Selección de Resúmenes de Menopausia

Semana del 3 a 9 de mayo, 2023

María Soledad Vallejo. Clínica Quilín. Universidad de Chile

Endocr Pract. 2023 May 4;S1530-891X(23)00400-7. doi: 10.1016/j.eprac.2023.04.011. Online ahead of print.

Bone mineral density response to long-term bisphosphonate treatment and discontinuation in a real-world clinical service

Diane E Powell 1, Sally F Evans 2, Chadi Rakieh 2

Objective: Bisphosphonate treatment does not increase bone mineral density (BMD) in all subjects particularly at the femoral neck (FN). Our aim was to evaluate the relationship between response to oral bisphosphonate (oBP) at the FN and change in BMD following discontinuation. Methods: Data was collected retrospectively from postmenopausal women on oBP for ≥3 years, attending a real-world metabolic clinic at initiation of oBP, discontinuation, and 1-2 years post discontinuation. Improvement in BMD ≥4% in the FN and ≥5% for the lumbar spine (LS) were deemed clinically meaningful and used as least significant change (LSC) values. We divided subjects based on FN BMD response and compared outcomes between responders and non-responders after oBP discontinuation. Results: Of the 213 subjects, 32.1% showed an increase ≥LSC at the FN compared to 57.1% at the LS on treatment (p<0.0001). FN responders had lower BMD levels at pre-treatment baseline than non-responders both at the FN (0.58 vs. 0.62 g/cm2; p=0.003) and LS (0.76 vs 0.79 g/cm2; p=0.044). Off-treatment, more subjects lost BMD ≥LSC at FN in the responder group than in the non-responder group (37.5% vs. 14.2%; p<0.001). BMD remained above pre-treatment levels in responders after a median follow-up of 1.52 years. Conclusion: BMD response at FN is suboptimal in patients on oBP and is much less common than LS response. FN responders tend to lose the accumulated bone quickly off-treatment, though BMD remains above pre-treatment levels. These observations suggest that new approaches may be needed to optimise osteoporosis management in real-world patients.

Ageing Res Rev. 2023 May 2;101943. doi: 10.1016/j.arr.2023.101943. Online ahead of print.

Exploring cellular senescence in the musculoskeletal system: any insights for biomarkers discovery?

Laura Gerosa 1, Amir Mohammad Malvandi 2, Marco Malavolta 3, Mauro Provinciali 4, Giovanni Lombardi 5

The locomotor system comprises skeletal muscles and bones with active metabolism and cellular turnover. Chronic locomotor system disorders gradually arising with aging are inversely associated with the correct function of bone and muscles. Senescent cells appear more frequently in advanced ages or pathological conditions, and the accumulation of senescent cells in muscle tissue negatively correlates with muscle regeneration, which is crucial for maintaining strength and preventing frailty. Senescence in the bone microenvironment, osteoblasts, and osteocytes affects bone turnover favoring osteoporosis. It is likely that in response to injury and age-related damage over the lifetime, a subset of niche cells accumulates oxidative stress and DNA damage beyond the threshold that primes the onset of cellular senescence. These senescent cells may acquire resistance to apoptosis that, combined with the weakened immune system, results in impaired clearance of senescent cells and their accumulation. The secretory profile of senescent cells causes local inflammation, further spreading senescence in neighboring niche cells and impairing tissue homeostasis. The resulting impairment of turnover/tissue repair in the musculoskeletal system reduces the efficiency of the organ in response to environmental needs that finally lead to functional decline. Management of the musculoskeletal system at the cellular level can benefit the quality of life and reduce early aging. This work discusses current knowledge of cellular senescence of musculoskeletal tissues to conclude with biologically active biomarkers effective enough to reveal the underlying mechanisms of tissue flaws at the earliest possible.

Epidemiol Health. 2023 May 1;e2023049. doi: 10.4178/epih.e2023049. Online ahead of print.

