GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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Week of September 25 - 29, 2023

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Remdesivir: Should We Use It?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Remdesivir for the Treatment of COVID-19

Grundeis F, Ansems K, Dahms K, et al. Remdesivir for the treatment of COVID-19. *Cochrane Database Syst Rev*. 2023;1(1):CD014962. Published 2023 Jan 25. doi:10.1002/14651858.CD014962.pub2

KEY TAKEAWAY: Remdesivir does not improve all-cause mortality or rate of adverse events among hospitalized patients with SARS-CoV-2 infection. However, it significantly increases the chances of clinical improvement and decreases the risk of clinical worsening.

STUDY DESIGN: Systematic review of nine randomized controlled trials (N=11,218)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Remdesivir is an antiviral medication commonly used to treat hospitalized patients with SARS-CoV-2 infection. It is thought to work by blocking RNA-polymerase and inhibiting virus replication. It was initially approved under Emergency Use Authorization, but more studies are needed to demonstrate clinical utility.

PATIENTS: Hospitalized patients with SARS-CoV-2 infection

INTERVENTION: Remdesivir

CONTROL: Standard care

PRIMARY OUTCOME: All-cause mortality, clinical improvement, clinical worsening, adverse events

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria:
  - Adult male or non-pregnant females
  - SARS-CoV-2 laboratory-confirmed symptomatic infection
  - Hospitalized patients
- Exclusion Criteria: Patients who attempted to treat other viral diseases including SARS, MERS, or Ebola
- The primary outcomes were assessed based on the Core Outcome Measures in Effectiveness Trials (COMET) initiative for people with COVID-19, and additional outcomes were prioritized by consumer representatives and the German guideline panel for SARS-CoV-2 therapy.
  - All-cause mortality was measured at 28 days, 60 days, and 150 days.
  - Clinical improvement was measured using the proportion of participants alive and ready to be discharged up to day 28, up to the longest follow-up, and time-to-event.
  - Clinical worsening was measured using the proportion of participants with a new need for invasive mechanical ventilation or decreased within 28 days, up to the longest follow-up, and time-to-event.
  - Adverse events of any grade were measured using the number of participants with any event.

INTERVENTION (# IN THE GROUP): 5,982

COMPARISON (# IN THE GROUP): 5,236

FOLLOW-UP PERIOD: Up to 150 days (longest available)

RESULTS:

Primary Outcome –

- Remdesivir did not significantly reduce all-cause mortality at:
  - 28 days (4 studies, n=7,142; risk ratio [RR] 0.93; 95% CI, 0.81–1.06)
  - 60 days (1 study, n=1,281; RR 0.85; 95% CI, 0.69–1.05)
  - 150 days (1 study, n=8,275; RR 0.93; 95% CI, 0.84–1.03)
- Remdesivir significantly increased chances of clinical improvement at:
  - Up to day 28 (4 studies, n=2,514; RR 1.1; 95% CI, 1.1–1.2).
- Remdesivir significantly decreased the risk of clinical worsening at:
  - Up to day 28 (2 studies, n=1,734; hazard ratio [HR] 0.67; 95% CI, 0.54–0.82).
- Remdesivir did not significantly decrease the rate of adverse events of any grade in hospitalized patients.

LIMITATIONS:

- Patients studied were primarily unvaccinated and infected with early SARS-CoV-2 strains as these studies were from early in the pandemic. Hence, more research is needed to determine if Remdesivir had any benefit in a population that was overall more vaccinated and in the setting of new emerging strains of SARS-CoV-2.
- There were some concerns about attrition bias as patients who died did not contribute information.

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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.

Taking the Pressure off Preeclampsia

Planned Delivery or Expectant Management in Preeclampsia: An Individual Participant Data Meta-Analysis

Beardmore-Gray A, Seed PT, Fleminger J, et al. Planned delivery or expectant management in preeclampsia: an individual participant data meta-analysis. *Am J Obstet Gynecol*. 2022;227(2):218-230.e8. doi:10.1016/j.ajog.2022.04.034

KEY TAKEAWAY: Planned delivery for patients with preeclampsia demonstrated improved maternal outcomes and decreased rates of premature infants who are small for gestational age (SGA). However, there is an increased risk of fetal perinatal mortality and morbidity.

