# Selección de Resúmenes de Menopausia

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María Soledad Vallejo. Obstetricia y Ginecología. Hospital Clínico. Universidad de Chile

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## Musculoskeletal Manifestations of Perimenopause: A Systematic Review and Meta-Analysis of 93,021 Women

Colin Kruse 1 2, Tyler McKechnie 2 3, Joshua Dworsky-Fried 1 4, Aariz Sardar 2, Georgia Hacker 4, et al.

Background: The prevalence and characterization of specific types of musculoskeletal (MSK) conditions associated with menopausal transition remains unclear and is often underreported. Our objectives were twofold: (1) to systematically review, and conduct meta-analysis whenever appropriate, to compare the prevalence of MSK symptoms across the different stages of menopause and (2) to characterize the specific MSK conditions associated with transition to menopause. Methods: We searched Medline, EMBASE, CENTRAL, and PubMed from inception to May 2024. Articles were eligible for inclusion if they included perimenopausal women and reported any primary data on MSK symptoms or pathology. The outcomes we aimed to find included muscle and joint pain, back pain, and the prevalence of various MSK conditions. A pairwise meta-analysis was performed using a DerSimonian-Laird random-effects model for all comparative data, and subgroup analyses were used to explore heterogeneity. Results: After screening 5,556 relevant records, 37 observational studies across 22 countries enrolling 93,021 women were included in the quantitative analysis. Four in 10 women experienced muscle or joint pain during the premenopausal phase (40% [95% confidence interval {CI}: 32%-49%]). Whereas over half of perimenopausal women (57% [95% CI: 48%-65%]) and postmenopausal women (59% [95% CI: 50%-67%]) experienced muscle or joint pain, representing a 1.35-fold increased risk (risk ratio [RR] 1.35, 95% CI: 1.25-1.46, $p < 0.001$, $I2 = 88.6\%$; absolute risk difference 130 more per 1,000 [95% CI: 93-171]) and a 1.40-fold increased risk (RR 1.40, 95% CI: 1.28-1.53, $p < 0.001$, $I2 = 95.0\%$; absolute risk difference 148 more per 1,000 [95% CI: 104-197]) on pairwise comparison with premenopausal women, respectively. Geographic study location nor measurement scale explained the considerable heterogeneity in the pooled analyses. There was underreporting of specific MSK conditions beyond the generic descriptors of muscle and/or joint pain. Conclusion: Women transitioning to menopause appear to be at increased risk of developing muscle or joint pain. However, as these findings are based on observational studies, specific causes of MSK pain are underreported, and there is significant heterogeneity. Further high-quality research is needed to confirm and clarify this association.

J Gerontol B Psychol Sci Soc Sci. 2026 Jan 10:gbag001. doi: 10.1093/geronb/gbag001. Online ahead of print.

## Associations of Lifetime Cumulative Estrogen Exposure with Lifecourse Social Exposures, Cognitive Decline, and Dementia Risk Among Postmenopausal White, Black, and Latina Women

Justina F Avila-Rieger 1 2, Benjamin Huber 1, Sarah E Tom 3, Whitney R Robinson 4, Tanisha G Hill-Jarrett 5 6, et al.

Objectives: Greater lifetime exposure to estrogen may protect women from cognitive decline and dementia later in life. Gender-related social factors also influence women's cognitive outcomes; however, little is known about how these biological and social influences work together. We examined the extent to which cumulative estrogen exposure and lifecourse social exposures jointly influence late-life memory trajectories and dementia risk among a community-based sample of White, Black, and Latina women. Methods: Participants were 3,688 postmenopausal women in the Washington Heights-Inwood Columbia Aging Project. Lifetime cumulative estrogen exposure was estimated based on age at menarche and menopause, breastfeeding duration, and hormone replacement therapy (HRT) use. Lifecourse social factors included birth cohort, childhood SES, educational and occupational attainment, and later-life income. Multiple-group growth models and Cox regression models were estimated across racial and ethnic groups. Results: Greater lifetime estrogen exposure was independently associated with higher baseline memory performance among Black and Latinx women, slower memory decline among White women, and lower dementia risk among Latinx women. Later birth year and higher lifecourse SES were associated with greater lifetime estrogen exposure, with associations varying in magnitude across racial and ethnic groups. Associations between lifecourse SES and each cognitive outcome were partially mediated by estrogen exposure indicators. Discussion: Cumulative estrogen exposure is socially patterned. We

found that lifecourse social factors and estrogen exposure synergistically contribute to women's late-life cognitive health outcomes. Understanding how sex-linked biology and gender-related social forces intertwine is essential for developing interventions to decrease dementia risk among women.

