Selección de Resúmenes de Menopausia

Semana del 31 de marzo al 6 de abril 2021

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J Womens Health (Larchmt). 2021 Apr 1.doi: 10.1089/jwh.2021.29037. Online ahead of print.

International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women

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Background: The Global Consensus Position Statement on the Use of Testosterone Therapy for Women (Global Position Statement) testosterone therapy for postmenopausal women with hypoactive sexual desire disorder (HSDD). Aim: To provide a clinical practice guideline for the use of testosterone including identification of patients, laboratory testing, dosing, post-treatment monitoring, and follow-up care in women with HSDD. Methods: The International Society for the Study of Women's Sexual Health appointed a multidisciplinary panel of experts who performed a literature review of original research, meta-analyses, review papers, and consensus guidelines regarding testosterone use in women. Consensus was reached using a modified Delphi method. Outcomes: A clinically useful guideline following a biopsychosocial assessment and treatment approach for the safe and efficacious use of testosterone in women with HSDD was developed including measurement, indications, formulations, prescribing, dosing, monitoring, and follow-up. Results: Although the Global Position Statement endorses testosterone therapy for only postmenopausal women, limited data also support the use in late reproductive age premenopausal women, consistent with the International Society for the Study of Women's Sexual Health Process of Care for the Management of HSDD. Systemic transdermal testosterone is recommended for women with HSDD not primarily related to modifiable factors or comorbidities such as relationship or mental health problems. Current available research supports a moderate therapeutic benefit. Safety data show no serious adverse events with physiologic testosterone use, but long-term safety has not been established. Before initiation of therapy, clinicians should provide an informed consent. Shared decision-making involves a comprehensive discussion of off-label use, as well as benefits and risks. A total testosterone level should not be used to diagnose HSDD, but as a baseline for monitoring. Government-approved transdermal male formulations can be used cautiously with dosing appropriate for women. Patients should be assessed for signs of androgen excess and total testosterone levels monitored to maintain concentrations in the physiologic premenopausal range. Compounded products cannot be recommended because of the lack of efficacy and safety data. Clinical Implications: This clinical practice guideline provides standards for safely prescribing testosterone to women with HSDD, including identification of appropriate patients, dosing, and monitoring. Strengths & Limitations: This evidence-based guideline builds on a recently published comprehensive meta-analysis and the Global Position Statement endorsed by numerous societies. The limitation is that testosterone therapy is not approved for women by most regulatory agencies, thereby making prescribing and proper dosing challenging. Conclusion: Despite substantial evidence regarding safety, efficacy, and clinical use, access to testosterone therapy for the treatment of HSDD in women remains a significant unmet need.

Clin Endocrinol (Oxf). 2021 Apr 2.doi: 10.1111/cen.14474. Online ahead of print.

Progesterone and estradiol may be active components of the sleep- wake regulatory mechanisms: an evidence-based hypothesis

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While multiple effects of progesterone in the brain are well documented,1 very few randomized placebo-controlled studies have investigated its effects on sleep architecture. In healthy young men2 and in healthy postmenopausal women,3 acute administration of a single dose of progesterone resulted in a significant increase in the duration of light non-REM (rapid eye movement) sleep and a decrease in wake after sleep-onset (WASO) duration. In a third study, daily evening oral administration of 300 mg of micronised progesterone for three weeks was associated with a decrease in WASO duration, without any other significant effect on overnight sleep architecture.4 Those data were consistent with a slight but significant hypnotic action of progesterone.

BMC Womens Health. 2021 Mar 31;21(1):133.doi: 10.1186/s12905-021-01275-8.

