Selección de Resúmenes de Menopausia

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Decline in endothelial function across the menopause transition in healthy women is related to decreased estradiol and increased oxidative stress

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Endothelial function declines progressively across stages of the menopause transition; however, the mechanisms contributing to this decline are unknown. We hypothesized that differences in endothelial function among pre-, peri, and postmenopausal women are related to differences in estradiol and oxidative stress. Brachial artery flow-mediated dilation (FMD) was measured in 87 healthy women categorized by menopause stage (24 premenopausal, 17 early and 21 late perimenopausal, and 25 postmenopausal) before and after 3 days of ovarian hormone suppression (gonadotropin releasing hormone antagonist [GnRHant]) alone, and an additional 3 days of GnRHant with concurrent transdermal estradiol or placebo add-back treatment. In 82 women, FMD during acute vitamin C (antioxidant) infusion was measured before and after GnRHant + add-back. Before GnRHant, FMD was different among groups ($p < 0.005$; reduced across stages of menopause). Vitamin C increased FMD in late peri- and post- ($p < 0.005$) but not pre- or early perimenopausal women ($p > 0.54$). After GnRHant alone, FMD decreased in pre- and peri- ($p < 0.01$), but not postmenopausal women, and was restored to premenopausal levels by estradiol add-back in the pre- and perimenopausal groups. Vitamin C improved FMD in pre-, peri-, and postmenopausal women on GnRHant + placebo. There was no effect of vitamin C on FMD in women on GnRHant + estradiol. These observations support the concept that the decline in endothelial function across the menopause transition is related to the loss of ovarian estradiol. The decline in estradiol may alter redox balance, thereby increasing oxidative stress and impairing endothelial function.

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Risk factors predicting osteosarcopenia in postmenopausal women with osteoporosis: A retrospective study

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There is growing interest in "osteosarcopenia" as the coexistence of osteoporosis and sarcopenia exacerbates negative outcomes. However, limited information is available regarding the risk factors of osteosarcopenia development in patients with osteoporosis. Therefore, we retrospectively reviewed 276 consecutive patients with postmenopausal osteoporosis who regularly visited Showa University Hospital. Patients were eligible for the study if they were ≥65 years of age and underwent dual-energy X-ray absorptiometry, blood sampling, and physical performance assessment. Patients were divided into the osteosarcopenia and osteoporosis alone groups according to the diagnostic criteria of the Asian Working Group for Sarcopenia. Of the 276 patients with osteoporosis, 54 patients (19.6%) had osteosarcopenia. Patients in the osteosarcopenia group had a greater risk of frailty than did those in the osteoporosis alone group (odds ratio 2.33; 95% confidence interval, 1.13-4.80, P = 0.028). Low body mass index seemed to be the strongest factor related to the development of osteosarcopenia, and none of the patients in the osteosarcopenia group were obese (BMI ≥27.5 kg/m2). Multiple logistic analyses revealed that patients aged 65-74 years who had comorbidities such as kidney dysfunction and high levels of HbA1c were at risk of developing osteosarcopenia. Thus, we strongly recommend the assessment of the key components of the diagnosis of osteosarcopenia in an osteoporosis clinic for patients with low body mass index. Furthermore, appropriate assessments, including comorbidities, will help in identifying patients at greater risk of developing osteosarcopenia.

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Reproductive history and osteoarthritis in the Women's Health Initiative

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Objective: To investigate the relationship between self-reported osteoarthritis (OA) and reproductive factors in the Women's Health Initiative (WHI). Method: We used multivariable logistic regression to study the association of self-reported OA and reproductive factors in the WHI Observational Study and Clinical Trial cohorts of 145 965

postmenopausal women, in a retrospective cross-sectional format. Results: In our cohort, we observed no clinically significant associations between reproductive factors and OA given small effect sizes. The following factors were associated with statistically significant increased likelihood of developing OA: younger age at menarche ($p < 0.001$), history of hysterectomy [adjusted odds ratio (aOR) 1.013, 95% confidence interval (CI) 1.004-1.022, $p = 0.04$ vs no hysterectomy], history of unilateral oophorectomy (aOR 1.015, 95% CI 1.004-1.026, $p < 0.01$ vs no oophorectomy), parity (aOR 1.017, 95% CI 1.009-1.026, $p < 0.001$), ever use of oral contraceptives (aOR 1.008, 95% CI 1.001-1.016, $p < 0.01$ vs never use), and current use of hormonal therapy (reference current users, aOR 0.951, 95% CI 0.943-0.959 for never users; aOR 0.981, 95% CI 0.972-0.989 for past users; global $p < 0.001$). Age at menopause, first birth, and pregnancy were not associated with OA. Among parous women, no clear pattern was observed with number of pregnancies, births, or duration of breastfeeding in relation to OA. Conclusion: Our study showed that reproductive factors did not have significant clinical associations with OA after controlling for confounders. This may be due to complex hormonal effects. Additional investigation is warranted in prospective cohort studies.

