Selección de Resúmenes de Menopausia

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Predominant Role of Nuclear Versus Membrane Estrogen Receptor α in Arterial Protection: Implications for Estrogen Receptor α Modulation in Cardiovascular Prevention/Safety.

Guivarc'h E, Buscato M, Guihot AL, Favre J, Vessières E, Grimaud L, Wakim J, Melhem NJ, et al.

BACKGROUND: Although estrogen receptor α (ERα) acts primarily as a transcription factor, it can also elicit membrane-initiated steroid signaling. Pharmacological tools and transgenic mouse models previously highlighted the key role of ERα membrane-initiated steroid signaling in 2 actions of estrogens in the endothelium: increase in NO production and acceleration of reendothelialization. METHODS AND RESULTS: Using mice with ERα mutated at cysteine 451 (ERaC451A), recognized as the key palmitoylation site required for ERα plasma membrane location, and mice with disruption of nuclear actions because of inactivation of activation function 2 (ERaAF20 = ERaAF2°), we sought to fully characterize the respective roles of nuclear versus membrane-initiated steroid signaling in the arterial protection conferred by ERα. ERaC451A mice were fully responsive to estrogens to prevent atheroma and angiotensin II-induced hypertension as well as to allow flow-mediated arteriolar remodeling. By contrast, ERαAF20 mice were unresponsive to estrogens for these beneficial vascular effects. Accordingly, selective activation of nuclear ERα with estetrol was able to prevent hypertension and to restore flow-mediated arteriolar remodeling. CONCLUSIONS: Altogether, these results reveal an unexpected prominent role of nuclear ERα in the vasculoprotective action of estrogens with major implications in medicine, particularly for selective nuclear ERα agonist, such as estetrol, which is currently under development as a new oral contraceptive and for hormone replacement therapy in menopausal women.

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Bone metabolism, density, and geometry in postmenopausal women with vitamin D insufficiency: a cross-sectional comparison of the effects of elevated parathyroid levels.

Rødbro LL, Bislev LS, Sikjær T, Rejnmark L.

INTRODUCTION: In vitamin D insufficiency, elevated parathyroid hormone (PTH) levels may contribute to adverse effect on bone. We assessed effects of PTH responses to vitamin D insufficiency on bone metabolism, density, and geometry. METHODS: Using a cross-sectional design, we investigated 102 healthy postmenopausal women with low 25-hydroxy-vitamin D (< 50 nmol/L) levels, who had either secondary hyperparathyroidism with elevated PTH levels (> 6.9 pmol/L, N = 51) or normal PTH levels (N = 51). Bone mineral density (BMD) and bone geometry were assessed by Dual-Energy X-ray absorptiometry (DXA), quantitative computed tomography (QCT) and high-resolution peripheral QCT (HRpQCT) scans. Bone metabolism was assessed by biochemistry including bone turnover markers. RESULTS: Levels of 25(OH)D were 38 (IQR 31-45) nmol/L with no differences between groups. PTH levels were 8.5 (IQR 7.5-9.5) in women with SHPT and 5.2 (4.4-6.6) pmol/L in women with normal PTH ($p < 0.001$). BMI and eGFR did not differ between groups. SHPT was associated with lower total- and trabecular bone area, lower cortical perimeter, and increased cortical area in tibia and radius. SHPT was associated with a lower weight-adjusted BMD at the lumbar spine ($p < 0.05$). High compared to normal PTH levels were associated with significantly lower plasma levels of 1,25(OH)2D, phosphate, but higher levels of osteocalcin and borderline higher levels of CTx. PTH correlated to osteocalcin and CTx. CONCLUSIONS: High PTH levels are associated with altered bone geometry, increased bone turnover, and reduced BMD at the spine. Whether an increased cortical thickness with a lower trabecular volume is an effect of PTH or not needs further elucidations.

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Timing of cyclic estradiol treatment differentially affects cognition in aged female rhesus monkeys.

