GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of May 6 - 10, 2024

SPOTLIGHT: Can GLP-1 Analogues Help Patients with Poor Weight Loss Following Metabolic Surgery?

- Olanzapine for Chemotherapy-Induced Anorexia
- OSA: Risk Factors and Comorbidities
- High-Volume Injections: Good or Bad for Achilles Tendinopathy?

Can GLP-1 Analogues Help Patients with Poor Weight Loss Following Metabolic Surgery?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Safety and Efficacy of Liraglutide, 3.0 mg, Once Daily vs Placebo in Patients with Poor Weight Loss Following Metabolic Surgery: The BARI-OPTIMISE Randomized Clinical Trial

Mok J, Adeleke MO, Brown A, et al. Safety and Efficacy of Liraglutide, 3.0 mg, Once Daily vs Placebo in Patients With Poor Weight Loss Following Metabolic Surgery: The BARI-OPTIMISE Randomized Clinical Trial. *JAMA Surg*. 2023;158(10):1003-1011. doi:10.1001/jamasurg.2023.2930

KEY TAKEAWAY: Liraglutide helps with weight loss in patients with poor weight loss after bariatric surgery.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Bariatric surgery has been known as the most effective weight loss method for those with obesity. 25% of patients who undergo metabolic surgery have <20% weight loss. Following bariatric surgery, patients are found to have higher levels of the satiety gut hormone GLP-1. Research has shown that individuals with less than 20% weight loss following bariatric surgery have decreased satiety with increased appetite, as well as a poor postoperative gut hormone profile, including less GLP-1 than those who had >20% weight loss.

PATIENTS: Patients with metabolic surgery and poor weight loss

INTERVENTION: Liraglutide

CONTROL: Placebo

PRIMARY OUTCOME: Body weight

Secondary Outcome: Changes in body fat, HbA1c, blood pressure (BP), bone density, low-density lipoprotein (LDL)

METHODS (BRIEF DESCRIPTION):

- Both men and women who had metabolic surgery and poor weight loss (<20% body weight lost) and a suboptimal nutrient-stimulated GLP-1 response at least 12 months following primary Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) were included.
- Patients were randomized to one of the following:
  - Liraglutide titrated to 3.0 mg subcutaneous injection once daily (Saxenda)
  - Matched placebo with saline solution
- The primary outcome was the mean change in body weight (measured in %) from baseline to week two.
  - The difference in mean percentage body weight change was adjusted for baseline weight, type of surgery, and diabetes status.

INTERVENTION (# IN THE GROUP): 35

COMPARISON (# IN THE GROUP): 35

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- In the intention-to-treat analysis, liraglutide resulted in greater weight loss than placebo (mean difference [MD] –8.0%; 95% CI, –10 to –5.7).
- In the per-protocol analysis, liraglutide resulted in greater weight loss than placebo (MD –7.7%; 95% CI, –10 to –5.2).

Secondary Outcome –

- Secondary outcomes favored liraglutide including:
  - Total body fat (MD –4.9 kg; 95% CI, –7.2 to –2.5)
  - HbA1c (MD –0.24; 95% CI, –0.32 to –0.16)
  - Systolic BP (MD –9.1; 95% CI, –16 to –1.9)
- There were no significant effects on bone density or LDL.

LIMITATIONS:

- This study included patients who had primary bariatric surgery and not revisional surgery.
- Homogeneous population of white females in the sample
- The study did not assess liraglutide's effect in patients who had a strong GLP-1 response following bariatric surgery, and only patients who had suboptimal GLP-1 responses.
- COVID-19 limited in-person weighing and relied on self-reported weight in seven patients.
- Due to the short treatment period, the study was unable to determine the maximal benefit of liraglutide.