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Anti-inflammatory effects of androgens in the human vagina

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Chronic inflammation is involved in the genitourinary syndrome of menopause (GSM) and beneficial effects of androgens in the vagina have been described. We investigated the potential involvement of human vagina smooth muscle cells (hvSMCs) in the inflammatory response and the immunomodulatory effect of androgen receptor (AR) agonist dihydrotestosterone (DHT). HvSMCs isolated from menopausal women were evaluated for sex steroids receptors and toll-like receptors mRNA expression, and left untreated or treated in vitro with lipopolysaccharide (LPS) or IFNγ, in the presence or absence of DHT. We evaluated mRNA expression (by RT-PCR) and secretion in cell culture supernatants (by a bead-based immunoassay) of pro-inflammatory markers. Nuclear translocation of NF-κB (by immunofluorescence) and cell surface HLA-DR expression (by flow cytometry) were also evaluated. Similar experiments were repeated in rat vSMCs (rvSMCs). In hvSMCs and rvSMCs, AR was highly expressed. DHT pre-treatment inhibited LPS induced-mRNA expression of several pro-inflammatory mediators (i.e. COX2, IL6, IL12A and IFNγ), effect significantly blunted by AR antagonist bicalutamide. DHT significantly counteracted the secretion of IL1RA, IL2, IL5, IL15, FGF, VEGF and TNFα. LPS-induced NF-κB nuclear translocation was significantly inhibited by DHT, an effect counteracted by bicalutamide. DHT pre-treatment significantly decreased IFNγ-induced expression of HLA-DR, mRNA expression of iNOS, COX2 and MCP1, and secretion of IL1, IL2, IL5, IL6, MCP1 and GCSF. Similar effects were observed in rvSMCs. The activation of AR suppresses the inflammatory response in hvSMCs, reducing their potential to be involved in the initiation and maintaining of inflammation, thus representing a therapeutic strategy in conditions like the GSM.

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Sex Hormones and Novel Corona Virus Infectious Disease (COVID-19)

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Given the rapid spread of the coronavirus disease 2019 (COVID-19) pandemic and its overwhelming effect on health care systems and the global economy, innovative therapeutic strategies are urgently needed. The proposed primary culprit of COVID-19 is the intense inflammatory response-an augmented immune response and cytokine storm-severely damaging the lung tissue and rendering some patients' conditions severe enough to require assisted ventilation. Sex differences in the response to inflammation have been documented and can be attributed, at least in part, to sex steroid hormones. Moreover, age-associated decreases in sex steroid hormones, namely, estrogen and testosterone, may mediate proinflammatory increases in older adults that could increase their risk of COVID-19 adverse outcomes. Sex hormones can mitigate the inflammation response and might provide promising therapeutic potential for patients with COVID-19. In this article, we explore the possible anti-inflammatory effects of estrogen and testosterone and the anabolic effect of testosterone, with particular attention to the potential therapeutic role of hormone replacement therapy in older men and women with COVID-19.

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Fracture risk assessment in celiac disease: a registry-based cohort study

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Celiac disease is associated with an increased fracture risk but is not a direct input to the FRAX® calculation. When celiac disease is considered as a secondary osteoporosis risk factor or BMD is included in the FRAX assessment, FRAX accurately predicts fracture risk. Introduction: The fracture risk assessment tool (FRAX®) uses clinical factors and bone mineral density (BMD) measurement to predict 10-year major osteoporotic (MOF) fracture probability. The study aim was to determine whether celiac disease affects MOF risk independent of FRAX score. Methods: The Manitoba BMD Registry includes clinical data, BMD measurements, 10-year probability of MOF calculated for each individual using the Canadian FRAX tool and diagnosed celiac disease. Using linkage to population-based healthcare databases, we identified incident MOF diagnoses over the next 10 years for celiac disease and general population cohorts. Results: Celiac disease (N = 693) was associated with increased fracture risk adjusted for FRAX score computed without secondary osteoporosis or BMD (adjusted hazard ratio [HR] 1.43, 95% confidence interval [CI] 1.11-1.86). Celiac disease was no longer a significant risk factor for fracture when secondary osteoporosis or BMD were included in the FRAX calculation ($p > 0.1$). In subjects with celiac disease, each SD increase in FRAX score (calculated with and without secondary osteoporosis or BMD) was associated with higher risk of incident MOF (adjusted HR 1.66 to 1.80), similar to the general population (p-interaction > 0.2). Including celiac disease as secondary osteoporosis or including BMD in FRAX 10-year MOF probability calculations (10.1% and 8.6% respectively) approximated the observed cumulative 10-year MOF probability (10.8%, 95% CI 7.8-13.9%). Conclusions: Celiac disease is associated with an increased risk of major osteoporotic fractures. When celiac disease is considered as a secondary osteoporosis risk factor or BMD is included in FRAX assessment, FRAX accurately predicts fracture risk.

