GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

Making STRIDES in Peripheral Arterial Disease

The Impact of Semaglutide on Walking Capacity

Putting Pressure on GLP-1 Nausea

A Hands-on Fix

GLP-1 RA, A Danger in Pregnancy?

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Making STRIDEs in Peripheral Arterial Disease: The Impact of Semaglutide on Walking Capacity

Semaglutide and Walking Capacity in People with Symptomatic Peripheral Artery Disease and Type 2 Diabetes (STRIDE): A Phase 3b, Double-blind, Randomized, Placebo-Controlled Trial

Bonaca MP, Catarig AM, Houlind K, et al. Semaglutide and Walking Capacity in People with Symptomatic Peripheral Artery Disease and Type 2 Diabetes (STRIDE): A Phase 3b, Double-blind, Randomized, Placebo-controlled Trial. *Lancet*. 2025;405(10489):1580-1593. doi:10.1016/S0140-6736(25)00509-4

KEY TAKEAWAY: Semaglutide improves walking distance without new safety concerns in adults with symptomatic peripheral artery disease (PAD) and type 2 diabetes mellitus (T2DM).

STUDY DESIGN: Phase 3b, multinational, double blinded randomized placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: PAD can cause symptoms of claudication and leg pain, limiting the patient's level of activity and quality of life. Unfortunately, the available treatments and interventions are limited. PAD results from chronic inflammatory changes in the blood vessels, which narrow the lumen and reduce the blood flow. Semaglutide, a glucagon-like peptide-1 (GLP-1) agonist, has been known to have anti-inflammatory vascular benefits and this study tried to prove whether it can be beneficial for patients with T2DM and PAD.

PATIENTS: Adults with T2DM and symptomatic PAD

INTERVENTION: Semaglutide

CONTROL: Placebo

PRIMARY OUTCOME: Improvement in maximum walking distance at 52 weeks

Secondary Outcome: Pain-free walking distance and quality of life, ankle brachial index, bodyweight, physical functioning, hemoglobin A1C (HbA1c)

METHODS (BRIEF DESCRIPTION):

- Adults with tT2DM and PAD with intermittent claudication, (Fontaine stage IIa, able to walk at least 200 m) and an ankle brachial index of ≤0.9 were included in the study.
- The sample was predominantly males (75%), and a median 68 years old. The median BMI was 29, and an A1C of approximately 7–7.2%. The sample was 70% White and 15% African American, and a smaller percentage of Hispanic, Asian and other races. Most had a history of smoking (current or former).
- Baseline testing used a flat treadmill with a fixed speed of 3.2 km/h to show that participants had limiting claudication and that their symptoms were consistent with Fontaine stage IIa.
- Participants that had a recently planned revascularization procedure or a condition that limited their functional capacity were excluded from the study.
- Participants were randomly assigned using interactive web response system to either semaglutide or placebo.
    - Participants receive 1 mg semaglutide subcutaneous or a matching placebo injection every week for 52 weeks.
    - Products containing active drug and placebo were similar in appearance.
- Both participants and investigators were masked to treatment (double blinded).
- Participants were contacted by the study team to ensure compliance and safety at weeks four, eight, 12, 26, 49, 52, and 57.
- The primary outcome was measured by change in ratio to baseline of the maximum walking distance at week 52, measured by the constant load treadmill with fixed speed (3.2 km/h [2 mph]) and a fixed inclination (12%).
- The secondary outcomes measured pain-free walking distance, quality of life, ankle brachial index, bodyweight, physical functioning, and HbA1c.

INTERVENTION (# IN THE GROUP): 396

COMPARISON (# IN THE GROUP): 396

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- Semaglutide increased maximum walking distance compared to placebo (estimated treatment ratio [ETR] 1.1; 95% CI, 1.1–1.2).

Secondary Outcome –

- Semaglutide improved quality of life compared to placebo (ETR 1.0; 95% CI, 0.48–1.5).

- Semaglutide increased pain-free walking distance compared to placebo (ETR 1.1, 95% CI, 1.03–1.2).
- Semaglutide reduced rescue therapy or all-cause death compared to placebo (hazard ratio [HR] 0.46; 95% CI, 0.24–0.85).
- Semaglutide resulted in greater weight loss (–5.2 kg vs –1.2 kg, respectively; *p*<.0001) and decreased HbA1c (ETR –1.0; 95% CI, –1.1 to –0.8) compared to placebo.
- Semaglutide improved physical functioning compared placebo (estimated treatment difference [ETD] 1.3; 95% CI, 0.26–2.3).
- Semaglutide improved the ankle brachial index compared to placebo (ETR 1.1; 95% CI, 1.02–1.1).

