GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of April 22- April 25, 2025

SPOTLIGHT:

Are SGLT2 Inhibitors Better for Diabetics with Gout?

- Less Is More: Home Blood Pressure Monitoring's Effect on Early Diagnosis of Hypertension in Pregnancy
- Heavy Slow Resistance: Good or Bad with Injections and Needling?
- Fish Oil Supplementation Alters HDL Composition, Cholesterol Efflux Capacity, and Expression of Anti-inflammatory Markers

Are SGLT2 Inhibitors Better for Diabetics with Gout?

Sodium-Glucose Cotransporter-2 Inhibitors vs Sulfonylureas for Gout Prevention Among Patients with Type 2 Diabetes Receiving Metformin

McCormick N, Yokose C, Lu N, et al. Sodium-Glucose Cotransporter-2 Inhibitors vs Sulfonylureas for Gout Prevention Among Patients With Type 2 Diabetes Receiving Metformin. *JAMA Intern Med*. 2024;184(6):650-660. doi:10.1001/jamainternmed.2024.0376

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KEY TAKEAWAY: Sodium-glucose cotransporter-2 inhibitors (SGLT2is) reduce the risk of developing recurring gout compared to use of sulfonylureas in individuals with type 2 diabetes mellitus (T2DM) on metformin.

STUDY DESIGN: Observational cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The frequency of gout is on the rise among people with T2DM. While SGLT2 medications have displayed potential in lowering risks and uric acid levels in this group of individuals, research is still needed to compare their effectiveness with used treatments like sulfonylurea in preventing gout for those with T2DM.

PATIENTS: Canadian adults with T2DM on metformin monotherapy

INTERVENTION: Initiation of SGLT2i

CONTROL: Initiation of sulfonylureas

PRIMARY OUTCOME: Development of gout

Secondary Outcome: Incidence of recurrent gout flares

METHODS (BRIEF DESCRIPTION):

- Adults with T2DM taken from a community-based record in British Columbia, Canada were included.
- Eligible patients included those who were on metformin for ≥1 year before beginning a glucose-lowering medication.
- Participants characteristics:
  - Mean age of 60 years old
  - 60% were male and 40% were female
  - Mean T2DM diagnosis duration was 9.7 years
- Participants in the intervention group received treatment with SGLT2is, specifically medications including canagliflozin, empagliflozin, and dapagliflozin.
  - The specific dosage and duration of treatment varied widely among participants and were not standardized.
  - Average dosing ranged from 10 mg to 25 mg once daily, but actual prescribed amounts differed based on individual patient needs and physician decisions.
  - The frequency of medication adherence and patient reports on treatment duration were collected, but no standard protocol was established across the cohort.
- Participants in the control group began treatment with sulfonylureas which included glimepiride or glyburide.
  - The dosages and treatment durations varied, reflecting individual patient circumstances rather than a uniform protocol.
  - Average dosing ranged from 1 mg to 8 mg daily, dependent on individual factors.
  - Treatment frequency and adherence data were gathered but not standardized among participants.
- The primary and secondary outcomes assessed gout incidence and recurrent flare outcomes via a combination of international classification of disease (ICD) codes and medication dispensing records related to gout from patients' emergency department (ED) visits, hospitalizations, and outpatient care.

INTERVENTION (# IN THE GROUP): 17,302

COMPARISON (# IN THE GROUP): 17,302

FOLLOW-UP PERIOD: Mean 1.4 years

RESULTS:

Primary Outcome –

- SGLT2is reduced the risk of developing gout compared to sulfonylureas (hazard ratio [HR] 0.62; 95% CI, 0.48–0.80).

Secondary Outcome –

- SGLT2is reduced the risk of recurrent gout flares compared to sulfonylureas in patients with a previous history of gout (HR 0.67; 95% CI, 0.55–0.82).

LIMITATIONS:

- The study's observational nature limits the ability to definitively establish causality between SGLT2i use and reduced gout risk; confounding remains a possibility.
- The study could not control variability in specific SGLT2i and sulfonylurea medications, dosages, and treatment durations due to its observational design.

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Less Is More: Home Blood Pressure Monitoring's Effect on Early Diagnosis of Hypertension in Pregnancy

Effect of Self-Monitoring of Blood Pressure on Diagnosis of Hypertension During Higher-Risk Pregnancy: The BUMP 1 Randomized Clinical Trial

Tucker KL, Mort S, Yu LM, et al. Effect of Self-monitoring of Blood Pressure on Diagnosis of Hypertension During Higher-Risk Pregnancy: The BUMP 1 Randomized Clinical Trial [published correction appears in JAMA. 2022 Jul 12;328(2):217. doi: 10.1001/jama.2022.11186.]. *JAMA*. 2022;327(17):1656-1665. doi:10.1001/jama.2022.4712

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KEY TAKEAWAY: Home blood pressure (BP) monitoring did not improve early identification of hypertension in pregnant patients compared to routine prenatal visits.

