GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 1 - Issue 25

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of June 21 - 25, 2021

SPOTLIGHT: Tirzepatide, Something to Talk about for Patients with Type 2 Diabetes?

- To C or Not to C
- Attainability of Early Post-Concussion Rehabilitation

Tirzepatide, Something to Talk about for Patients with Type 2 Diabetes?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Efficacy and tolerability of tirzepatide, a dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes: A 12-week, randomized, double-blind, placebo-controlled study to evaluate different dose-escalation regimens

Frias JP, Nauck MA, Van J, et al. Efficacy and tolerability of tirzepatide, a dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes: A 12-week, randomized, double-blind, placebo-controlled study to evaluate different dose-escalation regimens. *Diabetes Obes Metab*. 2020; 22:938–946.

KEY TAKEAWAY: Tirzepatide improves HbA1c and weight loss compared to placebo. The fewest adverse events (AEs) were seen with a lower starting dose and smaller dose increments.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: In patients with type 2 diabetes mellitus (DM), GLP-1RA improves HbA1c levels and weight loss but is associated with gastrointestinal AEs. In an effort to improve tolerability and efficacy, one emerging approach is combining a glucose-dependent insulinotropic peptide (GIP) with a glucagon-like peptide-1 receptor agonist (GLP-RA) like tirzepatide.

PATIENTS: Adults with type 2 DM inadequately controlled with diet and exercise alone or with stable metformin therapy

INTERVENTION: Subcutaneous tirzepatide

CONTROL: Placebo

OUTCOME: Change in HbA1c

Secondary: Reductions in mean body weight (BW), fasting blood glucose, waist circumference

METHODS (BRIEF DESCRIPTION):

- Patients were randomized 1:1:1:1
- Patient demographics:
  - Mean age: 57 years (range 18–75)
  - HbA1c: 8.4% (range 7.0–10.5%)
  - BMI: 32 kg/m^2 (range 23–45)
  - Mean time since diabetes diagnosis: 9.1 years
  - Male: 59.5%
  - Taking metformin: 86.5%
- Once weekly subcutaneous injection of tirzepatide, in one of the three dose-escalation regimens:
  - 12 mg: 4 mg for 4 weeks, 8 mg for 4 weeks, and then 12 mg for 4 weeks
  - 15 mg-1: 2.5 mg for 2 weeks, 5 mg for 2 weeks, 10 mg for 4 weeks, and then 15 mg for 4 weeks
  - 15 mg-2: 2.5 mg for 4 weeks, 7.5 mg for 4 weeks, then 15 mg for 4 weeks
- Secondary safety objectives included treatment emergent adverse events, serious adverse events, incidence of nausea, vomiting, and diarrhea.
- AEs were recorded in diaries and collected at every visit during the week after dose escalation.

INTERVENTION (# IN THE GROUP):

- 12 mg: 29
- 15 mg-1: 28
- 15 mg-2: 28

COMPARISON (# IN THE GROUP): 26

FOLLOW UP PERIOD: 12 week study with 4 weeks follow up

RESULTS:

Tirzepatide of any dosage lowered HbA1c more effectively than placebo:

- 12 mg: mean change –1.9% (95% CI, –2.5 to –1.4)
- 15 mg-1: mean change –2.2% (95% CI, –2.8 to –1.7)
- 15 mg-2: mean change –2.0% (95% CI, –2.5 to –1.4)

Tirzepatide of any dosage lowered body weight more effectively than placebo:

- 12 mg: mean change –4.8 kg (95% CI, –7.1 to –2.6)
- 15 mg-1: mean change –5.0 kg (95% CI, –7.2 to –2.7)
- 15 mg-2: mean change –5.2 kg (95% CI, –7.5 to –2.9)

Fasting blood glucose decreased in all tirzepatide groups compared to placebo:

- 12 mg: mean change –48.5 mg/dL (95% CI, –70.6 to –26.3)
- 15 mg-1: mean change –58.0 mg/dL (95% CI, –80.7 to –35.2)
- 15 mg-2: mean change –61.9 mg/dL (05% CI, –84.6 to –39.2)

Waist circumference decreased in the 15 mg-2 group: mean change –2.4 cm (95% CI, –4.9 to –0.2).

Adverse events were relatively common across all tirzepatide groups.

- In the 15 mg-2 group, 35.7% reported nausea, 32.1% diarrhea, and 28.6% decreased appetite (95% CI not reported).

LIMITATIONS:

- Study limited to 8 weeks
- Self-reported adverse events in diary format
- Small sample size

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To C or Not to C

The Efficacy and Safety of Vitamin C for Iron Supplementation in Adult Patients with Iron Deficiency Anemia

Nianyi L, Guangjie Z, Wanling W, et al. The Efficacy and Safety of Vitamin C for Iron Supplementation in Adult Patients with Iron Deficiency Anemia: A Randomized Clinical Trial. *JAMA Netw Open*. 2020; 3(11):e2023644.

KEY TAKEAWAY: Oral iron in combination with vitamin C is no better than oral iron alone in improving hemoglobin levels or ferritin stores in patients with iron deficiency anemia (IDA).

STUDY DESIGN: Randomized control trial (single blinded)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with IDA are often advised to take vitamin C with oral iron because it improves iron absorption. However, it is not known if adding vitamin C is actually more effective than iron replacement alone in improving the hemoglobin or ferritin levels in adult patients with IDA.