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Vasomotor symptoms and lipids/lipoprotein subclass metrics in midlife women: Does level of endogenous estradiol matter? The SWAN HDL Ancillary Study

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Background: A greater frequency of vasomotor symptoms (VMSs) has been associated with higher low-density lipoprotein cholesterol (LDL-C), but the association with high-density lipoprotein cholesterol (HDL-C) remains unclear. Endogenous estradiol (E2) levels are associated with both VMS and lipid levels and thus may confound such associations. Objectives: To assess the relationship of VMS frequency with HDL-C, LDL-C, and lipoprotein concentrations (HDL and LDL particles [HDL-P; LDL-P]) and lipoprotein sizes in midlife women and to evaluate whether these associations are explained by E2. Methods: Participants were from the Study of Women's Health Across the Nation (SWAN) HDL ancillary study who had both nuclear magnetic resonance (NMR) spectroscopy lipoprotein subclass metrics and self-reported frequency of VMS measured 2-5 times over the menopause transition. VMS frequency was categorized into none, 1-5 days (infrequent), or ≥6 days (frequent) within the past 2 weeks. Results: We evaluated 522 women [at baseline: mean age 50.3 (SD: 2.8) years; infrequent VMS: 29.8%, frequent VMS: 16.5%]. Adjusting for potential confounders except E2, frequent VMS was associated with smaller HDL size [β(SE): -0.06 (0.03); P = .04] and higher concentrations of LDL-C [β(SE): 3.58 (1.77); P = .04] and intermediate LDL-P [β(SE): 0.09 (0.05); P = .04] than no VMS. These associations were largely explained by E2, all P's > .05. Conclusions: Frequent VMSs were associated with smaller HDL size and higher concentrations of LDL-C and intermediate LDL-P. These associations were explained by endogenous E2. Whether treating frequent VMS with exogenous E2 could simultaneously improve lipids/lipoproteins profile should be assessed in future studies.

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Efficacy and safety of a low-dose continuous combined hormone replacement therapy with 0.5 mg 17β-estradiol and 2.5 mg dydrogesterone in subgroups of postmenopausal women with vasomotor symptoms

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Objectives: Various combinations of estrogens and progestogens are available for menopausal hormone therapy that differ in their efficacy and safety profile. We evaluated the efficacy and long-term safety of low-dose estradiol (0.5 mg) / dydrogesterone (2.5 mg) in subgroups of postmenopausal women with vasomotor symptoms. Analysis: Efficacy analysis was performed on data from 2 previously published studies for subgroups defined by age, duration of menopause, and body mass index at baseline. The primary efficacy variable was the number of moderate to severe hot flushes from baseline to week 13. Long-term safety was evaluated in relation to age and duration of menopause. Safety variables included adverse events to week 52 and change from baseline to endpoint in laboratory and vital sign values.

Results: The treatment difference seen in the overall population in favour of low-dose estradiol/dydrogesterone was also observed in the subgroups of patients aged 45 to < 55 years ($p < 0.01$) and ≥55 years ($p < 0.05$), with menopause duration of >12 months to <60 months ($p < 0.05$) and ≥ 60 months ($p < 0.005$), and with a BMI at baseline of <25 kg/m2 ($p < 0.05$) and 25 to <30 kg/m2 ($p < 0.01$). Low-dose estradilol/dydrogesterone was well tolerated across the different subgroups. The incidence of breast-related adverse events was very low. No breast malignancy was reported. Only one adverse endometrial outcome of simple hyperplasia was observed. Conclusion: The results of our analyses confirmed the consistent treatment effect on vasomotor symptoms and the favourable safety profile of 0.5 mg 17β estradiol and 2.5 mg dydrogesterone in different patient subgroups.

