GOOD EVIDENCE MATTERS

GEMs of the Week

Sleep Apnea

Breathing Room:
Tirzepatide for OSA and Obesity

Osteoarthritis

PRP, or Not to Be:
Questioning the Efficacy of PRP Injections

SPOTLIGHT: Gestational Diabetes

Delivering the Difference:
Metformin vs Insulin in Newborn Outcomes

Type 2 Diabetes

Taking the 'Manual' Out of Insulin:
Automated Delivery in T2DM

FPIN
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Delivering the Difference: Metformin vs Insulin in Newborn Outcomes

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Short-Term Neonatal Outcomes in Women with Gestational Diabetes Treated Using Metformin vs Insulin: A Systemic Review and Meta-Analysis of Randomized Controlled Trials

Sheng B, Ni J, Lv B, Jiang G, Lin X, Li H. Short-term neonatal outcomes in women with gestational diabetes treated using metformin versus insulin: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol*. 2023;60(5):595-608. doi:10.1007/s00592-022-02016-5

KEY TAKEAWAY: In pregnant patients with gestational diabetes mellitus (GDM), metformin reduces neonatal birth weight, risk of macrosomia, neonatal intensive care unit (NICU) admissions, and neonatal hypoglycemia compared to insulin, without increasing the risk of other short-term neonatal complications.

STUDY DESIGN: Systematic review and meta-analysis of 24 randomized controlled trials (RCTs) (N=4,355)

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

BRIEF BACKGROUND INFORMATION: While insulin is the standard of care in treating GDM, its cost and method of delivery have led to a desire for alternative therapies. With the increasing use of metformin in clinical practice and exposure to the medication during pregnancy, this study aimed to investigate if metformin is an effective and safe alternative to insulin in the treatment of GDM for short-term neonatal outcomes.

PATIENTS: Pregnant women with GDM

INTERVENTION: Metformin

CONTROL: Insulin

PRIMARY OUTCOME: Neonatal growth and neonatal adverse events

METHODS (BRIEF DESCRIPTION):

- A systematic search was conducted of RCTs involving pregnant women with GDM treated with either metformin or insulin that evaluated at least one neonatal outcome were included in the review.
- The search included PubMed, Embase, the Cochrane Library, and Web of Science databases, where 24 studies were eligible for inclusion.
- The studies included 4,355 patients with GDM and were conducted in Iran, Egypt, Pakistan, Finland, Australia, India, Spain, Brazil, New Zealand, and the USA.
    - Studies that included pregnant women with pre-existing diabetes were excluded.
    - Duplicate studies that were published in multiple journals were only included in the study once.
- Various dosages of metformin were included in the review, which consisted of 1,500 mg/day, 2,500 mg/day, and 3,000 mg/day.
- Various dosages of insulin were included, which ranged from 0.2–1.0 kg/day.
- The primary outcome measured neonatal growth and neonatal adverse events.
    - Neonatal growth was evaluated by birth weight, macrosomia (>4,000 g), large for gestational age (LGA) (>90th percentile), small for gestational age (SGA) (<10th percentile), and birth height.
    - Neonatal adverse events evaluated by NICU admission, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, premature birth, congenital anomalies, abnormal Apgar score at five minutes, neonatal death, neonatal sepsis, and birth trauma.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: At birth

RESULTS:

Primary Outcome –

- Metformin resulted in decreased neonatal weight at birth compared to insulin (22 studies, n=4,174; mean difference [MD] –123 g; 95% CI, –178 to –67; I^2=84%).
    - Grading of Recommendations, Assessment, Development and Evaluation (GRADE): Low
- Metformin reduced the risk of macrosomia compared to insulin (20 studies, n=3,484; risk ratio [RR] 0.75; 95% CI, 0.54–0.86; I^2=17%).
    - GRADE: Moderate
- Metformin did not result in a significant risk difference of LGA compared to insulin (12 studies, n=2,843; RR 0.86; 95% CI, 0.73–1.0; I^2=0%).
    - GRADE: Moderate