Changes in metabolic syndrome and risk of breast and endometrial cancers according to menopause

Thi Xuan Mai Tran 1, Soyeoun Kim 1, Boyoung Park 2

Objectives: This study investigated how changes in metabolic syndrome (MetS) are associated with the subsequent risk of breast and endometrial cancer according to menop ausal status.Methods: This cohort study, using data from the National Health Insurance Service database, included women aged ≥40 years who underwent 2 biennial cancer screenings (2009-2010 and 2011-2012) and were followed up until 2020. Participants were grouped into MetS-free, MetS-recovery, MetS-development, and MetS-persistent groups. Menopausal status (premenopausal, perimenopausal, and postmenopausal) was assessed at 2 screenings. Cox proportional hazard regression was used to assess the association between MetS changes and cancer risk. Results: In 3,031,980 women, breast and endometrial cancers were detected in 39,184 and 4,298, respectively. Compared with the MetS-free group, those who recovered, developed, or had persistent MetS showed an increased risk of breast cancer, with adjusted hazard ratios (aHRs) of 1.05, 1.05, and 1.11, respectively ($p<0.005$). MetS persistence was associated with an increased risk of breast cancer in postmenopausal women (aHR=1.12, 95% CI, 1.08-1.16) but not in premenopausal or perimenopausal women. MetS persistence was associated with an increased risk of endometrial cancer in premenopausal, perimenopausal, and postmenopausal women, with aHRs of 1.41 (95% CI, 1.17-1.70), 1.59 (95% CI, 1.19-2.12), and 1.47 (95% CI, 1.32-1.63), respectively. Conclusion: Increased breast cancer risk was associated with recovered, developed, and persistent MetS in postmenopausal women. Meanwhile, increased endometrial cancer risk was found in obese women who recovered from MetS or persistently had MetS, regardless of menopausal status, when compared to MetS-free women.

Curr Med Chem. 2023 May 1. doi: 10.2174/0929867330666230501231528. Online ahead of print.

Selective Activation of G protein-coupled Estrogen Receptor 1 Attenuates Atherosclerosis

Mohammad Zulqurnain Haider 1, Amirhossein Sahebkar 2, Ali H Eid 1

Atherosclerosis remains a leading contributor to cardiovascular disease-associated morbidity and mortality. Interestingly, the death rate is higher in men than women from atherosclerosis, and the risk increases for postmenopausal women. This suggested a protective role for estrogen in the cardiovasculature. These effects of estrogen were initially thought to be mediated by the classic estrogen receptors, ER alpha, and beta. However, genetic knockdown of these receptors did not abolish estrogen's vasculoprotective effects suggesting that the other membranous G-protein coupled estrogen receptor, GPER1, maybe the actual mediator. Indeed, in addition to its role in vasotone regulation, this GPER1 appears to play important roles in regulating vascular smooth cell phenotype, a critical player in the onset of atherosclerosis. Moreover, GPER1-selective agonists appear to reduce LDL levels by promoting the expression of LDL receptors as well as potentiating LDL re-uptake in liver cells. Further evidence also show that GPER1 can downregulate Proprotein Convertase Subtilisin/Kexin type 9, leading to suppression of LDL receptor breakdown. Here, we review how selective activation of GPER1 might prevent or suppress atherosclerosis, without the many undesired side effects of the non-selective estrogen.

BMJ. 2023 May 3;381:e074778. doi: 10.1136/bmj-2023-074778.

Association between SARS-CoV-2 vaccination and healthcare contacts for menstrual disturbance and bleeding in women before and after menopause: nationwide, register based cohort study

Rickard Ljung 1 2, YiYi Xu 3, Anders Sundström 4, Susannah Leach 5 6, Ebba Hallberg 4, Maria Bygdell 3 7, et al.