STUDY DESIGN: Meta-analysis including six randomized control trials (N=1790)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The prevalence of preeclampsia varies throughout the world but complicates between 2–3% of pregnancies in high-income settings and up to 12% of pregnancies in low-to-middle-income countries. Delivery of patients with preeclampsia is recommended at 37 weeks or upon diagnosis if term. Prior to 34 weeks, expectant management is recommended. Between 34–37 weeks there is no recommendation on the management of preeclampsia without severe features per ACOG. The aim of the meta-analysis was to determine if there is a benefit in planned delivery at 34 weeks.

PATIENTS: Women with late preterm preeclampsia

INTERVENTION: Early planned delivery

CONTROL: Expectant management

PRIMARY OUTCOME: Maternal morbidity, perinatal morbidity/mortality

Secondary Outcome: Size for gestational age, NICU admission

METHODS (BRIEF DESCRIPTION):

- Using the PROSPERO registry in accordance with PRISMA-IPD guidance, 1,950 studies were found, which were then narrowed down to six studies to assess the clinical question. Trials were excluded after title screening and full-text screening, all included trials were randomized control trials.
- There were 1,790 eligible participants with singleton or multifetal pregnancies presenting with preeclampsia or superimposed preeclampsia from 34 weeks gestation onward.
    - Participants were excluded from this meta-analysis due to having conditions other than preeclampsia or before 34 weeks gestation.
- The baseline maternal characteristics at enrollment were well-matched between the intervention and the control group.
    - These characteristics include maternal age, nulliparity, singleton pregnancy, diabetes, suspected fetal growth restriction, systolic blood pressure, and diagnosis of superimposed preeclampsia.
- Data was collected evaluating outcomes of both maternal and neonatal morbidity and mortality in the early planned delivery and expectant management groups.
- Late preterm gestation included gestational ages 34 weeks + zero days to 36 weeks + six days.
- The control group was expectantly managed during the late preterm period vs the intervention group was planned delivery during the late preterm period.
- The use of antenatal corticosteroids was varied across the studies, with 6.8%–65% of women receiving the antenatal corticosteroids depending on the trial, some trials did not report use.
- Risk ratios for the outcomes were calculated based on the method of delivery.
- Outcomes were evaluated at the time of delivery and participants were followed up until six weeks after delivery.

INTERVENTION (# IN THE GROUP): 901

COMPARISON (# IN THE GROUP): 889

FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- In patients with late preterm pre-eclampsia, planned delivery reduced the risk of maternal morbidity (RR 0.59; 95% CI, 0.73–0.87).
- Planned delivery increased fetal perinatal mortality/morbidity (RR 1.22; 95% CI, 1.01–1.47).

Secondary Outcome –

- Infants in the planned delivery group were less likely to be born small for gestational age, below the 10th percentile (RR 0.82; 95% CI, 0.70–0.97).

LIMITATIONS:

- Changes in clinical practice during the time period of the trials were included (antenatal corticosteroid use).
- Some perinatal outcomes were not collected due to rarity (bronchopulmonary dysplasia, cerebral infarction, intracerebral hemorrhage).
- There was no long-term follow-up up past six weeks.

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COVID-19: How is it Affecting Athletes?

Acute and Post-Acute COVID-19 Presentations in Athletes: A Systematic Review and Meta-Analysis

Lemes IR, Smaira FI, Ribeiro WJD, et al. Acute and post-acute COVID-19 presentations in athletes: a systematic review and meta-analysis. *Br J Sports Med*. 2022;56(16):941-947. doi:10.1136/bjsports-2022-105583

KEY TAKEAWAY: Most athletes with COVID-19 are asymptomatic or have mild disease, and there is little to no evidence in the study showing a causal relationship between COVID-19 and myocardial involvement.

STUDY DESIGN: Systematic review and meta-analysis of 43 observational studies (N=11,518)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The COVID-19 pandemic has been a focus of review and research in the last few years. It has impacted sports policies regarding return-to-play protocols for youth recreational leagues all the way to the professional leagues. This study looked at pooled event data in athletes diagnosed with COVID-19 to assess how the disease affects young athletes and if there is a relationship between COVID-19 illness and myocardial involvement.