Baxter MG1, Santistevan AC, Bliss-Moreau E, Morrison JH.

Some evidence suggests that there may be a limited "window of opportunity" for beneficial effects of hormone therapy after menopause in women. We tested whether the timing of cyclic estradiol (E2) treatment impacted its effect on cognitive function in aged, surgically menopausal (ovariectomized) rhesus monkeys. Monkeys were assigned to one of four treatment

conditions after ovariectomy: either vehicle or E2 treatment for the duration of the protocol, vehicle for the first 2 years of the protocol followed by E2 for the remainder (delayed treatment), or E2 for the first 11 months of the protocol followed by vehicle for the remainder (withdrawn treatment). Delayed treatment addressed the hypothesis that E2 treatment initiated more than 2 years postovariectomy would have a reduced effect on cognitive function. Withdrawn treatment mirrored current clinical advice to women to use hormone therapy in the initial postmenopausal period then discontinue it. Two periods of cognitive testing assessed treatment effects on cognition over time. E2 treatment predominantly affected a prefrontal cortex-dependent test of spatiotemporal working memory (delayed response). Monkeys with delayed E2 treatment modestly improved in delayed response performance over time, whereas vehicle-treated monkeys declined. Monkeys with withdrawn E2 treatment maintained their performance across assessments, as did monkeys treated with E2 across the entire protocol. These findings suggest that a "window of opportunity" for hormone treatment after cessation of ovarian function, if present in nonhuman primates, lasts longer than 2 years. They also support the notion that beneficial effects of hormone therapy may persist after discontinuation of treatment.

Front Endocrinol (Lausanne). 2018 Jun 13;9:326. doi: 10.3389/fendo.2018.00326. eCollection 2018.

Vitamin D Level and Activities of Daily Living in Octogenarians: Cross-Sectional Study.

Alekna V, Kilaite J, Mastaviciute A, Tamulaitiene M.

Introduction: Despite the growing number of octogenarians, little is known about their vitamin D status and activities of daily living (ADL) relations. Objective: The aim of this study was to investigate peculiarities of vitamin D and ADL and to assess their relations in octogenarians. Methods: A cross-sectional study was performed at the National Osteoporosis Centre located in Vilnius, Lithuania. Community-dwelling ambulatory persons aged ≥80 years were included. Current users of vitamin D supplements were excluded. Total 25 hydroxyvitamin D concentration in serum was measured with Cobas E411. Functional status was assessed by Katz ADL and the Lawton Instrumental Activities of Daily Living (IADL) scales. Subjects were divided into three groups according to age and into two groups according to vitamin D level. One-way analysis of variance with post hoc test was used to determine between-group comparisons. Associations between vitamin D and ADL score, and IADL score were assessed using Spearman's correlation. Results: The study was performed on 153 octogenarians: 81 (52.9%) women and 72 (47.1%) men. The average age of subjects was 83.9 ± 3.2 years. Mean total 25 OH Vit D concentration was 11.2 ± 7.0 ng/ml; 137 (89.5%) persons had vitamin D deficiency, 12 (7.8%) had insufficiency, and only 4 (2.6%) persons were vitamin D sufficient. Positive weak correlation between total 25 hydroxyvitamin D and ADL score ($r = 0.2$, $p = 0.01$) and very weak correlation between total 25 hydroxyvitamin D and IADL score ($r = 0.19$, $p = 0.02$) were found. Total 25 hydroxyvitamin D level was correlated with ADL score in women ($r = 0.23$, $p = 0.04$). In the 80-84 years group ADL score correlated with total 25 hydroxyvitamin D level ($r = 0.23$, $p = 0.02$). Conclusion: The majority of investigated octogenarians had vitamin D deficiency. The level of vitamin D was associated with the ADL score. There was no association between the vitamin D level and the IADL score, although a weak correlation was found between vitamin D level and category of food preparation.

