Selección de Resúmenes de Menopausia

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Hypothalamic neurokinin signalling and its application in reproductive medicine

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The discovery of the essential requirement for kisspeptin and subsequently neurokinin B signalling for human reproductive function has sparked renewed interest in the neuroendocrinology of reproduction. A key discovery has been a population of cells co-expressing both these neuropeptides and dynorphin in the hypothalamus, directly regulating gonadotropin hormone releasing hormone (GnRH) secretion and thus pituitary secretion of gonadotropins. These neurons also project to the vasomotor centre, and their overactivity in estrogen deficiency results in the common and debilitating hot flushes of the menopause. Several antagonists to the neurokinin 3 receptor, for which neurokinin B is the endogenous ligand, have been developed, and are entering clinical studies in human reproductive function and clinical trials. Even single doses can elicit marked declines in testosterone levels in men, and their use has elicited evidence of the regulation of ovarian follicle growth in women. The most advanced indication is the treatment of menopausal vasomotor symptoms, where these drugs show remarkable results in both the degree and speed of symptom control. A range of other reproductive indications are starting to be explored, notably in polycystic ovary syndrome, the most common endocrinopathy in women.

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Review of Allopregnanolone Agonist Therapy for the Treatment of Depressive Disorders

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Objective: This paper reviews the current literature available for the efficacy and safety of allopregnanolone agonists and discusses considerations for their place in therapy. Literature search: A literature search was conducted utilizing PubMed, clinicaltrials.gov, and the manufacturer's website. Data synthesis: One phase II trial and two phase III trials evaluating the efficacy and safety of brexanolone were identified. Brexanolone demonstrated efficacy through significantly reduced Hamilton Depression Rating Scale (HAM-D) scores compared to placebo in the treatment of postpartum depression (PPD). Noted adverse effects were somnolence and dizziness, excessive sedation, and loss of consciousness. One published phase II study and the interim results of two phase III trials and one phase II trial on zuranolone were included in this review. Zuranolone, an oral allopregnanolone agonist, is given as a single, 14-day course. A significant reduction in HAM-D scores was demonstrated in patients with major depressive disorder (MDD) at 15 and 28 days compared to placebo. Interim results for zuranolone in PPD and bipolar disorder (BPD) show promising reductions in HAM-D scores. Adverse effects included sedation, dizziness, and headache. Place in therapy: Allopregnanolone agonists seem to have a role in PPD when weighing the quick onset of action and potential risks of untreated PPD. The class of medications is limited by the single course for this indication and may fit as a bridge to maintenance therapy with selective serotonin reuptake inhibitors (SSRIs). Brexanolone, specifically, is hindered by the long infusion time, hospitalization associated with administration, and risk evaluation and mitigation strategy program. Zuranolone may also have a role in MDD or BPD, but more data are needed. Conclusion: Allopregnanolone agonists present a novel mechanism of action in the treatment of depressive disorders. Clinical trials and interim results support significant reductions in depression scores for brexanolone in PPD, and for zuranolone in PPD, MDD, and BPD.

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Aromatase inhibitors use and risk for cardiovascular disease in breast cancer patients: A population-based cohort study

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Background: Prior studies regarding use of Aromatase inhibitors (AIs) and risk for cardiovascular disease (CVD) have shown conflicting results. This retrospective cohort study aimed to investigate whether AIs use affects risk for CVD events in postmenopausal breast cancer survivors. Methods: Using a retrospective cohort study design, four CVD outcomes; heart failure or cardiomyopathy, arrhythmia, acute ischemic heart disease and ischemic stroke or Transient Ischemic Attack were compared with uni- and multivariate Cox regression analyses according to exposure to endocrine therapy (use of AI, tamoxifen or AI/tamoxifen sequentially) or no endocrine therapy. Results: In total 15815 postmenopausal women, surgically treated to early breast cancer during 2006-2012, were included. No significantly increased risk for CVD events was observed in patients with AI use in the whole cohort. However, two subgroup analyses showed increased risk for CVD events in the AI/tamoxifen sequential group; heart failure in patients older than 75 years (Hazard Ratio (HR) 2.44; 95% Confidence Interval (CI): 1.32-4.54) and arrhythmia in patients without prior CVD (HR 1.45; 95% CI: 1.01-2.10). An increased risk for arrhythmia and acute ischemic heart disease in patients with at least four years of AI treatment compared with no or short-time exposure was observed (HR 2.12; 95% CI: 1.40-3.25 for arrhythmia; HR 2.03; 95% CI: 1.15-3.58 for ischemic heart disease). Conclusion: Our results indicate an increased risk for ischemic heart disease and arrhythmia in patients treated for more than four years with AIs. This should be considered in the risk-benefit assessment concerning endocrine therapy.