Objectives: To evaluate the risks of any menstrual disturbance and bleeding following SARS-CoV-2 vaccination in women who are premenopausal or postmenopausal. Design: A nationwide, register based cohort study. Setting: All inpatient and specialised outpatient care in Sweden from 27 December 2020 to 28 February 2022. A subset covering primary care for 40% of the Swedish female population was also included. Participants: 2 946 448 Swedish women aged 12-74 years were included. Pregnant women, women living in nursing homes, and women with history of any menstruation or bleeding disorders, breast cancer, cancer of female genital organs, or who underwent a hysterectomy between 1 January 2015 and 26 December 2020 were excluded. Interventions: SARS-CoV-2 vaccination, by vaccine product (BNT162b2, mRNA-1273, or ChAdOx1 nCoV-19 (AZD1222)) and dose (unvaccinated and first, second, and third dose) over two time windows (one to seven days, considered the control period, and 8-90 days). Main outcome measures: Healthcare contact (admission to hospital or visit) for menstrual disturbance or bleeding before or after menopause (diagnosed with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes N91, N92, N93, N95). Results: 2 580 007 (87.6%) of 2 946 448 women received at least one SARS-CoV-2 vaccination and 1 652 472 (64.0%) 2 580 007 of vaccinated women received three doses before the end of

follow-up. The highest risks for bleeding in women who were postmenopausal were observed after the third dose, in the one to seven days risk window (hazard ratio 1.28 (95% confidence interval 1.01 to 1.62)) and in the 8-90 days risk window (1.25 (1.04 to 1.50)). The impact of adjustment for covariates was modest. Risk of postmenopausal bleeding suggested a 23-33% increased risk after 8-90 days with BNT162b2 and mRNA-1273 after the third dose, but the association with ChAdOx1 nCoV-19 was less clear. For menstrual disturbance or bleeding in women who were premenopausal, adjustment for covariates almost completely removed the weak associations noted in the crude analyses. Conclusions: Weak and inconsistent associations were observed between SARS-CoV-2 vaccination and healthcare contacts for bleeding in women who are postmenopausal, and even less evidence was recorded of an association for menstrual disturbance or bleeding in women who were premenopausal. These findings do not provide substantial support for a causal association between SARS-CoV-2 vaccination and healthcare contacts related to menstrual or bleeding disorders.

Drugs R D. 2023 May 3. doi: 10.1007/s40268-023-00419-5. Online ahead of print.

Estetrol: From Preclinical to Clinical Pharmacology and Advances in the Understanding of the Molecular Mechanism of Action

Céline Gérard 1, Jean-Michel Foidart 2 3

Estetrol (E4) is the most recently described natural estrogen. It is produced by the human fetal liver during pregnancy and its physiological function remains unclear. E4 is the estrogenic component of a recently approved combined oral contraceptive. It is also in development for use as menopausal hormone therapy. In the context of these developments, the pharmacological activity of E4, alone or in combination with a progestin, has been extensively characterized in preclinical models as well as in clinical studies in women of reproductive age and postmenopausal women. Despite the clinical benefits, the use of oral estrogens for contraception or menopause is also associated with unwanted effects, such as an increased risk of breast cancer and thromboembolic events, due to their impact on non-target tissues. Preclinical and clinical data for E4 point to a tissue-specific activity and a more selective pharmacological profile compared with other estrogens, including a low impact on the liver and hemostasis balance. This review summarizes the characterization of the pharmacological properties of E4 as well as recent advances made in the understanding of the molecular mechanisms of action driving its activity. How the unique mode of action and the different metabolism of E4 might support its favorable benefit-risk ratio is also discussed.

BJOG. 2023 May 2. doi: 10.1111/1471-0528.17511. Online ahead of print.

Care after premenopausal risk-reducing salpingo-oophorectomy in high-risk women: Scoping review and international consensus recommendations

Denise R Nebgen 1, Susan M Domchek 2, Joanne Kotsopoulos 3, Joanne A de Hullu 4, Emma J Crosbie 5, et al,

Women at high inherited risk of ovarian cancer are offered risk-reducing salpingo-oophorectomy (RRSO) from age 35 to 45 years. Although potentially life-saving, RRSO may induce symptoms that negatively affect quality of life and impair long-term health. Clinical care following RRSO is often suboptimal. This scoping review describes how RRSO affects short- and long-term health and provides evidence-based international consensus recommendations for care from preoperative counselling to long-term disease prevention. This includes the efficacy and safety of hormonal and non-hormonal treatments for vasomotor symptoms, sleep disturbance and sexual dysfunction and effective approaches to prevent bone and cardiovascular disease.

