GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of July 10 - 14, 2023

SPOTLIGHT: Exercise to Improve Body Mass Index and Inflammation

- Another Tool for COVID-19, or Wishful Thinking?
- Management of Gestational Diabetes Mellitus According to Intrauterine Fetal Growth
- Eosinophilic Esophagitis: Another Use for Human Monoclonal Antibodies?
- Medical Therapy Versus Metabolic Surgery: Is It Worth the Weight?

Exercise to Improve Body Mass Index and Inflammation

Effect of Exercise Training on Body Composition and Inflammatory Cytokine Levels in Overweight and Obese Individuals: A Systematic Review and Network Meta-Analysis

C Wang S, Zhou H, Zhao C, He H. Effect of Exercise Training on Body Composition and Inflammatory Cytokine Levels in Overweight and Obese Individuals: A Systematic Review and Network Meta-Analysis. *Front Immunol*. 2022;13:921085. Published 2022 Jun 23. doi:10.3389/fimmu.2022.921085

KEY TAKEAWAY: Combined aerobic and resistance training decreases inflammatory cytokines more than either alone.

STUDY DESIGN: Network meta-analysis of 38 randomized controlled trials (N=1,317)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to heterogeneity of studies)

BRIEF BACKGROUND INFORMATION: Research has shown that exercise can reduce chronic inflammation in obese individuals. However, the optimal type of exercise has not been identified. Types of exercise include aerobic, resistance training, combined aerobic and resistance training, and high-intensity interval training.

PATIENTS: Overweight or obese individuals

INTERVENTION: Exercise

CONTROL: Exercise intervention vs no-exercise control

PRIMARY OUTCOME: Body composition and inflammatory cytokine levels

METHODS (BRIEF DESCRIPTION):

- 38 studies involving 1,317 total patients were included and met the following criteria:
  - The study was a randomized, controlled trial.
  - Subjects had a body mass index (BMI) ≥25 kg/m^2.
- The intervention group had to use one of the exercise modalities for at least four weeks, most often three times per week for 12 weeks (about three months).
  - The intervention included: Aerobic exercise, resistance training, combined aerobic and resistance training, or high-intensity interval training.
  - Specific regimens within these interventions varied.
- Controls: Non-exercise routine vs no change from prior lifestyle.
- There were 58 interventional groups and 31 control groups in total.
- Outcomes included waist circumference, percentage body fat, as well as levels of inflammatory cytokines including CRP, TNF-α, IL-6, and IL-10.
  - The results of the interventions were measured using the area under the cumulative ranking probability diagram also known as SUCRA. The scores range from 0% to 100%; with the higher SUCRA values indicating better effects of an exercise intervention.

INTERVENTION (# IN THE GROUP): 868

COMPARISON (# IN THE GROUP): 449

FOLLOW-UP PERIOD: Average of 12 weeks (range 4–48 weeks)

RESULTS:

- Aerobic exercise significantly increased weight loss compared to no exercise.
  - SUCRA=78 vs SUCRA=32, respectively; SMD (standard mean difference) –0.51; 95% CI, –0.70 to –0.33).
- Combined aerobic and resistance reduced BMI compared to no exercise:
  - BMI (SUCRA=71; SMD –0.46; 95% CI, –0.81 to –0.10)
  - Weight circumference (SUCRA=93; SMD –1.9; 95% CI, –2.8 to –0.93)
  - Percent body fat (SUCRA=80 vs SUCRA=37, respectively; SMD –1.4; 95% CI, –2.3 to –0.48).
- All forms of exercise additionally improved levels of:
  - CRP (SMD –0.76; 95% CI, –1.1 to –0.41)
  - TNF-α (SMD –1.4; 95% CI, –1.9 to –0.82)
  - IL-6 (SMD –0.85; 95% CI, –1.4 to –0.27)
  - IL-10 (SMD 3.0; 95% CI, 1.4 to 4.5)
- Adiponectin was not significantly different between the intervention and control groups.
  - Control group (SMD 0.52; 95% CI, –0.11 to 1.2)
  - AE (SMD 0.51; 95% CI, –1.7 to 2.7)
  - RT (SMD 0.15; 95% CI, –3.0 to 3.3)

- CT (SMD 1.8; 95% CI, –1.4 to 4.9)
- HIIT (SMD 2.3; 95% CI, –1.3 to 5.9)

LIMITATIONS:

- The various studies did not clearly describe the intensity or specific regimen of the exercise.
- Due to the variability of intervention, results were at an increased risk of inconsistency and differences.
  - An attempt was made to break down the groups into subgroups, however, this did not resolve all differences.
- The number of studies on each exercise modality varied, so there was inconsistency for each exercise intervention.
- Some studies could not be included due to the small sample size.
- The intervention could not be blinded due to the study design.