Clin Calcium. 2018;28(7):863-971. doi: CliCa1807863971.

Body weight and bone/calcium metabolism. Glucose-lowering agents and fracture risk.

Watanabe R, Inoue D.

Diabetes is associated with increased fracture risk, involving a variety of factors. Besides poor glycemic control itself, some glucose-lowering agents are also associated with increased fracture risk. Thiazolidinediones increase fracture risk probably through inhibition of bone formation as well as increased resorption leading to decreased BMD. Sodium-glucose cotransporter (SGLT)-2 inhibitors have been reported to decrease BMD and increase fracture risk. However, the class effect of SGLT-2 inhibitors on bone metabolism remains to be established. In diabetic patients, especially in those with high fracture risk such as postmenopausal women, careful selection of glucose-lowering agents as well as appropriate and timely intervention for osteoporosis is necessary.

Clin Exp Obstet Gynecol. 2017;44(3):403-407.

Occurrence of climacteric symptoms in postmenopausal women after prophylactic bilateral ovariectomy.

Brodowski J, Jurczak A, Grochans E, Karakiewicz B, Laszczynska M, Ciecwiez S, et al.

PURPOSE OF INVESTIGATION: To analyse the quality of life in postmenopausal women after prophylactic bilateral ovariectomy depending on the time from menopause. MATERIALS AND METHODS: The study involved 252

postmenopausal women grouped according to the time from last menstruation: one to five years (group A), five to ten years (group B), and > ten years (group C). All women were ovariectomized during laparotomy performed for benign diseases of the uterus. Climacteric symptoms were measured with the Kupperman Index one day before and three months after surgery. RESULTS: Highly significant age differences and no substantial BMI differences were demonstrated among the study groups. Before and after surgery climacteric symptoms were reported by 17.06% and 57.8% of women, respectively. After surgery, group A women significantly more often had hot flushes, sweating, nervousness, and sleep disorders, the women in group B significantly more often reported sleep disorders, nervousness, and sweating, and the women in group C significantly more often complained of nervousness. CONCLUSION: In postmenopausal women, ovaries play the most important role during the first ten years from the last menstruation.

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Progression of frailailty and prevalence of osteoporosis in a community cohort of older women-a 10-year longitudinal study.

Bartosch P, McGuigan FE, Akesson KE.

In community dwelling, 75-year-old women followed 10 years, a frailty index was created at each of three visits. Frailty score increased by ~ 6-7% annually. A higher frailty score was equivalent to being 5-10 years chronologically older. Frailty was associated with low bone density and higher risk of dying. INTRODUCTION: To understand the distribution of frailty among a population-based sample of older community-dwelling women, progression over 10 years, and association with mortality and osteoporosis. METHODS: The study is performed in a cohort designed to investigate osteoporosis. The OPRA cohort consists of 75-year-old women, n = 1044 at baseline, and follow-up at age 80 and 85. A frailty index (scored from 0.0-1.0) based on deficits in health across multiple domains was created at all time-points; outcomes were mortality up to 15 years and femoral neck bone density. RESULTS: At baseline, the proportion least frail, i.e., most robust (FI 0.0-0.1) constituted 48%, dropping to 25 and 14% at age 80 and 85. On average, over 10 years, the annual linear frailty score progression was approximately 6-7%. Among the least frail, 11% remained robust over 10 years. A higher frailty score was equivalent to being 5 to 10 years older. Mortality was substantially higher in the highest quartile compared to the lowest based on baseline frailty score; after 10 years, 48.7% had died vs 17.2% ($p = 1.7 \times 10\text{-}14$). Mortality risk over the first 5 years was highest in the frailest (Q4 vs Q1; HRunadj 3.26 [1.86-5.73]; $p < 0.001$) and continued to be elevated at 10 years (HRunadj 3.58 [2.55-5.03]; $p < 0.001$). Frailty was associated with BMD after adjusting for BMI (overall $p = 0.006$; Q1 vs Q4 $p = 0.003$). CONCLUSIONS: The frailty index was highly predictive of mortality showing a threefold increased risk of death in the frailest both in a shorter and longer perspective. Only one in ten older women escaped progression after 10 years. Frailty and osteoporosis were associated.

