GOOD EVIDENCE MATTERS

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Rethinking the Standard: Weekly Tirzepatide or Daily Insulin?

Tirzepatide Outcompetes Long-Acting Insulin in Managing Type 2 Diabetes: A Meta-Analysis of Three Phase 3 Randomized Controlled Trials

Ala M, Mohammad Jafari R, Dehpour AR, Poursalehian M. Tirzepatide outcompetes long-acting insulin in managing type 2 diabetes: a meta-analysis of three phase 3 randomized controlled trials. *Int J Obes (Lond).* 2024 Dec;48(12):1684-1695. doi: 10.1038/s41366-024-01621-4. Epub 2024 Aug 29. PMID: 39210008.

KEY TAKEAWAY: Tirzepatide taken once a week may be as efficacious or more efficacious than daily long-acting insulin for treating type 2 diabetes mellitus (T2DM).

STUDY DESIGN: Systematic review and meta-analysis of three randomized multicenter, international, unblinded, open-label, phase 3, clinical trials, namely, SURPASS-3, SURPASS-4, and SURPASS-AP-Combo (N=4,339)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity, inclusion of only drug sponsored trials, and lack of blinding)

BRIEF BACKGROUND INFORMATION: T2DM is a prevalent disease in the United States. Recent clinical trials on tirzepatide on both glycemic control as well as improvement in comorbid conditions is a promising alternative medication to long-acting and ultra-long-acting insulin. Given the ease of using the once-weekly tirzepatide, it is beneficial to examine the relative efficacy of tirzepatide to the once-daily long-acting insulin.

PATIENTS: Adults with T2DM (>18 years old)

INTERVENTION: Once weekly tirzepatide at 5 mg, 10 mg, and 15 mg

CONTROL: Once-daily long-acting and ultra-long-acting insulin

PRIMARY OUTCOME: Blood glucose control, body weight, blood pressure, and lipid panel

METHODS (BRIEF DESCRIPTION):

- Clinical trials that compared tirzepatide with insulin in treating T2DM were gathered from a search of PubMed, Web of Science, Scopus, and Google Scholar.
- Studies using clinical trials or randomized controlled trials that compared the use of tirzepatide with long-acting or ultra-long-acting insulin to treat T2DM and reported outcomes on body weight, hemoglobin A1c (HbA1c), blood pressure, and lipid panels were included in the review.
- The Cochrane risk of bias tool was used to assess the included studies for selection, reporting, performance, attrition, and other biases.
- The outcomes were analyzed using weighted mean difference (WMD), odds ratio (OR), relative risk (RR), and I^2 statistics to assess heterogeneity of trials.

INTERVENTION (# IN THE GROUP): 2,759

COMPARISON (# IN THE GROUP): 1,580

FOLLOW-UP PERIOD: 40–52 weeks

RESULTS:

Primary Outcome –

- Tirzepatide reduced the following compared to long-acting and ultra-long-acting insulin:
  - HbA1c (WMD −1.1%, 95% CI, −1.4 to −0.8; I^2=95%)
  - Body weight (WMD −11 kg, 95% CI, –13 to –8; I^2=98%)
  - Blood pressure:
    - Systolic (WMD –6.5 mmHg; 95% CI, –8.3 to –4.6; I^2=83%)
    - Diastolic (WMD –2.3 mmHg; 95% CI, –3.1 to –1.6; I^2=61%)
- Tirzepatide improved lipid values compared to long-acting and ultra-long-acting insulin:
  - Triglyceride (WMD –14%; 95% CI, –20 to –9.4; I^2=73%)
  - Total cholesterol (WMD –4.8%; 95% CI, –7.1 to –2.5; I^2=64%)
  - LDL cholesterol (WMD –6%; 95% CI, –9.8 to –2.1; I^2=58%)
  - VLDL cholesterol (WMD –14%; 95% CI, –19 to –9.3; I^2=72%)
  - HDL cholesterol (WMD 7.1%; 95% CI, 5.8–8.4; I^2=0%)
- Adverse events leading to treatment discontinuation happened more often with tirzepatide compared to insulin (RR 3.3; 95% CI, 1.5–7.2; I^2=76%).
- Any serious adverse event was less common in patients who received tirzepatide compared to insulin for T2DM (RR 0.8; 95% CI, 0.7–0.9; I^2=33%).