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Another Tool for COVID-19, or Wishful Thinking?

VV116 versus Nirmatrelvir-Ritonavir for Oral Treatment of Covid-19

Cao Z, Gao W, Bao H, et al. VV116 versus Nirmatrelvir-Ritonavir for Oral Treatment of Covid-19. *N Engl J Med*. 2023;388(5):406-417. doi:10.1056/NEJMoa2208822

KEY TAKEAWAY: Oral remdesivir analogue VV116 is non-inferior to Nirmatrelvir-Ritonavir for outpatient treatment of adults with COVID-19.

STUDY DESIGN: Randomized, observer-blinded controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: COVID-19 continues to infect worldwide. Infected, high-risk patients cannot always obtain timely treatment due to limited resources. This study examines a potential new agent to expand access.

PATIENTS: Adults with mild or moderate SARS-CoV-2 infection and medical history placing them at risk for progression to severe disease

INTERVENTION: VV116

CONTROL: Nirmatrelvir-ritonavir

PRIMARY OUTCOME: Time to sustained symptom improvement

Secondary Outcome: Progression to severe COVID or death, time to viral clearance by PCR, safety events

METHODS (BRIEF DESCRIPTION):

- Subjects were selected to participate from seven hospitals in Shanghai.
  - Patients were 18 years and older with a positive SARS-CoV-2 PCR, mild to moderate disease as determined by a standardized symptom score, and a risk factor for progression to severe disease including a chronic condition or age >60.
  - The nirmatrelvir-ritonavir and experimental groups both included roughly 50% females and 50% males, and the median age of each group was 53. About a quarter of each group was unvaccinated, and a third was un-boosted.
  - Patients were excluded if they were judged to have severe COVID-19 by the investigator, a need for intubation was anticipated, ALT or AST was >1.5 times the upper limit of normal, estimated GFR was <60 ml/minute, or if they took medications which were contraindicated to use with nirmatrelvir-ritonavir.
- Patients were randomized but not blinded to receive either nirmatrelvir-ritonavir (300 mg–100 mg every 12 hours for five days) or VV116 (600 mg every 12 hours on day one, then 300mg days 2–5).
  - An unblinded team delivered treatment to subjects independent of researchers. Investigators were blinded.
- Symptom scores were obtained on day one prior to medication start, and daily until symptom resolution for two days or until the follow-up period expired.
- Multiple symptoms were scored for a total score range of 0 to 33.
  - Higher symptom scores indicated more severe disease.
  - Clinical recovery required a symptom score decrease to 0 or 1 for each symptom (the range was 0–3 for individual symptoms). The WHO Clinical Progression Scale was also used for secondary endpoints ranging from 0 to 10 (0 meaning uninfected and 10 meaning dead).

INTERVENTION (# IN THE GROUP): 411

COMPARISON (# IN THE GROUP): 411

FOLLOW-UP PERIOD: 28 days

RESULTS:

Primary Outcome –

- The time to sustained clinical recovery was equivalent in the intervention and control groups (HR 1.2; 95% CI, 1.0–1.4).
  - Median days to recovery were four and five days, respectively.

Secondary Outcome –

- No patients died or progressed to severe disease.
- The median time for the first negative PCR was seven days in both groups.
- The intervention group reported fewer adverse effects (67% vs 77%).

LIMITATIONS:

- Patients were only observed for up to 28 days, so long-term effects of the drug could not have been identified.

- The study did not include patients with an eGFR <60.
- Shanghai's population and SARS-CoV-2 infection may not accurately represent a U.S. population and infection.
- Patients were not blinded.

