GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 1 - Issue 47

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of November 22 - 26, 2021

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Compressive Forces of High-Intensity Strength Training in Adults with Knee Osteoarthritis: Helpful or Harmful?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Effect of High-Intensity Strength Training on Knee Pain and Knee Joint Compressive Forces Among Adults with Knee Osteoarthritis: The START Randomized Clinical Trial

Messier SP, Mihalko SL, Beavers DP, et al. Effect of High-Intensity Strength Training on Knee Pain and Knee Joint Compressive Forces Among Adults with Knee Osteoarthritis: The START Randomized Clinical Trial. *JAMA*. 2021; 325(7):646–657. doi:10.1001/jama.2021.0411.

KEY TAKEAWAY: Guided and interactive high-intensity strength training, low intensity strength training, and educational-attention intervention regimens are all equally capable of improving pain and function in adults with knee osteoarthritis (OA) without adversely affecting disease progression.

STUDY DESIGN: Single center assessor blinded randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: As one of the leading causes of disability and pain among older adults, OA of the knees can severely limit daily functioning. Conflicting evidence suggests that knee pain may improve with varying strength training regimens (particularly high versus low intensity) by increasing muscle strength and thereby decreasing joint load compressive forces.

PATIENTS: Ambulatory adults >50 years old with BMI 20–45 with self-reported disability due to OA

INTERVENTION: Supervised high-intensity strength training

CONTROL: Supervised low-intensity strength training or attention control

OUTCOME: Arthritis severity (knee pain and knee joint compressive force)

METHODS (BRIEF DESCRIPTION):

- Participants were ambulatory, >50 years-old, reported disability from mild-to-moderate patellofemoral OA with minimal or mild joint deformity.
- Those with severe OA, scores <20 on Montreal Cognitive Assessment, or had participated in formal strength training in the past six months were excluded.
- The strength training intervention and comparison group sessions were performed 3x/week for 18 months split into nine-week blocks.
  - The high-intensity group worked from 75% up to 90% of their determined 1-repetition max (1RM).
  - The low-intensity group stayed at 30–40% of their determined 1RM.
  - The attention control group attended guided educational workshops but had no exercise intervention.
- Primary Outcomes –
  - The level of knee pain in the past 48 hours was measured by the WOMAC scale (Western Ontario McMaster Universities Osteoarthritis index) where higher score indicates worse pain.
  - Knee joint compressive force (N) measured as the maximum tibiofemoral contact exerted on tibia's long axis while walking.

INTERVENTION (# IN THE GROUP): 127

COMPARISON (# IN THE GROUP):

- Low-intensity strength training: 126
- Attention control: 124

FOLLOW UP PERIOD: 18 months

RESULTS:

- There was no difference in knee pain between any of the groups.
  - High-intensity vs low-intensity (adjusted difference [AD] 0.7; 95% CI, –0.1 to 1.6)
  - High-intensity vs attention-control (AD 0.2; 95% CI, –0.6 to 1.1)
- All three groups clinically improved from baseline at 18 months.
  - Clinical improvement defined as a decrease of at least 2 on WOMAC scale.
  - High-intensity absolute change –2.0 (95% CI, –2.6 to –1.4)
  - Low-intensity –2.8 (95% CI, –3.5 to –2.2)
  - Attention-control –2.3 (95% CI, –2.9 to –1.6)
- There was no statistical difference in the compressive forces (N) of tibiofemoral joint load measurements between the three groups over the course of treatment.

LIMITATIONS:

- Majority were men (60%), white (79%), obese (mean BMI 31) with neutral/varus mechanically aligned knees.
- Measurements of joint mechanic compressive forces on the knee were oversimplified with many subjects lost to follow-up for this outcome.

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Constipation: A Hard Problem to Work Out

Senna Versus Magnesium Oxide for the Treatment of Chronic Constipation: A Randomized, Placebo-Controlled Trial

Morishita D, Tomita T, Mori S, et al. Senna Versus Magnesium Oxide for the Treatment of Chronic Constipation: A Randomized, Placebo-Controlled Trial. *Am J Gastroenterol*. 2021; 116(1):152–161.

