GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT:
Freedom From Finger Sticks?

Using Continuous Glucose Monitors to Detect Hypoglycemia

Can Antibiotics Replace an Appendicectomy in Children with Uncomplicated Appendicitis?

Surrogate Markers and Symptoms

Weight Loss in PCOS Patients

Unexpected Benefits

Multivitamins and Supplements Improve Cognition and Memory

FPIN
Family Physicians Inquiries Network

Volume 5 Issue 41

Does Using Continuous Glucose Monitors to Detect Hypoglycemia Mean Freedom from Finger Sticks?

Relationship Between Sensor-Detected Hypoglycemia and Patient-Reported Hypoglycemia in People with Type 1 and Insulin-Treated Type 2 Diabetes: The Hypo-METRICS Study

Divilly P, Martine-Edith G, Zaremba N, et al. Relationship Between Sensor-Detected Hypoglycemia and Patient-Reported Hypoglycemia in People With Type 1 and Insulin-Treated Type 2 Diabetes: The Hypo-METRICS Study. *Diabetes Care*. 2024;47(10):1769-1777. doi:10.2337/dc23-2332

KEY TAKEAWAY: Sensor-detected hypoglycemia (SDH) occurs more frequently than patient-reported hypoglycemia (PRH) in adults with type 1 diabetes (T1DM) and type 2 diabetes (T2DM), but both measures show similar duration of episodes. Fingerstick testing or symptom monitoring may still be necessary to fully assess hypoglycemia, even when using continuous glucose monitors (CGMs).

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: With multiple methods of glucose monitoring available to patients, including growing numbers of continuous glucose monitors, further investigation is warranted to determine their reliability and application to optimize diabetic treatment plans. This study aimed to investigate rates of SDH compared to PRH rates in patients with T1DM and insulin-treated T2DM.

PATIENTS: Adults with T1DM and insulin-treated T2DM

INTERVENTION: SDH

CONTROL: PRH

PRIMARY OUTCOME: Rates and duration of hypoglycemia

METHODS (BRIEF DESCRIPTION):

- This 10-week observational study was completed in nine sites in Austria, Denmark, France, the Netherlands, and the United Kingdom.
- Patients 18–85 years old with T1DM or insulin-treated T2DM who had at least one episode of hypoglycemia in the past three months were included in the study.
- Patients with an estimated glomerular filtration rate of <30 mL/min/1.73m^2 and patients who use automated insulin delivery systems were excluded from the study.
- Patients were monitored with a study-specific CGM device (Libre 2 sensor), but they were blinded to the CGM values.
- SDH was defined as blood glucose <70 mg/dL
- PRH included symptomatic hypoglycemia as well as blood glucose <72 mg/dL on routine checks
- Data from personal monitoring and study-specific sensors were analyzed to determine if PRH coincided with SDH.
- Patients recorded onset and duration of hypoglycemia symptoms in addition to their routine blood glucose monitoring (either CGM or capillary blood glucose checks).
- Coinciding hypoglycemic episodes were considered "associated" if they occurred within one hour of each other.

INTERVENTION (# IN THE GROUP):

- T1DM: 277
- Insulin-treated T2DM: 321

COMPARISON (# IN THE GROUP):

- T1DM: 277
- Insulin-treated T2DM: 321

FOLLOW-UP PERIOD: 10 weeks

RESULTS:

Primary Outcome –

- SDH events occurred more frequently in patients with T1DM compared to T2DM patients (6.7 vs 2.1 episodes per week, respectively; *P*<.001).
- PRH events occurred more frequently in patients with T1DM patients compared to patients with T2DM (3.9 vs 1.1 events per week, respectively; *P*<.001).
- Duration of hypoglycemia did not differ significantly between patients with T1DM and patients with T2DM (results presented via figure).
- SDH <70 mg/dL did not last longer in T1DM patients compared to T2DM patients (59 vs 59 min, respectively; *P*=.99).

- SDH <54 mg/dL did not last longer in T1DM patients compared to T2DM patients (38 vs 38 min, respectively; *P*=.66).
- SDH and PRH did not co-occur consistently.
  - SDH co-occurred with PRH only 35% of the time.
  - PRH co-occurred with SDH only 57% of the time.

