GOOD EVIDENCE MATTERS

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Family Physicians Inquiries Network

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Helping Kids Sleep: Is Melatonin the Answer?

Use of Melatonin in Children and Adolescents with Idiopathic Chronic Insomnia: A Systematic Review, Meta-Analysis, and Clinical Recommendation

Edemann-Callesen H, Andersen HK, Ussing A, et al. Use of Melatonin in Children and Adolescents with Idiopathic Chronic Insomnia: A Systematic Review, Meta-analysis, and Clinical Recommendation. *EClinicalMedicine*. 2023;61:102048. Published 2023 Jul 6. doi:10.1016/j.eclinm.2023.102048

KEY TAKEAWAY: In youth and adolescents with chronic idiopathic insomnia who have trialed sleep hygiene, the use of melatonin does not improve quality of sleep or daytime functioning.

STUDY DESIGN: Systematic review and meta-analysis of eight randomized controlled trials (RCTs) (N=1,118)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to limited sample sizes and small number of RCTs)

BRIEF BACKGROUND INFORMATION: Insomnia is a significant problem in children and adolescents, affecting as much as 25%, leading to impacts on not just school or work performance but health conditions such as depression, growth, diabetes, and obesity, yet it is difficult to treat effectively. Melatonin is a common over-the-counter sleep aid available for parents and easily recommended to children as a quick fix for sleep troubles. However, its long-term effects and efficacy are poorly understood. This meta-analysis aimed to review whether melatonin is an efficacious sleep aid to recommend to children with insomnia.

PATIENTS: Youth and adolescents 5–20 years old with chronic idiopathic insomnia who have trialed sleep hygiene

INTERVENTION: Melatonin

CONTROL: No treatment, placebo, or non-pharmacologic interventions

PRIMARY OUTCOME: Quality of sleep, daytime functioning, and serious adverse events

Secondary Outcome: Total sleep time, sleep latency, awakenings, drowsiness, dropouts, quality of life, non-serious adverse events

METHODS (BRIEF DESCRIPTION):

- Eight RCTs were included in the study with a total of 419 patients, 6–19 years old with chronic insomnia as defined by the International Classification of Sleep Disorders, version three (ICSD-3).
- Any study in children with a formal psychiatric diagnosis or somatic disorders was excluded due to differences in treatment.
- The impact of melatonin was studied with no restriction on formulation, frequency, protocol, duration, or dosage.
- Results were compared to placebo, no-treatment, or non-pharmacologic treatment that included physical activity, cognitive behavioral therapy, weighted blankets, and others.
- The primary outcomes measured the following:
  - Quality of sleep was measured by sleep efficiency percentage and actigraphy, with a higher score being better quality of sleep.
  - Daytime functioning was measured by the Functional Status II total score and the Children's Sleep Habits Questionnaire out of a total score of 41, with a lower score being better.
  - Serious adverse events were measured by report.
- The secondary outcomes measured the following:
  - Total sleep time was measured by a parent and self-reported sleep diary, with a higher score meaning more sleep time.
  - Sleep latency was assessed by a parent-reported sleep diary, with a lower score indicating improvement.
  - Awakenings after sleep onset as measured by actigraphy, with a lower score indicating improvement.
  - Drowsiness measured by the Karolinska Sleepiness Scale. Scores range from 0–10, with higher scores indicating falling asleep.
  - Dropouts were measured by report.
  - Quality of life as measured by actigraphy, with a higher score indicating improvement.
  - Non-serious adverse events were measured by report.

INTERVENTION (# IN THE GROUP): 291
COMPARISON (# IN THE GROUP): 206

FOLLOW-UP PERIOD: Variable (ranged between 2 weeks and 6 months)

RESULTS:

Primary Outcome –

- Melatonin did not significantly affect quality of sleep compared to placebo (1 study, n=56; mean difference [MD] –1.2; 95% CI, –3.5 to 1.1; I^2=Not applicable).
- Melatonin did not significantly affect daytime functioning compared to placebo (2 studies, n=122; standardized mean difference [SMD] –0.23; 95% CI, –0.60 to 0.14; I^2=0%).
- No studies provided information on the risk of serious adverse events secondary to the use of melatonin.

