Selección de Resúmenes de Menopausia

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Endogenous sex hormone levels and coronary heart disease risk in postmenopausal women: A meta-analysis of prospective studies.

Wang H, Li Y, Wang X, Bu J, Yan G, Lou D.

Background Low testosterone levels have been associated with coronary heart disease (CHD) morbidity and mortality in men, but the influence of hormones in postmenopausal women is unclear. This meta-analysis aimed to examine whether there is an association between endogenous sex hormones and CHD risk in postmenopausal women. Methods A systematic search of the PubMed and EMBASE databases from 1966 to 30 November 2016 was performed for prospective studies that reported an association between endogenous sex hormones and CHD in postmenopausal women. Summary relative risks (RRs) and 95% confidence intervals (CIs) were combined by using a random-effects model. Results A total of 13 publications (12 studies, including six prospective cohort and six nested case-control studies) were included. The summary RRs for CHD were 1.01 (95% CI 0.77-1.31) comparing the highest versus lowest tertile of total testosterone, with evidence of high heterogeneity ($I2 = 80.7\%$). In subgroup and meta-regression analyses, none of the variables were identified as contributing to significant heterogeneity. Based on a comparison of the highest versus lowest tertile models, the summary RRs (95% CIs) for CHD were 0.88 (0.63-1.23, $I2 = 48.7\%$) for free testosterone, 1.16 (0.82-1.63, $I2 = 47.8\%$) for estradiol, 0.98 (0.90-1.07, $I2 = 3.2\%$) for sex hormone-binding globulin and 1.19 (0.89-1.58, $I2 = 0$) for dehydroepiandrosterone. Conclusion There is limited evidence to suggest that endogenous levels of sex hormones are not significantly associated with CHD risk in postmenopausal women.

Pharmacoepidemiol Drug Saf. 2017 Mar 22. doi: 10.1002/pds.4197. [Epub ahead of print]

Bias from depletion of susceptibles: the example of hormone replacement therapy and the risk of venous thromboembolism.

Renoux C, Dell'Aniello S, Brenner B, Suissa S.

The data on the association between hormone replacement therapy and the increased risk of venous thromboembolism (VTE) in postmenopausal women are conflicting. The observed differences between oral estrogen and oral estrogen-progestogen combination formulations may be the result of bias from depletion of susceptibles. METHODS: We used United Kingdom's Clinical Practice Research Datalink to identify the cohort of all women aged 50 to 79 during 1987-2008, with all incident cases of VTE occurring during the study period identified. Using a nested case-control approach, the rate ratios (RRs) of VTE with current use of oral estrogen and oral estrogen-progestogen combinations were estimated as a function of duration of use using conditional logistic regression with cubic splines. RESULTS: The cohort of 955 582 postmenopausal women included 23 505 cases of VTE matched to 231 562 controls. The risk of VTE was increased with current use of oral estrogen (RR 1.49; 95% confidence interval: 1.37 to 1.63) and oral estrogen-progestogen (RR 1.54; 95% confidence interval: 1.44 to 1.65), relative to non-use. When assessed by duration of use, the risks with oral formulations were particularly elevated during the first year of use and were reduced subsequently. CONCLUSION: The phenomenon of depletion of susceptibles should be considered in cohort studies evaluating acute side effects of medications. This can be achieved by estimating the risk as a function not only of current use but also of duration of use.

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The Efficacy of Bisphosphonates for Prevention of Osteoporotic Fracture: An Update Meta-analysis.

Byun JH, Jang S, Lee S, Park S, Yoon HK, Yoon BH, Ha YC.

BACKGROUND: The efficacy of bisphosphonates for osteoporotic fracture has been consistently reported in recent randomized controlled trials (RCTs) enrolling hundreds of patients. The objective of this study was to update knowledge on the efficacy of available bisphosphonates in the prevention of vertebral and non-vertebral fractures.