LIMITATIONS:

- There were only three studies in this meta-analysis.
- The heterogeneity of the eligible studies was high.
- The risk for detection and performance bias was high as the included studies were open-label trials, and the participants and investigators were not blinded.
- The study trials were funded by Eli Lily and Company, the manufacturer of tirzepatide that was approved as Mounjaro for the treatment of T2DM.
- The cardiovascular, hepatic, and renal consequences of tirzepatide treatment were not examined in the studies.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the U.S. Government.

Fast and Safe: Correction Rates and Outcomes in Severe Hyponatremia

Correction Rates and Clinical Outcomes in Hospitalized Adults with Severe Hyponatremia: A Systematic Review and Meta-Analysis

Ayus JC, Moritz ML, Fuentes NA, et al. Correction Rates and Clinical Outcomes in Hospitalized Adults With Severe Hyponatremia: A Systematic Review and Meta-Analysis. *JAMA Intern Med*. 2025;185(1):38-51. doi:10.1001/jamainternmed.2024.5981

KEY TAKEAWAY: Rapid correction of severe hyponatremia is associated with significantly fewer in-hospital and 30-day deaths compared to slow or very slow corrections and may reduce hospital length of stay without significant increased risk for osmotic demyelination syndrome (ODS).

STUDY DESIGN: Systematic review and meta-analysis of 14 retrospective cohort studies and two prospective cohort studies (N=11,811)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to inclusion of only cohort studies)

BRIEF BACKGROUND INFORMATION: Severe hyponatremia (Na <125 mEq/L) has a prevalence of 20–30% among hospitalized patients and can result in encephalopathy requiring emergent treatment to prevent permanent neurological damage or even death. Current US guidelines stipulate a stringent rate of correction for severe hyponatremia which does not take mortality and morbidity of the patients into consideration and is based on low quality evidence. This systematic review and meta-analysis aimed to evaluate the association of the correction rate of severe hyponatremia with mortality, ODS and hospital length of stay (LOS) in hospitalized patients.

PATIENTS: Hospitalized patients with hyponatremia

INTERVENTION: Rapid correction rate

CONTROL: Slow or very slow correction rate

PRIMARY OUTCOME: In-hospital and 30-day mortality

Secondary Outcome: Intensive care unit (ICU), hospital LOS and ODS rate

METHODS (BRIEF DESCRIPTION):

- The authors conducted systematic review and meta-analysis of all related articles published from January 2013 to October 2023 using MEDLINE, Embase, the Cochrane Library, LILACs, Web of Science and CINAHL as well as international congress proceedings.
- Studies in the analysis included hospitalized adults with severe hyponatremia (Na <120 mEq/L) or hyponatremia (Na <125 mEq/L) with severe symptoms, including cardiorespiratory distress, seizures, Glasgow Coma Scale ≤8, or decreased level of consciousness.
- Common exclusion criteria in all the studies were pseudohyponatremia associated with hyperglycemia and hypertriglyceridemia, patient undergoing dialysis and hyperosmolar hyponatremia without clear etiology.
- A total of 5,010 records were retrieved of which 16 cohort studies met the inclusion criteria.
- The mean age of participants was >60 years old in 14 out of the 16 studies (the mean age for the other two studies were 48 and 59 years respectively) and most identified as women (57%).
- Among many strategies of rate of sodium correction studied, four categories were defined.
  - Very rapid (>12 mEq/L per 24 hours)
  - Rapid (≥8–10 mEq/L per 24 hours)
  - Slow (<8 or 6–10 mEq/L per 24 hours)
  - Very slow (<4–6 mEq/L per 24 hours)
- The primary comparison was between rapid vs slow and rapid vs very slow correction rates.
- Meta-analysis was performed for each comparison using the Cochrane methods and the random-effects meta-analysis for primary analysis.
- Outcomes were reported unadjusted as well as adjusted for age, sex, race, admission sodium levels, hospital setting (emergency, ICU and ward), alcohol use, cause of hyponatremia and comorbidity index.
- Substantial statistical heterogeneity was considered with I^2>60%.