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A cross-sectional study: an assessment of low muscle mass and osteoporosis in type 2 diabetes mellitus patients with a high glycated hemoglobin level

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Background: Low muscle mass and osteoporosis are commonly observed in individuals with type 2 diabetes mellitus (T2DM). We investigated the prevalence of low muscle mass and osteoporosis in patients with T2DM who had high glycated hemoglobin (HbA1c) levels. Methods: We included 187 Chinese patients with T2DM who were aged ⩾50 years and evaluated their body composition using dual-energy X-ray absorptiometry. We measured levels of fasting blood glucose, HbA1c, B collagen-specific sequences (B-CTX), osteocalcin (OC), propeptide of type 1 procollagen (P1NP), and 25-hydroxy vitamin D. Results: Of the total patients, 82 were men and 105 were women. The prevalence rates of low muscle mass, osteopenia, and osteoporosis were 35.8%, 38.0%, and 31.0%, respectively. The prevalence rate of low muscle mass was significantly higher in women with HbA1c levels >9.0% than in those with HbA1c levels <9.0%. The prevalence rates of osteopenia and osteoporosis in men with HbA1c levels >9.0% differed significantly from those with HbA1c levels <9.0%. The appendicular skeletal muscle mass index (ASMI), trunk muscle mass, lumbar spinal bone mineral content (BMC), lumbar spine BMD, femoral BMC, and femoral BMD were significantly decreased, and the serum levels of B-CTX, OC, and P1NP were significantly increased in patients with T2DM who had osteoporosis. The ASMI was associated with osteopenia/osteoporosis in men and women with T2DM. Conclusions: In patients with T2DM, high HbA1c levels were associated with higher prevalence rates of low muscle mass in women and osteoporosis in men, and ASMI was a risk factor of osteoporosis.

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Assessment of Coronary Artery Calcium Scoring to Guide Statin Therapy Allocation According to Risk-Enhancing Factors: The Multi-Ethnic Study of Atherosclerosis

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Importance: The 2018 American Heart Association/American College of Cardiology Guideline on the Management of Blood Cholesterol recommends the use of risk-enhancing factor assessment and the selective use of coronary artery calcium (CAC) scoring to guide the allocation of statin therapy among individuals with an intermediate risk of atherosclerotic cardiovascular disease (ASCVD). Objective: To examine the association between risk-enhancing factors and incident ASCVD by CAC burden among those at intermediate risk of ASCVD. Design, setting, and participants: The Multi-Ethnic Study of Atherosclerosis is a multicenter population-based prospective cross-sectional study conducted in the US. Baseline data for the present study were collected between July 15, 2000, and July 14, 2002, and follow-up for incident ASCVD events was ascertained through August 20, 2015. Participants were aged 45 to 75 years with no clinical ASCVD or diabetes at baseline, were at intermediate risk of ASCVD (≥7.5% to <20.0%), and had a low-density lipoprotein cholesterol level of 70 to 189 mg/dL. Exposures: Family history of premature ASCVD, premature menopause, metabolic syndrome, chronic kidney disease, lipid and inflammatory biomarkers, and