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## Comparative Study of Vitamin D Levels After Metabolic Bariatric Surgery in Women Under or Over 45 Years of Age

Diya Humeida Omer 1, Khiria Alsaghir 1, Aye A Thant 1, Siba Senapati 2 3, Basil J Ammori 2 4, Akheel A Syed 5 6

Background: Vitamin D deficiency is common in people with obesity and can worsen after bariatric surgery. As the reproductive years and post-menopausal status can place additional demands on vitamin D requirements, we studied vitamin D status after bariatric surgery in women under 45 years of age compared with women over 45. Methods: We conducted an observational cohort study of 305 women undergoing primary bariatric surgery at a university teaching hospital in North West England. Participants were stratified by age into women under 45 years (Wu45, n = 123) and over 45 years (Wo45, n = 182). Patients were routinely prescribed daily calcium and vitamin D supplementation after bariatric surgery. Serum 25-hydroxyvitamin D, adjusted calcium, parathyroid hormone (PTH) and metabolic parameters were measured preoperatively and at intervals over 24 months postoperatively. Results: After bariatric surgery, vitamin D levels rose significantly within 4 months but were lower in Wu45 at 12 and 24 months ($p < 0.05$). Adjusted calcium levels declined over time, with Wu45 showing significantly lower levels at 12 and 24 months. PTH levels, initially lower in Wu45, increased and equalized with Wo45's levels by 12 months. Conclusions: Women under 45 are at increased risk of vitamin D and calcium deficiencies after bariatric surgery. This may reflect higher physiological demands and variable adherence to supplementation. Patient education and tailored supplementation strategies may be required to prevent long-term micronutrient complications.

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## Subcutaneous Estradiol Pellets as Hormone Therapy in Menopause: Clinical Pharmacology, Patient Selection and Safety Considerations

Leonardo Jacobsen 1, Daniela Maia Fernandes 1, Maria Luiza Nagel 1, Eline Lobo de Souza 1, et al.

Background: Among hormone therapy options for menopause, subcutaneous estradiol pellets offer sustained hormone release, avoid first-pass hepatic metabolism, and maintain a near-physiological estradiol-to-estrone ratio. Despite clinical use since the 1940s, standardized protocols remain lacking. Methods: We performed a critical narrative review following SANRA criteria. PubMed, Scopus, Embase, and LILACS were searched from 1949 to 2024 for randomized trials, cohort studies, and case series on estradiol pellets and outcomes in symptom control, bone health, pharmacokinetics, and safety. Animal studies, editorials, and reports without primary clinical data were excluded. Results: Following an initial peak within the first week, pellets maintain stable serum estradiol levels within the early-to-mid follicular range (50-113 pg/mL depending on dose) for four to six months, with a near-physiological E2:E1 ratio of approximately 1.5:1. The 25 mg dose achieves mean levels of 50-70 pg/mL, effectively controls vasomotor symptoms, and increases bone mineral density. Compared with oral estradiol, pellets bypass hepatic first-pass metabolism, resulting in neutral or favorable metabolic and thrombotic profiles. Compared with transdermal therapy, pellets provide more predictable pharmacokinetics, especially in women with low skin absorption. Safety concerns, including bleeding, tachyphylaxis, and supraphysiological levels, are mainly associated with excessive dosing, premature reimplantation, or lack of endometrial protection in women with a uterus. Conclusions: Estradiol pellets are an effective option for women with poor transdermal absorption, low adherence to daily regimens, or surgical menopause. Safety depends on clinical management with individualized dosing, adequate endometrial protection, and laboratory monitoring. Long-term comparative studies are needed to standardize protocols and support broader evidence-based use.