LIMITATIONS:

- Despite the Libre 2 sensor having similar accuracy to other sensors, its accuracy might have contributed to a small proportion of the mismatch between SDH and PRH.
- At baseline, key variables such as glucose monitoring frequency and insulin delivery were statistically significant between patients with T1DM and T2DM, which could limit the accuracy of the observed differences.
- Inclusion criteria included patients who had at least one episode of hypoglycemia in the past three months. While this likely captured most patients with diabetes, it may have led to a higher rate of reported hypoglycemia in the study population compared to what is true of the general population with diabetes.
- Participants with their own CGM devices were allowed to continue using them during the study, which may have influenced their behavior related to diabetes management compared to the participants without their own CGM devices.
- Based on the population studied, results may not be applicable to non-white or non-Europeans.
- Given that data was collected during the COVID-19 pandemic, glycemic results may have been affected by abnormal daily life patterns.
- Funding for this study was provided in part by major pharmaceutical companies. Financial interests may have influenced study design and results.

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Multivitamins and Supplements Improve Cognition and Memory: Unexpected Benefits in Older Americans

Effect of Multivitamin-Mineral Supplementation vs Placebo on Cognitive Function: Results From the Clinic Sub-cohort of the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) Randomized Clinical Trial and Meta-Analysis of 3 Cognitive Studies Within COSMOS

Vyas CM, Manson JE, Sesso HD, et al. Effect of multivitamin-mineral supplementation versus placebo on cognitive function: results from the clinic subcohort of the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) randomized clinical trial and meta-analysis of 3 cognitive studies within COSMOS. *The American Journal of Clinical Nutrition*. 2024;119(3). doi:https://doi.org/10.1016/j.ajcnut.2023.12.011

KEY TAKEAWAY: Supplementation with multivitamins and minerals improves global cognition after two years compared to placebo in adults ≥60 years old.

STUDY DESIGN: Meta-analysis of three subsets of a randomized placebo-controlled clinical trial (RCT) (N=21,442)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Multivitamins and similar supplements have widespread use in the United States. Previous studies evaluating the effect of multivitamins on cognitive function have shown small or no effect in preventing cognitive decline from aging. Insufficient evidence exists to recommend multivitamin supplementation to prevent cognitive decline in older adults. This study evaluated changes in cognitive and memory functions with supplementation, compared with placebo.

PATIENTS: Adults in the United States ≥60 years old

INTERVENTION: Daily MVM and mineral supplementation

CONTROL: Placebo

PRIMARY OUTCOME: Global cognition composite

Secondary Outcomes: Episodic memory, executive functioning and attention

METHODS (BRIEF DESCRIPTION):

- Researchers evaluated three subgroup cohorts from the COSMOS trial (COSMOS-clinic, COSMOS-mind, and COSMOS-web).
- The COSMOS trial is a 2x2 factorial trial that included US adults ≥60 years old who were randomized to take daily multivitamin (MVM) and mineral supplementation vs placebo for cardiovascular disease and cancer prevention.
  - Mean age was 69 years old, with 98% non-Hispanic White, 60% post-college education, mean body mass index (BMI) of 27, and 55% never smokers.
- Exclusion criteria for the COSMOS trial comprised the following: History of myocardial infarction (MI) or stroke, diagnosis of cancer (except nonmelanoma skin cancer), other serious illness, unwillingness to forgo vitamins and supplements outside of the trial, extreme caffeine sensitivity, adherence <75% during the trial, and inability to communicate in English.
- The randomization was double blinded, with participants, examiners, and investigators masked regarding treatment group assignment.
- Participants randomized to supplements took cocoa extract (Mars Edge, 500 mg flavanols per day, and epicatechin 80 mg per day) and/or a daily MVI (Centrum Silver).
- Researchers performed detailed, in-person 45-minute neuropsychological testing at baseline and after two years for the COSMOS-clinic cohort.
- Detailed in person cognitive assessments included hearing screening, Clock-in-the-Box test, a 1–2 minute cognitive screening test, and the Modified Mini-Mental State.
- They calculated scores for the primary outcomes using standardized tests.
- Global cognition scores comprised the mean z-scores of 11 cognitive tests (Modified Mini-Mental Status [MMS], Consortium to Establish a Registry for Alzheimer's Disease [CERAD] immediate total learning, delayed recall, and recognition, East Boston Memory Test [EBMT] immediate and delayed recall trials, two category fluency tests [naming animals and vegetables], Trail-Making Test [TMT]-A and TMT-B, and Digit Span Backwards), with higher z-scores representing better cognition.
- Composite executive memory scores comprised the average z-scores of four memory tests (EBMT immediate and delayed recall, CERAD immediate total learning and delayed recall).
- Composite executive function/attention scores comprised the average z-scores of five tests (2