METHODS: An approach "using systematic reviews" on PubMed and Cochrane Library was taken. Twenty-four RCTs investigating the effects of bisphosphonates for the prevention of osteoporotic fracture were included in final analysis. A pairwise meta-analysis was conducted with a random effects model. Subgroup analysis was performed according to the type of bisphosphonate. RESULTS: The use of bisphosphonate decrease the risk of overall osteoporotic fracture (odds ratio [OR] 0.62; P<0.001), vertebral fracture (OR 0.55; P<0.001) and non-vertebral fracture (OR 0.73; P<0.001). Subgroup analysis indicated that zoledronic acid showed the lowest risk reduction (OR 0.61; P<0.001) for overall osteoporotic fractures but no significance was observed for etidronate (OR 0.34; P=0.127). CONCLUSIONS: This update meta-analysis re-confirmed that bisphosphonate use can effectively reduce the risk of osteoporotic fracture. However, there is a lack of evidence regarding etidronate for the prevention of osteoporotic fracture.

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Association between Sarcopenic Obesity and Metabolic Syndrome in Postmenopausal Women: A Cross-sectional Study Based on the Korean National Health and Nutritional Examination Surveys from 2008 to 2011.

Kang SY, Lim GE, Kim YK, Kim HW, Lee K, Park TJ, Kim J.

BACKGROUND: Menopause contributes to an increase in visceral fat mass and a decrease in muscle protein synthesis. Therefore, we performed this study to examine their relationship how effect the changes of body composition as obesity and sarcopenia on metabolic syndrome (MS) as a predictor of cardiovascular disease in postmenopausal women. METHODS: Using data from the Korean National Health and Nutrition Examination Survey (KNHANES) from 2008 to 2011, we estimated that 4,183 postmenopausal women underwent dual energy X-ray absorptiometry scans. Sarcopenia was defined as an appendicular skeletal muscle mass divided by body weight that was less than 1 standard deviation below the sex specific mean for the young reference group. After classification into four groups, the results were adjusted with menopausal age and hormonal treatment. The relationship between sarcopenic obesity (SO) and MS in postmenopausal women was analyzed by logistic regression analysis in a complex sampling. RESULTS: In an unadjusted model, the odds ratio (OR) of MS for sarcopenia was 1.94 (95% confidence interval [CI], 1.52-2.49); the obesity group had an OR of 4.55 (95% CI, 3.63-5.71); and distinctly, the SO group had an OR of 6.26 (95% CI, 5.10-7.70). Even though there was controlling for variable adjustment, no definite difference was seen in the results. CONCLUSIONS: Sarcopenia and obesity were associated with MS independent of other metabolic impairment risk factors in both early menopausal and postmenopausal women. The results showed that, in particular, the prevalence of MS has increased more in postmenopausal women compared with previous research.

J Bone Metab. 2017 Feb;24(1):1-8. doi: 10.11005/jbm.2017.24.1.1. Epub 2017 Feb 28.

Role of the Cytokine-like Hormone Leptin in Muscle-bone Crosstalk with Aging.

Hamrick MW.

The cytokine-like hormone leptin is a classic adipokine that is secreted by adipocytes, increases with weight gain, and decreases with weight loss. Additional studies have, however, shown that leptin is also produced by skeletal muscle, and leptin receptors are abundant in both skeletal muscle and bone-derived mesenchymal (stromal) stem cells. These findings suggest that leptin may play an important role in muscle-bone crosstalk. Leptin treatment in vitro increases the expression of myogenic genes in primary myoblasts, and leptin treatment in vivo increases the expression of microRNAs involved in myogenesis. Bone marrow adipogenesis is associated with low bone mass in humans and rodents, and leptin can reduce marrow adipogenesis centrally through its receptors in the hypothalamus as well as directly via its receptors in bone marrow stem cells. Yet, central leptin resistance can increase with age, and low circulating levels of leptin have been observed among the frail elderly. Thus, aging appears to significantly alter leptin-mediated crosstalk among various organs and tissues. Aging is associated with bone loss and muscle atrophy, contributing to frailty, postural instability, and the incidence of falls. Therapeutic interventions such as protein and amino acid supplementation that can increase muscle mass and muscle-derived leptin may have multiple benefits for the elderly that can potentially reduce the incidence of falls and fractures.

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Bone turnover is suppressed in insulin resistance, independent of adiposity.

Tonks KT, White CP, Center JR, Samocha-Bonet D, Greenfield JR.