KEY TAKEAWAY: Patients with chronic idiopathic constipation had significant improvement in constipation symptoms, stool frequency and form, and quality of life when treated with magnesium oxide or senna compared to placebo.

STUDY DESIGN: Double -blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Chronic constipation is a common problem, which can have negative impacts on the quality of life of those who experience it. It's unclear what is the most effective treatment for chronic idiopathic constipation.

PATIENTS: Constipated adults 20–75 years old

INTERVENTION: Daily magnesium oxide or senna

CONTROL: Placebo

OUTCOME: Improvement of constipation symptoms
Secondary Outcomes – Changes in number of and time until spontaneous bowel movements (SBM) and change in specific symptoms (bloating, straining, incomplete evacuation, abdominal discomfort)

METHODS (BRIEF DESCRIPTION):

- The study was completed in Japan, including 90 patients (93% female) with a mean age of 42 years old.
- For one week prior to initiation of study, participants discontinued any previous OTC constipation medications and noted their bowel symptoms, frequency, and stool form (based on Bristol Stool Form Scale).
- Participants were randomized to receive daily stimulant laxative (1 g Senna), daily osmotic laxative (1.5 g magnesium oxide), or placebo for four weeks.
    - All drugs and placebo were formulated into identical capsules for blinding.
- If abdominal symptoms or diarrhea occurred, participants were allowed to self-reduce the medication dose from six daily capsules to four or two.
- "Responders" to the intervention were defined as symptomatic improvement of >1 on a 5-point symptom scale (1-significantly improved, 2-improved, 3-slightly improved, 4-unchanged, 5-exacerbated) measured at weekly intervals.

INTERVENTION (# IN THE GROUP):

- Senna: 30
- Magnesium oxide: 30

COMPARISON (# IN THE GROUP): 30

FOLLOW UP PERIOD: Four weeks

RESULTS:

- The intervention groups had a greater proportion of individuals with overall symptom improvement compared to the placebo group (69% senna vs 68% magnesium oxide vs 12% placebo; *P*<.0001).
- The intervention groups had less time before their first SBM compared to placebo (19 hours senna vs 18 hours magnesium oxide vs 22 hours placebo; *P*<.002).
- Both intervention groups had significant improvements in bloating, straining, and feeling of incomplete evacuation.
    - The magnesium oxide group noted significant improvement in abdominal discomfort (*P*<.01 no specific outcome data provided by authors), but the senna group did not.

LIMITATIONS:

- Limited generalizability given study population of predominantly young, Japanese women (93%).
- 62% of patients self-reduced their dose (due to diarrhea or abdominal symptoms).
- Short duration of follow up.
- Short pre-trial "drug wash out period" of one week.
- Patients with severe constipation were excluded.
- No comparison to other common constipation treatments (ie polyethylene glycol, psyllium, etc).

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Lisfranc Injury: Can You Bear the Weight of Missing This Diagnosis?

Inter- and Intra-Observer Reliability of Non-Weight-Bearing Foot Radiographs Compared with CT in Lisfranc Injuries

Ponkilainen VT, Partio N, Salonen EE, et al. Inter- and intraobserver reliability of non-weight-bearing foot radiographs compared with CT in Lisfranc injuries. *Arch Orthop Trauma Surg*. 2020; 140(10):1423–1429. doi:10.1007/s00402-020-03391-w

KEY TAKEAWAY: 24% of Lisfranc injuries (LI) are missed when only non-weight-bearing radiographs (NWBR) are used.

STUDY DESIGN: Single blinded RCT

LEVEL OF EVIDENCE: STEP 3 (downgraded due to unclear gold-standard of testing)

BRIEF BACKGROUND INFORMATION: Lisfranc, or tarsometatarsal joint complex injury, is a commonly missed diagnosis. However, the reported literature on accuracy in diagnosis has been limited. The diagnostic accuracy of NWBR (an easily accessible imaging modality) has not been previously assessed among patients with LI.