INTERVENTION (# IN THE GROUP): 11,811

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- Rapid correction of severe hyponatremia was associated with a lower adjusted in-hospital mortality rate compared to slow correction (5

studies, n=6,017; odds ratio [OR] 0.67; 95% CI, 0.55–0.82; I^2=44%).

- Rapid correction of severe hyponatremia was associated with a lower adjusted in-hospital mortality rate compared to very slow correction (2 studies, n=372; OR 0.29; 95% CI, 0.11–0.79; I^2=59%).
- Similar outcomes were observed for unadjusted in-hospital mortality when comparing:
  - Rapid vs slow sodium correction (1 study, n=7,255; relative risk [RR] 0.72; 95% CI, 0.62–0.85; I^2=0%)
  - Rapid vs very slow sodium correction (11 studies, n=5,158; RR 0.50; 95% CI, 0.42–0.59; I^2=7%)

Secondary Outcome –

- No statistically significant difference was found for risk of ODS with a rapid correction rate for severe hyponatremia compared to slow and very slow correction rates.
- A faster correction was consistently associated with shorter hospital LOS, suggesting a potential dose-response effect:
  - Rapid vs slow (10 studies, n= 6,978; mean difference [MD] −1.2 days; 95% CI, −1.9 to −0.51; I^2=48%)
  - Rapid vs very slow (10 studies, n=5,110; MD −3.1 days; 95% CI, −5.0 to −1.2; I^2=85%)
- There was no statistically significant difference between groups in ICU LOS.

LIMITATIONS:

- There was heterogeneity in inclusion and exclusion criteria, comparison of correction rates and co-intervention, a reasonable range was agreed upon for comparing the correction rates rather than a discrete cut off value.
- The mean age of patients in majority of studies was >60 years and thus the results may not be generalizable to younger populations.
- Risk of bias overall was serious in 11 studies and moderate in the remaining studies.
- There were insufficient data to conduct analysis for ODS resulting from possible underreporting of ODS cases.
- Unadjusted potential confounding factors such as chronic illness (liver disease, heart failure or cancer) may have resulted in increased in mortality with slow correction rate in some patients.
- Duration of hyponatremia was not classified (e.g. as acute or chronic), which could have affected the results.

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One-Time Offer: Can a Single PSA Screening Invitation Reduce Prostate Cancer Mortality?

Prostate-Specific Antigen Screening and 15-Year Prostate Cancer Mortality: A Secondary Analysis of the CAP Randomized Clinical Trial

Martin RM, Turner EL, Young GJ, et al. Prostate-Specific Antigen Screening and 15-Year Prostate Cancer Mortality: A Secondary Analysis of the CAP Randomized Clinical Trial. *JAMA*. 2024;331(17):1460–1470. doi:10.1001/jama.2024.4011

KEY TAKEAWAY: A single invitation for prostate-specific antigen (PSA) screening slightly reduces prostate cancer mortality without affecting all-cause mortality compared to no screening invitation. It increases the detection of low grade and localized prostate cancer and decreases the detection of high grade and advanced stage prostate cancer.

STUDY DESIGN: Secondary analysis of the CAP cluster, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small absolute effect size)

BRIEF BACKGROUND INFORMATION: An increasing number of men are diagnosed with prostate cancer in England with population aging and increased PSA testing. However, it is unclear if there is a mortality benefit to PSA screening. The Cluster Randomized Trial of PSA Testing for Prostate Cancer showed that an invitation for PSA screening increased the number of prostate cancers diagnosed in the first 18 months of follow up but did not reduce prostate cancer mortality at 10 years follow up. This study aimed to evaluate mortality after 15 years.