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Management of Gestational Diabetes Mellitus According to Intrauterine Fetal Growth

Flexible Treatment of Gestational Diabetes Mellitus Adjusted According to Intrauterine Fetal Growth Versus Treatment According to Strict Maternal Glycemic Parameters: A Randomized Clinical Trial

Fernández-López M, Blanco-Carnero JE, Guardia-Baena JM, de Paco-Matallana C, Aragón-Alonso A, Hernández-Martínez AM. Flexible treatment of gestational diabetes mellitus adjusted according to intrauterine fetal growth versus treatment according to strict maternal glycemic parameters: a randomized clinical trial. *BMJ Open Diabetes Res Care*. 2022;10(6):e002915. doi:10.1136/bmjdrc-2022-002915

KEY TAKEAWAY: Using the fetal abdominal circumference measurement for the management of gestational diabetes is safe and decreases the number of pregnant women who may need insulin by almost 50%, without a significant change in the frequency of prenatal visits or ultrasound checks.

STUDY DESIGN: Prospective randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Treatment of Gestational Diabetes Mellitus (GDM) can improve pregnancy outcomes by minimizing maternal and neonatal morbidity (i.e., preeclampsia, macrosomia, polyhydramnios, shoulder dystocia, and stillbirth). The goal of management is to achieve strict control of the maternal blood sugar level through nutritional therapy, lifestyle changes, and self-blood glucose monitoring daily. If blood sugar targets cannot be achieved, insulin is considered the first line of treatment, which requires close monitoring. Additionally, only 20% of untreated women with GDM will have fetal macrosomia.

PATIENTS: Pregnant adult with gestational diabetes

INTERVENTION: Treating GDM based on fetal abdominal circumference (AC)

CONTROL: Treating GDM based on maternal blood sugar

PRIMARY OUTCOME: Neonatal and maternal complications

METHODS (BRIEF DESCRIPTION):

- Eligible subjects included pregnant women less than 34 weeks' gestation with a single fetus, and with a diagnosis of gestational diabetes in the second or third trimester.
    - Subjects were randomized to either the intervention group with management of GDM based on fetal AC, or the control group with management of GDM based on maternal blood glucose levels.
    - All subjects were instructed on lifestyle modifications and blood glucose levels self-check per protocol.
- In the intervention group where the GDM treatment was based on fetal AC, the glycemic target was set as:
    - If abdominal circumference p<75 (low risk for overgrowth): Glycemic targets are, fasting <120, one-hour post-prandial <180 mg/dL)
    - If abdominal circumference p>75 (high risk for overgrowth): Glycemic targets are, fasting <80, one-hour post-prandial <120 mg/dL)
    - Insulin was initiated for subjects who were unable to achieve the blood glucose targets listed above.
    - When treating GDM according to maternal criteria (capillary blood sugar), fasting glycemic targets were <95 mg/dL and one-hour postprandial <140 mg/dL.
- Outcomes:
    - Neonatal weight (large or small for gestational age)
    - Maternal insulin requirement
    - Perinatal complications (HTN with pregnancy, maternal weight gain, maternal hypoglycemia, preterm labor, cesarean section, instrumented delivery, induction of labor, shoulder dystocia, traumatic injuries, postpartum hemorrhage, respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia, admission to the neonatal intensive care unit, stillbirth)

INTERVENTION (# IN THE GROUP): 121

COMPARISON (# IN THE GROUP): 125

FOLLOW-UP PERIOD: Through delivery

RESULTS:

- Using fetal AC to monitor GDM did not affect neonatal outcomes compared to blood glucose monitoring except for neonatal hypoglycemia

- Neonatal hypoglycemia <40 mg/dL (1.7% vs 7.2%, respectively; *P*=.035)
- Intravenous glucose hypoglycemia (0.8% vs 0.8%, respectively; *P*=.982)
- Neonatal macrosomia (2.5% vs 6.4%, respectively; *P*=.162)
- Shoulder dystocia (0.0% vs 1.6%, respectively; *P*=.137)
- Clavicle fracture (0.8% vs 3.2%, respectively; *P*=.187)
- Brachial plexus injury (0.0% vs 1.6%, respectively; *P*=.162)
- Respiratory distress (2.5% vs 4.0%, respectively; *P*=.501)
- Hypoglycemia (1.7% vs 7.2%, respectively; *P*=.137)
- Hyperbilirubinemia (4.1% vs 4.8%, respectively; *P*=.800)
- NICU admission (0.8% vs 2.4%, respectively; *P*=.325)
- Stillbirth (2.5% vs 4.0%, respectively; *P*=.501)

- Fetal AC GDM monitoring resulted in a greater likelihood of glucose control compared to blood glucose monitoring (24% vs 12%, respectively; *P*=.018).
- Fetal AC GDM monitoring resulted in less insulin requirement compared to blood glucose monitoring (12.4% vs 24%, respectively; *P*=.018).