Secondary Outcome –

- Melatonin increased total sleep time compared to no melatonin (4 studies, n=184; difference 30 minutes; 95% CI, 19–42).
- Melatonin reduced sleep latency compared to no melatonin (3 studies, n=142; difference 18 minutes; 95% CI, –27 to –9.4) and when using actigraphy (1 study, n=72; 27 minutes; 95% CI, –38 to –16).
- Melatonin increased wakefulness after sleep onset as found by actigraphy compared to no melatonin (1 study, n=54; MD 18; 95% CI, 5.9–31).
- Melatonin increased the number of patients experiencing a non-serious adverse event compared to no melatonin (4 studies, n=212; relative risk [RR] 3.4; 95% CI, 1.3–9.4).
- Melatonin did not statistically affect quality of life, sleepiness, and all-cause dropouts compared to no melatonin.

LIMITATIONS:

- Only eight RCTs met inclusion criteria, which increases the risk of bias and limits external validity and generalizability.
- Included studies were restricted to the English or Scandinavian languages.
- Many secondary outcomes could not be measured as originally planned due to lack of data.
- Adverse events were not widely reported.

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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 Army Medical Department, the Army at large, or the Department of Defense.

Cure-iously Unavailable: A Transitional Palliative Study

Transitional Palliative Care for Family Caregivers: Outcomes from a Randomized Controlled Trial

Griffin JM, Mandrekar JN, Vanderboom CE, et al. Transitional Palliative Care for Family Caregivers: Outcomes from a Randomized Controlled Trial. *J Pain Symptom Manage*. 2024;68(5):456-466. doi:10.1016/j.jpainsymman.2024.07.030

KEY TAKEAWAY: Transitional palliative care in the era of video visits is a viable and effective option for both patients and caregivers when transitioning home from the hospital setting in the rural setting.

STUDY DESIGN: Randomized controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: For those who receive palliative care in the hospital, the transition home can often come with decreased quality of life, stress, increased burden, and even adverse events for both caregivers and patients. This study aimed to investigate the impact of transitional palliative care in the transition home using easily accessible video visits.

PATIENTS: Adult caregivers to patients in rural areas who transitioned home or to short-term rehabilitation after receiving inpatient palliative care

INTERVENTION: Palliative care nursing teaching/guidance via video visits at least weekly for eight weeks post discharge

CONTROL: Caregivers who received monthly phone calls but no other interventions

PRIMARY OUTCOME: Caregiver depression, caregiver burden, caregiver quality of life, care recipient quality of life

METHODS (BRIEF DESCRIPTION):

- Study participants were English-speaking adults in rural (<50,000 residents) Minnesota, Wisconsin, or Iowa who were most directly responsible for a patient who had received inpatient palliative care during hospital admission prior to transitioning home, to a short-term rehabilitation, or skilled nursing facility.
- Patients who required intensive out of hospital care (left ventricular assist devices [LVADs] or pain pumps) were excluded.
- Enrollment started in March 2018 and data collection concluded in July 2022.
- While study caregivers were identified in the hospital and provided consent prior to intervention assignment, inpatient palliative care teams were blinded to the study. Care recipients provided consent as well, however, they did not participate directly in the intervention.
- Participants were randomly assigned to the treatment arm or control using a computer-generated randomization.
- Transitional palliative care (addressing personalized social/emotional/spiritual/logistical needs) was started withing 24 hours of study enrollment, continued twice weekly while admitted, and continued in decreasing frequency at least weekly over the course of the eight-week study period post-discharge.
- The control group received monthly check-in phone calls during the same time-period, with no out of hospital coaching, however they did continue to receive usual palliative care services.
- Caregiver depression was measured using the Center for Epidemiological Studies Depression scale (CES-D). Scores range from 0–30, with higher scores indicating of more depressive symptoms.
- Caregiver burden was measured using the 15-point Bakas Caregiving Outcomes Scale-Revised which includes items that indicate challenges such as well-being and stress levels. Higher scores were indicative of less burden.
- Caregiver quality of life was measured using the 35-point Caregiver Quality of Life Index-Cancer, with 35 questions to assess aspects such as function and distress. Higher scores were indicative of worse quality of life.
- Care recipient quality of life was measured using the 10 item Palliative Care Outcomes Scale-Carer, with scores ranging from 0–40. Questions including pain, symptoms, and communication were composited into a total score, with higher score being indicative of more symptom burden.
- Scoring was adjusted to include gender, age, relationship between caregiver and care recipient,

relationship quality, preparedness at baseline, provision of other help, coping, time from palliative care consultation to hospital discharge, discharge disposition, and death during study period.