PATIENTS: Men 50–69 years old without prostate cancer

INTERVENTION: Single PSA screening invitation

CONTROL: Short phrase

PRIMARY OUTCOME: No screening invitation

Secondary Outcome: Prostate cancer mortality, all-cause mortality, prostate cancer stage, grade at diagnosis

METHODS (BRIEF DESCRIPTION):

- This was a non-blinded, randomized control trial across 573 practices in England and Wales.
- Clinics were blocked and stratified in groups of neighboring practices and randomized to intervention or control groups prior to recruitment.
- Men 50–69 years old in participating clinics were included.
    - 98% of patients in the intervention group were White and were a mean age of 59 years old.
- Men with prostate cancer were excluded from the analysis.
- The intervention was a single invitation for PSA testing.
    - Invitation entails an initial written invitation, followed by a 30-minute prostate check clinic appointment, where the participant received counselling and detailed information about the implications of PSA testing and subsequent treatment. If they consented, a PSA blood test was then collected after a further 'cooling-off' consent of at least 24 hours.
- If the patient underwent testing and had PSA level ≥3.0, they were offered further treatment.
- Men with PSA ≥ 3.0ng/ml were referred for further workup including repeat PSA, clinical examination, digital rectal examination (DRE) and trans-rectal ultrasound (TRUS)-guided biopsy.
    - Men found to have advanced disease were treated routinely but followed up within the comprehensive cohort.
- Men with a PSA level of ≥20 ng/mL were referred to a urologist and received standard care.
- Standard NHS management and no formal invitation for PSA testing for prostate cancer acted as the control.
- Primary outcome measured prostate cancer mortality after 15 years.
    - Other measured outcomes include total death rate, risk of diagnosis of high and low-grade prostate cancer, and risk of diagnosis of localized and advanced stage prostate cancer.
    - Outcomes were ascertained from death certificates and national registries.
    - Stage and grade were obtained from the National Disease Registration Service.

INTERVENTION (# IN THE GROUP): 189,326

COMPARISON (# IN THE GROUP): 219,395

FOLLOW-UP PERIOD: 15 years

RESULTS:

Primary Outcome –

- Patients invited to screen for prostate cancer with PSA testing had a decreased risk of prostate cancer mortality compared to no screening invitation (relative risk [RR] 0.92; 95% CI, 0.85−0.99).
- Patients invited to screen for prostate cancer with PSA testing had a lower cumulative risk of prostate cancer mortality compared to no screening invitation (risk difference [RD] −0.09%; 95% CI, −0.15 to −0.03).
- There was no significant difference in death rate for patients invited to screen for prostate cancer screening with PSA testing compared to no screening invitation (23% vs 23%; RR 0.97; 95% CI, 0.94–1.01).
- Patients invited to screen for prostate cancer with PSA testing had higher risk of diagnosis of low-grade prostate cancer compared to no screening invitation (RD 0.58%; 95% CI, 0.50–0.67).
- Patients invited to screen for prostate cancer with PSA testing had lower risk of diagnosis of high-grade prostate cancer compared to no screening invitation (RD −0.15%; 95% CI, −0.22 to −0.08).
- Patients invited to screen for prostate cancer with PSA testing had higher risk of localized prostate cancer compared to no screening invitation (RD 0.56%; 95% CI, 0.44–0.67).
- Patients invited to screen for prostate cancer with PSA testing had lower risk of advanced-stage tumors compared to no screening invitation (RD −0.16%; 95% CI, −0.22 to −0.10).

LIMITATIONS:

- The study included few Black men, who are at higher risk of both developing and dying from prostate cancer compared to the rest of the population, therefore limiting the generalizability of the study results.
- A single invitation for screening might not be enough of an intervention to provide an impact.
- The trial ran from 2002−2009; new methods of diagnosis and treatment for prostate cancer have been developed since then.