LIMITATIONS:

- The trial only included people with T2DM. The results in people without diabetes are still unknown.
- The long-term effect of semaglutide on major adverse limb events has not been studied beyond 52 weeks.
- The trial took place during COVID-19, so recruitment was slow and challenging.
- Despite the double blinded trial, the side effects of GLP1 receptor agonists (nausea and GI upset) may have been evident to participants, which could have affected quality of life or patient reports of safety outcomes.

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Putting Pressure on GLP-1 Nausea: A Hands-On Fix

Antiemetic Effect of Acupressure Wristbands for GLP-1 Medication Associated Nausea

Ziemke F, Belarj S, Esguerra J, Reyes A, Istfan N. Antiemetic Effect of Acupressure Wristbands for GLP-1 Medication Associated Nausea. *Obes Pillars*. 2025;15:100178. Published 2025 May 8. doi:10.1016/j.obpill.2025.100178

KEY TAKEAWAY: Acupressure wristbands (ACW) may relieve nausea in patients on glucagon-like peptide-1 receptor agonists (GLP-1as).

STUDY DESIGN: One arm, open-label, non-randomized, prospective interventional study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to lack of control arm and small sample size)

BRIEF BACKGROUND INFORMATION: Primary care physicians often prescribe GLP-1as, the most common side-effect of which is nausea. No direct interventions are considered first-line, leaving patients and their physicians to try various behavioral modifications and often disrupt treatment by reducing dosages or discontinuing the medication. This study aimed to test the efficacy of patient-administered acupressure wristbands for relief of nausea episodes in these patients.

PATIENTS: Adults taking GLP-1a

INTERVENTION: ACW

CONTROL: None

PRIMARY OUTCOME: Nausea episodes

Secondary Outcome: Time to nausea relief

METHODS (BRIEF DESCRIPTION):

- Patients included non-pregnant adults on GLP-1a.
- Patients were recruited during routine follow up appointments with nausea.
- Patients with other conditions potentially explaining nausea were excluded from the study.
- Patients were 55 years old average with a mean BMI 34, and a mean hemoglobin A1C (HbA1c) 5.9%.
- Patients were taking semaglutide or tirzepatide, and each remained on their individual current dosage over the four-week study period.
- Patients were provided with a pair of acupressure wristbands with two minutes of instruction on how to apply it at the P6 acupoint, located at three fingerbreadths proximal to the crease of each wrist.
- Patients were asked to record nausea episodes and apply the wristbands at onset of each and then record time to relief.

INTERVENTION (# IN THE GROUP): 31

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Four weeks

RESULTS:

Primary Outcome –

- Acupressure wristbands for one, two and three weeks did not significantly improve nausea compared to week four:
  - Week one (odds ratio [OR] 1.3; *p*=.24)
  - Week two (OR 1.7; *p*=.08)
  - Week three (OR 0.72; *p*=.08)
- Acupressure wristbands provided relief in over 80% of nausea episodes over four weeks.
  - Week one: 105 nausea episodes, 87% relieved with ACW.
  - Week two: 106 nausea episodes, 91% relieved with ACW
  - Week three: 81 nausea episodes, 80% relieved with ACW
  - Week four: 53 nausea episodes, 85% relieved with ACW

Secondary Outcome –

- Time to relief of nausea was between 5–20 minutes after application of the wristband (results presented via figure).

LIMITATIONS:

- The study included only 31 participants, which decreases generalizability and increases uncertainty in results, as it potentially produced false positives.
- The study was non-randomized, which increases potential selection bias.
- The study was not blinded, which increases chances of placebo effect.
- The study did not include a control group, which limits the comparison of the intervention to natural disease (nausea episode) progression (self-resolution).

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GLP-1 RA, A Danger in Pregnancy?

Use of GLP-1 Receptor Agonists in Early Pregnancy and Reproductive Safety: A Multicenter, Observational, Prospective Cohort Study Based on the Databases of Six Teratology Information Services

Dao K, Shechtman S, Weber-Schoendorfer C, et al. Use of GLP1 receptor agonists in early pregnancy and reproductive safety: a multicentre, observational, prospective cohort study based on the databases of six Teratology Information Services. *BMJ Open*. 2024;14(4):e083550. Published 2024 Apr 24. doi:10.1136/bmjopen-2023-083550

KEY TAKEAWAY: Exposure to glucagon-like peptide 1 receptor agonists (GLP-1 RAa) in the first trimester is not associated with a risk of major birth defects when compared with diabetic pregnant patients on ≥1 non-GLP-1 RAs, or to pregnant patients without diabetes who are overweight/obese.

