GOOD EVIDENCE MATTERS

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Volume 6 Issue 25

Let It Go! Frozen Shoulder, an Idiopathic Musculoskeletal Disorder

Casual Associations of Hypothyroidism with Frozen Shoulder: A Two-Sample Bidirectional Mendelian Randomization Study

Chen B, Zhu ZH, Li Q, Zuo ZC, Zhou KL. Causal Associations of Hypothyroidism with Frozen Shoulder: A Two-sample Bidirectional Mendelian Randomization Study. *BMC Musculoskelet Disord*. 2024;25(1):693. Published 2024 Sep 2. doi:10.1186/s12891-024-07826-y

KEY TAKEAWAY: Genetic evidence shows hypothyroidism is a modest, independent risk factor for frozen shoulder, reinforcing that it is a multifactorial condition.

STUDY DESIGN: Bidirectional Mendelian randomization (MR) study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Frozen shoulder (adhesive capsulitis) has traditionally been considered an idiopathic musculoskeletal disorder. Although the pathophysiology of frozen shoulder remains not fully understood, increased prevalence has been reported in association with diseases such as thyroid disorders, diabetes, and dyslipidemia. Prior studies linking hypothyroidism and frozen shoulder were largely observational, inconsistent, and susceptible to confounding thus limiting causal interpretation. This study aimed to use genetic variants as instrumental variables to infer causality.

PATIENTS: Adults with frozen shoulder

INTERVENTION: Genetically predicted hypothyroidism

CONTROL: No genetically predicted hypothyroidism

PRIMARY OUTCOME: Risk of developing frozen shoulder

Secondary Outcome: Reverse causation, risk of developing hypothyroidism in adults with frozen shoulder

METHODS (BRIEF DESCRIPTION):

- Bidirectional Mendelian randomization (MR) study using data from Genome-Wide Association Studies (GWAS) datasets based on European samples
- Summary-level GWAS data for hypothyroidism and frozen shoulder were analyzed.
- A total of 39 single nucleotide polymorphisms (SNPs) meeting genome-wide significance criteria were selected as instrumental variables.
- The inverse-variance weighted (IVW) method was used as the primary analysis.
- Sensitivity analyses, including MR-Egger to assess robustness and pleiotropy, were conducted.
- Bidirectional MR was performed to evaluate reverse causation.

INTERVENTION (# IN THE GROUP): 22,997

COMPARISON (# IN THE GROUP): 175,475

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Genetically predicted hypothyroidism was associated with a significant increase in frozen shoulder risk in the primary IVW analysis (odds ratio [OR] 1.1; 95% CI, 1.0–1.1).

Secondary Outcome –

- Sensitivity analyses using MR-Egger were consistent in direction and significance results (OR 1.2; 95% CI, 1.0–1.3).
- No evidence of reverse causation was observed, with genetically predicted frozen shoulder not associated with hypothyroidism in the primary IVW analysis (OR 0.94; 95% CI, 0.71–1.3).

LIMITATIONS:

- Findings are limited to individuals of European ancestry, thus limiting generalizability of findings to other populations.
- The causal effect is modest, indicating that frozen shoulder is multifactorial.
- The study does not identify specific biological pathways linking hypothyroidism to capsular fibrosis or frozen shoulder.
- There may be unobserved pleiotropy beyond vertical pleiotropy.

Tommy Brown, MD, MBChB, BSc
Kadlec Regional Medical Center Program
Richland, WA

Desmopressin: Tips and Drips for Nighttime Dryness

Desmopressin for Nocturnal Enuresis in Children
Hahn D, Stewart F, Raman G. Desmopressin for Nocturnal Enuresis in Children. *Cochrane Database Syst Rev*. 2025;7(7):CD002112. Published 2025 Jul 29. doi:10.1002/14651858.CD002112.pub2

KEY TAKEAWAY: Desmopressin may temporarily improve dry nights per week during treatment, but it is not superior to alarm training in the long-term after treatment cessation.

STUDY DESIGN: Systematic review of 95 randomized and quasi-randomized studies (N=8,473)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to overall poor quality of included studies, missing data, substantial heterogeneity and high risk of bias)

BRIEF BACKGROUND INFORMATION: Nocturnal enuresis (NE) is a distressing, stigmatizing condition affecting up to 20% children and can occasionally persist into adulthood. Desmopressin has historically been one of the most popular treatment options. This review aimed to evaluate the effectiveness of desmopressin in comparison to common therapies for NE.