JAMA. 2018 Jun 26;319(24):2521-2531. doi: 10.1001/jama.2018.7498.

Screening for Osteoporosis to Prevent Fractures: US Preventive Services Task Force Recommendation Statement. I

US Preventive Services Task Force, Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al.

By 2020, approximately 12.3 million individuals in the United States older than 50 years are expected to have osteoporosis. Osteoporotic fractures, particularly hip fractures, are associated with limitations in ambulation, chronic pain and disability, loss of independence, and decreased quality of life, and 21% to 30% of patients who experience a hip fracture die within 1 year. The prevalence of primary osteoporosis (ie, osteoporosis without underlying disease) increases with age and differs by race/ethnicity. With the aging of the US population, the potential preventable burden is likely to increase in future years. Objective: To update the 2011 US Preventive Services Task Force (USPSTF) recommendation on screening for osteoporosis. Evidence Review: The USPSTF reviewed the evidence on screening for and treatment of osteoporotic fractures in men and women, as well as risk assessment tools, screening intervals, and efficacy of screening and treatment in subgroups. The screening population was postmenopausal women and older men with no known previous osteoporotic fractures and no known comorbid conditions or medication use associated with secondary osteoporosis. Findings: The USPSTF found convincing evidence that bone measurement tests are accurate for detecting osteoporosis and predicting osteoporotic fractures in women and men. The USPSTF found adequate evidence that clinical risk assessment tools are moderately accurate in identifying risk of osteoporosis and osteoporotic fractures. The USPSTF found convincing evidence that drug therapies reduce subsequent fracture rates in postmenopausal women. The USPSTF found that the evidence is inadequate to assess the effectiveness of drug therapies in reducing subsequent fracture rates in men without previous fractures. Conclusions and Recommendation:

The USPSTF recommends screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in women 65 years and older. (B recommendation) The USPSTF recommends screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in postmenopausal women younger than 65 years at increased risk of

osteoporosis, as determined by a formal clinical risk assessment tool. (B recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures in men.

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Screening to Prevent Osteoporotic Fractures: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force.II

Viswanathan M, Reddy S, Berkman N, Cullen K, Middleton JC, Nicholson WK, Kahwati LC.