- Metformin did not result in a significant risk difference of SGA compared to insulin (12 studies, n=2,812; RR 1.0; 95% CI, 0.77–1.0; I^2=0%).
  - GRADE: Low
- Metformin did not result in a significant difference in neonatal birth height compared to insulin (3 studies, n=1,084; MD –0.24; 95% CI, –0.67 to 0.19; I^2=38%).
  - GRADE: Very low
- Metformin decreased the risk of NICU admissions compared to insulin (18 studies, n=3,527; RR 0.73; 95% CI, 0.61–0.88; I^2=23%).
  - GRADE: Moderate
- Metformin decreased the risk of hypoglycemia compared to insulin (20 studies; n=3,760; RR 0.65; 95% CI, 0.52–0.81; I^2=22%).
  - GRADE: Low
- Metformin minimally decreased the risk of respiratory distress compared to insulin (14 studies, n=2,708; RR 0.71; 95% CI, 0.51–0.99; I^2=0%).
- Metformin resulted in no difference for an abnormal five-minute Apgar score, hyperbilirubinemia, congenital anomalies, preterm birth, abnormal pH of the umbilical cord, neonatal death, neonatal sepsis, or birth trauma compared to insulin.
  - Abnormal five-minute Apgar score (15 studies, n=1,873; risk difference [RD] 0.0; 95% CI, –0.15 to 0.16; I^2=59%)
  - Hyperbilirubinemia (13 studies, n=1,820; RR 0.88; 95% CI, 0.69–1.1; I^2=0%)
  - Congenital anomalies (9 studies, n=2,027; RR 0.73; 95% CI, 0.44–1.2; I^2=0%)
  - Preterm birth (11 studies, 2,424; RR 1.1; 95% CI, 0.78–1.5; I^2=22%)
  - Neonatal death (10 studies, n=2,157; RR 0.52; 95% CI, 0.13–2.2; I^2=0%)
  - Neonatal sepsis (4 studies, n=1,329; RR 0.71; 95% CI, 0.34–1.5; I^2=0%)
  - Birth trauma (6 studies, n=1,694; RR 0.92; 95% CI, 0.57–1.5; I^2=0%)

LIMITATIONS:

- Some studies included women who received both metformin and insulin, introducing potential confounding factors that may have affected the outcomes.
- Measurements of neonatal growth and adverse outcomes varied widely across studies, and in some cases, data were unavailable or incompletely reported, limiting the ability to conduct a comprehensive analysis.
- Several included studies demonstrated high statistical heterogeneity, which may impact the reliability of the pooled estimates.

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Breathing Room: Tirzepatide for OSA and Obesity

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity [published correction appears in N Engl J Med. 2024 Oct 17;391(15):1464. doi: 10.1056/NEJMx240005.]. *N Engl J Med*. 2024;391(13):1193-1205. doi:10.1056/NEJMoa2404881

KEY TAKEAWAY: Tirzepatide reduces the apnea-hypopnea index (AHI) compared to placebo in patients with moderate to severe obstructive sleep apnea (OSA) and obesity.

STUDY DESIGN: Two double-blinded randomized control trials (RCTs)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to disease-oriented outcomes)

BRIEF BACKGROUND INFORMATION: OSA is associated with major cardiovascular complications. Obesity is one of the largest reversible risk factors for OSA. Trials of standard treatment of sleep apnea and continuous positive airway pressure (CPAP) have failed to improve cardiac outcomes. This study examined tirzepatide, a glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), to reduce weight and improve sleep apnea.