STUDY DESIGN: Unblinded, randomized clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to significant limitations)

BRIEF BACKGROUND INFORMATION: Hypertension affects approximately one in 10 pregnancies and is one of the most common complications of pregnancy. Gestational hypertension can progress to preeclampsia and may result in fetal growth restriction, placental abruption, and preterm delivery. In non-pregnant populations, home BP monitoring has been beneficial in diagnosing and managing hypertension. Existing studies of home hypertension monitoring in pregnant individuals have involved small samples and often lacked validated BP devices.

PATIENTS: Pregnant patients with elevated risk of pre-eclampsia

INTERVENTION: Self-monitoring BP with monitoring during routine prenatal visits

CONTROL: BP monitoring during routine prenatal visits

PRIMARY OUTCOME: Early detection of hypertension

Secondary Outcome: Incidence of severe hypertension, preeclampsia, spontaneous onset of labor, infants admitted to neonatal intensive care units (NICU)

METHODS (BRIEF DESCRIPTION):

- Patients from United Kingdom midwives' clinics were recruited at 16–24 weeks gestation and had ≥1 risk factor for pre-eclampsia.
  - Risk factors included women >40 years old, nulliparous, prior pregnancy >10 years ago, family history of preeclampsia, personal history of diabetes, gestational diabetes, preeclampsia, body mass index (BMI) ≥30, chronic kidney disease (CKD), autoimmune disorder, or current twin pregnancy.
- Patients with preexisting diagnoses of chronic hypertension were excluded from the trial.
- Participant characteristics:
  - Mean age of the participants: 33 years old
  - Mean gestational age: 20 years old
  - 39% of participants were multiparous
  - 77% of participants were White, 11% were Asian, and 8% were Black.
  - Baseline characteristics were similar between the control and intervention groups.
- Standard prenatal care included routine monitoring of BP at prenatal appointments.
- The home BP monitoring group received standard prenatal care and were also provided with a validated BP monitor, and were instructed to check their BP three times weekly, with two consecutive measures each session.
  - An elevated BP prompted a third check. If the reading remained elevated, patients were prompted to contact their provider for further guidance.
- Hypertension in the study was defined as sustained (>2 measurements) BP of >140/90 in one week.
- Patients were also considered to have hypertension if they were diagnosed with preeclampsia, gestational hypertension, or if they received treatment with antihypertensive medication.

INTERVENTION (# IN THE GROUP): 1,223

COMPARISON (# IN THE GROUP): 1,218

FOLLOW-UP PERIOD: Diagnosed with hypertension or delivery, whichever occurred first

RESULTS:

Primary Outcome –

- Self-monitoring BP did not affect early detection of hypertension compared to control (104 vs 106 days, respectively; mean difference [MD] –1.6 days; 95% CI, –8.1 to 4.9).

Secondary Outcome –

- The incidence of severe hypertension, pre-eclampsia, spontaneous onset of labor, and

newborns admitted to the NICU were not statistically significant between the two groups.

LIMITATIONS:

- The study was powered to detect a statistical significance based on a 12-day earlier presentation between self-monitoring and clinical diagnosis.
- White coat hypertension may have influenced BP readings, as 26% of diagnosed cases had elevated clinic measurements that were not observed during at-home monitoring.
- 61% of individuals in the intervention group diagnosed with hypertension had elevated home pressures up to one month before the official diagnosis.
- While participants were instructed to consult providers for elevated home readings, there is limited data on whether participants followed through.
- 27% of individuals were already monitoring their BP at home before randomization. It is unknown whether these individuals continued monitoring during the trial or not.

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Heavy Slow Resistance: Good or Bad with Injections and Needling?

Effects of Heavy Slow Resistance Training Combined with Corticosteroid Injections of Tendon Needling in Patients with Lateral Elbow Tendinopathy: A 3-Arm Randomized Double-Blinded Placebo-Controlled Study

Couppé C, Døssing S, Bülow PM, et al. Effects of Heavy Slow Resistance Training Combined With Corticosteroid Injections or Tendon Needling in Patients With Lateral Elbow Tendinopathy: A 3-Arm Randomized Double-Blinded Placebo-Controlled Study. *Am J Sports Med*. 2022;50(10):2787-2796. doi:10.1177/03635465221110214

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KEY TAKEAWAY: Heavy slow resistance (HSR) + corticosteroid injection (CI) improves pain and function compared to HSR + placebo needling (PN) but offers no benefit over HSR + tendon needling (TN).

