Selección de Resúmenes de Menopausia

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Progestins and breast cancer hallmarks: The role of the ERK1/2 and JNK pathways in estrogen receptor positive breast cancer cells

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Progestins used in hormonal contraceptives and menopausal hormone therapy (MHT) have been linked to increased breast cancer risk. Whether the association holds for all progestins is unclear and the underlying mechanisms remain poorly understood. We directly compared the effects of four progestins (medroxyprogesterone acetate (MPA), norethisterone acetate (NET-A), levonorgestrel (LNG) and drospirenone (DRSP)) to each other and the natural progestogen progesterone (P4) on selected cancer hallmarks. To provide mechanistic insight into these effects, we assessed the role of the progesterone receptor (PR), and the extracellular signal-related kinase (ERK1/2) and c-Jun N terminal (JNK) signaling pathways. We showed that the increased proliferation of the luminal T47D breast cancer cell line by P4 and all progestins, albeit to different extents, was inhibited by PR knockdown and inhibition of both the ERK1/2 and JNK pathways. While knockdown of the PR also blocked the upregulation of MKI67 and CCND1 mRNA expression by selected progestogens, only a role for the ERK1/2 pathway could be established in these effects. Similarly, only a role for the ERK1/2 pathway could be confirmed for progestogen-induced colony formation, whereas both the ERK1/2 and JNK pathways were required for cell migration in response to the three older progestins implicated in the etiology of breast cancer, MPA, NET-A and LNG. Together our results show that all the progestins elicit their effects on cell proliferation via a mechanism requiring the PR, ERK1/2 and JNK pathways. While the ERK1/2 and JNK pathways are also required for increased cell migration by the older progestins, only a role for the ERK1/2 pathway could be established in their effects on colony formation. Notably, the cytoplasmic PR was not needed for activation of the ERK1/2 pathway by the progestogens. Given that DRSP showed significantly lower proliferation than MPA and NET-A, and that it had no effect on breast cancer cell migration and colony formation, hormonal formulations containing the newer generation progestin DRSP may provide a better benefit/risk profile towards breast cancer than those containing the older generation progestins.

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Menopausal hormone therapy increases the risk of gallstones: Health Insurance Database in South Korea (HISK)-based cohort study

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Objective: To determine whether menopausal hormone therapy (MHT) increases the risk of gallstones and gallbladder cancer. Design: A retrospective cohort study. Patients or other participants: Data from the Korea National Health Insurance Corporation was obtained between January 1, 2002, and December 31, 2019. Interventions: Participants were divided into MHT and non-MHT groups; the MHT group was analyzed in detail by dividing participants into tibolone, combined estrogen plus progestin by the manufacturer (CEPM) or physician (CEPP), oral estrogen alone, and topical estrogen subgroups. Main outcome measures: The incidence of gallstones and gallbladder cancer was compared between the two groups. Results: This study enrolled 1,004,034 and 381,711 patients in the non-MHT and the MHT groups, respectively. The incidence of gallstones was 2.6% in the non-MHT group and 3.4%, 2.6%, 3.4%, 3.2%, and 4.4% in the tibolone, CEPM, oral estrogen alone, CEPP, and topical estrogen groups, respectively. Cox proportional hazard analysis revealed that all hormones increased the risk of gallstones ([tibolone] hazard ratio [HR]: 1.347, 95% confidence interval [CI]: 1.309-1.387, [CEPM] HR: 1.146, 95% CI: 1.1-1.19, [oral estrogen alone] HR: 1.241, 95% CI: 1.18-1.305, [CEPP] HR: 1.164, 95% CI: 1.01-1.341, [topical estrogen] HR: 1.602, 95% CI: 1.295-1.983). However, the risk of gallbladder cancer did not change with any hormone therapy. Conclusions: All types of MHT including tibolone, increased the risk of gallstones. This risk was the highest with topical estrogen, which may be a result of selection bias due to concerns regarding the adverse effects of CEE and MPA.