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Olanzapine for Chemotherapy-Induced Anorexia

Randomized Double-Blind Placebo-Controlled Study of Olanzapine for Chemotherapy-Related Anorexia in Patients with Locally Advanced or Metastatic Gastric, Hepatopancreativcobillary, and Lung Cancer

Sandhya L, Devi Sreenivasan N, Goenka L, et al. Randomized Double-Blind Placebo-Controlled Study of Olanzapine for Chemotherapy-Related Anorexia in Patients With Locally Advanced or Metastatic Gastric, Hepatopancreaticobiliary, and Lung Cancer. *J Clin Oncol.* 2023;41(14):2617-2627. doi:10.1200/JCO.22.01997

KEY TAKEAWAY: Daily olanzapine may improve weight gain and appetite in patients undergoing chemotherapy for some metastatic cancers. Additionally, olanzapine may improve quality of life, nutritional status, and calorie intake while reducing chemotherapy toxicity.

STUDY DESIGN: Randomized, double-blind, parallel-group placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with newly diagnosed malignancies are frequently affected by anorexia, which is worsened by chemotherapy. To treat anorexia, current guidelines recommend dietary intervention; however, there is limited information on how pharmacologic agents can be utilized. Primary care physicians can play a key role by managing a patient's appetite, enhancing chemotherapeutic regimens, and improving their quality of life. This study aimed to address how olanzapine can be used to address these concerns.

PATIENTS: Cancer patients receiving chemotherapy

INTERVENTION: Olanzapine

CONTROL: Placebo

PRIMARY OUTCOME: Weight gain and appetite stimulation

Secondary Outcome: Quality of life, change in nutritional status, calorie intake, chemotherapy toxicity

METHODS (BRIEF DESCRIPTION):

- Patients on long-term steroids and antipsychotics were excluded from the study.
- Patients were blinded and randomized to one of the following groups:
  - Olanzapine 2.5 mg daily
  - Placebo tablets
- A protocol was given to all patients detailing the incorporation of high-calorie foods into their diet.
- Patients were evaluated at baseline, during chemotherapy appointments, and at the end of the study.
- Weight, height, BMI, and arm circumference/thickness were measured at the start of the study.
- The primary outcome measured weight gain (goal for >5%) and appetite stimulation.
- Appetite stimulation was assessed using the visual analog scale (VAS), with scores ranging from 1–10 (normal appetite=10).
  - The Functional Assessment of Chronic Illness Therapy system of Quality-of-Life questionnaires Anorexia Cachexia Subscale (FAACT ACS) measured anorexia-associated symptoms (scores range from 0–48; scores <37 defined anorexia).
- Nutritional status was measured using the subjective global assessment (SGA) and ranged from well-nourished, moderately malnourished, to severely malnourished.
- Quality of life (QOL) was measured by the Cancer Institute Quality of Life questionnaire (CI-QOL) and ranged from poor to high.
- Calorie intake was assessed at every appointment with a self-reporting food diary.
- Toxicities to chemotherapy were assessed at every visit and included drowsiness, headache, hyperglycemia, suicidal tendencies, constipation, and dizziness.

INTERVENTION (# IN THE GROUP): 58

COMPARISON (# IN THE GROUP): 54

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- Patients receiving olanzapine were more likely to experience at least 5% weight gain compared to placebo (60% vs 9%, respectively; *P*<.001).
- Appetite stimulation was higher in the olanzapine group compared to placebo (43% vs 13%, respectively; *P*<.001).

Secondary Outcome –

- Nutrition status improved in the olanzapine group compared to placebo (43% vs 9%, respectively; *P*<.0001).
- The proportion of patients who achieved >75% calorie intake was higher in the olanzapine group compared to placebo (52% vs 18%, respectively; *P*<.001).
- Quality of life improved more in the olanzapine group compared to placebo (70% vs 50%, respectively; *P*=.003).
- Chemotherapy toxicity was less in the olanzapine group than placebo (12% vs 37%, respectively; *P*=.002).

LIMITATIONS:

- The malignancies studied involved different chemotherapeutic regimens.
- The study was limited to 12 weeks.
- There was a small sample size due to recruitment challenges.
- Anorexia measurement is subjective; various measures were used to gauge the success of the intervention.
- There were twice as many males as females in each group.

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OSA: Risk Factors and Comorbidities

Association and Risk Factors for Obstructive Sleep Apnea and Cardiovascular Disease: A Systematic Review

Mitra AK, Bhuiyan AR, Jones EA. Association and Risk Factors for Obstructive Sleep Apnea and Cardiovascular Diseases: A Systematic Review. *Diseases*. 2021;9(4):88. Published 2021 Dec 2. doi:10.3390/diseases9040088

KEY TAKEAWAY: This systematic review identified associations between several risk factors and comorbidities, especially cardiovascular comorbidities, and obstructive sleep apnea (OSA).

