Selección de Resúmenes de Menopausia

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Plain vitamin D or active vitamin D in the treatment of osteoporosis: where do we stand today?

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Osteoporosis is a major cause of morbidity and mortality worldwide and its prevention in order to avert fractures was considered of great importance in maintaining well-being and independence among the elderly. Strategies for osteoporosis prevention are well delineated, but research shows that the treatment options offered today could still be improved. The role of plain vitamin D (cholecalciferol) in bone health and the prevention of osteoporosis are well documented; however, as a treatment for osteoporosis, either with or without calcium, it has been shown to be ineffective. This is due in part to the strong negative feedback mechanisms in place in vitamin D-replete patients. However, other factors linked directly to ageing such as oestrogen depletion, reduced kidney or liver function may also be involved in reducing the body's capability to activate plain vitamin efficiently. This is why active vitamin D analogues such as alfacalcidol, 1-α-(OH)D3, are of clinical interest. Alfacalcidol requires only one hydroxylation reaction to become active 1,25-(OH)2-vitamin D3, and the 25-hydroxylase catalyzing this reaction is found in the liver and also interestingly in osteoblasts suggesting a local effect. Registered for use in postmenopausal osteoporosis, in most countries worldwide, alfacalcidol has also shown efficacy in glucocorticoid-induced and male osteoporosis. The present review provides compelling evidence for the efficacy of this compound in the treatment of osteoporosis and prevention of fractures both in monotherapy and when combined with other osteoporotic drugs where additive effects are clear. The safety profile of alfacalcidol is shown to be highly acceptable and it is considered less likely to induce hypercalcaemia than another more widely used analogue, calcitriol. Therefore, it remains unclear as to why alfacalcidol is not more widely used in clinical practice.

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Determinants of attained estradiol levels in response to oral estradiol plus progesterone therapy

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Objectives: Among postmenopausal women taking hormone therapy (HT), the estradiol (E2) dose and E2 levels were differentially associated with change in metabolic measures. We evaluated determinants of attained E2 levels in response to HT. Methods: Postmenopausal women from the REPLENISH trial tested four formulations of oral combined E2 and progesterone compared with placebo. Mixed-effects linear models assessed characteristics associated with E2 levels among women with ≥80% HT compliance, adjusted for E2 dose and baseline E2 level. Results: Among 1173 postmenopausal women with mean (standard deviation) age 55 (4.3) years and 5.2 (4.8) years since menopause, higher treated E2 levels were significantly related to younger age, more recent menopause, and current alcohol use, while lower E2 levels were related to current smoking. Both age and time since menopause were significantly inversely associated with E2 levels; time since menopause had a stronger association with E2 levels. In the final multivariable model, E2 levels were positively associated with current alcohol use, and inversely associated with time since menopause and current smoking. Conclusion: Adjusting for E2 dose and baseline E2 level, on-trial E2 levels were significantly associated with time since menopause, current smoking, and current alcohol use. Practitioners should consider these factors in individual women to achieve a desirable E2 level during HT.

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Endocrine therapy use and cardiovascular risk in postmenopausal breast cancer survivors

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Objective: Examine the effect of tamoxifen and aromatase inhibitors (AIs) on the risk of 12 clinically relevant cardiovascular outcomes in postmenopausal female breast cancer survivors. Methods: We carried out two prospective

cohort studies among postmenopausal women with breast cancer in UK primary care and hospital data (2002-2016) and US Surveillance, Epidemiology and End Results-Medicare data (2008-2013). Using Cox adjusted proportional hazards models, we compared cardiovascular risks between AI and tamoxifen users; and in the USA, between users of both drug classes and women receiving no endocrine therapy. Results: 10 005 (UK) and 22 027 (USA) women with postmenopausal breast cancer were included. In both countries, there were higher coronary artery disease risks in AI compared with tamoxifen users (UK age-standardised incidence rate: 10.17 vs 7.51 per 1000 person-years, HR: 1.29, 95% CI 0.94 to 1.76; US age-standardised incidence rate: 36.82 vs 26.02 per 1000 person-years, HR: 1.29, 95% C I1.06 to 1.55). However, comparisons with those receiving no endocrine therapy (US data) showed no higher risk for either drug class and a lower risk in tamoxifen users (age-standardised incidence rate tamoxifen vs unexposed: 26.02 vs 35.19 per 1000 person-years, HR: 0.74, 95% 0.60 to 0.92; age-standardised incidence rate AI vs unexposed: 36.82 vs 35.19, HR: 0.96, 95% CI 0.83 to 1.10). Similar patterns were seen for other cardiovascular outcomes (arrhythmia, heart failure and valvular heart disease). As expected, there was more venous thromboembolism in tamoxifen compared with both AI users and those unexposed. Conclusions: Higher risks of several cardiovascular outcomes among AI compared with tamoxifen users appeared to be driven by protective effects of tamoxifen, rather than cardiotoxic effects of AIs.

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Sexual dimorphism in cardiometabolic health: the role of adipose tissue, muscle and liver

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Obesity is associated with many adverse health effects, such as an increased cardiometabolic risk. Despite higher adiposity for a given BMI, premenopausal women are at lower risk of cardiometabolic disease than men of the same age. This cardiometabolic advantage in women seems to disappear after the menopause or when type 2 diabetes mellitus develops. Sexual dimorphism in substrate supply and utilization, deposition of excess lipids and mobilization of stored lipids in various key metabolic organs (such as adipose tissue, skeletal muscle and the liver) are associated with differences in tissue-specific insulin sensitivity and cardiometabolic risk profiles between men and women. Moreover, lifestyle-related factors and epigenetic and genetic mechanisms seem to affect metabolic complications and disease risk in a sex-specific manner. This Review provides insight into sexual dimorphism in adipose tissue distribution, adipose tissue, skeletal muscle and liver substrate metabolism and tissue-specific insulin sensitivity in humans, as well as the underlying mechanisms, and addresses the effect of these sex differences on cardiometabolic health. Additionally, this Review highlights the implications of sexual dimorphism in the pathophysiology of obesity-related cardiometabolic risk for the development of sex-specific prevention and treatment strategies.

