Diabetes, Metabolic Syndrome and Obesity

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LETTER

Metabolic Insights and Reproductive Health Challenges: High-Protein Hypocaloric Diets in PCOS Management [Letter]

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Dear editor

Wang et al's randomized trial[1] comparing high-protein hypocaloric diets (HPD) with conventional restricted diets (CRD) in overweight/obese PCOS women offers critical metabolic insights but underscores unresolved reproductive health challenges. While HPD's superior preservation of fat-free mass (FFM) aligns with its anabolic potential via mTORC1 pathway activation, the equivalent reductions in HOMA-IR and testosterone between groups suggest macronutrient modulation alone may insufficiently address androgen excess or ovarian dysfunction.[2] Future longitudinal studies must track ovulatory frequency and serum anti-Müllerian hormone (AMH) levels to determine whether sustained FFM retention translates to restored reproductive axis function—an outcome absent in current short-term trials.

The reliance on whey protein isolates (50% of HPD intake) introduces practical limitations. Whole-food alternatives like legumes or soy not only provide equivalent protein quality but also deliver phytoestrogens and fiber, which may modulate gut dysbiosis, a contributor to PCOS-related inflammation.[3] Moreover, the study's exclusion of non-obese PCOS phenotypes overlooks 30–50% of cases characterized by metabolic dysfunction despite normal BMI. Stratified analyses by waist-to-hip ratio or fasting insulin could identify subgroups where HPD exerts disproportionate benefits, particularly given evidence that lean PCOS patients exhibit unique adipokine profiles and insulin signaling defects.

Critically, the absence of structured exercise protocols represents a missed opportunity. Resistance training synergizes with dietary protein to augment FFM synthesis and insulin receptor substrate-1 (IRS-1) phosphorylation. Future trials should incorporate supervised strength training (3x/week) to test whether HPD's metabolic advantages are amplified by concurrent myofibrillar hypertrophy.[4] Additionally, patient-reported outcomes—such as dietary satisfaction and disordered eating patterns (Eating Attitudes Test)—require quantification, as PCOS patients frequently exhibit binge-eating behaviors that undermine adherence to restrictive diets.

Mechanistic gaps persist in understanding HPD's endocrine effects. While reduced adiposity may lower aromatase activity, the parallel decline in testosterone observed in both groups implies weight loss itself, not protein composition—drives androgen reduction.[5] To dissect dietary-specific impacts, future studies should integrate hyperinsulinemic-euglycemic clamps to isolate insulin sensitivity changes and liquid chromatography-mass spectrometry to profile steroid hormone metabolites.

Suggestions

To advance translation, we advocate for pragmatic randomized controlled trials (RCTs) co-designed by gynecologists, endocrinologists, and nutrition scientists. These should (1) track reproductive endpoints (eg, spontaneous ovulation, live birth rates), not just metabolic surrogates; (2) compare HPD against CRD combined with first-line pharmacological agents (eg, metformin, GLP-1 agonists); and (3) incorporate biomarker panels (eg, adiponectin, inflammatory cytokines) to elucidate mechanisms linking protein intake to ovarian function. Until such evidence emerges, clinicians should

Received: 11 July 2025
Accepted: 19 July 2025
Published: 25 July 2025

emphasize HPD as a complementary strategy within multimodal PCOS management—valuable for body composition but not yet proven superior for core reproductive outcomes.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

WL: Conceptualization, Writing – original draft, Writing – review and editing. LS: Writing – review and editing. SZ: Writing – review and editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts of interest in this communication.

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https://doi.org/10.2147/DMSO.S552390