PATIENTS: Athletes from various countries and divisions

INTERVENTION: Infection from COVID-19

CONTROL: Not applicable

PRIMARY OUTCOME: Incidence of COVID-19 based on severity, most common post-acute infection symptoms

Secondary Outcome: Myocardial involvement

METHODS (BRIEF DESCRIPTION):

- Utilizing PRISMA and PERSiST guidelines, a literature review was performed focusing on the population of interest: 11,518 athletes across professional, amateur, or collegiate/university teams from various countries in North America, South America, Africa, Asia, and Europe.
- This study included data on self-reported symptoms during or after the acute phase of infection using an observational design.
    - 11 of the 43 studies included control parameters such as non-infected athletes, health controls (healthy non-athletes and/or pre-infection data, or baseline imaging).
    - Data reported on symptoms were pulled by the researchers and pooled estimates (number of events per sample size) were collected.
    - Symptoms were self-reported, and each study made their own criteria for what was defined as asymptomatic, mild, moderate, or severe COVID-19 symptoms while some studies (8), did not describe disease severity and were not included in the pooled event rate estimate.
    - Symptoms were followed anywhere from 90 days to 12 weeks.
    - Myocardial involvement was assessed based on EKG findings, abnormalities on echocardiogram and/or cardiac MRI (CMRI), with or without elevated cardiac troponin (cTn).

INTERVENTION (# IN THE GROUP): 11,518

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 90 days to 12 weeks

RESULTS:

Primary Outcome –

- The pooled event rates of acute and post-acute COVID-19 based on severity:
    - Asymptomatic: 0.26 (95% CI, 0.21–0.31)
    - Mild Symptoms: 0.69 (95% CI, 0.58–0.77)
    - Moderate Symptoms: 0.07 (95% CI, 0.04–0.11)
    - Severe Symptoms: 0.01 (95% CI, 0.01–0.02)
    - Post-acute Symptoms: 0.08 (95% CI, 0.04–0.17)
- The most common acute symptoms reported were anosmia/dysgeusia, fever/chills, headache, fatigue, and cough.
- The most common post-acute symptoms reported were anosmia/dysgeusia, cough, fatigue, and headache.

Secondary Outcome –

- The pooled estimate for myocardial involvement was 0.05 (95% CI, 0.03–0.08).

LIMITATIONS:

- The lack of control groups in most of the studies affected the ability to make meaningful comparisons.
- Though a small portion of athletes showed myocardial involvement after recovery from infection, it was unclear if these were due to COVID-

19 illness versus pre-existing cardiac abnormalities given the lack of control parameters.

- There was no data included in the study as to how severity of illness ratings were assigned nor a clear and standardized criteria to define symptom presentation.
- Symptoms are subjectively reported by the study participants, which affects the interparticipant grading reliability.
- Many studies did not identify potential confounders or strategies to deal with possible confounders.
- All the studies were done prior to the Omicron strain of SARS-COVID-19, and the role of this variant on symptom presentation versus the other strains affecting the patients who were studied may explain patient presentation and disease severity.
- Immunization and baseline health status were not reported, which may have influenced symptom severity in athletes.

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Cognitive Behavioral Therapy and Chronic Pain: When Long-Term Opioids Just Aren't Enough

A Primary Care-Based Cognitive Behavioral Therapy Intervention for Long-Term Opioid Users with Chronic Pain: A Randomized Pragmatic Trial

DeBar L, Mayhew M, Benes L, et al. A Primary Care-Based Cognitive Behavioral Therapy Intervention for Long-Term Opioid Users With Chronic Pain: A Randomized Pragmatic Trial. *Ann Intern Med*. 2022 Jan;175(1):46-55. doi: 10.7326/M21-1436.

KEY TAKEAWAY: Cognitive behavioral therapy (CBT) for the management of chronic pain in patients receiving long-term opioid therapy is effective for decreasing pain intensity, disability due to pain, and improving satisfaction of care but does not significantly affect opioid use.