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Turning Up the Metabolism Dial for Heart Health!

Novel Controlled Metabolic Accelerator for Obesity-Related HFpEF: The HuMAIN-HFpEF Randomized Clinical Trial

Pandey A, Lewis GD, Borlaug BA, et al. Novel Controlled Metabolic Accelerator for Obesity-Related HFpEF: The HuMAIN-HFpEF Randomized Clinical Trial. *JAMA Cardiol*. 2025;10(6):609-616. doi:10.1001/jamacardio.2025.0103

KEY TAKEAWAY: HU6 treatment in patients with obesity-related heart failure with preserved ejection fraction (HFpEF) resulted in modest weight loss driven by reductions in fat mass while preserving lean muscle.

STUDY DESIGN: Randomized, double-blind, placebo-controlled, dose-escalation phase 2A trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: HFpEF is prevalent among individuals with obesity and is associated with increased morbidity. HU6, a novel metabolic accelerator, enhances mitochondrial uncoupling and fat-specific weight loss, which could provide a new treatment strategy for obesity-related HFpEF. This study aimed to evaluate the safety and efficacy of HU6 in reducing body weight and improving body composition in patients with obesity-related HFpEF.

PATIENTS: Adult patients with obesity-related HFpEF

INTERVENTION: HU6

CONTROL: Placebo

PRIMARY OUTCOME: Change in body weight

Secondary Outcome: Change in peak volume of oxygen consumption (VO_2)

METHODS (BRIEF DESCRIPTION):

- Adults >30 years old with chronic, stable HFpEF, obesity defined as BMI ≥30 with no recent cardiac events and were able to complete cardiopulmonary exercise testing were included in the study.
- Patients with unstable medical conditions or inability to tolerate the study protocol were excluded from the study.
- Patients in the intervention group started on HU6 150 mg daily and titrated up to 450 mg based on tolerability.
- The medication was administered for 19 weeks.
- A matching oral placebo was administered daily for 19 weeks under the same protocol.
- The primary outcome was the change in body weight from baseline to day 134 (approximately 19 weeks).
- Body composition was assessed using the InBody BWA bioimpedance scale, including measurements of total body weight, percentage change in total body fat, percentage change in visceral fat, and the percentage change in dry lean mass.
- The secondary outcome measured the change in peak VO_2, measured through standardized cardiopulmonary exercise testing (CPET) at baseline and at the end of treatment.

INTERVENTION (# IN THE GROUP): 33

COMPARISON (# IN THE GROUP): 33

FOLLOW-UP PERIOD: 19 weeks

RESULTS:

Primary Outcome –

- HU6 significantly reduced body weight compared to placebo (mean difference [MD] −2.9 kg; 95% CI, −4.7 to −1.04).
- HU6 significantly reduced total fat mass compared to placebo (MD −3.0 kg; 95% CI, −4.5 to −1.4).
- HU6 significantly reduced visceral fat compared to placebo (MD −1.3%; 95% CI, −2.1 to −0.5).
- HU6 did not significantly affect lean mass compared to placebo (MD 0.05 kg; 95% CI, −0.85 to 0.96).

Secondary Outcome –

- HU6 did not significantly affect peak VO_2 compared to placebo.

LIMITATIONS:

- The study had a small sample size, which may limit the generalizability of the findings.
- The treatment duration was short, which may not have been sufficient to detect long-term effects.
- There were baseline imbalances between groups, particularly a higher prevalence of diabetes in the HU6 group.
- No significant improvements were observed in exercise capacity or quality of life measures.

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Cracks in the Foundation: Adults with T2DM May Have a Greater Risk of Osteoporosis and Fractures

Association of type 2 diabetes with osteoporosis and fracture risk: A systematic review and meta-analysis.
Cao Y, Dong B, Li Y, Liu Y, Shen L. Association of type 2 diabetes with osteoporosis and fracture risk: A systematic review and meta-analysis. *Medicine (Baltimore).* 2025 Feb 7;104(6):e41444. doi: 10.1097/MD.0000000000041444. PMID: 39928813; PMCID: PMC11813021.