INTERVENTION (# IN THE GROUP): 183

COMPARISON (# IN THE GROUP): 184

FOLLOW-UP PERIOD: Eight weeks

RESULTS:

Primary Outcome –

- Transitional palliative care improved caregiver depression and quality of life compared to control.
  - Depression (0.62 vs 2.5, respectively; *p*=.04).
  - Quality of life (–0.16 vs 5.7, respectively; *p*=.04).
- Transitional palliative care increased the care recipient's quality of life compared to control (–2.5 vs –0.20, respectively; *p*=.05).
- There was no statistically significant improvement in the level of caregiver burden between those receiving transitional palliative care compared to control (–0.002 vs 0.10, respectively; *p*=.05).

LIMITATIONS:

- Data was limited to an eight-week time-period, with no long term follow up.
- Follow up calls for the control group may not have provided a true control scenario.
- There was noted difficulty in retaining those recruited to the study.
- It is unclear if the population recruited is truly representative of the broader patient population physicians serve due to cultural/ethnic groups surveyed and willingness to share personal information.
- Caregivers were surveyed for quality of life of the patients which may have led to skewed perceptions of true changes.

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Lower Urinary Tract Symptoms? There's an App for That!

A Randomized Trial of an App-Based Therapeutic for Lower Urinary Tract Symptoms

Gratzke C, Schönburg S, Eger S, et al. A Randomized Trial of an App-Based Therapeutic for Lower Urinary Tract Symptoms. *NEJM Evid*. 2025;4(4):EVIDoa2400290. doi:10.1056/EVIDoa2400290

KEY TAKEAWAY: For men with benign prostatic enlargement and/or overactive bladder, an app-based program utilizing behavioral therapy significantly improves urinary tract symptoms and quality of life (QoL).

STUDY DESIGN: Prospective, two-center, single-blinded, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Lower urinary tract symptoms are prevalent in older men and negatively impact quality of life. While behavioral therapy is recommended as first-line treatment, it is often underutilized. This study investigated the efficacy of using an app with integrated behavioral therapy to improve symptoms and QoL.

PATIENTS: Men with lower urinary tract symptoms

INTERVENTION: App-based program

CONTROL: Standard medical care

PRIMARY OUTCOME: Symptom severity

Secondary Outcome: Symptom bother, health-related QoL

METHODS (BRIEF DESCRIPTION):

- Patients (mean age 58 years old) diagnosed with benign prostatic enlargement and/or overactive bladder were recruited from two centers in Germany.
- Patients with recurrent urinary tract infections, recent micturition drug initiation, and impaired renal function were excluded.
- Patients were randomized 1:1 to the app-based therapeutic with standard medical care or standard medical care only.
    - The app-based therapeutic was a 12-week personalized program combining physical, psychological, and behavioral approaches.
- The primary outcome was measured with the International Prostate Symptom Score (IPSS). Scores range from 0–35, with higher scores indicating more severe symptoms. The minimal clinically important difference (MCID) is a change of ≥3.0.
- The secondary outcomes were measured using two parts of the Overactive Bladder Questionnaire - Short Form (OAB-q-SF).
    - Part one measured symptom bother. Scores range from 6–36 transformed to 0–100, with higher scores indicating greater symptom bother.
    - Part two measured health-related QoL. Scores range from 13–78 transformed to 0–100, with higher scores indicating better QoL.

INTERVENTION (# IN THE GROUP): 112

COMPARISON (# IN THE GROUP): 125

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- App-based program reduced symptom severity compared to standard care (least square means [LSM] −7.0; 95% CI, −8.1 to −5.9).