Importance: Osteoporotic fractures cause significant morbidity and mortality. Objective: To update the evidence on screening and treatment to prevent osteoporotic fractures for the US Preventive Services Task Force. Data Sources: PubMed, the Cochrane Library, EMBASE, and trial registries (November 1, 2009, through October 1, 2016) and surveillance of the literature (through March 23, 2018); bibliographies from articles. Study Selection: Adults 40 years and older; screening cohorts without prevalent low-trauma fractures or treatment cohorts with increased fracture risk; studies assessing screening, bone measurement tests or clinical risk assessments, pharmacologic treatment. Data Extraction and Synthesis: Dual, independent review of titles/abstracts and full-text articles; study quality rating; random-effects meta-analysis. Main Outcomes and Measures: Incident fractures and related morbidity and mortality, diagnostic and predictive accuracy, harms of screening or treatment. Results: One hundred sixty-eight fair- or good-quality articles were included. One randomized clinical trial (RCT) (n = 12 483) comparing screening with no screening reported fewer hip fractures (2.6% vs 3.5%; hazard ratio [HR], 0.72 [95% CI, 0.59-0.89]) but no other statistically significant benefits or harms. The accuracy of bone measurement tests to identify osteoporosis varied (area under the curve [AUC], 0.32-0.89). The pooled accuracy of clinical risk assessments for identifying osteoporosis ranged from AUC of 0.65 to 0.76 in women and from 0.76 to 0.80 in men; the accuracy for predicting fractures was similar. For women, bisphosphonates, parathyroid hormone, raloxifene, and denosumab were associated with a lower risk of vertebral fractures (9 trials [n = 23 690]; relative risks [RRs] from 0.32-0.64). Bisphosphonates (8 RCTs [n = 16 438]; pooled RR, 0.84 [95% CI, 0.76-0.92]) and denosumab (1 RCT [n = 7868]; RR, 0.80 [95% CI, 0.67-0.95]) were associated with a lower risk of nonvertebral fractures. Denosumab reduced the risk of hip fracture (1 RCT [n = 7868]; RR, 0.60 [95% CI, 0.37-0.97]), but bisphosphonates did not have a statistically significant association (3 RCTs [n = 8988]; pooled RR, 0.70 [95% CI, 0.44-1.11]). Evidence was limited for men: zoledronic acid reduced the risk of radiographic vertebral fractures (1 RCT [n = 1199]; RR, 0.33 [95% CI, 0.16-0.70]); no studies demonstrated reductions in clinical or hip fractures. Bisphosphonates were not consistently associated with reported harms other than deep vein thrombosis (raloxifene vs placebo; 3 RCTs [n = 5839]; RR, 2.14 [95% CI, 0.99-4.66]). Conclusions and Relevance: In women, screening to prevent osteoporotic fractures may reduce hip fractures, and treatment reduced the risk of vertebral and nonvertebral fractures; there was not consistent evidence of treatment harms. The accuracy of bone measurement tests or clinical risk assessments for identifying osteoporosis or predicting fractures varied from very poor to good.

Thromb Res. 2018 Jun 19;168:83-95. doi: 10.1016/j.thromres.2018.06.014. [Epub ahead of print]

Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: A systematic review and meta-analysis.

Rovinski D, Ramos RB, Fighera TM, Casanova GK, Spritzer PM.

INTRODUCTION: Hormone therapy (HT) is an effective treatment for climacteric symptoms. Nevertheless, combined estrogen-progestin therapy and the oral route seem to entail higher risk of venous thromboembolism (VTE) than estrogen-only therapy and transdermal administration. The present study aimed to investigate the risk of thromboembolic events in postmenopausal women using non-oral estrogen compared to women using oral estrogen and control groups (women receiving placebo or non-users of HT), as well as to assess the thrombotic impact of estrogens alone vs. combined estrogen-progestin therapy.MATERIALS AND METHODS: Systematic review of MEDLINE, Cochrane CENTRAL, EMBASE, and ClinicalTrials.gov according to PRISMA guidelines. RESULTS: Twenty-two studies were included in the meta-analyses (9 case-control studies, 9 cohort studies, and 4 randomized controlled trials). As compared to control groups, VTE risk was not increased with non-oral HT, including users of estrogens and estrogens plus progestins (OR 0.97 [0.9-1.06]), non-oral estrogen therapy (ET)-only (OR 0.95 [0.81-1.10]), and non-oral combined estrogen-progestin therapy (OR 0.92 [0.77-1.09]). Conversely, increased risk of VTE was observed as compared with control groups in users of oral HT, including users of estrogens and estrogens plus progestins HT (OR 1.72 [1.47-2.01]), oral ET-only (OR 1.43 [1.34-1.53]), and combined oral estrogen-progestin HT (OR 2.35 [1.9-2.9]). The comparison of non-oral vs. oral HT showed increased VTE risk with oral HT (OR 1.66 [1.39-1.98]). CONCLUSIONS: VTE risk was increased in postmenopausal women with no previous thromboembolic events using oral HT. Non-oral HT did not significantly affect this risk. The quality of the

evidence produced in our meta-analyses is low to moderate, and further clinical trials are needed to sort out the impact of different types of progestin and different estrogen doses and administration routes on VTE risk.