

Selección de Resúmenes de Menopausia

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Association of Subclinical Hypothyroidism and Cardiovascular Disease With Mortality.

Inoue K1, Ritz B1,2, Brent GA3,4, Ebrahimi R5, Rhee CM6, Leung AM3,4.

Importance: Subclinical hypothyroidism is a common clinical entity among US adults associated in some studies with an increase in the risk of cardiovascular disease (CVD) and mortality. However, the extent to which CVD mediates the association between elevated serum thyrotropin (TSH) and mortality has not yet been well established or sufficiently quantified. Objective: To elucidate the extent to which subclinical hypothyroidism, elevated serum TSH and normal serum free thyroxine, or high-normal TSH concentrations (ie, upper normative-range TSH concentrations) are associated with mortality through CVD among US adults. Design, Setting, and Participants: This cohort study relied on representative samples of US adults enrolled in the National Health and Nutrition Examination Survey in 2001 to 2002, 2007 to 2008, 2009 to 2010, and 2011 to 2012 and their mortality data through 2015. Data were analyzed from January to August 2019. Main Outcomes and Measures: Cox proportional hazards regression models were used to investigate associations between the TSH concentration category (subclinical hypothyroidism or tertiles of serum TSH concentrations within the reference range; low-normal TSH, 0.34-1.19 mIU/L; middle-normal TSH, 1.20-1.95 mIU/L; and high-normal TSH, 1.96-5.60 mIU/L) and all-cause mortality. Mediation analysis was used within the counterfactual framework to estimate natural direct associations (not through CVD) and indirect associations (through CVD). Results: Of 9020 participants, 4658 (51.6%) were men; the mean (SD) age was 49.4 (17.8) years. Throughout follow-up (median [interquartile range], 7.3 [5.4-8.3] years), serum thyroid function test results consistent with subclinical hypothyroidism and high-normal TSH concentrations were both associated with increased all-cause mortality (subclinical hypothyroidism: hazard ratio, 1.90; 95% CI, 1.14-3.19; high-normal TSH: hazard ratio, 1.36; 95% CI, 1.07-1.73) compared with the middle-normal TSH group. Cardiovascular disease mediated 14.3% and 5.9% of the associations of subclinical hypothyroidism and high-normal TSH with all-cause mortality, respectively, with the CVD mediation being most pronounced in women (7.5%-13.7% of the association) and participants aged 60 years and older (6.0%-14.8% of the association). Conclusions and Relevance: In this study, CVD mediated the associations of subclinical hypothyroidism and high-normal TSH concentrations with all-cause mortality in the US general population. Further studies are needed to examine the clinical benefit of thyroid hormone replacement therapy targeted to a middle-normal TSH concentration or active CVD screening for people with elevated TSH concentrations.

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The role of testosterone in menopausal hormone treatment. What is the evidence?

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About 40% of postmenopausal women have decreased sexual desire causing distress. Estrogen therapy attenuates vaginal complaints, but has no effect on sexual desire. Although sexual function has been linked to testosterone, there is no clear relation between sexual desire and circulating levels of testosterone. Nevertheless, treatment with transdermal (patch) testosterone improved sexual function in several randomized controlled trials. Women with hypoactive sexual desire disorder who were treated with testosterone reported more satisfying sexual episodes and sexual desire compared with the placebo group. Adverse effects were mild. However, there is no testosterone drug designed for women available on the European market. Consequently, women who opt for testosterone treatment have to use preparations made for men with high drug concentration. Adequate dosage for women is therefore challenging. A trial of 5 mg transdermal testosterone (gel or cream) daily or less has been suggested, followed by close monitoring of side effects and hormone level.

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Cost-effectiveness of five versus ten years of alendronate treatment prior to drug holiday for women with osteoporosis.