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Nutrition Interventions on Muscle-Related Components of Sarcopenia in Females: A Systematic Review of Randomized Controlled Trials

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Sarcopenia is a skeletal muscle disease categorized by low muscle strength, muscle quantity or quality, and physical performance. Sarcopenia etiology is multifaceted, and while resistance training is widely agreed upon for prevention and treatment, disease progression is also highly related to poor diet. The incidence of sarcopenia appears sex-specific and may be increased in females, which is problematic because dietary quality is often altered later in life, particularly after menopause. Identifying effective nutrition or supplementation interventions could be an important strategy to delay sarcopenia and related comorbidities in this vulnerable population. This systematic review examined randomized controlled trials (RCTs) of nutrition strategies on muscle-related components of sarcopenia in middle-aged and older females. A protocol was registered (PROSPERO CRD42022382943) and a systematic search of MEDLINE and CINAHL was undertaken. RCTs from 2013 to 2023 that assessed nutrition-only interventions on muscle mass, muscle strength, and physical function in female participants were included. Fourteen RCTs were included based on selection criteria. Study designs and interventions were heterogeneous in supplementation type and amount, age, and duration. Six RCTs reported beneficial effects of protein, Vitamin D, Vitamin D and Magnesium (Mg), and fish oil on muscle protein synthesis, muscle strength, and/or muscle function. Eight studies that examined various protein interventions, VitD alone, Mg alone, and dairy derivatives did not demonstrate any effect. Exercise appeared to modulate results in several studies. Nutrition interventions alone are likely to have a limited but positive effect on muscle-related components of sarcopenia in females. Current evidence suggests that a combination of dietary intervention and exercise is likely to be key to preventing and treating sarcopenia in middle aged and older females and there is a need for well-designed nutrition based studies in this population.

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A Cross-sectional Assessment of Depression, Anxiety, and Cognition in Perimenopausal and Menopausal Women

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Introduction: Menopausal transition involves failure of ovarian function followed by cessation of menstruation. This has been said to lead to psychiatric comorbidities such as depression and anxiety. Estrogen also has beneficial effects on cognition and thus fluctuation in the same can lead to cognitive decline. Given the number of women undergoing menopause, timely screening of the comorbidities is of importance.Aims and objectives: Our study aimed at assessment of anxiety, depression, and cognitive impairment in perimenopausal and postmenopausal women presenting in the medicine and gynecology units of a tertiary care hospital. The objectives were to screen the peri- and postmenopausal women presenting with medical and gynecological complaints for the presence of depression and anxiety and assess their cognitive function. To find association of their symptoms with psychosocial and menopausal factors with the psychiatric parameters. Settings and design: Our study was conducted among the perimenopausal and postmenopausal women visiting gynecology and medicine units in a tertiary care hospital. One hundred and five women in the age group of 45-55 were assessed using a specialized pro forma, Beck's Anxiety Inventory, Beck's Depression Inventory, and Addenbrooke's Cognitive Examination III. Statistical analysis used: The results were analyzed using SPSS software (version 20.0). Results: 21.9% of females had moderate levels of anxiety, 24.76% had clinical depression, and 13.33% had mild cognitive impairment. The presence of psychosocial stressors had a significant impact on the anxiety, depression, and cognitive impairment. There was no significant association found between psychiatric parameters and peri- and postmenopausal stage as well between natural or surgical menopause.

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Association of the visceral adiposity index with femur bone mineral density and osteoporosis among the U.S. older adults from NHANES 2005-2020: a cross-sectional study

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Background: The visceral adiposity index (VAI) is a marker of abdominal fat distribution and adipose tissue function. However, the association between VAI and femur bone mineral density (BMD) and osteoporosis is unclear among the U.S. older adults. Methods: Cross-sectional data for adults aged 60 years and older from the 2007-2020 National Health and Nutrition Examination Survey (NHANES) were included. Multivariable linear and logistic regression were used to evaluate the association between VAI and femur BMD and osteoporosis. We used the smooth curve fitting to address nonlinearity. Moreover, a two-piecewise linear regression model was used to explain the nonlinearity further. Results: The findings of the multivariable logistic regression models showed that as the VAI value increased by one unit, the prevalence

of osteoporosis decreased by 1.2% after adjusting for covariates associated with osteoporosis. The multivariable linear regression models demonstrated that VAI was positively correlated with femur BMD. Further analysis revealed an inverted L-shaped and inverted U-shaped relationship between VAI and femur BMD at different sites. Conclusions: Our findings indicated that an increased VAI is independently linked to a higher prevalence of osteoporosis among the U.S. older adults. Further analysis reveals that once VAI reaches a certain threshold, femur BMD no longer increases and may even decrease. This suggests that a moderate accumulation of visceral fat may be beneficial for bone health, while excessive visceral fat could potentially have detrimental effects.