PATIENTS: Adult patients with newly diagnosed IDA

INTERVENTION: 100 mg ferrous succinate plus 200 mg oral vitamin C given every 8 hours

CONTROL: 100 mg ferrous succinate given every 8 hours

OUTCOME: Change in hemoglobin level from baseline after 2 weeks of treatment

Secondary Outcomes: Change in reticulocyte percentage after 2 weeks of treatment; increase in hemoglobin level after 4, 6, and 8 weeks of treatment; increase in serum ferritin levels after 8 weeks of treatment

METHODS (BRIEF DESCRIPTION):

Included patients were 18 years or older (mean 38; range 18–90) with newly diagnosed IDA meeting the following criteria:

- Hemoglobin <13 g/dL in males and <12 g/dL in females
- Mean corpuscular volume less than 80 um^3
- Mean corpuscular hemoglobin less than 27 pg/cell
- Mean corpuscular hemoglobin concentration < 32g/dL
- Serum ferritin <14 ng/mL for women or <30 ng/mL for men
- Serum iron <39 ug/dL for women or <56 ug/dL for men
- Transferring saturation <20%
- Total iron-binding capacity (TIBC) exceeding 428 ug/dL

Randomized 1:1 to receive either 100 mg ferrous succinate with or without 200 mg oral vitamin C every 8 hours.

- Patients were assessed every 2 weeks for 2 months with a complete blood count, serum iron, transferring saturation, TIBC ,and ferritin at 8 weeks

INTERVENTION (# IN THE GROUP): 220

COMPARISON (# IN THE GROUP): 220

FOLLOW UP PERIOD: 3 months

RESULTS:

Primary Outcomes:

- No significant difference in hemoglobin levels at two weeks between the two groups (Mean Difference [MD] 0.16 g/dL; 95% CI, –0.03 to 0.35 g/dL)

Secondary Outcomes:

- No significant differences occurred between the groups in:
    - Ferritin levels at eight weeks (MD 1.3 ng/mL; 95% CI, –0.70 to 3.24 ng/mL)
    - Change in reticulocyte percentage at two weeks (MD 0.11; 95% CI, –0.10 to 0.32)
    - In addition, no significant difference in hemoglobin levels at 4, 6, or 8 weeks

LIMITATIONS:

- 97% of patients were female (426 of the 440)
- Observation period was too short

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Attainability of Early Post-Concussion Rehabilitation

Feasibility of Early Active Rehabilitation for Concussion Recovery in Youth: A Randomized Trial

Dobney DM, Grilli L, Beaulieu C, et al. Feasibility of Early Active Rehabilitation for Concussion Recovery in Youth: A Randomized Trial. *Journal of Sport Medicine*. 2020: 30(6)519–25.

KEY TAKEAWAY: Starting active rehabilitation as early as 2 weeks after a concussion may lead to quicker resolution of post-concussion symptoms compared to the standard of care. This small RCT indicates the need for a larger clinical trial to fully understand these benefits.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: The standard treatment for concussions is active rehabilitation beginning at 4 weeks. However, conflicting evidence exists on when to begin activity. Immediate exercise post-concussion has been demonstrated to prolong recovery, but prolonged activity restrictions lead to an increase in concussion-like symptoms causing further limitations in activity.

PATIENTS: Youth ages 9–17 with post-concussion symptoms for at least 2 weeks

INTERVENTION: Active rehabilitation (AR) beginning 2 weeks post-concussion

CONTROL: AR beginning 4 weeks post-concussion

OUTCOME: Post-concussion symptoms

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: Concussion diagnosed by a physician; active symptoms 2 weeks after concussion; 6–17 years old
- Exclusion Criteria: Previous concussion within 6 months of current concussion; accompanying injury that limits participation; prior engagement in physical activity; exercise/sports that were moderate to vigorous prior to enrollment
- In this feasibility trial, participants were randomized to either receive early active rehabilitation (2 weeks post injury) or standard care active rehabilitation (4 weeks post injury)
  - Randomization was withheld from patients and clinicians until the intervention was initiated
  - Active rehabilitation whether it was early or standard was identical
- Components of active rehabilitation: Aerobic activity, coordination/skills practice, visualization, education
- Post-concussion symptoms measured with PCSI-SR13 scale (possible score of 156; higher scores indicating greater severity of symptoms)
  - Symptoms: Headache, nausea, balance problems, dizziness, fatigue, sadness, and nervousness/anxiety

INTERVENTION (# IN THE GROUP): 10

COMPARISON (# IN THE GROUP): 10

FOLLOW UP PERIOD: 8 weeks after concussion

RESULTS:

Early active rehabilitation compared to usual care may hasten concussion recovery:

- 2 weeks (mean 21 vs 21; range 4-59 vs 6-35)
- 4 weeks (mean 3 vs 11; range 0-49 vs 0-35)
- 6 weeks (mean 2 vs 8; range 0-21 vs 0-27)
- 8 weeks (mean 3 vs 2.25; range 0-9 vs 0-24)

This is a feasibility trial to examine the safety and acceptability of early active rehabilitation, therefore, no direct comparisons were made. The results from this study provide a base from which future studies should be conducted, leading to an important impact concussion rehabilitation protocol. Additional studies will need to be completed to measure early active rehabilitation's superiority compared to standard care.

LIMITATIONS:

- No blinded outcomes
- No legitimate control group
- Lack of variety of ages in participants
- Data collection methods may not have been appropriate for younger participants
- Lack of direct measuring of physical activity (over- or under-estimating)
- Coordination and visualization not measured

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