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category fluency tests, TMT-A and TMT-B, and Digit Span Backwards).

- Researchers conducted telephone cognitive assessments at baseline, before randomization, and annually for three years in the COSMOS-mind cohort, and similarly, computer-based cognitive assessments at baseline and annually for three years for the COSMOS-web cohort.
- Investigators performed a meta-analysis of two subgroup results for global cognition using COSMOS-clinic and COSMOS-mind, and all three subgroups for episodic memory (COSMOS- clinic, COSMOS-mind, and COSMOS-web).

INTERVENTION (# IN THE GROUP):

- COSMOS-clinic: 272
- COSMOS-MIND: 2,158
- COSMOS-web: 2,472

COMPARISON (# IN THE GROUP): 301

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- Daily MVM supplementation improved global cognition composite compared to placebo (mean difference [MD] 0.07; 95% CI, 0.03–0.11), which is equivalent to two years of less cognitive aging.

Secondary Outcomes –

- Daily MVM supplementation produced no difference in composite episodic memory scores, compared with placebo.
- Daily MVM supplementation did not significantly change executive functioning and attention compared to placebo.

LIMITATIONS:

- Participants represented a relatively low racial and ethnic diversity.
- The study design made it difficult to determine which specific vitamins and minerals produced the benefits. The use of one type of multivitamin (Centrum Silver) may not generalize results with other multivitamins with minerals supplements.
- Researchers did not control type one error in secondary outcomes and subgroup analyses for one of the included studies (COSMOS-clinic).
- Translating the clinical relevance of MVM supplements using years of aging has inherent limitations.

Surrogate Markers and Symptoms: Weight Loss in PCOS Patients

Effect of Weight Loss Interventions on the Symptomatic Burden and Biomarkers of Polycystic Ovary Syndrome: A Systematic Review of Randomized Controlled Trials

Scragg J, Hobson A, Willis L, Taylor KS, Dixon S, Jebb SA. Effect of Weight Loss Interventions on the Symptomatic Burden and Biomarkers of Polycystic Ovary Syndrome: A Systematic Review of Randomized Controlled Trials. *Ann Intern Med*. 2024;177(12):1664-1674. doi:10.7326/M23-3179

KEY TAKEAWAY: Weight loss interventions in polycystic ovary syndrome (PCOS) patients improve biomarkers, but have little effect on symptoms and quality of life.

STUDY DESIGN: Systematic review of 26 randomized controlled trials (RCTs) (N=1,529)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity and statistical incongruity)

BRIEF BACKGROUND INFORMATION: PCOS is a common condition seen by primary care providers that affects about 10% of adult females. Of those 10 %, anywhere from 50–80% of women can experience obesity, insulin resistance, and increased blood androgens. PCOS is also strongly associated with reproductive health issues and menstrual irregularities. Due to the lack of evidence that demonstrates the impact of weight loss for patients with PCOS, this review aimed to evaluate many weight loss interventions and their impact on PCOS related co-morbidities.