PATIENTS: Adults with OSA

INTERVENTION: Tirzepatide

CONTROL: Placebo

PRIMARY OUTCOME: Change in AHI

Secondary Outcome: Participants with reduced AHI episodes, body weight

METHODS (BRIEF DESCRIPTION):

- The authors conducted two multi-center, multi-country double-blind RCTs, which included adults with moderate to severe OSA and obesity not using CPAP (Trial 1) and adults with moderate to severe OSA and obesity using CPAP (Trial 2).
- Participants were adults who received the diagnosis of moderate to severe OSA (AHI ≥15 events per hour) and had obesity.
- Patients with type 1 or type 2 diabetes, a change in body weight of >5 kg in the three months prior to screening, and central/mixed sleep apnea were excluded from the study.
- Participants in Trial 1 had a mean of 48 years old, most were male (67%), identified as White (66%), had an average BMI of 39, and a mean AHI of 52 events per hour.
- Participants in Trial 2 had a mean of 52 years old, most were male (72%), identified as White (73%), had an average BMI of 39, and a mean AHI of 50 events per hour.
- Patients were randomly divided to receive tirzepatide or a placebo subcutaneously each week.
    - CPAP therapy was continued in those already using the device (Trial 2).
- All patients received regular lifestyle counseling while adhering to a 500-kcal deficit per day and achieving 150 minutes of physical activity per week.
- The primary outcome measured the change in AHI events per hour from baseline at 52 weeks and included all participants who injected at least one dose of the treatment or placebo.
- Secondary outcomes included the percentage of participants who had a reduction in AHI ≥50% and the percentage change in body weight.

INTERVENTION (# IN THE GROUP):

- Trial 1: 114
- Trial 2: 120

COMPARISON (# IN THE GROUP):

- Trial 1: 120
- Trial 2: 115

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- Tirzepatide decreased AHI events compared to placebo in both trials.
    - Trial 1 (estimated treatment difference –20 events; 95% CI, –26 to –14)
    - Trial 2 (estimated treatment difference –24 events; 95% CI, –30 to –18)

Secondary Outcome –

- More participants in the tirzepatide group had a reduced AHI of ≥50% compared to placebo in both trials.
    - Trial 1 (relative risk [RR] 3.3; 95% CI, 2.1–5.1)

    - Trial 2 (RR 3.1; 95% CI, 2.1–4.5)
- Tirzepatide decreased body weight compared to placebo in both trials.
    - Trial 1 (estimated treatment difference –16%; 95% CI, –18 to –14)
    - Trial 2 (estimated treatment difference –17%; 95% CI, –19 to –15)

LIMITATIONS:

- The study's findings may not be generalizable for long-term use of tirzepatide.
- The trial excluded patients with a normal or overweight body mass index (BMI), some of whom have OSA.
- The trial protocol did not establish if patients were adherent to CPAP treatment.
- The trial did not determine if patients at baseline had OSA symptoms and how these were affected.
- The trial did not have a threshold for minimal clinically meaningful change.

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PRP, or Not to Be: Questioning the Efficacy of PRP Injections

Does the Combination of Platelet-Rich Plasma and Supervised Exercise Yield Better Pain Relief and Enhanced Function in Knee Osteoarthritis? A Randomized Controlled Trial

Karaborklu Argut S, Celik D, Ergin ON, Kilicoglu OI. Does the Combination of Platelet-rich Plasma and Supervised Exercise Yield Better Pain Relief and Enhanced Function in Knee Osteoarthritis? A Randomized Controlled Trial. *Clin Orthop Relat Res*. 2024;482(6):1051-1061. doi:10.1097/CORR.0000000000002993

KEY TAKEAWAY: Platelet-rich plasma (PRP) injections alone or in combination with a structured exercise program offers no additional benefit to knee pain in patients with mild-to-moderate knee osteoarthritis (OA) compared to exercise alone.

STUDY DESIGN: Randomized, controlled, three-arm clinical trial

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

BRIEF BACKGROUND INFORMATION: Knee OA is a common source of pain and poor quality of life (QoL) leading to numerous primary care visits. Various treatments exist for addressing pain associated with knee OA. This study aimed to assess which of the treatment options: PRP injections alone, exercise alone, or PRP injections + exercise therapy, yielded the greatest benefit to pain reduction and QoL.