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## Estimating the effect of hypothetical dietary protein interventions on changes in body composition of postmenopausal women over 3 years using data from the Women's Health Initiative (WHI) Study: an emulated target trial

Jiarui Li 1, Luohua Jiang 1 2, Nazmus Saquib 3, Philippe Jean-Luc Gradidge 4, Simin Liu 1 2, Linda Van Horn, et al. Background: Postmenopausal women tend to experience significant changes in body composition, particularly abdominal adipose tissue (AAT) deposition patterns, which are hypothesized to be critical factors influencing future chronic disease risk. The level of protein intake to maintain or achieve a more favorable body composition for health in postmenopausal women is a central, largely unanswered question relating to the appropriateness of current dietary guideline recommendations for sufficient protein intake (set at 0.8 g/kg/day). Objective: To estimate the hypothetical effect of a range of protein intake levels on 3-year mean changes in body composition measures in postmenopausal women.Methods: We analyzed data from 3789 postmenopausal women aged 50-79 enrolled in the Women's Health Initiative (WHI) to emulate a 3-year target trial of adhering to increasing levels of protein intake: ≥0.8 g/kg/d, ≥1.0 g/kg/d, ≥1.2 g/ kg/d, and ≥1.5 g/kg/d. All participants had repeated Dual X-Ray Absorptiometry (DXA) scans with derived abdominal visceral (VAT) and subcutaneous adipose tissue (SAT). The measured differences in average levels of VAT, SAT, and other body composition measures determined at end of follow-up were estimated with the parametric-g formula. Results: Over 3 years, hypothetical interventions of increasing levels of dietary protein intake are estimated to have dose-dependent reductions in abdominal VAT, SAT, and overall body fat, and increases in lean soft tissue, with potential benefits observed at ≥1.2 g/kg/day and the greatest estimated benefit at ≥1.5 g/kg/day of dietary protein. Compared to no intervention, if all participants hypothetically adhered to a total daily protein intake of ≥1.5 g/kg/day over 3 years, they would be estimated to have lower levels of VAT (-13.1 cm2, 95% Confidence Interval [CI] -18.9, -7.3), SAT (-25.3 cm2, 95% CI -39.7, -11.0), total body fat % (-1.0%, 95% CI -1.7, -0.3), body weight (-2.5 kg, 95% CI -3.7, -1.2) and greater lean soft tissue % (0.9%, 95% CI 0.3, 1.6) over 3 years. Conclusion: This hypothetical emulated intervention suggests that postmenopausal women who maintain a hypothetical total protein intake of at least 1.2 g/kg/day could experience beneficial changes in abdominal VAT, SAT, and overall body composition over three years, with even greater estimated benefits observed at an intake of 1.5 g/kg/day. These findings suggest that protein intake higher than guideline recommendations may better support healthier body composition and lower chronic disease risk in postmenopausal women.

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## Complementary therapies for management of menopausal symptoms: a systematic review to inform the update of the International Menopause Society recommendations on women's midlife health

Alison Maunder 1, Amelia K Mardon 1 2, Vibhuti Rao 1, Sophia Torkel 3, Najwa-Joelle Metri 1, Jing Liu 1, et al.
Objective: Menopausal hormone therapy is standard treatment, but some women use complementary therapies. This review examines complementary therapies for menopause to inform International Menopause Society (IMS) recommendations. Method: A systematic search of six databases (January 2022-December 2024) identified randomized controlled trials (RCTs) and systematic reviews on complementary therapies for menopause. Outcomes included menopausal, vasomotor, genitourinary, cardiometabolic, sleep symptoms, bone health and safety. The study quality and certainty of evidence were evaluated using Cochrane Risk of Bias (RoB2), A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2) and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). Results: From 3187 citations, 158 studies were included: one overview, 36 meta-analyses, seven systematic reviews and 114 RCTs. While promising evidence was found for acupuncture, Chinese herbal medicine (CHM), herbs, nutrients, mind-body/touch therapies for a variety of symptoms, most was of low/very low certainty. High-certainty evidence supports vitamin D safety; and moderate-certainty evidence supports black cohosh (vasomotor/menopausal symptoms), CHM (menopausal symptoms, sleep, blood pressure), acupuncture + CHM (sleep) and vitamin D (fracture risk). Most complementary therapies are safe.Conclusion: Vitamin D, black cohosh, CHM and acupuncture + CHM may improve some menopausal symptoms, but o verall evidence remains limited. More rigorous research is needed on the efficacy and safety of complementary therapies for menopause.