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We performed a cost-effectiveness analysis comparing 5 versus 10 years of alendronate treatment prior to 5-year drug holiday for US postmenopausal women with hip BMD T-scores between -2.5 and -3.5. We found that for most postmenopausal women 5 years of treatment prior to drug holiday is the more effective and cost-effective option. **INTRODUCTION:** We performed a cost-effectiveness analysis to compare 5 versus 10 years of alendronate treatment prior to 5-year drug holiday for postmenopausal osteoporotic women. **METHODS:** We created an individual-level state-transition microsimulation model to compare 3 treatment strategies for US postmenopausal women with osteoporosis and femoral neck BMD T-scores between -2.5 and -3.5 at baseline: recurrent periods of 5 years of alendronate followed by 5 years of drug holiday (alendronate 5/5), recurrent periods of 10 years of alendronate followed by 5 years of drug holiday (alendronate 10/5), and no alendronate treatment. **RESULTS:** Base-case analysis revealed for women initiating treatment at ages 50, 60, and 70, the alendronate 5/5 strategy dominated (was more effective and less costly than) the alendronate 10/5 strategy and no treatment. For women age 80, the alendronate 10/5 strategy dominated. When assuming a lower relative risk of nonvertebral fracture during years 6-10 of alendronate treatment than the base-case assumption, the alendronate 10/5 strategy became the most cost-effective strategy even at younger treatment initiation ages. Probabilistic sensitivity analysis results supported the base-case findings; for treatment initiation ages of 50, 60, and 70, the alendronate 5/5 strategy was favored, whereas for treatment initiation age of 80, the alendronate 10/5 strategy was favored; however, there was uncertainty in these findings. **CONCLUSIONS:** After 5 years of alendronate treatment, younger postmenopausal women (ages 50-70) with osteoporosis would likely benefit from a drug holiday, whereas older women (age 80) are likely to benefit from treatment for 10 years before a drug holiday.

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Muscle and bone mass in middle-aged women: role of menopausal status and physical activity.

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BACKGROUND: Women experience drastic hormonal changes during midlife due to the menopausal transition. Menopausal hormonal changes are known to lead to bone loss and potentially also to loss of lean mass. The loss of muscle and bone tissue coincide due to the functional relationship and interaction between these tissues. If and how physical activity counteracts deterioration in muscle and bone during the menopausal transition remains partly unresolved. This study investigated differences between premenopausal, early perimenopausal, late perimenopausal, and postmenopausal women in appendicular lean mass (ALM), appendicular lean mass index (ALMI), femoral neck bone mineral density (BMD) and T score. Furthermore, we investigated the simultaneous associations of ALM and BMD with physical activity in the above-mentioned menopausal groups. **METHODS:** Data from the Estrogen Regulation of Muscle Apoptosis study were utilized. In total, 1393 women aged 47-55 years were assigned to premenopausal, early perimenopausal, late perimenopausal, and postmenopausal groups based on follicle-stimulating hormone concentration and bleeding diaries. Of them, 897 were scanned for ALM and femoral neck BMD by dual-energy X-ray absorptiometry and ALMI (ALM/height²) and neck T scores calculated. Current level of leisure-time physical activity was estimated by a validated self-report questionnaire and categorized as sedentary, low, medium, and high. **RESULTS:** Appendicular lean mass, appendicular lean mass index, femoral neck bone mineral density, and T score showed a significant linear declining trend across all four menopausal groups. Compared with the postmenopausal women, the premenopausal women showed greater ALM (18.2, SD 2.2 vs. 17.8, SD 2.1, $P < 0.001$), ALMI (6.73, SD 0.64 vs. 6.52, SD 0.62, $P < 0.001$), neck BMD (0.969, SD 0.117 vs. 0.925, SD 0.108, $P < 0.001$), and T score (-0.093, SD 0.977 vs -0.459, SD 0.902, $P < 0.001$). After adjusting for potential confounding pathways, a higher level of physical activity was associated with greater ALM among the premenopausal [$\beta = 0.171$; confidence interval (CI) 95% 0.063-0.280], late perimenopausal ($\beta = 0.289$; CI 95% 0.174-0.403), and postmenopausal ($\beta = 0.278$; CI 95% 0.179-0.376) women. The positive association between femoral neck BMD and level of physical activity was significant only among the late perimenopausal women ($\beta = 0.227$; CI 95% 0.097-0.356). **CONCLUSIONS:** Skeletal muscle and bone losses were associated with the menopausal transition. A higher level of physical activity during the different menopausal phases was beneficial, especially for skeletal muscle. Menopause-related hormonal changes predispose women to sarcopenia and osteoporosis and further to mobility disability and fall-related fractures in later

life. New strategies are needed to promote physical activity among middle-aged women. Longitudinal studies are needed to confirm these results.

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Heart fat and carotid artery atherosclerosis progression in recently menopausal women: impact of menopausal hormone therapy: The KEEPS trial.

El Khoudary SR1, Venugopal V1, Manson JE2, Brooks MM1, Santoro N3, Black DM4, Harman M5, et al.