Secondary Outcome –

- App-based therapy reduced symptom bother compared to standard care (LSM −19; 95% CI, −22 to −15).
- App-based therapy increased health-related QoL compared to standard care (LSM 17; 95% CI, 14–20).

LIMITATIONS:

- Participants were unable to be blinded to the treatment.
- There was no long-term follow-up.
- Patients who signed up for the study had smartphone or tablet access, as well as technological competency, and were likely more motivated to follow the plan, introducing recruitment bias.
- There is limited generalizability since the app is not available in the United States.
- Given the multimodal component of the app, it is unclear which features were most effective, making it difficult to replicate similar results.

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Bleeding Risk in Acute VTE: Does Apixaban Outperform Rivaroxaban?

Bleeding Risk with Apixaban vs Rivaroxaban in Acute Venous Thromboembolism

Castellucci LA, Chen VM, Kovacs MJ, et al. Bleeding Risk with Apixaban vs. Rivaroxaban in Acute Venous Thromboembolism. *N Engl J Med*. 2026;394(11):1051-1060. doi:10.1056/NEJMoa2510703

KEY TAKEAWAY: Apixaban lowers the risk of clinically significant bleeding for patients with acute venous thromboembolism (VTE) compared to rivaroxaban.

STUDY DESIGN: Prospective, randomized, open-label, blinded endpoint design

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: One of the most serious side effects that is clinically relevant when prescribing anticoagulation for an acute VTE is the risk of bleeding during treatment. This study evaluated the two most prescribed direct oral anticoagulants (DOACs) used in the treatment of acute VTE to determine which had a lower risk of bleeding.

PATIENTS: Patients with acute VTE

INTERVENTION: Apixaban

CONTROL: Rivaroxaban

PRIMARY OUTCOME: Risk of clinically relevant bleeding
Secondary Outcome: Major bleeding, clinically relevant nonmajor bleeding, death from bleeding, recurrent symptomatic VTE, death from recurrent VTE, death from any cause

METHODS (BRIEF DESCRIPTION):

- Patients were adults with no history of VTE chosen from Canada, Australia, and Ireland presenting with acute VTE.
- These patients also weighed <120 kg, did not have severe renal or hepatic dysfunction, no active cancer, acute bleeding on presentation, or receive therapeutic anticoagulation >72 hours prior to enrollment.
- Patients who were pregnant, breastfeeding, or had any other indication for long-term anticoagulant therapy were excluded.
- Patients were randomized 1:1 to receive either three months of apixaban (10 mg BID for 1 week followed by 5 mg BID until 3 months) or three months of rivaroxaban (15 mg BID for 21 days followed by 20 mg daily until 3 months).
- The primary outcome of clinically relevant bleeding was checked at 1–3 weeks and three months after randomization.
- The following were measured as the secondary outcomes: Major bleeding, clinically relevant nonmajor bleeding, death from bleeding, recurrent symptomatic VTE (defined by a noncompressible area in the popliteal vein or more proximal vein on compression ultrasonography that was not present at the time of diagnosis or by a constant intraluminal filling defect in the popliteal vein or more proximal veins on venography), death from recurrent VTE (confirmed on the basis of a death certificate or autopsy findings), and death from any cause.

INTERVENTION (# IN THE GROUP): 1,345

COMPARISON (# IN THE GROUP): 1,355

FOLLOW-UP PERIOD: Three months

RESULTS:

Primary Outcome –

- Apixaban decreased the risk of clinically relevant bleeding compared to rivaroxaban (relative risk [RR] 0.46; 95% CI, 0.33–0.65).

Secondary Outcome –

- Apixaban decreased the risk of major bleeding compared to rivaroxaban RR 0.16; 95% CI, 0.06–0.40).
- Apixaban decreased the risk of clinically relevant nonmajor bleeding compared to rivaroxaban (RR 0.59; 95% CI, 0.40–0.86).
- There was no significant difference in recurrent symptomatic VTE or death from recurrent VTE for apixaban compared to rivaroxaban.
- No deaths due to bleeding from any cause were reported for either group.