PATIENTS: Children 5–16 years old

INTERVENTION: Desmopressin monotherapy, desmopressin combination therapy

CONTROL: Placebo, other intervention, desmopressin monotherapy (compared to combination therapy)

PRIMARY OUTCOME: Mean number of wet nights per week and number of children with 14 consecutive dry nights at the end of treatment

Secondary Outcome: Mean number of wet nights and mean number of children remaining dry for 14 consecutive nights at follow-up (after stopping treatment), relapse after treatment, adverse events

METHODS (BRIEF DESCRIPTION):

- Relevant trials were identified from the Cochrane Incontinence Specialized Register using the Cochrane Incontinence Review Group strategy with searches performed until January 2023. International Children's Continence Society nomenclature and definitions were applied for standardization.
- Included studies addressed children with NE and used a randomized, quasi-randomized, cluster-randomized or cross-over design.
- Excluded studies focused on adults, daytime-only incontinence, organic causes of incontinence, pharmacokinetic outcomes or non-relevant conditions (eg., respiratory disorders).
- Interventions included desmopressin monotherapy or in combination with another intervention. Studies included desmopressin at different dosages and routes of administration.
- Comparator groups received placebo or no treatment, other intervention (alarm training, anticholinergics, tricyclics, NSAIDs, behavioral therapy, laser acupuncture), or desmopressin with other intervention.
- Primary outcomes measured the number of wet nights per week and number of children having 14 consecutive dry nights during treatment.
- Secondary outcomes included the number of wet nights per week and number of children maintaining dryness for 14 nights in a row at follow-up, relapse rate after stopping treatment, and adverse events.
- Selected studies were assessed based on Cochrane Handbook for Systematic Reviews of Interventions. Each study was screened using Cochrane 'Risk of bias' tool.
- Data analysis was completed using REVMAN 5.4.1 tool and Excel was used for number collation. Primary and secondary outcomes were assessed for evidence certainty using the GRADE approach.

INTERVENTION (# IN THE GROUP): 5,434 total participants (variable number depending on outcome)

COMPARISON (# IN THE GROUP): 3,039 total comparators (variable number depending on outcome)

FOLLOW-UP PERIOD: Variable (no follow-up to at least 3 months)

RESULTS:

Primary Outcome –

- Desmopressin reduced the number of wet nights at the end of treatment compared to placebo (16 studies, n=1,257; mean difference [MD] –1.8; 95% CI, –2.2 to –1.4).

- Desmopressin minimally reduced the number of wet nights at the end of treatment in combination with alarm therapy (2 studies, n=156; MD –0.88, 95% CI, –1.4 to –0.38).
- Desmopressin increased the number of children achieving 14 consecutive dry nights by the end of treatment compared to placebo (11 studies, n=922; risk ratio [RR] 3.2; 95% CI, 1.8–5.8; I^2=42%).
- Desmopressin minimally increased the number of children achieving 14 consecutive dry nights at the end of treatment in combination with alarm therapy (5 studies, n=370; RR 1.3; 95% CI, 1.1–1.5).
- The results comparing effectiveness of desmopressin monotherapy or combination therapy with other interventions such as anticholinergics, tricyclics, NSAIDs, behavioral therapy, and laser acupuncture were inconclusive.

Secondary Outcome –

- Desmopressin with either alarm training or behavioral training decreased the number of wet nights at follow-up compared to desmopressin monotherapy.
  - Alarm training (2 studies, n=149; MD –1.4; 95% CI, –1.9 to –0.94)
  - Behavioral training (1 study, n=146; MD –1.5; 95% CI, –2.2 to –0.9)
- There was no significant difference in the mean number of wet nights at follow-up between desmopressin monotherapy and desmopressin combined with laser acupuncture.
- Desmopressin combined with alarm training may improve dryness for 14 nights in a row compared to desmopressin monotherapy (2 studies, n=161; RR 2.3; 95% CI, 1.2–4.1) but there was no significant difference when this combination was compared with alarm training alone.
- Desmopressin combined with anticholinergics slightly increased dryness for 14 nights in a row compared to desmopressin monotherapy (1 study, n=99; RR 2.2; 95% CI, 1.1–4.6).
- There was no significant difference in dryness for 14 consecutive nights for desmopressin combined with tricyclics, behavioral therapy, and laser acupuncture compared to desmopressin monotherapy.
- There was no significant difference in outcome between various methods of desmopressin withdrawal and placebo withdrawal.
- Desmopressin was more likely to be associated with adverse events than placebo or alarm training but not necessarily tricyclics.