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Discontinuation of hormone therapy and bone mineral density: does physical activity modify that relationship?

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Objective: Hormone therapy can positively impact bone mineral density after menopause. We explored bone mineral density change in postmenopausal women who discontinued hormone therapy after the Women's Health Initiative landmark 2002 trial results were published. We secondarily explored whether usual physical activity modified the results. Methods: Postmenopausal women participating in the Buffalo OsteoPerio study with information on hip bone density, hormone therapy use, and self-reported physical activity at two time points (1997-2001; 2002-2007) were included (N = 961). Hormone therapy included three groups according to use at baseline and year 5 (non/non; current/non; current/current). Results: At baseline (mean age, 65.9 years; SD, 6.7 years), 480 women were not using hormone therapy, while 481 were current users. Between the baseline and 5-year visits, 336 women using hormone therapy discontinued. Baseline total hip bone density was highest in current users. After 5 years, those who continued hormone therapy exhibited no bone loss; those who discontinued exhibited the greatest loss at the total hip of -0.021 gm/cm2. Women who never used hormone therapy exhibited some loss of -0.012 gm/cm2. Usual physical activity did not appreciably impact change in bone density in any group. Conclusions: This prospective observational study explored the 5-year change in bone mineral density among older postmenopausal women after the landmark 2002 hormone therapy trial findings were released. We found bone density decreased in never-users and in women who discontinued use. Bone density was maintained in current users. Although usual physical activity did not mitigate bone loss, targeted physical activity regimens should be investigated.

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Systematic review and network meta-analysis comparing the efficacy of fezolinetant with hormone and nonhormone therapies for treatment of vasomotor symptoms due to menopause

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Importance: The neurokinin 3 receptor antagonist fezolinetant 45 mg/d significantly reduced frequency/severity of moderate to severe vasomotor symptoms (VMS) of menopause compared with placebo in two phase 3 randomized controlled trials. Its efficacy relative to available therapies is unknown. Objective: We conducted a systematic review and Bayesian network meta-analysis to compare efficacy with fezolinetant 45 mg and hormone therapy (HT) and non-HT for VMS in postmenopausal women. Evidence review: Using OvidSP, we systematically searched multiple databases for phase 3 or 4 randomized controlled trials in postmenopausal women with ≥7 moderate to severe VMS per day or ≥50 VMS per week published/presented in English through June 25, 2021. Mean change in frequency and severity of moderate to severe VMS from baseline to week 12 and proportion of women with ≥75% reduction in VMS frequency at week 12 were assessed using fixed-effect models. Findings: The network meta-analysis included data from the pooled phase 3 fezolinetant trials plus 23 comparator publications across the outcomes analyzed (frequency, 19 [34 regimens]; severity, 6 [7 regimens]; ≥75% response, 9 [15 regimens]). Changes in VMS frequency did not differ significantly between fezolinetant 45 mg and any of the 27 HT regimens studied. Fezolinetant 45 mg reduced the frequency of moderate to severe VMS events per day significantly more than all non-HTs evaluated: paroxetine 7.5 mg (mean difference [95% credible interval {CrI}], 1.66 [0.63-2.71]), desvenlafaxine 50 to 200 mg (mean differences [95% CrI], 1.12 [0.10-2.13] to 2.16 [0.90-3.40]), and gabapentin ER 1800 mg (mean difference [95% CrI], 1.63 [0.48-2.81]), and significantly more than placebo (mean difference, 2.78 [95% CrI], 1.93-3.62]). Tibolone 2.5 mg (the only HT regimen evaluable for severity) significantly reduced VMS severity compared with fezolinetant 45 mg. Fezolinetant 45 mg significantly reduced VMS severity compared with desvenlafaxine 50 mg and placebo and did not differ significantly from higher desvenlafaxine doses or gabapentin ER 1800 mg. For ≥75% responder rates, fezolinetant 45 mg was less effective than tibolone 2.5 mg

(not available in the United States) and conjugated estrogens 0.625 mg/bazedoxifene 20 mg (available only as 0.45 mg/20 mg in the United States), did not differ significantly from other non-HT regimens studied and was superior to desvenlafaxine 50 mg and placebo. Conclusions: The only HT regimens that showed significantly greater efficacy than fezolinetant 45 mg on any of the outcomes analyzed are not available in the United States. Fezolinetant 45 mg once daily was statistically significantly more effective than other non-HTs in reducing the frequency of moderate to severe VMS.