PATIENTS: Adults with mild-to-moderate knee OA

INTERVENTION: PRP injection alone and PRP injection + exercise therapy

CONTROL: Exercise therapy

PRIMARY OUTCOME: Knee pain

Secondary Outcome: Knee function, health-related QoL

METHODS (BRIEF DESCRIPTION):

- Adults 40–70 years old were recruited based on radiographic evidence of mild-to-moderate knee OA and a pain score of ≥3 on a 0–10 pain scale.
- Participants were randomly assigned 1:1:1 into groups receiving PRP injection alone, exercise therapy alone, or PRP injection + exercise.
  - The PRP groups received three total intra-articular knee injections administered in weekly intervals.
  - Injections were prepared using a commercially available kit (T Lab, T-Biotechnology Laboratory).
  - The platelet concentration was 3.4 times higher than whole blood.
  - 6 mL injections were administered by an experienced orthopedic surgeon using an ultrasound-guided, medial patellofemoral approach.
- The exercise groups received twice weekly therapeutic exercise sessions for six weeks with gradual progression of resistance or weight.
- The primary outcome was knee pain measured on a 0–10 rating scale at 24 weeks, with higher scores indicating more subjective pain.
  - The minimum clinically important difference (MCID)=2 points.
- The secondary outcomes were knee function and health-related QoL.
  - Functional difficulty was measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and two performance tests:
    - Scores on the WOMAC range from 0–100, with higher scores indicating worse function; MCID=12 points.
    - Performance tests included a 40-meter fast-paced walk test and the stair climbing test.
  - Health-related QoL was measured using the Short Form-12 health-related QoL score (SF-12). Scores range from 0–100 with higher scores indicating better health; MCID=5 points.

INTERVENTION (# IN THE GROUP):

- PRP injection alone: 28
- PRP injection + exercise therapy: 28

COMPARISON (# IN THE GROUP): 28

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- PRP alone did not clinically improve knee pain compared to exercise alone (mean difference [MD] 1.9; 95% CI, 1.2–2.7).

- PRP injection + exercise therapy did not improve knee pain compared to exercise alone (MD –0.5; 95% CI, –1.2 to 0.4).

Secondary Outcome –

- PRP alone increased functional difficulty compared to exercise alone (MD 16; 95% CI, 5–22).
- PRP alone increased performance compared to exercise alone:
  - 40-meter walk test (MD 0.1; 95% CI, 0.2–1.2)
  - Stair climbing test (MD 6; 95% CI, 2–10)
- PRP alone did not affect mental or physical health related QoL compared to exercise alone.
- PRP + exercise improved physical health related QoL compared to exercise alone (MD 4; 95% CI, 2–13).
- PRP + exercise did not affect functional difficulty, 40-meter walk test, stair climbing test, or mental health related QoL compared to exercise alone.

LIMITATIONS:

- The study had a small sample size which limits generalizability and statistical power.
- This study did not include individuals with severe knee OA.
- Formulations of PRP injections available are varied and may not reflect what patients received in this study.
- The 24-week follow-up period may not be sufficient to fully assess the effect of the treatment groups on knee pain and QoL.

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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.

Taking the 'Manual' Out of Insulin: Automated Delivery in T2DM

A Randomized Trial of Automated Insulin Delivery in Type 2 Diabetes

Kudva YC, Raghinaru D, Lum JW, et al. A Randomized Trial of Automated Insulin Delivery in Type 2 Diabetes. *N Engl J Med*. 2025;392(18):1801-1812. doi:10.1056/NEJMoa2415948

KEY TAKEAWAY: In adults with insulin treated type 2 diabetes mellitus (T2DM), automated insulin delivery (AID) reduces glycated hemoglobin levels compared to standard insulin delivery over 13 weeks.

