GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of October 4 - 8, 2021

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Azithromycin for COVID-19 Symptoms in the Outpatient Setting?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Effect of Oral Azithromycin vs Placebo on COVID-19 Symptoms in Outpatients with SARS-CoV-2 Infection: A Randomized Clinical Trial

Oldenburg CE, Pinsky BA, Brogdon J, et al. Effect of Oral Azithromycin vs Placebo on COVID-19 Symptoms in Outpatients With SARS-CoV-2 Infection: A Randomized Clinical Trial. *JAMA*. 2021; 326(6):490–498. doi:10.1001/jama.2021.11517

KEY TAKEAWAY: Single dose Azithromycin for outpatient treatment of COVID-19 infection does not result in resolution of symptoms at 14 days.

STUDY DESIGN: Double blinded randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Azithromycin is a macrolide antibiotic with anti-inflammatory properties. It has been theorized to have activity against SARS-CoV-2. However, no trials to date study the efficacy of azithromycin alone for the treatment of COVID-19.

PATIENTS: Symptomatic COVID-19 positive adult patients 18–55 years old

INTERVENTION: Azithromycin 1.2 grams one time orally

CONTROL: Placebo

OUTCOME: Absence of symptoms at 14 days

Secondary Outcomes: Adverse effects on day 3 and emergency or urgent care use, death, or hospitalization by day 21

METHODS (BRIEF DESCRIPTION):

- 604 patients with a positive SARS-CoV-2 Nucleic Acid Amplification Test within 7 days prior to enrollment were assessed for eligibility.
  - Patients were not required to have symptoms at time of enrollment.
  - Recruited through flyers, social media, and letters sent to patients who had positive laboratory tests.
- Exclusion Criteria: Taking warfarin or nelfinavir, macrolide allergy, concurrently taking hydroxychloroquine, or pregnant
- 264 patients were included in the study and randomized in a 2:1 ratio to receive Azithromycin or placebo, with 76% completing the study by day 14 (n=201).
  - Participants and investigators were blinded.
  - The Azithromycin group had 36 participants lost to follow up and 4 with no outcome data.
  - The placebo group had 18 participants lost to follow up and 4 with no outcome data.
- Patients were sent either a single 1.2 gram dose of Azithromycin or matching placebo through overnight mail.
- Patients self-reported symptoms through online surveys on days 3, 7, 14, and 21.

INTERVENTION (# IN THE GROUP): 171

COMPARISON (# IN THE GROUP): 92

FOLLOW UP PERIOD: 21 days

RESULTS:

Primary Outcome –

- The Azithromycin group did not vary from the placebo group in symptom resolution (50% vs 50%; prevalence difference 0%; 95% CI, –14% to 15%).

Secondary Outcomes –

- The Azithromycin group had more adverse effects on day 3 than the placebo group. However, statistical significance was not tested.
  - At least one adverse event: 57% of Azithromycin group vs 26% of placebo group
  - At least two adverse events: 26% of Azithromycin group vs 7% of placebo group
- The Azithromycin group had more emergency department or urgent care visits at day 21 than the placebo group (14% vs 3% respectively; prevalence difference 12%; 95% CI, 3% to 20%).
- The two groups had no difference in hospitalizations (prevalence difference 4%; 95% CI, –1% to 9%).
- No serious adverse events or deaths were reported.

LIMITATIONS:

- Underpowered due to small sample size.
- High loss to follow-up in both groups.
- Medication non-compliance may have biased results to show Azithromycin had no effect on symptoms.
- Online surveys may have been difficult for older patients.
- Patients received Azithromycin 1 day (median) later than the placebo group and patients could have already been improving.

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Ketogenic Diet Not Just a Fad but Helpful in Glycemic Control and Insulin Resistance in Type II Diabetics

Effect of the Ketogenic Diet on Glycemic Control, Insulin Resistance, and Lipid Metabolism in Patients with T2DM: A Systematic Review and Meta-Analysis

Yuan X, Wang J, Yang S, et al. Effect of the ketogenic diet on glycemic control, insulin resistance, and lipid metabolism in patients with T2DM: a systematic review and meta-analysis. *Nutr Diabetes*. 2020; 10(1):38. Published 2020 Nov 30. doi:10.1038/s41387-020-00142-z

KEY TAKEAWAY: Ketogenic diets improve glycemic control and lipid metabolism and promote weight loss in type II diabetics.