low ankle-brachial index. Main outcomes and measures: Incident ASCVD over a median follow-up of 12.0 years. Results: A total of 1688 participants (mean [SD] age, 65 [6] years; 976 men [57.8%]). Of those, 648 individuals (38.4%) were White, 562 (33.3%) were Black, 305 (18.1%) were Hispanic, and 173 (10.2%) were Chinese American. A total of 722 participants (42.8%) had a CAC score of 0. Among those with 1 to 2 risk-enhancing factors vs those with 3 or more risk-enhancing factors, the prevalence of a CAC score of 0 was 45.7% vs 40.3%, respectively. Over a median follow-up of 12.0 years (interquartile range [IQR], 11.5-12.6 years), the unadjusted incidence rate of ASCVD among those with a CAC score of 0 was less than 7.5 events per 1000 person-years for all individual risk-enhancing factors (with the exception of ankle-brachial index, for which the incidence rate was 10.4 events per 1000 person-years [95% CI, 1.5-73.5]) and combinations of risk-enhancing factors, including participants with 3 or more risk-enhancing factors. Although the individual and composite addition of risk-enhancing factors to the traditional risk factors was associated with improvement in the area under the receiver operating curve, the use of CAC scoring was associated with the greatest improvement in the C statistic (0.633 vs 0.678) for ASCVD events. For incident ASCVD, the net reclassification improvement for CAC was 0.067. Conclusions and relevance: In this cross-sectional study, among participants with CAC scores of 0, the presence of risk-enhancing factors was generally not associated with an overall ASCVD risk that was higher than the recommended treatment threshold for the initiation of statin therapy. The use of CAC scoring was associated with significant improvements in the reclassification and discrimination of incident ASCVD. The results of this study support the utility of CAC scoring as an adjunct to risk-enhancing factor assessment to more accurately classify individuals with an intermediate risk of ASCVD who might benefit from statin therapy.

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Aging and changes in adiposity indices: the impact of menopause

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Purpose: Aging is associated with significant changes in fat distribution and menopause may alter this process. This study aimed to investigate the longitudinal effect of menopause on changes in adiposity indices (AI). Methods: A total number of 3876 non-menopausal women, aged > 20 years, who participated in the Tehran Lipid and Glucose study, were selected for the present study. They were followed from 1998 to 2018 at a 3-year interval and their adiposity indices were measured. Throughout the study, participants were categorized into two groups according to their menopausal status as group 1): women who reached menopause and group 2): women who did not reach menopause. The generalized estimation equation (GEE) models were used to compare the trend of changes in AIs between these two groups. Results: At the end of the study, a total number of 1479 (38.2%) participants reached menopause. The odds of general obesity decreased by 5% (OR: 0.95, 95% CI: 0.90-0.99), and the odds of central obesity increased by 6% in group1 compared to group2 (OR: 1.06, 95% CI: 1.01-1.12). Conclusions: Menopause alters the impact of aging on central fat distribution. Increasing awareness of the related risk in menopausal women and their healthcare professional may prevent adverse related outcomes.

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Meta-analysis of clinical fracture risk reduction of anti-osteoporosis drugs: direct and indirect comparisons and meta-regressions

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Objective: Anti-osteoporotic drug (AOD) trials have variabilities in duration and fracture risks. This study evaluated AOD's versus controls regarding reduction in relative rates (rr) and rate differences (rd) of vertebral and hip fractures and comparative costs. Methods: Primary randomized-controlled trials (RCT's) of AOD's in post-menopausal women with documentation of vertebral fracture rates (VFR) or hip fracture rates (HFR) were extracted from meta-analyses and PubMed through February 2021. Direct and indirect meta-analysis and meta-regression analyzed fracture reductions. Results: There were 24 RCT's of drug-versus-placebo (73,862 women) and 10 drug-versus-drug trials. Reduction in rr of VFR were significant for anti-resorptive (alendronate, risedronate, zoledronate, denosumab, raloxifene) and anabolic (teriparatide, abaloparatide, romosozumab) drugs. Denosumab, teriparatide and abaloparatide were more effective in reducing VFR compared to oral bisphosphates (all p <0.05) but not to zoledronate. Reduction in HFR were significant for alendronate, denosumab and zoledronate (all p <0.05), without significant differences among drugs. Anabolic drugs did not show significant HFR reduction. Meta-regression of rd's allowed for calculation of costs per vertebral fracture prevented, which were estimated at >$100,000 for anabolic drugs and between $2,289-$28,947 for anti-resorptive drugs. Drug-versus-drug trials were underpowered to demonstrate changes. Conclusions: This study suggests goal-directed, cost-effective therapy relative to a patient's risk for vertebral and hip fractures.

Anabolic drugs are better at preventing vertebral fractures compared to oral bisphosphonates. Anabolic drugs are not superior to zoledronate or denosumab, and at substantially higher cost. In comparing drugs which prevented hip fractures, there was no statistical benefit of any drug.