STUDY DESIGN: Multicenter, nonblinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding and small sample size)

BRIEF BACKGROUND INFORMATION: Insulin treatment via AID devices is well-established in the treatment of type 1 diabetes mellitus (T1DM), but there is little evidence regarding AID in T2DM requiring insulin therapy. This study aimed to evaluate whether AID could improve glycemic control in T2DM and explores the potential benefits of precise, adaptive insulin management for overall better outcomes in diabetes care.

PATIENTS: Adults with insulin treated T2DM

INTERVENTION: AID

CONTROL: Pretrial insulin delivery

PRIMARY OUTCOME: Glycated hemoglobin levels

Secondary Outcome: Hyperglycemic and hypoglycemic events

METHODS (BRIEF DESCRIPTION):

- Patients were recruited from one US Veterans affair hospital and 21 clinics in the US and Canada.
- Patients ≥18 years old with a T2DM diagnosis for at least six months, on a stable diabetes medication regimen for at least three months, and required multiple daily injections of insulin, one of which was rapid acting insulin (concurrent use of non-insulin medications were permitted, provided the patient was stable on that dose for the previous three months) were included in the study.
- Patients were randomized 2:1 to AID or pre-trial standard insulin delivery method
    - Patients receiving AID were given a t:slim X2 insulin pump with insulin aspart for 13 weeks with CGM via Dexcom G6 sensor
    - Patients receiving pre-trial insulin delivery were instructed to continue their pre-trial regimen with continuous glucose monitoring (CGM) via Dexcom G6 sensor
- The primary outcome measured glycated hemoglobin levels after 13 weeks.
- The following were measured as the secondary outcomes:
    - CGM time spent in the target glucose range (70–180 mg/dL)
    - CGM value of >180 mg/dL and 259 mg/dL
    - CGM value >300 mg/dL for 90 minutes (prolonged hyperglycemia)
    - CGM value of <70 mg/dL and 54 mg/dL
    - CGM value <54 mg/dL for 15 minutes (prolonged hypoglycemia)

INTERVENTION (# IN THE GROUP): 215

COMPARISON (# IN THE GROUP): 104

FOLLOW-UP PERIOD: 13 weeks

RESULTS:

Primary Outcome –

- AID significantly decreased glycated hemoglobin levels compared to standard insulin delivery (mean adjusted difference –0.6; 95% CI, –0.8 to –0.4).
- For patients with a higher baseline glycated hemoglobin level (≥9.0%), AID significantly reduced glycated hemoglobin levels compared to standard insulin delivery (mean adjusted difference –1.0; 95% CI, –1.5 to –0.5).

Secondary Outcome –

- AID increased the time patients spent in the target glucose range compared to standard insulin delivery (adjusted between group difference 14%; 95% CI, 11–17).
- AID decreased the amount of time patients had a CGM value >180 mg/dL compared to standard insulin delivery (adjusted between group difference –14%; 95% CI, –17 to –11).
- AID decreased the amount of time patients spent with a CGM value >250 mg/dL compared to

standard insulin delivery (adjusted between group difference –9.1%; 95% CI, –12 to –6.6).

- AID decreased the number of prolonged hyperglycemia events compared to standard insulin delivery (adjusted between group difference –0.7; 95% CI, –1.0 to –0.4).
- There was no difference in the number of prolonged hypoglycemic events, the amount of time patients had a CGM value <70 mg/dL or <54 mg/dL for AID compared to standard insulin delivery.

LIMITATIONS:

- Due to the nature of the treatment method, patients and researchers were unable to be blinded to the results of the study.
- The study being performed in the United States and Canada made the study largely representative of the causation population limited its generalizability.
- The trial's 13-week duration may not capture long-term effects and potential challenges associated with automated insulin delivery over extended periods of time.
- There is an overall lack of data regarding the amount of training required for participants to safely use the AID system, which could be a barrier in routine practice.
- The AID group experienced modest weight gain, and the study did not address this outcome, which could be a consideration for patients and clinicians.

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