STUDY DESIGN: Meta-analysis model of random effects or of fixed effects of randomized and non-randomized trials (N=567)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Classic ketogenic diet consists of 90% of caloric intake from fat, 6% from protein, and 4% from carbohydrates. Initially proposed to mitigate seizures in a niche pediatric population, the ketogenic diet has since evolved into a food trend. Despite a conventional belief that fats are predominantly "bad", this study evaluated a measurable, favorable impact of a ketogenic diet on health metrics in diabetics.

PATIENTS: Patients with type II diabetes

INTERVENTION: Ketogenic diet

CONTROL: Comparison of biometrics prior to ketogenic diet and after starting ketogenic diet

OUTCOME: Fasting glucose, HbA1c, total cholesterol, triglycerides, HDL, LDL, body weight, BMI, and waist circumference

METHODS (BRIEF DESCRIPTION):

- Keywords T2DM, diabetes mellitus, ketogenic diet, obesity, and human were used to find relevant English articles in PubMed and MEDLINE databases.
- Inclusion Criteria:
  - Having T2DM on a ketogenic diet
  - Study was done on humans not animals
  - Summary statistics of the average difference before and after ketogenic diet
- Exclusion Criteria:
  - Case reports
  - Meta-analysis or review studies
  - Any other disease than T2DM
- Effects estimated by mean difference after ketogenic diet vs prior to ketogenic diet.
- Heterogeneity evaluated via Cochranes Q statistics corresponding to P and I^2 statistics.
- If $P<.05$ or $I^2>.05$ then a random effect meta-analysis model was used; otherwise, a fixed-effect model was used.

INTERVENTION (# IN THE GROUP): 567

COMPARISON (# IN THE GROUP): Consisted of the same patients as the intervention group

FOLLOW UP PERIOD: 1 week – 56 weeks

RESULTS: Compared to baseline, ketogenic diets caused:

- A decrease in:
  - Fasting blood glucose (10 studies; mean difference [MD] 23 mg/dL; 95% CI, –32 to –14)
  - HbA1c (8 studies; MD 1.1%; 95% CI, –1.4 to –0.78)
  - Triglycerides (8 studies; MD –64 mg/dL; 95% CI, –89 to –38)
  - Weight (11 studies; MD –8.7 kg; 95% CI, –11 to –6)
  - Waist circumference (6 studies; MD 9.2 cm; 95% CI, –11 to –7.7)
  - BMI (8 studies; MD 3.1 kg/m^2; 95% CI, –3.3 to –3.0)
- An increase in:
  - HDL (8 studies; MD 5.4 mg/dL; 95% CI, 1.2 to 9.7)
- No change in:
  - Total cholesterol (5 studies; MD –13 mg/dL; 95% CI, –26 to 0.4)
  - LDL (8 studies; MD –1.9 mg/dL; 95% CI, –9.7 to 5.8)

LIMITATIONS:

- Although 13 studies were included in the meta-analysis, evidence for each of the outcomes varied from 5 to 11 studies.
- Patient population predominantly Caucasian.
- No consistent follow-up intervals.
- Outcomes focused on biometrics rather than morbidity, mortality, or quality of life.

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Manual Therapy with Stabilizing Exercises Improves Pain and Function

The Effect of Manual Therapy and Stabilizing Exercises on Forward Head and Rounded Shoulder Postures: A Six-Week Intervention with a One-Month Follow-Up Study

Fathollahnejad K, Letafatkar A, Hadadnezhad M. The effect of manual therapy and stabilizing exercises on forward head and rounded shoulder postures: a six-week intervention with a one-month follow-up study. *BMC Musculoskelet Disord*. 2019; 20(1):86. Published 2019 Feb 18. doi:10.1186/s12891-019-2438-y

KEY TAKEAWAY: Combined manual therapy and stabilizing exercises improve neck pain and function more than home exercise or stabilizing exercises alone.
STUDY DESIGN: Randomized controlled trial with blinded assessors
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Forward head posture (FHP) leads to significant pain and decreased function. Stabilizing exercises (SE) and manual therapy (MT) have been shown to have considerable effects on pain, posture, and range of motion. This study assessed combined modalities of therapy compared to individual modalities.