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## Individualized Fracture Prevention for Postmenopausal Women with Osteopenia

Jisu Mun 1, Meeran Kim 2, Jaeyen Song 1, Younjee Chung 1, Jungyoon Park 1, Junghyun Park 1
Osteopenia-defined by a bone mineral density T-score between -1.0 and -2.5-is more common than osteoporosis and accounts for most fragility fractures in postmenopausal women. Approximately 50% of Korean women aged ≥ 50 years

have osteopenia. Despite this high prevalence, optimal therapeutic strategies remain unclear. This review summarizes the clinical significance and management of osteopenia. Clinical practice often categorizes osteopenia into mild, moderate, and severe based on specific T-score ranges. Studies indicate that women transitioning from normal or moderate osteopenia to lower bone density experience more fractures. One study reported that approximately 10% of women with normal BMD or osteopenia progressed to osteoporosis, mostly from moderate to severe osteopenia groups. Fracture risks, particularly for hip and vertebral fractures, are elevated mainly in moderate to severe osteopenia. The National Osteoporosis Foundation and the American Association of Clinical Endocrinologists incorporate FRAX® scores alongside T-scores and clinical history to guide pharmacological intervention. Accordingly, South Korean guidelines classify fracture-risk groups as low, moderate, high, or very high, allowing treatment of patients with osteopenia in the high-risk categories. Evidence supporting medications for fracture prevention remains limited. However, growing interest in preventing fractures has directed the ongoing studies to evaluate various drugs. Food and Drug Administration-approved treatments include menopausal hormone therapy, bisphosphonates, and selective estrogen receptor modulators. To reduce fractures in postmenopausal women, treatment should not be restricted to osteoporosis alone. Women with moderate to severe osteopenia may also benefit from medications used for osteoporosis. Clinicians should assess individual fracture risks and select preventive treatments based on risk level, fracture site, menopausal symptoms, patient preference, and cost-effectiveness.

**Biol Reprod. 2026 Jan 5:ioaf292. doi: 10.1093/biolre/ioaf292. Online ahead of print.**

## Injectable contraceptives differentially affect the hypothalamic-pituitary-gonadal axis and amenorrhea incidence†

Alexis J Bick 1, Chanel Avenant 1, Carole-Keza Capitaine 1, Sharoné Eck 1, Mu-Tien Lee 2, Johnson M Moliki, et el.

Hormonal contraceptives modulate the hypothalamic-pituitary-ovarian (HPO) axis; however, underlying mechanisms and differences between contraceptives are underexplored. The Women's Health Injectable Contraception and HIV trial randomised 521 women to intramuscular depot medroxyprogesterone acetate (DMPA-IM) or norethisterone enanthate (NET-EN) and showed similar decreased estradiol levels, but more amenorrhea for DMPA-IM users. This secondary study excluded for misreporting contraceptive use for 128 participants (DMPA-IM n = 65; NET-EN n = 63). Peripheral blood serum collected at initiation and one week after the 24-week injection (25W), at peak progestin levels, was analysed for gonadal steroids, progestins and peptide hormones. While no changes were detected in peripheral gonadotropin-releasing hormone levels, DMPA-IM decreased luteinising hormone (LH) less than NET-EN. DMPA-IM increased, while NET-EN decreased follicle-stimulating hormone (FSH). Both contraceptives substantially decreased gonadal steroid levels, more so in NET-EN users for testosterone and estradiol. Post-menopausal-like hypoestrogenic effects were greater than previously reported, consistent with the substantial reduction in LH levels. Whether reduced LH levels are due to direct pituitary, hypothalamic, or supra-hypothalamic effects by progestins, is unclear. MPA, unlike NET, increased fsh expression in LβT2 cells, likely via the glucocorticoid receptor, consistent with direct effects on the pituitary by MPA in women. Amenorrhea associated in a time-varying manner with MPA and HPO hormone levels and LH/FSH, for DMPA-IM but not NET-EN users. HPO hormone profiles differ between DMPA-IM and NET-EN users and compared to pre- and post-menopausal women. Mechanisms affecting amenorrhea likely differ between contraceptives, with lower 25W LH/FSH being consistent with more amenorrhea for DMPA-IM.