STUDY DESIGN: Multicenter, observational, prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: GLP-1 RAs have gained popularity as a treatment option of type 2 diabetes mellitus(T2DM) and obesity. With 50% of pregnancies worldwide being unplanned, the risk of exposure to GLP-1 RA during early pregnancy is high. This study aimed to evaluate the outcomes of GLP-1 RA exposure during the first trimester of pregnancy.

PATIENTS: Pregnant women

INTERVENTION: Pregnancies exposed to GLP-1 RA in first trimester

CONTROL: Pregnant women with diabetes exposed to non-GLP-1 RA in first trimester and pregnant women with overweight/obesity diagnosis in first trimester

PRIMARY OUTCOME: Major fetal birth defects, spontaneous pregnancy loss, and pregnancy termination
Secondary Outcome: Preterm births, gestational age at birth, birth weight

METHODS (BRIEF DESCRIPTION):

- Patients were randomly selected across six participating medical centers who are members of the European Network of Teratology Information Services (ENTIS) across five countries: Germany, Israel, Italy, Switzerland, and UK.
- Pregnancies of women exposed to a GLP-1 RA during the first trimester and pregnancies of women with diabetes who were exposed to non GLP-1 RA antidiabetic medication in the first trimester and pregnancies of nondiabetic women who were overweight/obese (BMI >25) were included in the study.
- Exposure to any teratogenic drugs, cytotoxic agents, as well as presence of malignancies or malignancy related conditions, multiple pregnancies and duplicate cases were excluded.
- Maternal characteristics of the groups were generally similar with the diabetic control group being slightly older and with more medical comorbidities, and the overweight/obese control group having more overweight and obese patients.
- Liraglutide (n=99) was the most prescribed medication in the intervention group, followed by semaglutide (n=51), dulaglutide (n=11), and exenatide (n=7).
    - Dosages were not included.
- Primary outcomes analyzed included major birth defects, incidence of elective terminations, and pregnancy losses.
- Secondary outcomes analyzed included pre-term births, gestational age at delivery, and birth weight.

INTERVENTION (# IN THE GROUP): 167

COMPARISON (# IN THE GROUP):

- Diabetes control: 154
- Obese control: 162

FOLLOW-UP PERIOD: Patients were followed from first contact with ENTIS to soon after expected due date

RESULTS:

Primary Outcome –

- There was no significant difference in rates of major birth defects in the GLP-1 RA group compared to the diabetes group (2.6% vs 3.9%, respectively; adjusted odds ratio [aOR] 0.54; 95% CI, 0.11–2.8).
- There was no significant difference in major birth defects in the GLP-1 RA group compared to the overweight/obese group (irrespective of etiology) (2.6% vs 3.9%, respectively; aOR 0.54; 95% CI, 0.11–2.8).

- There was a higher incidence of elective terminations for personal reasons in the GLP-1 RA group, compared to both control groups (adjusted hazard ratio [aHR] 3.9; 95% CI, 1.5–10).
- There was no significant difference in pregnancy losses between the GLP-1 RA and obese control groups (aHR 1.4; 95% CI, 0.66–2.4).
- There was no significant difference in pregnancy loss for GLP-1 RA compared to the diabetic group (aHR 1.7; 95% CI, 0.93–3.0).
- There was no significant difference in pregnancy loss for GLP-1 RA compared to the obese group (aHR 0.90; 95% CI, 0.48–1.3).

Secondary Outcome –

- There were fewer preterm births in the GLP-1 RA group (8%) compared to the diabetes control group (15%) and the obese control groups (15%).
- Gestational age at birth was similar between the GLP-1 RA group and the two control groups.
- There were fewer larger gestational age births in the GLP-1 RA group (18%) than the diabetes control group (23).

LIMITATIONS:

- This study focused on first trimester exposure and did not analyze the potential risks with gestational diabetes.
- Treatment of GLP-1 RA was discontinued in early gestational ages in majority of cases.
- Due to the low sample size, the power of the study is diminished.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the U.S. Government.