PATIENTS: Women with neck pain, forward head, round-shoulder posture (FHRP)
INTERVENTION: MT + SE or SE alone
CONTROL: Home exercise (HE)
OUTCOME: Pain, function, and head and shoulder angles

METHODS (BRIEF DESCRIPTION):

- Iranian women ages 32–40 with non-specific neck pain (excluding that from cervical injury, surgery, or other conditions) and FHRP greater than 3 months.
- Participants were recruited through private physiotherapists and physicians in outpatient settings with random, blinded assignment to treatment group.
- SEs were performed by a physiotherapist and two exercise trainers 3 times weekly. MT was performed by a "skilled manual therapist" for 10 min 3 times weekly for 6 weeks.
- The HE group performed postural correction on daily activities 3 times weekly, irregularly met for lectures, and were given information on activities promoting general health.
- Data was analyzed by an analyst blinded to the treatment modality.
- Pain was measured with the visual analog scale (0=no pain at all; 10=unbearable pain).
- Function was assessed using the Progressive Iso-inertial Lifting Evaluation (PILE) test which measures how many times a person can lift increasing loads over a specified period of time.
    - The reference did not describe how a numerical score was obtained.
- All were measured pre-study and after 6 weeks of intervention.
- Lower pain numbers, higher function scores, and head and shoulder angles indicate improvement.

INTERVENTION (# IN THE GROUP):

- MT + SE = 20
- SE alone = 20

COMPARISON (# IN THE GROUP): 20

FOLLOW UP PERIOD: 1-month post-intervention

RESULTS:

- The MT + SE group had a statistically significant greater improvement in pain and function compared to the SE alone group and the HE group:
    - Pain
        - MT + SE vs SE alone: Mean Difference [MD] –2.6 vs –1.9 respectively (P<.05)
        - MT + SE vs HE: MD –2.6 vs 0.41 respectively (P<.05)
    - Function
        - MT + SE vs SE alone: MD 1.3 vs 0.95 respectively (P<.05)
        - MT + SE vs HE: MD 1.3 vs 0.07 respectively (P<.05)
- Compared to directly post-intervention, at one month follow up:
    - The MT + SE group experienced a further reduction in pain (MD= –1.3; P≤.05), but no additional improvement in function.
    - The SE alone group did not experience further improvement in pain or function.
- The HE group did not experience improvement at post-intervention or one-month follow up.

LIMITATIONS:

- Small sample size.
- Unclear how many physiotherapists and analysts involved.
- Unclear training of “skilled manual therapist”.
- 95% CIs were not presented in the paper.

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Vestibular Ocular System: The Window into the Adolescent Concussion

Derivation of a Focused, Brief Concussion Physical Examination for Adolescents with Sport-Related Concussions

Leddy J, Lesh K, Haider MN, et al. Derivation of a Focused, Brief Concussion Physical Examination for Adolescents with Sport-Related Concussion. *Clin J Sport Med*. 2021; 31(1):7–14. doi:10.1097/JSM.0000000000000686

KEY TAKEAWAY: In adolescents that have suffered sports related concussion (SRC), a focused and brief physical exam can be done to aid in diagnosis and may have prognostic value.
STUDY DESIGN: Prospective cohort study
LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: SRC is a commonly seen injury in clinics and emergency rooms. Adolescent patients are most at risk for long term consequences and recovery is generally longer than other age groups. Currently, there is no universal method for physicians to diagnose SRC or track recovery. Typically, history is used to make a diagnosis. Many studies have shown that ocular and vestibular deficits are associated with prolonged recovery. This study analyzes if these deficits are effective in the diagnosis of SRC.

PATIENTS: Adolescent athletes 13–19 years old
INTERVENTION: Concussion with normal or delayed recovery
CONTROL: Healthy adolescents
OUTCOME: Positive findings (symptoms) during physical examination
Secondary Outcomes: Delayed recovery vs normal recovery and positive findings between the groups

METHODS (BRIEF DESCRIPTION):

- Concussed patients were evaluated by an independent blinded physician at visit 1 (1-10 days from injury).
  - Concussion diagnosis based on 4th International Conference on Concussion in Sport.
- Heathy patients were recruited from the same schools as the concussed patients and did not have a concussion within the previous year.
- Physical examinations examined the number of positive findings that were present in the concussed group vs the healthy group and the delayed recovery group vs the normal recovery group.
  - Cervical Examinations: Range of motion, occipital and cervical muscle tenderness, muscle spasm
  - Oculomotor Examinations: Near-point convergence, smooth pursuits, and horizontal saccades
  - Vestibular Systems Examinations: Vestibular ocular reflex, Romberg test, Tandem gait with tandem stance
- Findings were analyzed using fisher exact test.
- Bonferroni correction was used to counter the multiple comparisons.
- Normal recovery: Resolution of symptoms at second visit (≤21 days after injury)
- Delayed recovery: Persistent symptoms at second visit (>21 days).
  - Regression analysis used to determine significant difference between normal and delayed recovery.