LIMITATIONS:

- Quality of included studies was generally low with high- risk of biases and incomplete or missing data related to key factors. Some studies included small numbers of subjects.
- Significant heterogeneity further compromised the study results.
- Long-term effectiveness of treatment and adverse events could not be assessed due to limited follow-up information for majority of the studies.

Deena Sunny, MD
Amgad Abdelhady, MBBCh
University of Iowa Hospitals and Clinics
Sioux City, IA

High-Fat Fads and Fertility: Can Ketogenic Diet Improve Hormonal Health in Women with PCOS?

Effects of Ketogenic Diet on Reproductive Hormones in Women with Polycystic Ovary Syndrome

Khalid K, Apparow S, Mushaddik IL, Anuar A, Rizvi SAA, Habib A. Effects of Ketogenic Diet on Reproductive Hormones in Women with Polycystic Ovary Syndrome. *J Endocr Soc*. 2023;7(10):bvad112. Published 2023 Sep 7. doi:10.1210/jendso/bvad112

KEY TAKEAWAY: Among women with polycystic ovary syndrome (PCOS), a ketogenic diet (KD) consisting of high fat and low carbohydrate may improve reproductive hormone profiles and weight loss.

STUDY DESIGN: Systematic review and meta-analysis of two randomized controlled trials, one prospective cohort study, and four nonrandomized single-arm studies

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size, heterogeneity of studies reviewed, not including control or comparison groups, and disease-oriented primary outcome)

BRIEF BACKGROUND INFORMATION: PCOS is one of the most common medical pathologies in women of reproductive age. It is often treated with hormonal contraceptive therapies, but this is not ideal for many women who are trying to conceive. PCOS is also often treated with weight loss and metformin because it is generally understood that insulin resistance contributes to PCOS and that improvement of insulin resistance and accompanying weight loss can alleviate PCOS symptoms. The effect of a KD, a low insulinogenic diet, on reproductive hormonal profiles of women with PCOS remains unclear.

PATIENTS: Women diagnosed with PCOS

INTERVENTION: KD

CONTROL: Various

PRIMARY OUTCOME: Improvement in hormonal profiles

Secondary Outcome: Weight change

METHODS (BRIEF DESCRIPTION):

- Eligible studies were extracted from online databases that included MEDLINE, ScienceDirect, Scopus, and Web of Science from inception through January 20, 2023.
- The Revised Cochrane risk of bias tool was used to assess the methodological quality of the included studies, and each was rated as fair overall.
- Women, diagnosed with PCOS, were included.
- Outcomes of KD were reported as follows:
  - Four single arm studies (n=61)
  - The KD arm of one study (n=8) that compared KD to conventional treatment
  - The KD arm of one study that compared KD to Mediterranean diet (MD) (n=73)
  - The non-hyperuricemia group of a two-group study (n=28)
- The mean age of the participants ranged from 25–35 years old.
- KD composition comprised classical KD, low-carbohydrate KD, and very low-calorie KD.
- Participants' daily calorie allowance ranged from 600–2,000 or a self-chosen number of kcals daily of a KD.
- Pre-post measures included levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG), free testosterone, and weight change.
- Statistical analyses were conducted using a random-effects model to combine data and generate 95% confidence intervals for each outcome. If at least two studies looked at a particular outcome, analysis was performed.

INTERVENTION (# IN THE GROUP): 170

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied (45 days to 24 weeks)

RESULTS:

Primary Outcome –

- KD was associated with a significant reduction in:
  - LH/FSH ratio (4 studies, n=112; overall effect size [d] –0.9; 95% CI, –1.0 to –0.7).
  - Free testosterone (4 studies, n=112; d –0.2; 95% CI, –0.3 to –0.1).
- KD was associated with a significant increase in serum SHBG (3 studies, n=104; d 9.1; 95% CI, 3.4–15).

Secondary Outcome –

- KD was associated with significant weight loss (5 studies, n=92; d –12; 95% CI, –15 to –8.1).

LIMITATIONS:

- Some of the studies included caloric restriction, a confounder that very likely contributed to weight

loss and improvement of hormonal profiles regardless of diet composition.

- There was not a control or comparison group included in the meta-analysis.
- Due to the nature of dietary studies, participants could not be blinded.
- Heterogeneity existed between studies.