LIMITATIONS:

- Application of this study to non-White populations is limited due to approximately 90% of the study population being White.
- The exclusion criteria excluded patients with a weight of >120 kg, which excluded a growing

number of people who are likely at a higher risk than average for VTE.

- The exclusion criteria also eliminated patients with significant kidney and liver disease.
- Complete adherence to the medication regimen was only reported by 66% of the apixaban group and 75% of the rivaroxaban group.

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A New Metabolic Tune-Up: Recalibrating Diabetes and Metabolic Dysfunction-Associated Steatotic Liver Disease with Tirzepatide

Effects of Tirzepatide on Patients with Type 2 Diabetes and Metabolic Dysfunction-Associated Steatotic Liver Disease: A Retrospective Cohort Study

Okuma H. Effects of Tirzepatide on Patients with Type 2 Diabetes and Metabolic Dysfunction-associated Steatotic Liver Disease: A Retrospective Cohort Study. *Cureus*. 2025 May 8;17(5):e83712. doi:10.7759/cureus.83712

KEY TAKEAWAY: Switching from glucagon-like peptide-1 receptor agonists (GLP-1 RAs) to tirzepatide is an effective way to manage metabolic dysfunction-associated steatotic liver disease (MASLD) in patients with type 2 diabetes mellitus (T2DM).

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: MASLD is increasing globally and can progress to cirrhosis and liver cancer. GLP-1 RAs improve metabolic dysfunction-associated steatohepatitis (MASH) without clear benefits on fibrosis. Tirzepatide improves MASH and fibrosis biomarkers. This study aimed to evaluate the effects of switching from a GLP-1 RA to tirzepatide on glycemic control, liver disease parameters, and inflammation markers in patients with T2DM and MASLD.

PATIENTS: Patients with T2DM and MASLD

INTERVENTION: Tirzepatide after use of GLP-1 RA

CONTROL: GLP-1RA use prior to switch to tirzepatide

PRIMARY OUTCOME: Changes in liver disease markers

Secondary Outcome: Changes in glycemic control

METHODS (BRIEF DESCRIPTION):

- This study included 54 Japanese adults (29 men and 25 women) >20 years old with T2DM and MASLD.
- Patients were excluded if they were <20 years old, had HbA1c >10%, or could not tolerate tirzepatide ≥5 mg/week.
- Patients were switched to tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, administered as a once-weekly subcutaneous injection with dose titration to a minimum of 5 mg/week, for a total duration of six months.
- Prior to switching, all patients had been treated with GLP-1 RAs, specifically dulaglutide or semaglutide, administered as once-weekly subcutaneous injections for at least six months. These therapies served as the comparator to assess changes after initiating tirzepatide.
- The primary outcomes were changes in liver disease markers, including the Fatty Liver Index (FLI) and Fibrosis-4 (FIB 4) index, measured at baseline and after six months of treatment.
    - The FLI is a noninvasive scoring system calculated using body mass index, waist circumference, triglycerides, and gamma-glutamyl transferase levels. Scores range from 0–100, with higher values indicating a greater likelihood of hepatic steatosis.
    - The FIB-4 index is a validated marker of liver fibrosis derived from age, AST, ALT, and platelet count. Higher values are associated with more advanced liver fibrosis.
- Secondary outcomes included changes in glycemic control, assessed by HbA1c, body weight, and systemic inflammation measured by high-sensitivity C-reactive protein (hsCRP).
    - Higher hsCRP levels reflect increased systemic inflammatory activity.
- All secondary outcomes were evaluated at baseline and at six months following initiation of tirzepatide.

INTERVENTION (# IN THE GROUP): 54

COMPARISON (# IN THE GROUP):

- Dulaglutide: 24
- Semaglutide: 30

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Tirzepatide decreased FLI six months after the switch compared to before the switch (mean 48 vs 67, respectively; $p<.0001$).
- Tirzepatide decreased FIB-4 six months after the switch compared to before the switch (mean 0.96 vs 1.3, respectively; $p<.0001$).

Secondary Outcome –

- Tirzepatide decreased HbA1c six months after the switch compared to before the switch (mean 7.3 vs 8.2, respectively; $p<.0001$).