INTERVENTION (# IN THE GROUP): 52
COMPARISON (# IN THE GROUP): 30

FOLLOW UP PERIOD: Average of 13 days after first visit

RESULTS:
Primary Outcome –

- AC patients had significantly worse symptoms, indicated by more deficits, during examination than HC patients (2.8 vs 0.07 respectively; *P*<.0001).

Secondary Outcomes –

- The delayed recovery group had more residual physical exam deficits than the normal recovery group (2.5 vs 0.17 respectively; *P*<.0001).
- When retrospectively reviewing the first visit, those with delayed recover (n=11) did not exhibit different deficits than those with normal recovery (n=41) (2.6 vs 3.5, respectively; *P*=.246).

LIMITATIONS:

- Diagnosis of delayed recovery was defined as >21 days from injury in the study, however, visit 2 was on average only 13 days after visit 1 (1 to 10 days after injury). Newer guidelines define delayed recovery as >30 days from injury.

- Limited powered study with n=52 in intervention group and n=30 in comparison group.

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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.

Glycemic Index vs Load: Which Lands the Greater Sucker-Punch for Cardiovascular Disease?

Glycemic Index, Glycemic Load, and Cardiovascular Disease and Mortality

Jenkins DJA, Dehghan M, Mente A, et al. Glycemic Index, Glycemic Load, and Cardiovascular Disease and Mortality. *N Engl J Med*. 2021; 384(14):1312–1322. doi:10.1056/NEJMoa2007123

KEY TAKEAWAY: Individuals from low to middle income countries who consume a diet with a high glycemic index (GI) are at increased risk of cardiovascular disease (CVD) or death.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Previously, the association between GI and CVD was only studied in Western countries. Therefore, there is an information gap to understand this association in non-Western countries.

PATIENTS: Adults from geographically diverse countries

INTERVENTION: Diet with lowest GI

CONTROL: Diet with highest GI

OUTCOME: Composite of cardiovascular death, nonfatal myocardial infarction, stroke, and heart failure or death from any cause

METHODS (BRIEF DESCRIPTION):

- Participants were 35–70 years old and from 20 countries (n=137,581).
  - Four high-income countries, 11 middle-income countries, five low-income countries
  - Data regarding vital status and CVD available for 98% and 95% of participants respectively.
- Participants completed a standardized, country-specific food questionnaire in 2003 and were followed through 2019.
- Primary analysis based on the presence or absence of pre-existing CVD.
- Participants were divided into quintiles based on GI and glycemic load (GL).
  - Quintile 1 had the lowest GI, and quintile 5 the highest.
- GI reflects the food's ability to raise the blood glucose level.
- GL reflects the amount of glucose delivered per serving.

INTERVENTION (# IN THE GROUP): Lowest quintile – 27,517

COMPARISON (# IN THE GROUP): Highest quintile – 27,570

FOLLOW UP PERIOD: Median of 9.5 years

RESULTS:

- High glycemic index diets are associated with an increased risk of a major cardiovascular event or death when comparing quintile 5 and quintile 1 (HR 1.3; 95% CI, 1.2–1.4).
  - Participants with pre-existing CVD (HR 1.5; 95% CI, 1.3–1.8)
  - Participants without CVD (HR 1.2; 95% CI, 1.1–1.3)
- High glycemic load diets only cause a significantly greater risk of a major cardiovascular event or death in patients with pre-existing CVD (HR 1.3; 95% CI, 1.1–1.7).
  - All participants (HR 1.1; 95% CI, 0.97–1.2)
  - Participants without CVD (HR 1.0; 95% CI, 0.91–1.1)

LIMITATIONS:

- Categorized carbohydrate foods may decrease precision of GI calculations.
- Inclusion of many different populations may limit ability to draw uniform conclusions.
- Overall number of participants was high, but the number of participants were not large enough to complete geographical analysis.
- Reliance on one baseline measure of dietary intake may not reflect current patterns in various countries.

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