PATIENTS: Patients with non-displaced Lisfranc injury (NDLFI), displaced Lisfranc injury (DLFI), and no Lisfranc injury (NLFI)

INTERVENTION: Evaluation of NWBR accuracy to diagnose DLFI, NDLFI, NLFI

CONTROL: Confirmed LI (or NLFI) via CT scan

OUTCOME: Inter- and intra-observer accuracy in diagnosing LI with NWBR

Secondary Outcome: Accuracy between senior and junior orthopedic surgeons

METHODS (BRIEF DESCRIPTION):

- Patients who had received a CT were selected:
  - 34 patients with NLFI
  - 33 patients with DLFI (defined as TMT joint dislocation of 2 mm or more)
  - 33 patients with NDLFI
- NWBR were blinded and assessed independently twice by:
  - Three senior orthopedic surgeons with at least 10 years of experience
  - Three junior orthopedic surgery residents with 4–6 years of experience
- Three months were between the initial and subsequent assessments.
- Observers viewed images of the foot in the antero-posterior, 30^{o} oblique, and lateral view.
- The order of images was randomly sorted during the second assessment period.

INTERVENTION (# IN THE GROUP): 66

COMPARISON (# IN THE GROUP): 34

FOLLOW UP PERIOD: Three months

RESULTS:

- The mean specificity of NWBR was 85% (range 53–100).
- The mean sensitivity of NWBR was 76% (range 61–92).
- Sensitivity of NDLFI diagnosis was lower than DLFI diagnosis (65% vs 87%; *P*=.003).
- There were no statistically significant differences in diagnostic accuracy between senior and junior orthopedic observers.

LIMITATIONS:

- Radiographs were assessed by orthopedic surgeons and residents who are more familiar with LI than non-orthopedic physicians.
- MRI and weight-bearing x-rays were not used to assess injury.
- Class 1 LI are unable to be diagnosed using radiographs.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.

Sharing is Caring: Fecal Microbiota Transplant Can Improve IBS Symptoms

Efficacy of Faecal Microbiota Transplantation for Patients with Irritable Bowel Syndrome in a Randomised Double-Blind, Placebo-Controlled Study

El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A, Hausken T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. *Gut*. 2019; 69(5):859–867. doi: 10.1136/gutjnl-2019-319630

KEY TAKEAWAY: Fecal microbiota transplant (FMT) improved symptoms of irritable bowel syndrome (IBS) when compared with placebo.

STUDY DESIGN: Double-blind randomized placebo-controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and short follow up)

BRIEF BACKGROUND INFORMATION: IBS is a common condition that significantly decreases quality of life. The etiology is not entirely clear but may be related to low bacterial diversity in the gut. Prior studies involving treatment of IBS with FMT have yielded conflicting results.

PATIENTS: Patients 18–85 years old with IBS based on Rome IV criteria

INTERVENTION: 30g or 60g FMT

CONTROL: 30g FMT of own feces

OUTCOME: Abdominal pain, fatigue, quality of life

Secondary Outcomes: Stool bacterial composition and intestinal bacterial profiles

METHODS (BRIEF DESCRIPTION):

- Patients that met Rome IV criteria for IBS with moderate to severe symptoms (≥175 on IBS-SSS) at baseline were recruited from single medical center in Norway.
- The primary outcome was improvement in abdominal pain, fatigue, and quality of life as measured by a reduction in IBS Symptom Severity Score (IBS-SSS) of at least 50 points at 3 months.
- Participants randomized in 1:1:1 ratio to 30 g FMT, 60 g FMT, or placebo (30 mg FMT of own feces).
- The intervention groups received stool from a single donor with normobiosis in the distal duodenum via gastroscope. Stool bacterial composition was analyzed using GA-map Dysbiosis Test, which determines the bacterial profile and assigns a dysbiosis index (DI) score, before and after FMT.

INTERVENTION (# IN THE GROUP):

- 30 g FMT group: 54
- 60 g FMT group: 55

COMPARISON (# IN THE GROUP): 55

FOLLOW UP PERIOD: Three months

RESULTS:

Primary Outcome –

- More participants in the 30 g treatment group successfully improved abdominal pain, fatigue, and quality of life compared to the control group at two weeks (69% vs 49%, respectively; *P*<.001).
- This persisted at one month (76% vs 26%, respectively; *P*<.0001) and three months (77% vs 24%, respectively; *P*<.0001).
- More participants in the 60 g treatment group successfully improved abdominal pain, fatigue, and quality of life compared to the control group at two weeks (80% vs 49%, respectively; *P*<.0001).
- This persisted at one month (86% vs 26%, respectively; *P*<.0001) and three months (89% vs 24%, respectively; *P*<.0001).