Context: The contribution of insulin resistance vs. adiposity to bone mineral density (BMD), bone turnover and fractures in humans remains unclear. Objective: Evaluate BMD and bone turnover markers (BTM) in lean (n=18) and overweight/obese individuals with (n=17) and without type 2 diabetes (n=34, deemed insulin-sensitive [Obsensitive, n=15] or insulin-resistant [Obresistant, n=19] by HOMA-IR). Design: Observational study. Outcome measures: Insulin sensitivity assessed by hyperinsulinemic-euglycemic clamp; whole body BMD and fat mass (FM) by DXA; and BTM (osteocalcin [OC], procollagen type-1 propeptide [P1NP] and collagen type-1 cross-linked C-telopeptide [CTx]) fasting and during clamp hyperinsulinemia. Results: Fasting BTM correlated with glucose infusion rate/fat free mass (GIR/FFM) and adiponectin, and inversely with fasting insulin and visceral fat (all $p \leq 0.04$). Obsensitive, Obresistant and diabetes individuals were matched for FM%. Clamp GIR/FFM was similar in lean and Obsensitive ($p=1$) and ~2-fold higher ($p<0.001$) than Obresistant and diabetes. BMD was higher in Obresistant than Obsensitive ($p=0.04$) and lean ($p=0.001$). At baseline, compared to Obsensitive and lean, Obresistant and diabetes individuals had lower OC, P1NP and CTx levels. This reached statistical significance for Obresistant vs lean, and Obresistant vs Obsensitive for both OC and CTx; and diabetes vs lean for CTx (all $p \leq 0.04$). During hyperinsulinemia, lean individuals suppressed CTx more than diabetes individuals ($p=0.03$). On multiple regression analysis visceral adiposity explained 16.7% and 19.3% of baseline OC and CTx variability, respectively. Conclusions: Increased visceral adiposity and higher fasting insulin in insulin-resistant states is associated with lower fasting OC and CTx, and failure to further suppress with more insulin.

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Menopausal hormone therapy and type 2 diabetes prevention: Evidence, mechanisms and clinical implications.

Mauvais-Jarvis F, Manson JE, Stevenson JC, Fonseca VA.

Type 2 diabetes has reached epidemic proportions in the US. Large randomized controlled trials suggest that menopausal hormone therapy (MHT) delays the onset of type 2 diabetes in women. Still, the mechanisms and clinical implications of these associations are a matter of controversy. This review provides an up-to-date analysis and integration of epidemiological, clinical and basic studies, and proposes a mechanistic explanation for the effect of menopause and MHT on type 2 diabetes development and prevention. We discuss the beneficial effects of endogenous estradiol in insulin secretion, insulin sensitivity and glucose effectiveness, as well as energy expenditure and adipose distribution that are lost at menopause and improved by MHT, which decreases the incidence of type 2 diabetes. We reconcile differences among studies of the effect of menopause and MHT formulations on type 2 diabetes. We argue that discrepancies arise from physiological differences in methods used to assess glucose homeostasis, ranging from clinical indices of insulin sensitivity to steady state methods to assess insulin action. We also discuss the influence of the route of estrogen administration and the addition of progestogens. We conclude that, although MHT is not approved or appropriate for the prevention of type 2 diabetes due to its complex balance of risks and benefits, it should not be withheld from women with or at increased risk for type 2 diabetes who seek treatment for menopausal symptoms.

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Menopause is a determinant of breast aromatase expression and its associations with BMI, inflammation and systemic markers.

Brown KA, Iyengar NM, Zhou XK, Gucalp A, Subbaramaiah K, Wang H, Giri DD, Morrow M, Falcone DJ, et al.

Most estrogen-dependent breast cancers occur after menopause despite low levels of circulating estrogens. Breast expression of the estrogen-biosynthetic enzyme, aromatase, is proposed to drive breast cancer development after menopause. However, the effects of menopause on breast aromatase expression are unknown. OBJECTIVE: To determine the effect of menopause on breast aromatase expression in relation to body mass index (BMI), white adipose tissue inflammation (WATi) and systemic markers of metabolic dysfunction. DESIGN, SETTING AND PARTICIPANTS: Cross-sectional study of 102 premenopausal (aged 27-56) and 59 postmenopausal (aged 45-74) women who underwent mastectomy for breast cancer treatment/prevention (2010-2015). OUTCOME: Breast tissue was assessed for the presence of crown-like structures (CLS), and the expression and activity of aromatase. Systemic