LIMITATIONS:

- Ultrasound availability among different healthcare systems.
- Small sample size which may impact outcome data when the prevalence of certain complications is low.

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Eosinophilic Esophagitis: Another Use for Human Monoclonal Antibodies?

Dupilumab in Adults and Adolescents with Eosinophilic Esophagitis

Dellon ES, Rothenberg ME, Collins MH, et al. Dupilumab in Adults and Adolescents with Eosinophilic Esophagitis. *N Engl J Med*. 2022;387(25):2317-2330. doi:10.1056/NEJMoa2205982

KEY TAKEAWAY: Subcutaneous dupilumab was shown to improve histologic outcomes and reduce symptom severity for patients with eosinophilic esophagitis.

STUDY DESIGN: Single-blinded randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Eosinophilic Esophagitis (EoE) is a chronic, progressive disease that can severely impact the quality of life of those affected. If left untreated, it can lead to permanent and debilitating complications. Dupilumab is a monoclonal antibody that blocks interleukin-4 and interleukin-13, which are key drivers in the inflammation seen in EoE. As current treatments have varied response rates, dupilumab is hypothesized to decrease symptoms and improve histological outcomes for patients with EoE.

PATIENTS: Patients 12 or older with EoE treated with PPI

INTERVENTION: Weekly or biweekly dupiluamb

CONTROL: Placebo

PRIMARY OUTCOME: Histologic remission and improvement in Dysphagia Symptom Questionnaire (DSQ) Score

METHODS (BRIEF DESCRIPTION):

- Phase three, a three-part, study of patients with biopsy-confirmed EoE despite high dose PPI for 8 weeks and baseline DSQ ≥10.
- Participants were recruited from 96 sites across Australia, Canada, Europe, and the United States.
  - Participants had EoE diagnosis for a mean of five years, 23–33% were adolescents, and 89–98% were White.
- Part A: Participants were randomized 1:1 to receive either weekly dupilumab 300 mg or a placebo for 24 weeks.
- Part B: Participants were randomized 1:1:1 to receive dupilumab 300 mg either every week or every other week or placebo for 24 weeks.
- At the end of 24 weeks, participants were assessed for histological remission via EGD and for changes to the baseline DSQ score.
  - (Range: 0–84; higher score indicates more frequent or severe dysphagia)

INTERVENTION (# IN THE GROUP): Part A: 42, Part B: 161

COMPARISON (# IN THE GROUP): Part A: 39, Part B: 79

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- Histologic remission occurred in more patients in the dupilumab groups as compared to placebo.
  - Part A: 60% in the weekly group vs 5% in the placebo group (adjusted between-group difference of 55%; 95% CI, 40%–71%)
  - Part B: 59% in the weekly group vs. 60% in the biweekly group vs 6% in the placebo group (weekly group adjusted between-group difference of 54 percentage points; 95% CI, 41%–66%) and (biweekly group adjusted between-group difference of 56 percentage points; 95% CI, 43%–69%).
- DSQ scores improved in weekly dupilumab groups as compared to placebo.
  - Part A: Difference of –12 (95% CI, –19 to –5.5)
  - Part B: Difference of –9.9 (95% CI, –15 to –5.0)
- There was no significant improvement seen in those in the biweekly group.

LIMITATIONS:

- A high percentage of the participants were White.
- The study used a relatively short placebo-controlled treatment period.
- Partial funding was provided by Sanofi Pharmaceuticals which produces dupilumab.
- Histologic improvement seen in the experimental group may not always correlate with symptom severity.

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Medical Therapy Versus Metabolic Surgery: Is it Worth the Weight?

Metabolic Surgery Versus Conventional Medical Therapy in Patients with Type 2 Diabetes: 10-year Follow-up of an Open-label, Single-centre, Randomized Controlled Trial

Mingrone G, Panunzi S, De Gaetano A, et al. Metabolic Surgery Versus Conventional Medical Therapy in Patients with Type 2 Diabetes: 10-year Follow-up of an Open-label, Single-centre, Randomized Controlled Trial. *Lancet*. 2021;397(10271):293-304. doi:10.1016/S0140-6736(20)32649-0

KEY TAKEAWAY: Metabolic surgery may be more effective than medical therapy for long-term control of type 2 diabetes, including remission.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size, bias, and no blinding)

BRIEF BACKGROUND INFORMATION: About 6.3% of the world's population suffers from type 2 diabetes. Before this study, there were no studies on the treatment of diabetes for remission with metabolic surgery with a ten-year follow-up. However, metabolic surgery would not benefit patients who have type 2 diabetes without obesity.