PATIENTS: Adult females with PCOS

INTERVENTION: Various weight loss interventions

CONTROL: Standard weight loss advice without support, oral contraceptive (OCP), metformin, and placebo medications

PRIMARY OUTCOME: Biological markers and symptoms of PCOS

Secondary Outcome: Adverse events

METHODS (BRIEF DESCRIPTION):

- Two reviewers identified RCTs that included female adults diagnosed with PCOS from MEDLINE, Emboss, and Cochrane.
  - Of the 3,948 studies that were initially identified, 39 studies were included in the review, but only 26 studies were used in the primary analysis.
  - Data from 1,529 participants were used in the primary analyses
  - Data from 2,308 participants were used in the secondary analyses.
- Studies with a high risk of bias, similar interventions, studied weight loss medications that are no longer commercially available, had incomplete data, non-randomized control trial study design, and had a non-desired patient population were excluded from the review.
- Weight loss interventions included behavioral intervention (cognitive behavioral therapy, diets, exercise), weight loss medications (GLP1 agonists, orlistat, etc.), and bariatric surgery.
- Interventions were compared to standard care which included metformin, OCP, weight loss advice (low calorie diets and physical exercise) or placebo.
- The primary outcomes assessed biological markers and symptoms of PCOS measured via the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), free androgen index (FAI) and menstrual frequency (number of menses per year) due to their medium to high certainty level of evidence.
  - HOMA-IR is a calculation using blood levels of insulin and glucose to estimate insulin resistance with generally accepted reference range of 0.7–2.
  - FAI uses blood levels of total testosterone and sex-hormone binding globulin to estimate biologically active testosterone with age-variable reference ranges between 0.1–7.1.
- The secondary outcomes measured adverse events.
- Outcomes were reported as mean difference with standard deviation and 95% confidence interval and plotted on forest plots.
  - I^2 was reported to demonstrate statistical heterogeneity.

INTERVENTION (# IN THE GROUP): 895

COMPARISON (# IN THE GROUP): 729

FOLLOW-UP PERIOD: Varied (mean 21 weeks)

RESULTS:

Primary Outcome –

- Weight loss interventions improved insulin resistance compared to control (mean difference [MD] –0.45; 95% CI, –0.75 to –0.15; I^2=24%).
- Weight loss interventions improved free testosterone levels compared to control (MD –2.0; 95% CI, –3.0 to –1.1; I^2=48%).
- Weight loss interventions increased menstrual frequency compared to control (MD 2.6 menses per year; 95% CI, 0.65–4.6; I^2=43%)
- Weight loss interventions did not result in a clinically significant change in the following compared to control:
  - Fasting glucose (MD –0.11; 95% CI, –0.22 to 0; I^2=89%)
  - FSH (MD –0.19; 95% CI, –0.41 to 0.02; I^2=7%)
  - LH (MD –0.61; 95% CI, –1.6 to 0.38; I^2=45%)
  - Hirsutism (MD –1.5; 95% CI, –4.9 to 1.2; I^2=51%)

Secondary Outcome –

- Adverse events were more common in interventions involving pharmacotherapy due to the increase in reports of gastrointestinal (GI) side effects. However, due to variability in report from different studies it was difficult to analyze the adverse event data.

LIMITATIONS:

- The study had a high statistical heterogeneity.
- The numbers of patients in the intervention and control arms of the study do not match the total number of patients included in the systematic review.
- Clinical uncertainty was present due to inconsistent data reporting between the randomized control trials.
- Long term effects of weight loss on PCOS symptoms and biomarkers are unclear since most studies did not exceed 20 weeks or roughly six months.
- It was reported that “no trials were conducted in primary care or community settings.” However, it is unclear where these studies were conducted if not in the primary care setting.

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Can Antibiotics Replace an Appendicectomy in Children with Uncomplicated Appendicitis?

Appendicectomy Versus Antibiotics for Acute Uncomplicated Appendicitis in Children: An Open-label, International, Multicenter, Randomized, Non-inferiority Trial

St Peter SD, Noel-MacDonnell JR, Hall NJ, et al. Appendicectomy versus antibiotics for acute uncomplicated appendicitis in children: an open-label, international, multicentre, randomised, non-inferiority trial. *Lancet*. 2025;405(10474):233-240. doi:10.1016/S0140-6736(24)02420-6

KEY TAKEAWAY: Antibiotic therapy increases treatment failure within one year compared to appendicectomy in children 5–16 years with acute uncomplicated appendicitis.