STUDY DESIGN: Pragmatic, cluster randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Chronic pain is amongst the most common complaints in primary care. Many patients have a significant impact on their lifestyle due to pain despite being on long-term opioid therapy. Few studies have examined the effect of CBT specifically for the management of chronic pain in such patients.

PATIENTS: Adults with chronic pain on long-term opioid therapy

INTERVENTION: CBT

CONTROL: Usual pharmacologic and nonpharmacologic care

PRIMARY OUTCOME: Patient-reported pain impact
Secondary Outcome: Patient-related disability, patient satisfaction, opioid and benzodiazepine use

METHODS (BRIEF DESCRIPTION):

- Included patients were adults who had filled ≥2 long-acting opioid prescriptions in the last six months or 90 days or more of short-acting opioids in the last four months with a pain diagnosis in the last year.
    - Exclusion criteria: ≥2 cancer diagnoses, oncology visit in the last 60 days, hospice or palliative care in the last year, diagnosis of or treatment for substance abuse, cognitive impairment
- High-need chronic pain patients were prioritized (≥120 MME, concurrent benzodiazepine prescriptions, high primary care utilization)
- 67% women; 77% White; average age 60 years old; median MME 29.6
- CBT was delivered by a team (behavioral health specialist, nurse care manager, physical therapist, pharmacist) in collaboration with primary care physician (PCP).
- Four components of intervention:
    - Intake evaluation: Three sessions with medication reconciliation
    - Core skills: 12 weekly 90-minute group sessions (relaxation techniques, activity modification, distraction techniques, relapse prevention and maintenance)
    - PCP Consultation: CBT team and PCP met before and after group sessions to discuss patient's goals of care.
    - Patient Monitoring: Physical activity changes, post-treatment assessment, guidance in developing maintenance plan.
- PCP clusters assigned to usual care were encouraged to continue to provide pharmacologic and nonpharmacologic treatments without restriction.
- Pain measured via Pain, Enjoyment, General Activity scale (PEGS, 0–10, higher scores indicating worse pain impact).
- Pain-related disability measured via Roland Morris Disability Questionnaire (RMDQ; 0= better function 1=worse function).
- Patient satisfaction was assessed via Likert scale (0–5, higher scores indicating greater satisfaction).
- Opioid use was calculated as the average daily dose of MME per 90 days in a 12-month period.
- Benzodiazepine use was assessed through medical record review.
- All outcomes were measured at baseline, 3, 6, 9, and 12 months.

INTERVENTION (# IN THE GROUP): 433

COMPARISON (# IN THE GROUP): 417

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- CBT reduced pain impact compared to usual care.
  - Three months: –0.57 point difference (95% CI, –0.76 to –0.33)
  - 12 months: –0.43 point difference (95% CI, –0.69 to –0.18)
  - There was no significant difference in pain impact scores at six or nine months.

Secondary Outcome –

- CBT reduced pain-related disability compared to usual care.
  - Three months: –0.043 point difference (95% CI, –0.064 to –0.021)
  - 12 months: –0.06 point difference (95% CI, –0.084 to –0.035)
- CBT resulted in greater patient satisfaction in primary care services than usual care (0.23 point difference; 95% CI, 0.053–0.041).
- CBT resulted in greater patient satisfaction in pain services than usual care (0.34 point difference; 95% CI, 0.13–0.54).
- At 12 months, CBT resulted in less benzodiazepine use than usual care (ARR –0.055; 95% CI, –0.099 to –0.011).
- There was no significant difference in average daily opioid use between the groups.

LIMITATIONS:

- The study specifically targeted high-need chronic pain patients with insurance and access to care in large health care systems, limiting generalizability.
- Due to a narrow enrollment window (4 weeks), volunteer bias may skew the results towards those who were more open to behavioral therapy.

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DAPT vs Thrombolysis in Minor Acute Stroke: What's Really Needed?