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Polycystic ovary syndrome and aging: Health implications after menopause

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder with heterogenous clinical manifestations. The evidence indicates that PCOS is associated with long-term health risks including type 2 diabetes, metabolic syndrome, obstructive sleep apnea, endometrial cancer, and mood disorders. Although cardiometabolic risk factors are more common among women with PCOS, currently there is no strong evidence for increased cardiovascular morbidity and mortality in these patients. The effect of menopausal transition on the long-term health consequences of PCOS is mostly uncertain. The PCOS phenotype improves with aging in affected women. Accordingly, the differences in the cardiometabolic risk profiles of PCOS patients and of the general population seem to disappear after menopause. However, it is not clear whether this phenotype amelioration is associated with changes in other long-term health risks after the menopause. There are also gaps in our knowledge about the impact of long-term use of oral contraceptives on the prevalence of PCOS-related comorbidities. This review summarizes the current knowledge regarding the long-term health consequences of PCOS and their clinical implications in peri- and postmenopause, and highlights areas for future research.

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17β-estradiol/progesterone in a single, oral, softgel capsule (TX-001HR) significantly increased the number of vasomotor symptom-free days in the REPLENISH trial

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Objective: To examine responder rates and vasomotor symptom-free days with oral 17β-estradiol/progesterone (E2/P4; TX-001HR) versus placebo in the REPLENISH trial. Methods: REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial, evaluating single, oral, softgel E2/P4 capsules in postmenopausal women (40-65 y) with a uterus and vasomotor symptoms (VMS). Women with moderate to severe hot flushes (≥7/d or ≥50/wk) were randomized (VMS substudy) to daily E2/P4 (mg/mg) of 1/100, 0.5/100, 0.5/50, 0.25/50, or placebo. Proportions of women with ≥50% or ≥75% reductions in moderate to severe VMS (responders), and those with no severe VMS as well as the weekly number of days without moderate to severe VMS with TX-001HR versus placebo were determined. Mixed model repeated measures was used to analyze data and Fisher exact test was employed to compare E2/P4 versus placebo. Results: Seven hundred twenty-six women were eligible for the VMS efficacy analysis (E2/P4 1/100 [n = 141], 0.5/100 [n = 149], 0.5/50 [n = 147], 0.25/50 [n = 154], or placebo [n = 135]). Significantly more women treated with all E2/P4 doses versus placebo were ≥50% responders and ≥75% responders at weeks 4 and 12 ($P < 0.05$) and also had significantly more days per week without moderate to severe VMS at week 12 (1.9-3.0 d for E2/P4 versus 1.3 d for placebo; $P < 0.05$). The proportion of women without severe hot flushes at week 12 was 43% to 56% for all E2/P4 doses versus 26% for placebo ($P \leq 0.01$). Conclusions: Women treated with E2/P4 had a greater response to treatment with more VMS-free days than with placebo. The E2/P4 1/100 dose (Bijuva [E2 and P4] capsules) represents an oral treatment option for postmenopausal women with moderate to severe VMS and a uterus.

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A selective serotonin receptor agonist for weight loss and management of menopausal vasomotor symptoms in overweight midlife women: a pilot study

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Objective: Weight gain and vasomotor symptoms (VMS) are common complaints in midlife women going through the menopause transition. A selective serotonin 2C (5-HT2C) receptor agonist, lorcaserin, which was previously approved by the Food and Drug Administration for weight loss, has unreported observational evidence suggesting improvement in VMS with its use. The goal of this pilot study was to evaluate the efficacy of lorcaserin for weight loss and management of VMS in overweight midlife women. Methods: This was a 24-week open label pilot study of 20 overweight midlife women, aged 45-60 years, who were experiencing severe VMS. Participants received lorcaserin at the standard dose of 10 mg twice daily for 12 weeks, followed by 12 weeks of observation off the drug. The primary outcomes were changes in weight and subjectively reported VMS. Results: At the end of 12 weeks, mean change in weight was -2.4 kg (90% CI, -3.2 to -1.7, $P < 0.001$). However, the participants returned to the baseline weight at 24 weeks. Participants also reported significant subjective improvement in VMS, with a mean ± SD change in self-reported hot flash frequency from baseline to week 12 of -5.4 ± 3.9 (decrease of 1.4 standard deviations). There was a rapid increase in the frequency of VMS within 2 weeks of discontinuation of lorcaserin with a tendency to approach the baseline frequency of VMS. Conclusions: In addition to its weight loss-inducing effect, 5-HT2C receptor modulation may have an additional beneficial effect on VMS in midlife women. A treatment option that targets both weight and VMS in midlife women is attractive.