STUDY DESIGN: Systematic review of 34 studies which included 21 cross-sectional, 10 prospective cohort, and three retrospective studies (N=37,599)

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: It is understood that OSA is a risk factor for major cardiovascular diseases including heart disease, heart failure, and cerebral stroke. This study aims to evaluate evidence for the association between OSA and cardiovascular disease morbidities and review risk factors.

PATIENTS: Adult patients

INTERVENTION: OSA diagnosis

CONTROL: No OSA diagnosis

PRIMARY OUTCOME: Risk factors and comorbidities

METHODS (BRIEF DESCRIPTION):

- This study reviewed recently published peer-reviewed studies on cardiovascular disease and OSA.
- Article inclusion criteria included: (1) English language, (2) human studies, (3) scholarly papers, (4) patients who were ≥19 years old, (5) cardiovascular diseases with or without comorbidities, and (6) sleep apnea. The time limit for the review was from 2018–2021.
- The primary search engines included PubMed, EBSCO-host, Scopus, Cochrane Library, Google Scholar, Medline, Alt HealthWatch, CINAHL Consumer Health Complete, and Health Source.
- The Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) guidelines were followed to document the review process. Three researchers independently screened the titles and reviewed the abstracts. Studies were included in the review if a consensus was achieved by all three researchers.
- All three researchers separately graded the studies using a rating scale from 0–4 based on study design (cross-sectional, case-control, or cohort study vs other), sample size (large vs small), selection of sample (random vs non-random), and analyses (robust vs otherwise).
- The mean standard deviation score for the quality of the studies was 2.82±1.06. 13 studies scored high, 20 scored moderate and one scored low.
- Severe OSA was defined as an apnea-hypopnea index >30.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Risk factors associated with OSA:
  - Age >35 years old (odds ratio [OR] 4.5; 95% CI, 1.4–14)
  - BMI >25 kg/m^2 (adjusted odds ratio [aOR] 3.5; 95% CI, 1.2–11)
  - Alcoholism (aOR 4.5; 95% CI, 1.8–11)
  - Elevated daytime sleepiness (OR 1.2; 95% CI, 1.1–1.3)
  - Mean apnea duration (OR 1.1; 95% CI, 1.0–1.1)
  - Sleeping oxygen levels (OR 1.1; 95% CI, 1.0–1.1)
  - Nocturnal oxygen desaturation (OR 2.4; 95% CI, 1.2–5.1)
- Severe OSA was significantly associated with the following:
  - Daytime sleepiness (OR 20; 95% CI, 1.6–27)
  - Oxygen desaturation index (OR 4.1; 95% CI, 1.9–8.8)
- The most common comorbidities reported with OSA included:
  - Hypertension: 88% of studies
  - Obesity: 50% of studies
  - Diabetes mellitus: 35% of studies
  - Heart disease: 17% of studies
  - Stroke: 9% of studies
  - Kidney disease: 9% of studies

- Psychological disorders, such as depression and anxiety: 9% of studies
- Comorbidities identified in 6% of studies: Asthma, COPD, acute heart failure, chronic heart failure, hyperlipidemia, thyroid disease, cerebral infarct or embolism, and myocardial infarction

LIMITATIONS:

- Due to the nature of the studies, no causal association could be made between OSA and the disease.
- With the use of 10 search sources, there is a possibility that some important articles could have been missed.
- This study did not aim to identify any relationships between specific traits of the population with OSA or any gender differences in OSA.

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High-Volume Injections: Good or Bad for Achilles Tendinopathy?