PATIENTS: Adults 30–60 years old with type 2 diabetes

INTERVENTION: Metabolic surgery

CONTROL: Standard medication treatment

PRIMARY OUTCOME: Diabetes remission

Secondary Outcome: Metabolic factors

METHODS (BRIEF DESCRIPTION):

- Adults 30–60 years old in Rome, Italy with type 2 diabetes, BMI ≥35%, and A1C ≥7%.
- Patients were randomly assigned to treatment groups.
  - Roux-en-Y Gastric Bypass (RYGB)
  - Biliopancreatic diversion with duodenal switch (BPD)
  - Medical therapy included oral antihyperglycemic agents, insulin, GLP-1 analogues, and SGLT2 inhibitors.
- Diabetes remission was measured by using the standards of fasting plasma glucose <100 mg/dL and A1C <=6.5% without ongoing medication therapy.

INTERVENTION (# IN THE GROUP): BPD group: 20 patients, RYGB group: 20 patients

COMPARISON (# IN THE GROUP): 20 patients

FOLLOW-UP PERIOD: 10 years

RESULTS:

Primary Outcome –

- BPD improved the likelihood of diabetes remission at 10 years compared to medical therapy.
  - (Relative Risk [RR] 7.5; 95% CI, 1.1–52)
- RYGB improved the likelihood of diabetes remission at 10 years compared to medical therapy.
  - (Relative Risk [RR] 3.8; 95% CI, 0.50–29).

Secondary Outcome –

- Metabolic surgeries improved most metabolic factors compared to medical therapy at 10 years.
  - Fasting glucose, mmol/L
    - BPD (RR) –2.1; 95% CI, –2.5 to –1.6
    - RYGB (RR) –1.6; 95% CI, –2.1 to –1.1
  - A1C%
    - BPD (RR) –1.2; 95% CI, –1.5 to –0.90
    - RYGB (RR) –0.90; 95% CI, –1.2 to –0.60
  - Weight, Kgs
    - BPD (RR) –35; 95% CI, –44 to –27
    - RYGB (RR) –34; 95% CI, –43 to –26
  - BMI, Kg/m^2
    - BPD (RR) –12; 95% CI, –15 to –9.0
    - RYGB (RR) –11.0; 95% CI, –14 to –8.0
  - Waist circumference, cm
    - BPD (RR) –15; 95% CI, –23 to –7.0
    - RYGB (RR) –13; 95% CI, –22 to –5.0
  - Total cholesterol, mmol/L
    - BPD (RR) –1.5; 95% CI, –2.0 to –1.0
  - LDL cholesterol, mmol/L
    - BPD (RR) –1.2; 95% CI, –2.0 to –1.0
  - Triglycerides, mmol, L
    - BPD (RR) –0.80; 95% CI, –0.90 to –0.60
    - RYGB (RR) –0.40; 95% CI, –0.60 to –0.30
  - Diastolic blood pressure, mmHg
    - BPD (RR) –5.8; 95% CI, –9.0 to –3.0
  - Systolic blood pressure, mmHg
    - BPD (RR) –8.9; 95% CI, –13 to –5.0
    - RYGB (RR) –5.0; 95% CI, –9.0 to –1.0
  - GFR, mL/min per 1.773m^2
    - RYGB (RR) 16; 95% CI, 5.0 to 26

- Diabetic medications, total
  - BPD (RR) –2.2; 95% CI, –3.0 to –1.5
- Insulin resistance (Homeostatic Model Assessment of Insulin Resistance)
  - BPD (RR) –3.4; 95% CI, –4.3 to –2.4
  - RYGB (RR) –3.1; 95% CI, –4.0 to –2.0

LIMITATIONS:

- The study was exposed to bias in the assessment of participants due to the open-labeled design.
- The study had a small population size.
- Patient masking was not an option between study groups due to laparoscopic vs open technique procedures.

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