markers examined include IL-6, insulin, glucose, leptin, adiponectin, hsCRP, cholesterol, and triglycerides. Multivariable analysis was performed for aromatase mRNA in relation to BMI, WATi and blood markers. RESULTS:
Postmenopausal women had higher BMI and more breast WATi than premenopausal women. Fasting levels of IL-6, glucose, leptin, hsCRP and HOMA2 IR score were higher in the postmenopausal group. BMI was positively correlated with aromatase mRNA in both pre- and postmenopausal women. Aromatase levels were higher in breast tissue of postmenopausal women, with levels being higher in inflamed vs non-inflamed, independent of BMI. Adipocyte diameter and levels of leptin, hsCRP, adiponectin and HDL cholesterol, were more strongly correlated with aromatase in postmenopausal than premenopausal women. CONCLUSIONS: Elevated aromatase in the setting of adipose dysfunction provides a possible mechanism for the higher incidence of hormone-dependent breast cancer in obese women after menopause.

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High dose vitamin d may improve lower urinary tract symptoms in postmenopausal women.

Oberg J, Verelst M, Jorde R, Cashman K, Grimnes G.

Lower urinary tract symptoms (LUTS) are common in postmenopausal women, and have been reported inversely associated with vitamin D intake and serum 25-hydroxyvitamin D (25(OH)D levels. The aim of this study was to investigate if high dose vitamin D supplementation would affect LUTS in comparison to standard dose. In a randomized controlled study including 297 postmenopausal women with low bone mineral density, the participants were allocated to receive capsules of 20 000 IU of vitamin D3 twice a week (high dose group) or similar looking placebo (standard dose group). In addition, all the participants received 1g of calcium and 800 IU of vitamin D daily. A validated questionnaire regarding LUTS was filled in at baseline and after 12 months. At baseline, 76 women in the high dose group and 82 in the standard dose group reported any LUTS. Levels of serum 25(OH)D increased significantly more in the high dose group (from 64.7 to 164.1 nmol/l compared to from 64.1 to 81.8 nmol/l, $p<0.01$). No differences between the groups were seen regarding change in LUTS except for a statistically significant reduction in the reported severity of urine incontinence in the high dose group as compared to the standard dose group after one year ($p<0.05$). The results need confirmation in a study specifically designed for this purpose.

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Comparison of intravaginal 0.5% prasterone, 0.3mg conjugated estrogens and 10µg estradiol on estrogen-related symptoms of vulvovaginal atrophy.

Archer DF, Labrie F, Montesino M, Martel C.

The objective is to compare the effect of intravaginal dehydroepiandrosterone (DHEA, prasterone), conjugated equine estrogens (CEE) and estradiol (E2) on moderate to severe dyspareunia and/or vaginal dryness. In a review of available data, independent prospective, randomized, double-blind and placebo-controlled Phase III 12-week clinical trials involved daily administration of 6.5mg (0.50%) prasterone, daily (21days on/7days off) 0.3mg CEE, twice weekly 0.3mg CEE or 10 µg E2 daily for 2 weeks followed by twice weekly for 10 weeks. Vulvovaginal atrophy symptoms were evaluated by questionnaires. The total severity score decreased from 1.27 to 1.63 units with prasterone treatment, 1.4 with CEE and 1.23 in one statistically significant study with E2. Decreases over placebo ranged from 0.36 to 1.21 with prasterone, 0.7 to 1.0 with CEE and 0.36 for the E2 study. The total decreases in vaginal dryness severity ranged from 1.44 to 1.63 units for prasterone, 1.1 unit for CEE and 1.23 unit for E2. The decreases over placebo of vaginal dryness intensity ranged from 0.27 to 0.43 unit for prasterone and 0.40 unit for CEE with no statistically significant difference over placebo for E2. Daily 0.50% prasterone appears to be at least as efficacious as 0.3mg CEE or 10 µg E2 for treatment of the VVA symptoms. In summary, the beneficial effects on the VVA symptomatology can be obtained by the addition of a small amount of intravaginal prasterone to compensate for the low serum concentration of prasterone observed in the majority of women after menopause without concerns about systemic effects.