OBJECTIVE: Heart fat deposition has been linked to atherosclerosis, and both accelerate after menopause. Hormone therapy (HT) may differentially slow heart fat deposition and progression of atherosclerosis, depending on the specific HT agent or its route of administration. Our objective was to evaluate the effects of different HT agents, oral and transdermal, on associations between heart fat accumulation and atherosclerosis progression, measured by carotid intima-media thickness (CIMT), in recently menopausal women from the Kronos Early Estrogen Prevention Study (KEEPS) trial. **METHODS:** KEEPS was a randomized, placebo-controlled trial of the effects of 0.45mg/d oral conjugated equine estrogens (o-CEE) or 50mcg/d transdermal 17 β -estradiol (t-E2), compared with placebo, on 48 months progression of CIMT. Epicardial adipose tissue (EAT) and paracardial adipose tissue (PAT) volumes were quantified by computed tomography. **RESULTS:** In all, 467 women (mean age [SD] 52.7 [2.5]; 78.2% White; 30% on o-CEE, 30.8% t-E2, 39.2% placebo) with heart fat volumes and CIMT at baseline and 48 months were included. EAT and PAT changes were not associated with CIMT progression; however, the assigned treatment significantly modified the association between PAT (but not EAT) change and CIMT progression. In the o-CEE group, adjusted CIMT progression was 12.66 μ m (95% confidence interval [CI] 1.80, 23.52) lower than in t-E2 group (P=0.02), and 10.09 μ m (95% CI 0.79, 19.39) lower than in placebo group (P=0.03), as per 1-SD increase in PAT. **CONCLUSION:** Compared with t-E2, o-CEE appears to slow down the adverse effect of increasing PAT on progression of atherosclerosis. Whether this beneficial association is specific to CEE or to the oral route of CEE administration is unclear and should be assessed further.

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Adult weight change and premenopausal breast cancer risk: A prospective pooled analysis of data from 628,463 women.

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Early-adulthood body size is strongly inversely associated with risk of premenopausal breast cancer. It is unclear whether subsequent changes in weight affect risk. We pooled individual-level data from 17 prospective studies to investigate the association of weight change with premenopausal breast cancer risk, considering strata of initial weight, timing of weight change, other breast cancer risk factors, and breast cancer subtype. Hazard ratios (HR) and 95% confidence intervals (CI) were obtained using Cox regression. Among 628,463 women, 10,886 were diagnosed with breast cancer before menopause. Models adjusted for initial weight at ages 18-24 years and other breast cancer risk factors showed that weight gain from ages 18-24 to 35-44 or to 45-54 years was inversely associated with breast cancer overall (e.g. HR per 5kg to ages 45-54: 0.96, 95% CI: 0.95-0.98) and with oestrogen-receptor(ER)-positive breast cancer (HR per 5kg to ages 45-54: 0.96, 95% CI: 0.94-0.98). Weight gain from ages 25-34 was inversely associated with ER-positive breast cancer only and weight gain from ages 35-44 was not associated with risk. None of these weight gains were associated with ER-negative breast cancer. Weight loss was not consistently associated with overall or ER-specific risk after adjusting for initial weight. Weight increase from early-adulthood to ages 45-54 years is associated with a reduced premenopausal breast cancer risk independently of early-adulthood weight. Biological explanations are needed to account for these two separate factors.

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Ultrasound detection of endometrial cancer in women with postmenopausal bleeding: Systematic review and meta-analysis.

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OBJECTIVE: To assess the performance of endometrial thickness (ET) cut-offs for detecting endometrial cancer (EC) in women with postmenopausal bleeding (PMB) and evaluate the clinical utility of additional ultrasound measures

such as endometrial volume (EV), vascular flow index (VFI), vascularization index (VI), and uterine artery flow index (FI). **METHODS:** Clinicaltrials.gov and MEDLINE database via PubMed were queried for studies published between 1/1990 and 3/2016 using specific MeSH terms. Original, peer-reviewed cohort studies reporting EC outcomes and specific ultrasound findings by PMB status were included. **RESULTS:** Study design, country, clinical setting inclusion/exclusion criteria, aggregate study-level demographic and clinical data were extracted from 44 studies including 17,339 women with PMB and 1341 cases of EC (7.7%). In women with PMB and EC (n = 417), pooled mean ET was 16.4 mm (95% CI, 14.8-18.1 mm). In women with PMB without EC, pooled mean ET was 4.1 mm. 31 studies reported outcomes using different ET cut-off values ranging from 3 to 20 mm. Compared to ≥ 3 or 4 mm, a cutoff of ≥ 5 mm had similar sensitivity (96.2, 95%CI 92.3, 98.1) with improved specificity for EC (51.5, 95%CI 42.3-60.7), allowing to reduce the rate of invasive workup for PMB by 17%. EV, VI, VFI, and FI were significantly correlated with EC, but performance of specific cut-offs was not analyzed due to limited data. **CONCLUSION:** Among women with PMB mean ET is substantially higher in women with EC compared to those without EC. An ET cutoff of ≥ 5 mm shows an acceptable tradeoff between sensitivity and specificity for diagnosis of EC.