 127(2), 213-222