**Endocr J. 2025 Dec 26. doi: 10.1507/endocrj.EJ25-0483. Online ahead of print.**

## Anti-aging effects of the adrenal androgens dehydroepiandrosterone and dehydroepiandrosterone sulfate: mechanisms of action and beneficial effects in older people

Hajime Nawata 1 2, Toshihiko Yanase 2 3, Ken-Ichirou Morohashi 4 5, Masatoshi Nomura 5, Kazuo Muta 2

We review the recent remarkable progress of the molecular mechanisms of action of the adrenal androgens dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) regarding their beneficial effects on older people and adrenal regenerative therapy by looking back on our research extending over 50 years since 1971. DHEAS is the most abundant circulating steroid hormone in humans and apes. DHEAS is essential for brain development in adrenarche and for anti-aging in adrenopause as shown by the evolutionary process in primates. The molecular mechanisms of action of DHEA and DHEAS have been clarified by the discovery of many membrane receptors and by the concept of intracrinological action, which is especially important in menopausal women. The genes associated with serum DHEAS concentrations were identified by genome-wide association study meta-analysis of

cohort studies. Recent advances in aging research have shown that DHEA and DHEAS have anti-aging action via antioxidants, anti-inflammation, telomere protection, p38MAPK inhibition, anti-cortisol effects, and chaperone induction. DHEA has beneficial effects on the prevention of atherosclerosis based on visceral obesity-induced metabolic syndrome in middle-aged people. DHEA also prevents infection, frailty via reverse metabolism, sarcopenia, and osteoporosis in older people, with a marked decrease in serum DHEAS concentrations. This review discusses adrenal regenerative therapy using steroid-producing cell replacement by overexpressing Ad4BP/steroidogenic factor 1 in mouse or human bone marrow mesenchymal stem cells. This therapy replaces cortisol and DHEAS treatment for the prevention of sudden death by adrenal crisis and severe infection in primary adrenal insufficiency (Addison's disease).

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## Modulation of blood pressure by estrogen: A modeling analysis

Anita T Layton 1

Hypertension is a global health challenge: it affects one billion people worldwide and is estimated to account for >60% of all cases or types of cardiovascular disease. Premenopausal women have lower blood pressure and hypertension prevalence compared to age-matched men, but that female protection is lost after menopause, the onset of which marks the beginning of a rapid decline in estrogen levels. The precise mechanisms by which estrogen protects premenopausal women from hypertension have yet to be elucidated. What is known is that estrogen has a plethora of interactions with other hormone systems as well as physiological processes known or hypothesized to impact the regulation of blood pressure. Thus, an objective of this study is to identify the primary contributors to the estrogen-mediated cardiovascular protection. To accomplish that goal, we develop a blood pressure regulation model that incorporates the effects of estrogen on the renin-angiotensin system, the reactivity of renal sympathetic nervous activity, vascular tone, and renal epithelial transport. Model simulations suggest that estrogen's vasodilatory effect, especially on the afferent arterioles, is the largest cause of premenopausal women's lower blood pressure and resistance to developing hypertension. Furthermore, the model predicts that angiotensin receptor blockers are more effective than angiotensin converting enzyme inhibitors in treating hypertensive women throughout their lifespan, even as estrogen levels decline.