Dual Antiplatelet Therapy vs Alteplase for Patients with Minor Nondisabling Acute Ischemic Stroke: The ARAMIS Randomized Clinical Trial

Chen HS, Cui Y, Zhou ZH, et al. Dual antiplatelet therapy vs alteplase for patients with minor nondisabling acute ischemic stroke: The ARAMIS randomized clinical trial. *JAMA*. 2023;329(24):2135-2144

KEY TAKEAWAY: Dual antiplatelet therapy (DAPT) is as effective as IV alteplase (thrombolysis) with regard to functional outcome at 90 days in patients presenting with minor nondisabling acute ischemic stroke within 4.5 hours. In addition, DAPT results in significantly less early neurological deterioration and bleeding events than IV alteplase.

STUDY DESIGN: Multi-center, open-label, blinded, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: IV alteplase is often given to patients presenting with minor ischemic stroke; however, it carries a greater risk of hemorrhagic events. Few studies have analyzed the efficacy of DAPT, instead of thrombolysis, in patients presenting with minor ischemic stroke.

PATIENTS: Adult patients with non-disabling ischemic stroke

INTERVENTION: DAPT

CONTROL: IV alteplase

PRIMARY OUTCOME: Excellent functional outcome at 90 days

Secondary Outcome: Early neurological deterioration, bleeding events

METHODS (BRIEF DESCRIPTION):

- Study participants were 69% male with a median age of 64 years old.
- Adults with acute ischemic stroke with NIHSS score ≤5 who presented within 4.5 hours of symptom onset were included.
  - NIHSS: National Institutes of Health Stroke Scale (0–42; 0=no stroke, 42=severe stroke)
- Patients were randomized to:
  - DAPT: 300 mg Clopidogrel and 100 mg Aspirin on day one followed by 75 mg Clopidogrel and 100 mg Aspirin daily for 12 days and guideline-based antiplatelet treatment for 90 days
  - IV alteplase: 0.9 mg/kg IV Alteplase (10% bolus, 90% infused over 1 hour) with a maximum dose of 90 mg followed by guideline-based antiplatelet treatment
- Clinical assessments were performed at baseline, 24 hours, seven days, 12 days/discharge, and 90 days after treatment.
- Early neurological deterioration at 24-hours was defined as an increase in at least 2 on the NIHSS.

INTERVENTION (# IN THE GROUP): 369

COMPARISON (# IN THE GROUP): 350

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- DAPT was noninferior to IV alteplase with regard to excellent functional outcome at 90 days (risk difference [RD] 2.3%; adjusted 95% CI, –1.6% to 6.1%; *P*<.001 for noninferiority).

Secondary Outcome –

- There was significantly less early neurological deterioration at 24 hours in the DAPT group compared to the alteplase group (RD –4.6%; adjusted 95% CI, –8.3% to –0.9%; *P*=.02 for noninferiority).
- There were significantly fewer bleeding events in the DAPT group compared to the alteplase group (RD –3.6%; adjusted 95% CI, –6.4% to –0.7%; *P*=.01 for noninferiority).

LIMITATIONS:

- The study was conducted in China and 69% of participants were men, limiting the generalizability of the results.
- There was a high crossover rate (20%), which might have compromised study integrity.
- High rates of the primary outcome in both groups could have resulted in a ceiling effect.

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Is High-Dose Exercise More Beneficial Than Low-Dose Exercise for Knee Osteoarthritis?

High Versus Low Dose Exercise Therapy for Knee Osteoarthritis: A Randomized Controlled Multicenter Trial

Torstensen TA, Østerås H, LoMartire R, Rugelbak GM, Grooten WJA, Äng BO. High- Versus Low-Dose Exercise Therapy for Knee Osteoarthritis: A Randomized Controlled Multicenter Trial. *Ann Intern Med*. 2023;176(2):154-165. doi:10.7326/M22-2348

KEY TAKEAWAY: In adults with chronic symptomatic knee osteoarthritis, high-dose exercise is not superior to low-dose exercise for knee pain and most knee-function outcomes, though small benefits are noted in knee function in sports/recreation and quality of life domains.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Knee osteoarthritis is a commonly encountered disorder in primary care. Exercise is a well-established and recommended treatment option for knee osteoarthritis, though previous studies have been limited in determining the ideal exercise amount. In this study, the authors compare high-dose exercise versus low-dose exercise for the management of symptomatic knee osteoarthritis.