Christina Bassette, MD
Womack Army Medical Center FMR
Fort Bragg, NC

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.

Sweet Spot: Pioglitazone as an Add-On to Metformin and Dapagliflozin Lowers A1C

Pioglitazone as Add-On Therapy in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Dapagliflozin and Metformin: Double-Blind, Randomized, Placebo-Controlled Trial

Heo JH, Han KA, Hong JH, et al. Pioglitazone as Add-on Therapy in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Dapagliflozin and Metformin: Double-Blind, Randomized, Placebo-Controlled Trial. *Diabetes Metab J*. 2024;48(5):937-948. doi:10.4093/dmj.2023.0314

KEY TAKEAWAY: In patients with type 2 diabetes inadequately controlled on metformin and dapagliflozin, adding pioglitazone significantly improves glycemic control but is associated with weight gain.

STUDY DESIGN: Multisite, double-blind, randomized, placebo-controlled trial

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

BRIEF BACKGROUND INFORMATION: When metformin and a sodium-glucose co-transporter 2 (SGLT2) fail to achieve glycemic control in patients with type 2 diabetes (T2DM), a third agent is often needed. Pioglitazone is effective in lowering the hemoglobin A1C (HbA1C), but its use is limited due to side effects like weight gain and edema.

PATIENTS: Adults with poorly controlled T2DM

INTERVENTION: Pioglitazone

CONTROL: Placebo

PRIMARY OUTCOME: Change in HbA1C at 24 weeks

Secondary Outcome Change in A1C at 12 weeks, fasting plasma glucose (FPG), insulin resistance, blood pressure, body weight

METHODS (BRIEF DESCRIPTION):

- The phase 3 randomized, controlled trial, conducted at 31 sites in South Korea between October 2021 and September 2022, included an eight-week single blind treatment period and a two-week run-in period to ensure tolerability prior to randomization.
- Participants were ≥19 years old with inadequately controlled T2DM (defined as HbA1C of 7–11%) and body mass index (BMI) ≤45 kg/m^2 on stable metformin (≥1,000 mg daily) and dapagliflozin (10 mg daily) for at least eight weeks prior to study participation.
- Patients with cardiovascular event in the past six months, HIV infection, renal and liver dysfunction, or FPG >270 were excluded from the study.
- After the two-week run-in period of placebo + dapagliflozin + metformin, participants with at least 70% compliance were assigned to receive either pioglitazone 15 mg daily or placebo daily for 24 weeks.
- Participants in both groups had similar demographics (mean age of 57 years old, mean T2DM duration of 9.1 years, mean HbA1C of 7.7%±0.67%) and continued to maintain their diet and exercise programs.
- Follow-up assessments were completed at weeks 12 and 24 with insulin resistance measured using the homeostasis model assessment for insulin resistance (HOMA-IR), a calculated value derived from FPG and serum insulin levels (range from 0–3 with ≥2 indicating insulin resistance).

INTERVENTION (# IN THE GROUP): 125

COMPARISON (# IN THE GROUP): 125

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- Adding pioglitazone resulted in a greater reduction in HbA1C at 24 weeks compared to placebo (adjusted mean change –0.47%; 95% CI, –0.61 to –0.33).

Secondary Outcome –

- The pioglitazone group achieved a greater reduction in the following compared to placebo:
  - FPG (placebo-adjusted mean change –14 mg/dL; 95% CI, –18 to –9.2)
  - Insulin resistance (placebo-adjusted mean change –0.78; 95% CI, –1.1 to –0.45)
  - Triglycerides (placebo-adjusted mean change –16; 95% CI, –28 to –3.9)
- The pioglitazone group achieved a higher high-density lipoprotein cholesterol compared to placebo (placebo-adjusted mean change 3.7 mg/dL; 95% CI, 2.0–5.3).

- The pioglitazone group experienced a significant increase in body weight compared to placebo (placebo-adjusted mean change 2.9 kg; 95% CI, 2.3–3.5).
- There was no significant difference in total cholesterol, LDL cholesterol, blood pressure, or adverse events between the two groups.

LIMITATIONS:

- The study's short duration of 24 weeks limits the assessment of long-term efficacy and safety.
- Only a single, low dose of pioglitazone (15 mg) was evaluated.
- The study population consisted exclusively of Korean patients and those who achieved >70% compliance during a run-in period, limiting generalizability of the findings.
- The results focused on disease-oriented outcomes and did not include patient-oriented outcomes.