KEY TAKEAWAY: Individuals with type 2 diabetes mellitus (T2DM) may have an increased risk of osteoporosis and fractures when compared to those without T2DM.

STUDY DESIGN: Systematic review and meta-analysis of 18 cohort, 6 case-control, and 2 cross-sectional studies (N = 14,976,637)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to heterogeneity of study outcomes)

BRIEF BACKGROUND INFORMATION: For aging individuals, T2DM and fractures present a great threat to morbidity and mortality. Individuals who are screened or counseled on their risk for fractures can take proper mitigating steps to decrease this risk. T2DM increases bone mineral density (BMD) while paradoxically increasing the risk of fractures in men and women. Previous research has shown conflicting results between the association of T2DM and osteoporosis and fractures.

PATIENTS: Adults

INTERVENTION: Adults with T2DM requiring diabetes medication

CONTROL: Adults without T2DM

PRIMARY OUTCOME: Prevalence of osteoporosis or fractures

METHODS (BRIEF DESCRIPTION):

- Studies were extracted from four databases that included Embase, PubMed, Web of Science, and Cochrane Library from inception through March 2023.
- The quality of the cohort and case-control studies was examined using the Newcastle-Ottawa Scale and the quality of the cross-sectional studies was evaluated using an 11-item checklist from the Agency for Healthcare Research and Quality.
- I^2 statistics were used to quantify heterogeneity across studies.
- T2DM was defined as fasting blood glucose ≥ 7.0 mmol/L, 2-hour plasma glucose ≥ 11.1 mmol/L or anyone not T1DM but on diabetes medication.
- Individuals with T2DM, regardless of intervention or blood glucose status, were included.
- Studies that displayed inconsistencies or unclear data were excluded from the meta-analysis.

INTERVENTION (# IN THE GROUP): 14, 976,637

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- The T2DM group had a significantly higher prevalence of:
  - osteoporosis (odds ratio [OR]: 1.8; 95% confidence interval [CI], 1.2-2.8; five studies, n = 105,132, I^2 = 95%, P < .001)
  - fractures (OR: 1.2; 95% CI, 1.1-1.3; 21 studies, n = 14,871,505, I^2 = 99%, P < .001)

Secondary Outcome -

- The T2DM group had a significantly higher prevalence of osteoporosis in:
  - data analysis method
    - univariate (three studies, n = 11,969)
    - multivariate (two studies, n = 93,163)
  - study type
    - cross-sectional studies (one study, n = 530)
    - cohort studies (two studies, n = 13,640)
    - case-control studies (two studies, n = 90,962)
  - geographic region
    - Asia (four studies, n = 15,300)
    - North America (one study, n = 89,832)
- The T2DM group had a significantly higher prevalence of fractures in:
  - data analysis method
    - multivariate analysis (16 studies, n = 14,489,058)
  - study type
    - cohort studies (16 studies, n = 7,665,218)
    - case-control studies (four studies, n = 7,154,957)
  - geographic region
    - North America (seven studies, n = 852,881)

- A significant correlation was found between T2DM and:
    - hip fractures (13 studies, n = 14,138,289)
    - female sex (11 studies, n = 6,920,539)

LIMITATIONS:

- The systematic review did not disclose the breakdown of numbers between the intervention and control groups.
- The overall heterogeneity was high at I^2>95% for the association between T2DM and osteoporosis and T2DM and fractures.
- The observational design of the studies reviewed precluded conclusions about causality.
- Multivariable factors such as environments, access to healthcare, comorbidities, and medications might have played a role in fracture prevalence.
- The timeline between onset of T2DM and fractures or development of osteoporosis was not clearly defined.
- The inclusion criteria of "diabetes medication" was not defined as some medications can be used off-label for non-diabetes conditions.

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