PATIENTS: Adults with chronic symptomatic knee osteoarthritis

INTERVENTION: High-dose exercise therapy

CONTROL: Low-dose exercise therapy

PRIMARY OUTCOME: Knee function score

Secondary Outcome: Knee pain and quality of life

METHODS (BRIEF DESCRIPTION):

- Adults 45–85 years old with chronic knee osteoarthritis causing knee pain and decreased knee function were included in this study.
- Patients lived in Norway and Sweden, with an average age of 62 years old.
- Patients were excluded if they had physiotherapy in the prior three months, had a history of major knee trauma, or had comorbidities that prevented exercise.
- 189 patients were randomized to one of the following treatment groups, and blinded from group allocation:
    - High-dose exercise: performed 11 exercises for 70–90 minutes three times per week for 12 weeks.
    - Low-dose exercise: performed five exercises for 20–30 minutes three times per week for 12 weeks.
- The following outcomes were measured at baseline, every two weeks during the intervention, at three months (end of intervention period), six months, and 12 months:
    - Knee function was measured using the Knee Injury and Osteoarthritis Outcome Score (KOOS) 0–100 with higher scores indicating better function.
    - Knee pain was measured using visual analogue scales (VAS) of 0–100 mm with higher scores indicating worse pain.
    - Health-related quality of life was measured using the visual analogue scale 0–100 and index 0–1 score from the EuroQol Group 5-Dimension (EQ-5D) tool, with higher scores indicating better QoL.

INTERVENTION (# IN THE GROUP): 98

COMPARISON (# IN THE GROUP): 91

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Knee function (KOOS scores)
    - At three months (end of treatment), high-dose exercise was not superior to low-dose exercise in KOOS scores of pain, other symptoms, activities of daily living (ADL), or quality of life (QoL).
        - Pain (MD 1; 95% CI, –4 to 5)
        - Other symptoms (MD 2; 95% CI, –2 to 6)
        - ADL (MD 2; 95% CI, –2 to 6)
        - QoL (MD 2; 95% CI, –3 to 6)
    - At three months, there was a greater increase in the KOOS Sport/Recreation score in the high-dose group (MD 8; 95% CI, 2–14).
    - At six months, the high-dose exercise group still had higher KOOS Sport/Recreation scores (MD 11; 95% CI, 4–17) as well as higher KOOS QoL scores (MD 8; 95% CI, 3–14).
    - At 12 months there was no difference in KOOS scores between the groups.

Secondary Outcome –

- Knee pain (VAS scores)
  - There was no difference in VAS score between the high-dose and low-dose exercise groups at any period of follow-up.
- Health-related Quality of Life (EQ-5D scores)
  - At 12 months, the high-dose group had a greater increase in EQ-5D score (MD .04; 95% CI, 0.0–0.1) and VAS (MD 7; 95% CI, 2–11), though this did not meet the authors' threshold for clinical significance.

LIMITATIONS:

- The dropout rate was higher in the high-dose group during the intervention.
- There was no control group that did not exercise.
- Floor and ceiling effects were noted in sensitivity analyses.
- Physiotherapist blinding was impossible due to the study design.
- The response rate on follow-up was lower than expected.

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Donor Kidneys: To Cool, or Not To Cool

Hyperthermia or Machine Perfusion in Kidney Donors

Malinoski D, Saunders C, Swain S, et al. Hypothermia or Machine Perfusion in Kidney Donors. *N Engl J Med*. 2023;388(5):418-426. doi:10.1056/NEJMoa2118265

KEY TAKEAWAY: Machine perfusion of kidneys obtained from brain-dead donors provides better protection against delayed graft function than targeted mild hypothermia alone. The combination of hypothermia and machine perfusion is not superior to machine perfusion alone in decreasing the incidence of delayed graft function.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Data from a prior study suggested a significant reduction in the risk of delayed graft function in brain-dead donors treated with mild hypothermia before organ recovery as opposed to no intervention. This study was designed to compare this intervention to the relatively expensive practice of ex-situ machine perfusion. If indeed mild hypothermia was not inferior to machine perfusion, this finding would lead to considerable cost reduction in kidney transplants.