- Tirzepatide decreased body weight six months after the switch compared to before the switch (median 67 kg vs 71 kg, respectively; $p<.0001$).
- Patients previously treated with dulaglutide experienced greater reductions in body weight, body mass index, and HbA1c compared to those previously treated with semaglutide, but changes in FLI and FIB-4 index were not significantly different between groups after adjustment for age.

LIMITATIONS:

- The study was conducted at a clinic in Japan, which may limit applicability to other patient populations.
- Tirzepatide dose was limited to 5 mg/week, which is less than the maximum recommended dose, due to limited medication shipments.
- The study had a small sample size.
- Although the study focused on tirzepatide's effect on management of MASLD, FLI and FIB-4 index were used rather than including imaging tests.
- The study lacked a control group that did not use tirzepatide.
- Differences in prior GLP-1 RA treatment between dulaglutide and semaglutide groups may have influenced the comparative outcomes following the switch to tirzepatide.

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One Lump or Two, Dear? Observed Effects of Raspberry Leaf Tea on Blood Glucose and Insulin Levels in Healthy Individuals

Effects of Raspberry Leaf Tea Polyphenols on Postprandial Glucose and Insulin Responses in Healthy Adults

Alkhudaydi HMS, Spencer JPE. Effects of Raspberry Leaf Tea Polyphenols on Postprandial Glucose and Insulin Responses in Healthy Adults. *Nutrients*. 2025;17(17):2849. Published 2025 Sep 1. doi:10.3390/nu17172849

KEY TAKEAWAY: Raspberry leaf tea (RLT) reduces early postprandial glucose and insulin after sucrose, but not when consumed with glucose in healthy adults.

STUDY DESIGN: Randomized controlled crossover design

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and short-term randomized crossover trial in humans)

BRIEF BACKGROUND INFORMATION: Postprandial (after-meal) spikes in blood glucose and insulin are increasingly recognized as important contributors to the risk of type 2 diabetes development, cardiovascular disease (CVD), and long-term metabolic dysfunction. Even in healthy people, repeated sharp glucose spikes may have negative effects over time. RLT was chosen to investigate whether its high polyphenol content, which inhibits carbohydrate-digesting enzymes, affects postprandial glucose levels in humans.

PATIENTS: Healthy adults 18–65 years old

INTERVENTION: Glucose + RLT and sucrose + RLT after carbohydrate intake

CONTROL: Glucose alone and sucrose alone

PRIMARY OUTCOME: Postprandial blood glucose levels

METHODS (BRIEF DESCRIPTION):

- This study used a randomized crossover design that included healthy adults, 18–65 years old.
- Patients consumed RLT or a control drink alongside sucrose or glucose on separate occasions.
- Blood glucose checks 15 minutes before the test meal and tea, 15, 30, 60, 90, and 120 minutes after carbohydrate and tea consumption.
- A 2–4-week washout period between sessions to allow vein recovery and eliminate crossover effects.
- The primary outcomes measured postprandial blood glucose levels. Blood samples were collected over two hours to measure postprandial glucose and insulin responses.

INTERVENTION (# IN THE GROUP): 22

COMPARISON (# IN THE GROUP): 22

FOLLOW-UP PERIOD: 15 minutes before test meal and tea, 15, 30, 60, 90, and 120 minutes after carbohydrate and tea consumption

RESULTS:

Primary Outcome –

- There was no statistically significant difference in postprandial blood glucose levels at 15, 30, 60, 90, or 120 minutes between glucose + RLT compared to glucose alone.
  - 15 minutes (41% vs 43%, respectively; p=.64)
  - 30 minutes (65% vs 64%, respectively; p=.94)
  - 60 minutes (44% vs 51%, respectively; p=.36)
  - 90 minutes (20% vs 22%, respectively; p=.78)
  - 120 minutes (0.64% vs –0.57%, respectively; p=.79)
- These findings suggest the tea specifically slows sucrose digestion, likely via inhibition of carbohydrate-digesting enzymes, rather than affecting glucose absorption directly.
- Sucrose + RLT decreased postprandial blood glucose at 15 and 30 minutes compared to sucrose alone.
  - 15 minutes (26% vs 38%, respectively; p=.001)
  - 30 minutes (44% vs 61%, respectively; p=.0004)
- Sucrose + RLT did not significantly change postprandial blood glucose at 60, 90, and 120 minutes compared to sucrose alone.
  - 60 minutes (26% vs 27%, respectively; p=.23)
  - 90 minutes (2.9% vs –5.7%, respectively; p=.06)
  - 120 minutes (–3.4% vs –20%, respectively; p=.16)