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

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

BRIEF BACKGROUND INFORMATION: Prior studies have shown that eccentric and HSR programs effectively treat lateral elbow tendinopathy. HSR provides an advantage with higher patient compliance given the lower volume and frequency of this exercise protocol. This study aimed to provide additional insight into the statistical significance of HSR + CIs or dry needling for the treatment of lateral elbow tendinopathy.

PATIENTS: Adults with lateral elbow tendinopathy

INTERVENTION: HSR + CI

CONTROL: HSR + TN and HSR + PN

PRIMARY OUTCOME: Function and symptoms

Secondary Outcome: Modified function and symptoms, pain, pain-free grip strength, hypervascularity

METHODS (BRIEF DESCRIPTION):

- Adults 18–70 years old in the outpatient setting with lateral elbow and forearm pain symptoms with >3 months duration, tenderness on palpation, two of three positive Cozen test, Maudsley test, or forearm supination test, DASH score >30, ultrasonography with increased tendon thickness were included.
- Patients were excluded if they had a history of elbow fractures or osteoarthritis, bilateral symptoms and/or systemic arthritis, diabetes, or CI or dry needling within three months.
- Patients were randomized and stratified by sex and baseline DASH score (<50 or >50 points), with higher scores indicating worse disability.
- Participants, statisticians, research assistants, and physical therapists were blinded to group allocations.
    - Trial physicians performing injections were not blinded.
- HSR training consists of three exercises, including extension, flexion, and supination/pronation, to be performed every other day with training diaries to track compliance.
    - Progressive overload was used for training and patients followed up with physical therapy at four weeks.
- Patients assigned to the intervention group received 1 mL of depo-medrol (40 mg/mL) and 1 mL of lidocaine (10 mg/mL) injected beneath the tendon.
- Patients assigned to the control group received either:
    - PN: 1 mL of 0.9% isotonic saline above the tendon
    - TN: 1 mL of 0.9% isotonic solution inserted through the affected tendon at 2–3 sites
- The primary outcome measured function and symptoms using the Disabilities of the Arm, Shoulder, and Hand (DASH). Scores range from 0–100, with higher scores indicating severe disability.
- The following were measured as the secondary outcomes:
    - Modified function and symptoms were measured using the shortened version of DASH, the QuickDASH score. Scores range from 0–100, with higher scores indicating severe disability.
    - Pain was measured using the Numerical Rating Scale (NRS). Scores range from 0–10, with higher scores indicating worse pain.
    - Hypervascularization was measured using a power doppler ultrasound.
    - Pain free grip strength was measured using a digital hand dynamometer to assess strength in the affected hand and forearm.

- DASH, QuickDASH, and NRS measures were repeated at 12, 26 and 52 weeks.
- Grip strength and hypervascularity were repeated at 12 weeks.

INTERVENTION (# IN THE GROUP): 21

COMPARISON (# IN THE GROUP):

- HSR + TN: 17
- HSR + PN: 20

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- HSR + CI significantly improved function and pain assessed via DASH compared to HSR + PN at 52 weeks (mean difference [MD] 14; 95% CI, 2.5–26).
- HSR + CI did not significantly improve function and pain assessed via DASH compared to HSR + TN at 52 weeks (MD –7.7; 95% CI, –19 to 3.8).

Secondary Outcome –

- HSR + CI significantly improved function and pain assessed via QuickDASH compared to HSR + PN at 52 weeks (MD 15; 95% CI, 2.5–26).
- HSR + CI did not significantly improve function and pain assessed via QuickDASH compared to HSR + TN at 52 weeks.
- HSR + CI significantly improved pain compared to HSR + PN at 52 weeks (MD 1.8; 95% CI, 0.22–3.4).
- HSR + CI did not significantly improve pain compared to HSR + TN at 52 weeks.
- HSR + CI improved pain-free grip strength compared to HSR + PN at 12 weeks (MD 10 kg; 95% CI, 0.16–20).
- HSR + CI did not improve pain-free grip strength compared to HSR + TN at 12 weeks.
- HSR + CI decreased hypervascularization compared to HSR + PN at 12 weeks (MD –2,251; 95% CI, –4,416 to –87).
- HSR + CI decreased hypervascularization compared to HSR + TN at 12 weeks (MD –3,333; 95% CI, –1,114 to –5,551).

LIMITATIONS:

- The study did not include a power analysis to account for the small sample size, which may limit the reliability of the outcome results.
- There was no control for previous interventions used prior to participation. Although patients with prior CIs or needling were excluded, other preceding treatments such as physical therapy, dextrose prolotherapy, or platelet-rich plasma (PRP) injections were not accounted for.
- There was variability in the load magnitude applied during the intervention.
- The study lacked a "wait-and-see" control group to compare the natural progression of the disease.
- Assessing functional limitations as an outcome may have limited utility, as lateral tendinopathy is unlikely to significantly impair function.
- Although the DASH questionnaire has been validated for lateral elbow tendinopathy, more specific elbow assessments could have been employed.