PATIENTS: Kidney transplant recipients

INTERVENTION: Mild hypothermia in donors prior to organ recovery or a combination of hypothermia and ex-situ machine perfusion

CONTROL: Ex-situ machine perfusion of kidney

PRIMARY OUTCOME: Delayed graft function in kidney transplant recipients

Secondary Outcome: Graft survival at one year after transplant

METHODS (BRIEF DESCRIPTION):

- Selected donors were deidentified with the criteria of being greater than 18 years old with no ESRD, hemodynamic instability, and coagulopathy. They were also determined to have neurological death. Recipients were chosen in accordance with standard Organ Procurement and Transplantation Network practices.
- The Organ Procurement and Transplantation Network governs the operation of all transplant hospitals, organ procurement organizations, and histocompatibility labs in the United States. All of the kidneys used in the trial were managed by six organ procurement organizations across seven states.
- This trial was conducted from August 10, 2017–May 21, 2020. Brain-dead donors who had kidneys that were eligible for machine perfusion were managed clinically by organ procurement organizations in these states.
- Donors were split into three groups: Normothermia and machine perfusion of both kidneys, hypothermia and machine perfusion of the left kidney, and hypothermia and machine perfusion of the right kidney in a 1:1:1 ratio. This allowed the formation of three recipient groups: machine perfusion, hypothermia, and a combination of hypothermia and machine perfusion in a 1:1:1 ratio.
- The primary outcome, delayed graft function, was determined by personnel at the organ transplant center and was signified by the initiation of dialysis during the first week after transplantation. Relative risk (RR) was calculated to measure the risk of delayed graft function; RR <1 indicates a lower risk of delayed graft function vs RR >1 indicates a higher risk.
- The secondary outcome, allograft survival after one year, was estimated using the Kaplan-Meier method which statistically estimated the survival function from lifetime data measured in the follow-up period. A hazard ratio (HR) <1 indicates a lower risk of graft failure.

INTERVENTION (# IN THE GROUP): 359 hypothermia only; 479 combination therapy of hypothermia and machine perfusion

COMPARISON (# IN THE GROUP): 511 ex-situ machine perfusion only

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Hypothermia was inferior to machine perfusion in protecting kidney-graft recipients from delayed graft function (adjusted RR 1.72; 95% CI, 1.35–2.17).
- Combination therapy was not superior to machine perfusion in protecting kidney graft recipients from

delayed graft function (adjusted RR 1.09; 95% CI, 0.85–1.40).

Secondary Outcome –

- The frequency of kidney graft survival was similar among the three groups at one year.
- Among 1,348 kidney recipients, 45 recipients died within one year of follow-up.
- Of these recipients, eight (2%) were in the hypothermia group, 19 (4%) were in the machine perfusion group, and 18 (4%) were in the combination therapy group.

LIMITATIONS:

- The trial was terminated early after the first interim analysis established the inferiority of hypothermia alone due to the impact.
- This study had an open design in which all healthcare providers were aware of the group assignments.
- Six organ procurement organizations were involved in the study, increasing the likelihood of lapses in the standardization of procedures (i.e. machines used for perfusion, and differences in transplant teams).

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Incidence of Type 2 Diabetes: Not All Plant-Based Diets Are Created Equal

Healthful Plant-Based Diet and Incidence of Type 2 Diabetes in Asian Population

Kim J, Giovannucci E. Healthful Plant-Based Diet and Incidence of Type 2 Diabetes in Asian Population. *Nutrients*. 2022;14(15):3078. Published 2022 Jul 27. doi:10.3390/nu14153078

KEY TAKEAWAY: Diets focused on increased consumption of healthy plant-based foods and decreased consumption of nutrient-deficient plant and animal foods are associated with a lower incidence of developing type 2 diabetes in the Korean population.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Diets focused on whole foods can help individuals manage both their weight and health outcomes. Organizations such as the World Health Organization, American Cancer Society, and U.S. Dietary Guidelines for Americans encourage the consumption of plant-based foods and caution against the consumption of high amounts of added sugar, highly refined foods, saturated fats, and processed meats. Patients may be counseled by primary care providers to implement a plant-based diet to improve health outcomes. However, it is important to remember that not all plant-based foods are created equally. The goal of this study was to evaluate how different plant-based diets can affect the risk of developing type 2 diabetes, one of the most common health conditions in our modern society.