Charles Goodman, MD
Naval Medical Center Camp Lejeune
Jacksonville, NC

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From Clinic to Couch: Validating Vaginal Self-Sampling for HPV

Clinical Validation of a Vaginal Cervical Cancer Screening Self-Collection Method for At-Home Use: A Nonrandomized Clinical Trial

Fitzpatrick MB, Behrens CM, Hibler K, et al. Clinical Validation of a Vaginal Cervical Cancer Screening Self-Collection Method for At-Home Use: A Nonrandomized Clinical Trial. *JAMA Netw Open*. 2025;8(5):e2511081. Published 2025 May 1. doi:10.1001/jamanetworkopen.2025.11081

KEY TAKEAWAY: The FDA approved self-collection vaginal device for high-risk human papillomavirus (hrHPV) testing is an effective and valid tool that should be considered to decrease barriers and increase access to cervical cancer screening.

STUDY DESIGN: Non-randomized clinical trial with a prospective comparison study design

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Before the Papanicolaou screening test, which was introduced in the 1950s, cervical cancer was the leading cause of cancer-related death for women in the United States (US). While advancements have been made with hrHPV testing, there continues to be an increase in the percent of women overdue for cervical cancer screenings in the U.S due to both logistical and emotional barriers to screening. To overcome these barriers, this study aimed to validate an at-home self-collection vaginal device.

PATIENTS: Females 25–65 years old with intact cervix

INTERVENTION: Self-collection (SC) using a vaginal device

CONTROL: Clinician-collected (CC) vaginal sample for hrHPV, as well as the histopathology results for those that required a colposcopy with a biopsy or excisional procedure (loop electrosurgical procedure or conization)

PRIMARY OUTCOME: Positive percent agreement (PPA) and negative percent agreement (NPA) for the SC device vs the CC method and/or histopathology results

METHODS (BRIEF DESCRIPTION):

- Patients 25–65 years old with an intact cervix, from 16 US sites (both academic and community settings), recruited from two specific groups: A general screening population and a group with positive hrHPV results or abnormal Papanicolaou cytology within the past six months were included.
- Exclusion criteria included pregnancy, vaginal bleeding, and cervical alteration in the past five months.
- Participants were provided with a SC device in a private room with standardized instructions for use in 5th to 6th grade language followed immediately by participants entering an exam room for a CC sample.
- Samples were run using the same Roche Cobas hrHPV test on the Roche Cobas 8800 System.
- The primary outcome measures were PPA and NPA values for detection of hrHPV between the SC sample and the CC sample.

INTERVENTION (# IN THE GROUP):

- Total participants: 609
- HrHVP group: 362
- General screening population: 247

COMPARISON (# IN THE GROUP):

- Total participants: 609
- HrHVP group :362
- General screening population: 247

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- The PPA for any hrHPV was 95% (n=278 of 292; 95% CI, 92–97).
- The PPA for hrHPV 16 or hrHPV 18 only was 96% (n=69 of 72; 95% CI, 89–98).
- The PPA for other hrHPV only was 94% (n=207 of 220; 95% CI, 90–97)
- The NPA for any hrHPV was 90% (n=261 of 290; 95% CI, 86–93).

Secondary Outcome –

- The absolute clinical sensitivity for SC detection of high-grade cervical dysplasia (CIN2) was 96% (n=46 of 48; 95% CI, 86–99). The relative sensitivity compared with CC was 1.0.
- The absolute clinical sensitivity for SC detection of cervical dysplasia (CIN3) was 97% (n=28 of 29; 95% CI, 83–99). The relative sensitivity compared with CC was 0.97.
- For usability, 92% of participants (n=555 of 601) reported easy or very easy understanding.
- For screening preferences, 46% (276 participants) preferred at-home SC, 34% (206 participants)

preferred in-clinic speculum collection, and 20% (118 participants) preferred in-clinic SC. Lastly, 93% (560 participants) indicated they would prefer an at-home SC options if they knew the results were equivalent to CC.

LIMITATIONS:

- It was a non-randomized clinical trial.
- The study was designed by the study sponsor Teal Health with feedback from the FDA.
- The samples were not collected at home but in a simulated at-home environment, which could alter real-life utilization of the tool.

Rachel Eckelkamp, DO
Loyola MacNeal FMRP
Berywn, IL