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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 Air Force, Defense Health Agency, Department of Defense, or the US Government.

Fish Oil Supplementation Alters HDL Composition, Cholesterol Efflux Capacity, and Expression of Anti-inflammatory Markers

Fish Oil Supplementation Modifies the Proteome, Lipidome, and Function of High-Density Lipoprotein: Findings From a Trial in Young Healthy Adults

Mueller PA, Bergstrom P, Rosario S, Heard M, Pamir N. Fish Oil Supplementation Modifies the Proteome, Lipidome, and Function of High-Density Lipoprotein: Findings from a Trial in Young Healthy Adults. *J Nutr*. 2024;154(4):1130-1140. doi:10.1016/j.tjnut.2024.01.007

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KEY TAKEAWAY: Fish oil supplementation alters the expression of proteins and phospholipids composing high-density lipoprotein (HDL) and increases in vitro measurements of reverse cholesterol transport but does not significantly decrease inflammatory markers.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Supplementation with omega-3 fatty acids found in fish oil is an FDA-approved treatment for hypertriglyceridemia >500 mg/dL and reduces plasma triglycerides by 30%, making supplementation with fish oil a candidate for use in the reduction of cardiovascular risk. Although large clinical trials showed no decrease in cardiovascular disease (CVD) risk with fish oil supplementation, other studies suggest fish oil supplementation reduces myocardial infarction (MI), fatal myocardial infarction, coronary artery disease (CAD), and mortality. Regardless of the controversy regarding outcomes, little is known regarding the epigenetic changes of HDL that are associated with increased transport of cholesterol from peripheral tissues.

PATIENTS: Healthy young adults

INTERVENTION: Oral fish oil supplementation with EPA and DHA

CONTROL: Baseline

PRIMARY OUTCOME: Plasma EPA, DHA, cholesterol, triglycerides, cholesterol efflux capacity, inflammatory cytokine expression

METHODS (BRIEF DESCRIPTION):

- Normolipidemic adults 26–37 years old without a history of CVD and not currently taking fish oil supplements were included in the study.
- Participants received oral fish oil supplementation containing 1,125 mg eicosapentaenoic acid (EPA) and 875 mg docosahexaenoic acid (DHA) daily for 30 days.
  - EPA and DHA are long-chain omega-3 fatty acids found in fish, shellfish, and some algae.
- Study participants were used as their own controls using a 30-day washout period between measurements**.**
- The following were measured as the primary outcomes:
  - Plasma EPA, DHA, cholesterol, and triglycerides were measured after isolation via ultracentrifugation and compared to baseline.
  - Cholesterol efflux capacity was measured using baby hamster kidney cells exposed to control HDL or HDL from study subjects.
  - Anti-inflammatory capacity was measured by exposing human macrophage cells to HDL from study subjects, extracting ribonucleic acid (RNA), and using that RNA to generate complementary deoxyribose nucleic acids (cDNA) that could be targeted for the following inflammatory markers: Interleukin-1b, interleukin-10, and interleukin-6.

INTERVENTION (# IN THE GROUP): 7

COMPARISON (# IN THE GROUP): The same 7 patients

FOLLOW-UP PERIOD: 30 days

RESULTS:

Primary Outcome –

- Oral fish oil supplementation increased EPA levels compared to baseline (86 vs 18, respectively; *P*=.002).
  - Following washout, EPA levels returned to baseline.
- Oral fish oil supplementation increased DHA levels compared to baseline (110 vs 58, respectively; *P*=.004).
  - Following washout, DHA levels remained elevated compared to baseline (81 vs 58, respectively; *P*=.026).
- Oral fish oil supplementation did not significantly change serum cholesterol compared to baseline (188 vs 187, respectively; *P*=.92).

- Oral fish oil supplementation did not significantly change serum triglycerides compared to baseline (84 vs 103, respectively; *P*=.080).
- Oral fish oil supplementation increased cholesterol efflux capacity compared to baseline (16 vs 13, respectively; *P*=.002).
- Oral fish oil supplementation did not affect HDL anti-inflammatory capacity compared to baseline (results presented via figure).

LIMITATIONS:

- Small sample size limits generalizability of the study's findings
- Limited applicability to only healthy young adults
- There may have been changes in the dietary habits of studied individuals that were not accounted for.
- The study was limited by the use of in-vitro measurements of cholesterol efflux and anti-inflammatory capacities.

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