PATIENTS: Resident ages 40–69 years old without type 2 diabetes

INTERVENTION: Consumption of a healthful plant-based diet

CONTROL: Consumption of a regular diet

PRIMARY OUTCOME: Incidence of type 2 diabetes

METHODS (BRIEF DESCRIPTION):

- Individuals included 7,393 Korean adults aged 40–69, specifically community residents living in Ansung and Ansan, near Seoul.
- Individuals were excluded from the study if they had:
  - Type 2 diabetes. The incidence of type 2 diabetes was defined as a self-reported doctor's diagnosis, use of oral hypoglycemic drugs, or by an elevated plasma glucose of 126.
  - Cardiovascular disease
  - Cancer
- Dietary data was obtained from the KoGES (Korean Genome and Epidemiology Study), which was a prospective cohort study initiated between 2001 and 2002.
- A validated 106-item semi-quantitative food frequency questionnaire was used to assess the dietary intake of the participants.
  - The food frequency questionnaire consisted of a list of beverages and foods with response categories to indicate the usual frequency of consumption over one year.
  - The food items from the questionnaire were sorted into 17 food groups based on culinary and nutrient similarities. The study distinguished between less healthy plant foods and healthy plant foods by looking at the associations of a food item with disease risk.
  - The food frequency questionnaire was given out to participants twice throughout the study.
- Once the participant's diets were assessed from the questionnaire, they were further measured by comparing the results of plant-based diet indices to determine the incidence of developing type 2 diabetes. The plant-based diet index is a scoring system used to assess data collected from the food frequency questionnaire. This scoring index gives the consumption of certain foods either positive or negative markers.
  - The three plant-based indices were an overall plant-based diet index, a healthful plant-based diet index, and an unhealthful plant-based diet index.
- In each of the diet indices, all individuals' food frequency data was scored and assessed based on the nutrients consumed. For each of the three diet indices, the data was split into five quintiles. Food group consumption was compared between the lowest and highest quintile of each of the three diet indices.

- In the plant-based diet index (PDI), individuals had a higher score for increased consumption of any plant foods, these individuals were in the 5th quintile. Individuals who consumed more animal products were in the 1st quintile.
- In the healthful plant-based diet index (hPDI), individuals with a higher score for increased consumption of only healthy plant foods were in the 5th quintile vs individuals who consumed greater amounts of unhealthy plant foods such as refined grains and salty foods were in the 1st quintile.
- For the unhealthful plant-based diet index (uPDI), individuals received a higher score for increased consumption of less healthy plant foods and were placed in the 1st quintile vs individuals with a lower score were in the 5th quintile.
- Within each diet index group, a Hazard Ratio (HR) and 95% confidence interval was used to determine how often individuals developed type 2 diabetes.

- The incidence of type 2 diabetes was defined as having at least one of the following criteria: An elevated plasma glucose level above or equal to 126 mg/dL, current treatment with insulin, or the use of an oral hypoglycemic drug.
- Medication use, medical history, and biochemical assessment were identified at follow-up visits that occurred biennially (every other year).

INTERVENTION (# IN THE GROUP): 7,363

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: 14 years

RESULTS:

Primary Outcome –

- There was no significant risk associated with individuals in the plant-based group with the risk of developing type 2 diabetes (HR 0.99; 95% CI, 0.88–1.12).
- Individuals in the healthful plant-based group a significantly lower risk of developing type 2 diabetes over 14 years (HR 0.86; 95% CI, 0.77–0.95).
- There was no significant risk associated with individuals in the unhealthful plant-based group with the risk of developing type 2 diabetes (HR 1.06; 95% CI, 0.96–1.18).

LIMITATIONS:

- The study is not generalizable to all populations because the participants only included Korean adults.
- The data is subject to error because it is based on a patient questionnaire, which is subject to accurate reporting of their diet.
- When differentiating between a healthy plant food versus a less healthy plant food, the processing and cooking method was not considered.

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