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Body Shape Trajectories And Risk Of Breast Cancer: Results From The SUN ('Seguimiento Universidad De Navarra') Project

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Objective: The aim of this study was to assess body shape trajectories in childhood and midlife in relation to subsequent risk of breast cancer in a Mediterranean cohort. Design: The SUN Project is a dynamic prospective cohort study of university graduates initiated in 1999. With a group-based modelling approach, we assessed body shape trajectories from age 5 to 40 years. Multivariable Cox regression models were used to estimate the hazard ratio (HR) for breast cancer after the age of 40 years according to the body shape trajectory. Setting: City of Pamplona, in the North of Spain. Participants: 6498 women with a mean age of 40 years (standard deviation: 9 years). Results: We identified four distinct body shape trajectories ['childhood lean-midlife increase' (19.9%), 'childhood medium-midlife stable' (53%), 'childhood heavy-midlife stable' (21%), and 'childhood heavy-midlife increase' (6.1%)]. Among 54,978 women-years of follow-up, we confirmed 82 incident cases of breast cancer. Women in the 'childhood lean-midlife increase' group showed a higher risk of breast cancer (HR=1.84, 95%CI 1.11, 3.04) compared to women in the 'childhood medium-midlife stable' category. This association was stronger for postmenopausal breast cancer (HR=2.42, 95%CI 1.07, 5.48).

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Controversies Regarding Post-Menopausal Hormone Replacement Therapy for Primary Cardiovascular Disease Prevention in Women

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The debate over the safety and benefit of hormone replacement therapy (HRT) in postmenopausal women for primary prevention of cardiovascular disease has been ongoing for the past several decades. Observational trials in the 1980's suggested a benefit of HRT for primary cardiovascular disease prevention. However, randomized controlled trials in the 1990's suggested potential harm. Because of these discrepancies, recommendations from authorities on the usage of postmenopausal HRT have fluctuated. Many believed that the timing of HRT initiation relative to the onset of menopause, also known as the "timing hypothesis," was the factor that could explain the differences among these studies. Some recent investigations have concluded that HRT initiated in postmenopausal women near the onset of menopause confers a cardioprotective benefit, while others simply showed that HRT does not cause harm. Research has expanded to evaluate alternative doses, preparations, routes, and formulations, including selective estrogen receptor modulators, to demonstrate their suitability for this purpose. This article is a review of the major research studies of HRT in postmenopausal women with respect to its safety and efficacy for the primary prevention of cardiovascular disease.

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Premature Menopause, Clonal Hematopoiesis, and Coronary Artery Disease in Postmenopausal Women

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Background: Premature menopause is an independent risk factor for cardiovascular disease in women, but mechanisms underlying this association remain unclear. Clonal hematopoiesis of indeterminate potential (CHIP), the age-related expansion of hematopoietic cells with leukemogenic mutations without detectable malignancy, is associated with accelerated atherosclerosis. Whether premature menopause is associated with CHIP is unknown. Methods: We included postmenopausal women from the UK Biobank (N=11,495) aged 40-70 years with whole exome sequences and from the Women's Health Initiative (WHI, N=8,111) aged 50-79 years with whole genome sequences. Premature menopause was defined as natural or surgical menopause occurring before age 40 years. Co-primary outcomes were the presence of (1) any CHIP and (2) CHIP with variant allele frequency (VAF) >0.1. Logistic regression tested the association of premature menopause with CHIP, adjusted for age, race, the first 10 principal components of ancestry, smoking, diabetes mellitus, and hormone therapy use. Secondary analyses considered natural vs. surgical premature menopause and gene-specific CHIP subtypes. Multivariable-adjusted Cox models tested the association between CHIP and incident coronary artery disease (CAD). Results: The sample included 19,606 women, including 418 (2.1%) with natural premature menopause and 887 (4.5%) with surgical premature menopause. Across cohorts, CHIP prevalence in postmenopausal women with vs. without a history of premature menopause was 8.8% vs. 5.5% (P<0.001), respectively. After multivariable adjustment, premature menopause was independently associated with CHIP (all CHIP: OR 1.36, 95% 1.10-1.68, P=0.004; CHIP with VAF >0.1: OR 1.40, 95% CI 1.10-1.79, P=0.007). Associations were larger for natural premature menopause (all CHIP: OR 1.73, 95% CI 1.23-2.44, P=0.001; CHIP with VAF >0.1: OR 1.91, 95% CI 1.30-2.80, P<0.001) but smaller and non-significant for surgical premature menopause. In gene-specific analyses, only DNMT3A CHIP was significantly associated with premature menopause. Among postmenopausal middle-aged women, CHIP was independently associated with incident coronary artery disease (HR associated with all CHIP: 1.36, 95% CI 1.07-1.73, P=0.012; HR associated with CHIP with VAF >0.1: 1.48, 95% CI 1.13-1.94, P=0.005). Conclusions: Premature menopause, especially natural premature menopause, is independently associated with CHIP among postmenopausal women. Natural premature menopause may serve as a risk signal for predilection to develop CHIP and CHIP-associated cardiovascular disease.