STUDY DESIGN: Randomized non-inferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Appendicitis is the most frequent surgical emergency in children. Although appendectomy is well-recognized as the standard of care, there have long been examples of treating appendicitis with antibiotics alone. The study aimed to find whether treatment of uncomplicated appendicitis with antibiotics alone in children is inferior to appendectomy.

PATIENTS: Children 5–16 years old with acute uncomplicated appendicitis

INTERVENTION: Antibiotics

CONTROL: Appendicectomy

PRIMARY OUTCOME: Treatment failure within one year
Secondary Outcome: Adverse events, extended length of hospital stays, associated complications, pain medication use

METHODS (BRIEF DESCRIPTION):

- Children 5–16 years old with appendicitis were recruited from 11 children's hospitals in Canada, the United States, Finland, Sweden, and Singapore.
- Exclusion criteria included suspicion of perforated appendicitis, appendiceal mass or phlegmon, previous antibiotic treatment to at least a second dose, pregnancy, prior episode of appendicitis, current treatment for malignancy, or comorbid condition that would alter the length of stay.
- Patients were randomized 1:1 to the antibiotic or appendicectomy group using an online stratified randomization tool.
- In the antibiotic group:
  - Following at least 12 hours of intravenous therapy, patients were discharged if they tolerated a regular diet, had adequate pain control, and maintained stable vital signs.
  - If patients had not improved sufficiently to advance care or be discharged by the day after admission, they either received another day of antibiotics or were scheduled for the next available appendicectomy.
  - Patients whose clinical condition deteriorated on the first day or those who did not show improvement on the second day were taken for appendectomy.
  - At discharge, patients received a 10-day oral course of either amoxicillin-clavulanic acid or ciprofloxacin plus metronidazole.
- In the appendectomy group:
  - Patients received intravenous fluids and antibiotics and were scheduled for laparoscopic appendectomy in the next available slot in the operating room.
  - In the absence of appendiceal perforation, postoperative antibiotics were not administered, and patients were discharged once clinically stable.
- The primary outcome was treatment failure, defined in the antibiotic group as the need for appendicectomy within one year and in the appendicectomy group as a normal appendix based on pathology. For both groups, treatment failure additionally included additional appendicitis-related procedures under general anesthesia.
- The secondary outcomes were defined as appendicitis-related adverse events requiring additional interventions without general anesthesia, prolonged hospitalization, or associated complications.
- Researchers utilized a non-inferiority design with a 20% margin, and interim analysis was employed to

see if inferiority could be declared halfway through the study.

INTERVENTION (# IN THE GROUP): 452

COMPARISON (# IN THE GROUP): 394

FOLLOW-UP PERIOD: One year

RESULTS:

Primary Outcome –

- Patients receiving antibiotics had higher treatment failure compared to patients who underwent appendicectomy (34% vs 7%, respectively; difference 27%; 90% CI, 22–31).
- As the upper bound of the confidence interval (31%) was greater than the selected inferiority margin of 20%, the null hypothesis that antibiotic treatment alone is inferior to appendicectomy was not rejected.

Secondary Outcome –

- Patients receiving antibiotics had a longer median length of hospital stay compared to patients who underwent appendicectomy during the initial hospitalization (1.3 days vs 1.0 day, respectively; p<.0001).
- Patients receiving antibiotics had a longer total length of hospital stay compared to patients who underwent appendicectomy (1.6 days vs 1.0 days, respectively; p<.0001).
- Patients receiving antibiotics had a higher risk of mild-to-moderate adverse events (risk ratio [RR] 4.3; 95% CI, 2.1–8.7).
    - Most adverse events in the antibiotic group involved gastrointestinal symptoms.
- Patients receiving antibiotics took pain medication fewer days compared to patients who underwent appendectomy (0 days vs 3 days, respectively; p<.0001).

LIMITATIONS:

- Declined consents and the reason for refusal were not well tracked.
- Approximately 10% of data was missing, with a higher proportion of missing data in the appendicectomy group compared with the antibiotic group.
- The final analysis of the primary outcome included only those patients who could be contacted at 12 months to verify treatment failure status.
- The research did not assess ethnicity nor include countries with more limited healthcare resources.

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