Arch Osteoporos. 2023 May 2;18(1):60. doi: 10.1007/s11657-023-01247-5.

Global prevalence of osteosarcopenic obesity amongst middle aged and older adults: a systematic review and meta-analysis

Ying Liu 1, Yi Song 2, Qinjian Hao 1, Jinhui Wu 3

Purpose: Osteosarcopenic obesity syndrome (OSO) is a recently recognized disorder encompassing osteopenia/osteoporosis, sarcopenia, and obesity. However, evidence in pooling knowledge regarding the prevalence of OSO worldwide is scarce. Hence, this review aimed to determine the pooled prevalence of OSO in middle-aged and older adults. Methods: We conducted systematic searches in Scopus, Embase, PubMed Central, MEDLINE, ScienceDirect, and Google Scholar from inception until October 2022. We evaluated the quality of the included studies using the Newcastle-Ottawa scale. The meta-analysis results using a random-effects model included the pooled

prevalence and 95% confidence intervals (CIs). Results: We included 20 studies with a total of 23,909 participants. Most of the studies were of good quality. The final pooled prevalence of OSO in middle-aged and older adults worldwide was 8% (95% CI: 6%-11%; n = 20). Females (pooled prevalence = 9%; 95% CI:7%-12%; n = 17) had a higher burden of OSO than males (pooled prevalence = 5%; 95% CI:3%-8%; n = 11). We also found that the burden was higher among studies reporting OSO prevalence only in the elderly population (pooled prevalence = 13%; 95% CI: 9%-17%). The asymmetric nature of the funnel plot indicates the presence of publication bias. Additional sensitivity analysis did not reveal any significant variation in the pooled effect size estimation. Conclusion: Approximately one in ten middle-aged and older adults suffer from OSO. The burden was highest among females and older adults. Diagnostic and intervention packages targeting such patients should be developed and implemented in high-risk settings.

Iran J Public Health. 2023 Mar;52(3):534-541. doi: 10.18502/ijph.v52i3.12136.

Early Menopause and Risk of Fractures-A Preventable Gap

Ivana Minaković 1 2, Jelena Zvekić-Svorcan 1 3, Tanja Janković 1 3, Miljanka Vuksanović 4 5, et al

Background: Osteoporosis is a chronic disease that results in microarchitectural changes to the bone, thereby reducing its density and increasing the risk of fractures. This retrospective cross-sectional study aimed to examine the link between the risk of major osteoporotic fractures and hip fractures with the age of menopause onset, as well as the impact of menopause duration on fracture incidence. Methods: This retrospective cross-sectional study was conducted at the Special Hospital for Rheumatic Diseases, Novi Sad, Serbia. The data required for meeting the study objectives were obtained from patients' medical records spanning the 2015-2018 period. The sample for the study comprised of 985 postmenopausal women aged ≥ 50 yr who underwent bone mineral densitometry examination and received a FRAX score for major osteoporotic fractures and hip fractures with and without bone mineral density. The obtained FRAX scores were compared across the subjects with respect to the age of menopause onset and menopause duration. Results: The group that entered into menopause before the age of 45 had a high risk of hip fracture (OR: 1,652; 95% CI: 1,138 - 2,399; P<.01) and a higher mean FRAX score for hip fracture compared to women in whom menopause started after the age of 45 (Me=1.60 vs. 1.30, P<.004). FRAX scores were also correlated with menopause duration, and the difference between the groups with the longest (over 20 yr) and the shortest (1-10 yr) duration was statistically significant at P<.001. Conclusion: As menopause duration could contribute to the prediction of fracture risk, its inclusion in the FRAX algorithm should be considered, while also taking into account the age of menopause onset.