Do High-Volume Injections Affect the Ultrasonopgrahic Neovascularization in Chronic Achilles Tendinopathy? A Randomized Placebo-Controlled Clinical Trial

van Oosten CCM, van der Vlist AC, van Veldhoven PLJ, van Oosterom RF, Verhaar JAN, de Vos RJ. Do High-Volume Injections Affect the Ultrasonographic Neovascularization in Chronic Achilles Tendinopathy? A Randomized Placebo-Controlled Clinical Trial. *Clin J Sport Med.* 2022;32(5):451-457. doi:10.1097/JSM.0000000000000998

KEY TAKEAWAY: There is no significant difference between high-volume injections (HVI) of 50 mL and placebo low-volume injections of 2 mL on ultrasonographic neovascularization in chronic Achilles tendinopathy (AT).

STUDY DESIGN: Double-blind, randomized, placebo-controlled, clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to underpowered study)

BRIEF BACKGROUND INFORMATION: Achilles tendinopathy is common in the general population with the highest incidence among athletes. Current therapies for AT are mainly symptomatic based on little high-quality evidence. Current common practices include avoiding aggravating activities, ice when symptomatic, a short course of NSAIDs lasting approximately 7–10 days, and heel lift to support the Achilles. Using high-volume injections aims to improve recovery and muscle repair by obliterating neovascularization and sensory nerves and working at getting back to normal activities.

PATIENTS: Adults with AT

INTERVENTION: High-volume saline with lidocaine

CONTROL: Low-volume placebo

PRIMARY OUTCOME: Tendinopathy improvement

Secondary Outcome: Patient-perceived improvement of tendinopathy symptoms

METHODS (BRIEF DESCRIPTION):

- Patients diagnosed with chronic midportion AT were selected from Haaglanden Medical Centre in the Netherlands.
- Main inclusion criteria included AT pain for at least two months, nonresponse to a calf-muscle exercise program for at least six weeks, aged 18–70 years old, and presence of peritendinous/intratendinous Doppler flow on Power Doppler Ultrasonography (PDUS) examination.
- Main exclusion criteria included suspicion of other musculoskeletal disorders, previous Achilles tendon rupture or surgery, and inability to complete an exercise program.
- Patients were randomized into the intervention group or the placebo group. Patients were stratified by Ankle-activity scoring which could then match patients against those of similar scoring.
    - The intervention group received high-volume injections with five syringes filled with 8 mL sodium chloride and 2 mL of 1% lidocaine for a total of 50 mL.
    - The placebo group received a total of 2 mL of the same solution, but the syringe was switched four times without any additional volume.
- Patients were injected once at the start of the 24-week course with all patients participating in a gradually increased training program.
- Patients were re-evaluated at baseline, post-injection, two, six, 12, and 24 weeks with ultrasound surface area quantification (SAQ), Victorian Institute of Sports Assessment-Achilles (VISA-A), and visual analog scale (VAS) to quantify the severity of AT.
- Ultrasound SAQ detected the maximum degree of vascular Doppler flow with each evaluation suggestive of AT Improvement.
- The SAQ scores measured ultrasonographic neovascularization which was determined by Doppler flow on PDUS.
- The VISA-A scoring showed the severity of AT pain with 0 being the worst pain and 100 being the least amount of pain.
- VAS 10-hop-scores are another pain rating scale where the patient makes a mark on a 10-cm line between most pain and least pain; a low score in cm means a low amount of pain while a high score means more pain at any given time.

INTERVENTION (# IN THE GROUP): 30

COMPARISON (# IN THE GROUP): 32

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- HVI did not improve tendinopathy at 24 weeks compared to placebo (adjusted difference –0.1; 95% CI, –4.9 to 4.7).

Secondary Outcome –

- HVI improved patient-reported perceived pain compared to baseline at 24 weeks.
  - VISA-A (44 vs 65, respectively; P<.01)
  - VAS 10-hop score (42 vs 16, respectively; P<.01)

LIMITATIONS:

- The sample size had low power with only 38 patients, indicating the results are likely to be distorted by random or systematic error.
- 18 of the 62 PDUS images could not be used due to poor study quality further limiting the analysis quantity and concern that SAQ may not be the most accurate way to measure neovascularization.
- The study also had a relatively homogenous population of those who sought and participated in medical care at Haaglanden Medical Centre in the Netherlands.
- Blinding of both the patients and providers during analysis was also compromised due to the nature of administration. Providers could visually see the amount given during the procedure and on ultrasound imaging, given volume changes.

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