LIMITATIONS:

- The study is limited by its small sample size (n=22), short-term follow-up, and inclusion of only healthy adults, reducing generalizability.
- It assessed acute glycemic responses rather than long-term outcomes and used controlled conditions that may not reflect real-world eating patterns.
- Physiological mechanisms of polyphenol effects on postprandial glucose levels were inferred rather than directly measured in vivo.

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Extra Protein, Zero Gains

Augmented Enteral Protein During Critical Illness: The TARGET Protein Randomized Clinical Trial

Summers MJ, Chapple LS, Karahalios A, et al. Augmented Enteral Protein During Critical Illness: The TARGET Protein Randomized Clinical Trial. *JAMA*. 2025;334(4):319-328. doi:10.1001/jama.2025.9110

KEY TAKEAWAY: An augmented protein (100 g/L) formula does not significantly improve hospital-free days within 90 days compared to usual protein (63 g/L) formula in intensive care unit (ICU) patients requiring enteral nutrition.

STUDY DESIGN: Multicenter open-label randomized crossover trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Several formulations of enteral nutrition are marketed to hospital systems. Higher protein formulations are theorized to improve critically ill patients' long-term outcomes by reducing muscle atrophy. Prior studies have shown no difference in recovery outcomes between augmented and usual protein formulas.

PATIENTS: ICU patients who require enteral nutrition

INTERVENTION: Augmented protein of 100 g/L protein

CONTROL: Usual protein of 63 g/L protein

PRIMARY OUTCOME: Hospital-free days within 90 days

Secondary Outcome: Survival at 90 days, duration of invasive ventilation, admission duration, risk of tracheostomy, incidence of new dialysis requirement, discharge destination

METHODS (BRIEF DESCRIPTION):

- This study included ICU patients ≥16 years old who required enteral nutrition and excluded patients with a contraindication to enteral nutrition as well as those who had already received ≥12 hours of an enteral nutrition formulation that was not being studied.
- Eight ICUs in Australia and New Zealand were randomized to provide either augmented protein parenteral formula with Nutrison Protein Intense (100 g/L) or usual protein formula with Nutrison Protein Plus (63 g/L) for all patients requiring tube feeds who met inclusion criteria for a three-month block, then alternated formula type every three months over a 12-month period.
- The trial formula was administered in each patient while clinically indicated, for up to 90 days or until the patient was discharged from the ICU or died.
- If there was a clinical need for a different formula, the trial formula was discontinued, and a protocol deviation was recorded. Patients were analyzed with an intention-to-treat model.
- The primary outcome of hospital-free days was measured by 90 minus the total number of days hospitalized within a 90-day period. Patients who did not survive within 90 days were assigned zero hospital-free days.
- The secondary outcomes included survival at 90 days, duration of invasive ventilation, admission duration, risk of tracheostomy, incidence of new dialysis requirement, and discharge destination.

INTERVENTION (# IN THE GROUP): 1,681

COMPARISON (# IN THE GROUP): 1,716

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- In ICU patients requiring enteral nutrition, augmented protein formula did not improve the number of hospital-free days compared to usual protein enteral nutrition formula (adjusted median difference −2.0 days; 95% CI, −7.2 to 3.3).

Secondary Outcome –

- Augmented protein formula did not significantly change survival at 90 days, difference in mean duration of invasive ventilation, hospital admission duration, risk of tracheostomy, incidence of new dialysis requirement, or discharge destination.

LIMITATIONS:

- Patients were not individually randomized; rather, randomization occurred for an entire patient cluster.
- Interventions were not blinded.
- Could not account for re-admission to a different hospital other than the index hospital.
- The daily protein dose differed by only 19 g between the interventional and comparison groups.
- The follow-up period was only 90 days.

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