Secondary Outcomes: There were no significant differences between the groups in stool bacterial composition.

Adverse effects: Patients in the donor FMT groups experienced more GI side effects vs placebo.

- Abdominal pain: 19% vs 0% (*P*<.01)
- Diarrhea: 24% vs 4% (*P*<.01)
- Constipation: 22% vs 2% (*P*<.01)

LIMITATIONS:

- The primary endpoint is less than the minimal clinically important change score of 175 points in IBS-SSS.
- Small sample size and limited patient population.
- Use of single super donor limits generalizability.
- Short follow up period, unclear if benefits persist beyond 3 months.

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SMS Reminders Do Not Increase Adherence to PrEP in Women with High Rates of HIV Acquisition in Kenya

Effect of SMS reminders on PrEP Adherence in Young Kenyan Women (MPYA Study): A Randomised Controlled Trial

Haberer JE, Bukusi EA, Mugo NR, et al. Effect of SMS reminders on PrEP adherence in young Kenyan women (MPYA study): a randomised controlled trial. *Lancet HIV*. 2021; 8(3):e130-e137. doi:10.1016/S2352-3018(20)30307-6

KEY TAKEAWAY: SMS text messages did not increase adherence to PrEP therapy in women 18–24 years old with a high risk of HIV acquisition in Kenya.
STUDY DESIGN: Randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Women in Sub-Saharan Africa are at increased risk of acquiring HIV. PrEP is highly effective, yet multiple trials show that adherence is low. One intervention shown to improve adherence to medication is SMS reminders. A Ugandan study indicated an improvement in ART therapy compliance with SMS, but it has not been studied with PrEP.

PATIENTS: Women 18–24 years old in Kenya
INTERVENTION: SMS messages
CONTROL: No SMS reminders
OUTCOME: PrEP adherence

METHODS (BRIEF DESCRIPTION):

- Participants had a VOICE (risk score of 5 or higher) or were in a sero-discordant relationship.
  - VOICE is an evidence-based risk score that considers multiple social, demographic, and economic factors.
- Exclusion criteria were breastfeeding and pregnancy, although those who became pregnant during the study could continue.
- Participants were randomly assigned to SMS or non-SMS group.
  - SMS messages were sent by an automated platform and study visits were conducted in clinics in Thika and Kisumu.
  - During visits, patients were given their medication (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) and completed a questionnaire.
- Visits were held at one month, three months, and then quarterly (every 3 months) over a two-year period.
- Wisepill RT2000, a real time electronic monitor, measured device opening, as a mark for medication ingestion.
- Drug concentrations of tenofovir diphosphate were collected among 15% of non-pregnant women to reflect average adherence to the medication.
- Statistical analysis was done for the primary outcome, electronically monitored adherence, defined as monitor openings among days of functional monitoring.
- Two sub-analyses were done based on who refilled PrEP regularly, as well as within the group, regardless of medication refills. The different locations were also evaluated for statistical differences.

INTERVENTION (# IN THE GROUP): 173
COMPARISON (# IN THE GROUP): 175

FOLLOW UP PERIOD: Two years

RESULTS:
The SMS reminders did not improve PrEP adherence.

- At the six-month mark, PrEP adherence was 39%.
  - 40% in SMS group vs 37% in control group (adjusted incidence rate ratio [aIRR] 1.1; 95% CI, 0.9–1.4)
- At the two-year mark, PrEP adherence was 27%.
  - 27% in SMS group vs 27% in control group (aIRR 1.2; 95% CI, 0.93–1.5)
- There was no statistically significant difference for refills or site location.

LIMITATIONS:

- The risk of becoming HIV positive might not be adequately represented with the VOICE risk score. This may represent the lack of generalizability of the study, which also is the case of the electronic adherence monitors.
- Drug levels were used to correlate with opening the monitor, but individuals could have taken medication without opening the monitor or opened the monitor and not taken the medicine.

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