Perimenopausal women show modulation of excitatory and inhibitory neuromuscular mechanisms

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Background: Menopausal transition exposes women to an early decline in muscle force and motor function. Changes in muscle quality and function, especially in lower limbs, are crucial, as they expose individuals to increased risk of falls. To elucidate some of the related neuromuscular mechanisms, we investigated cortical inhibition and peripheral muscle twitch force potentiation in women during the early and late stages of perimenopause. Methods: Participants were 63 women aged 48-55 years categorized as early (EP, n = 25) or late (LP, n = 38) perimenopausal according to serum follicle-stimulating hormone (FSH) levels and menstrual diaries. EP women had an irregular menstrual cycle and FSH < 25 IU/L, while LP women had an irregular cycle and > 25 IU/L. We examined motor evoked potential (MEP) and silent period (SP) elicited by transcranial magnetic stimulation (TMS), in the tibialis anterior muscle at 20%, 40%, and 60% of maximal voluntary contraction (MVC) levels, and twitch force potentiation in plantar flexors. Results: EP group showed a longer SP duration in 40% MVC condition and larger motor evoked potential amplitude in 20% MVC condition compared to the LP group. No group difference was detected in twitch force potentiation; however, it correlated negatively with FSH levels. Other factors, such as age, height, body mass index, or physical activity did not explain group differences. Conclusions: Our preliminary results indicate subtle modulation in both TMS-induced inhibitory and excitatory mechanisms and twitch force potentiation in women already in the late perimenopausal stage. This suggests that the reduction of estrogens may have an accelerating role in the aging process of neuromuscular control.

Clin Transl Med. 2021 Mar;11(3):e368.doi: 10.1002/ctm2.368.

A novel modified RANKL variant can prevent osteoporosis by acting as a vaccine and an inhibitor

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Background: The discovery of receptor activator of nuclear factor-κB ligand (RANKL) as the final effector in the pathogenesis of osteoporosis has led to a better understanding of bone remodeling. When RANKL binds to its receptor (RANK), osteoclastic differentiation and activation are initiated. Herein, we propose a strategy using a novel RANKL variant as a competitive inhibitor for RANKL. The RANKL variant activates LGR4 signaling, which competitively regulates RANK and acts as an immunogen that induces anti-RANKL antibody production. Methods: We modified the RANK-binding site on RANKL using minimal amino acid changes in the RANKL complex and its counterpart receptor RANK and tried to evaluate the inhibitory effects on osteoclastogenesis. Results: The novel RANKL variant did not bind RANK in osteoclast progenitor cells, but activated LGR4 through the GSK3-β signaling pathway, thereby suppressing activated T cell cytoplasmic nuclear factor calcineurin-dependent 1 (NFATc1) expression and activity during osteoclastogenesis. Our RANKL variant generated high levels of RANKL-specific antibodies, blocked osteoclastogenesis, and inhibited osteoporosis in ovariectomized mouse models. Generated anti-RANKL antibodies showed a high inhibitory effect on osteoclastogenesis in vivo and in vitro. Conclusions: We observed that the novel RANKL indeed blocks RANKL via LGR4 signaling and generates anti-RANKL antibodies, demonstrating an innovative strategy in the development of general immunotherapy.

J Am Heart Assoc. 2021 Mar 27;e019173.doi: 10.1161/JAHA.120.019173. Online ahead of print.

Adipokines and Subclinical Cardiovascular Disease in Post-Menopausal Women: Study of Women's Health Across the Nation

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Background The menopausal transition is characterized by increased cardiovascular risk, weight gain, and increased adiposity for many women. The adipose-derived secretory proteins adiponectin and leptin are associated with insulin resistance, metabolic syndrome, and cardiovascular disease but their role in subclinical atherosclerotic disease is unclear. This cross-sectional study evaluated the associations of adiponectin and leptin with carotid artery intima-media thickness, adventitial diameter, presence of carotid plaques, and brachial-ankle pulse wave velocity (baPWV) in women aged 54 to 65 years. Methods and Results Participants were 1399 women from SWAN (Study of Women's Health Across the Nation), a community-based study of women transitioning through menopause. Carotid ultrasound and baPWV measures were obtained at SWAN follow-up visits 12 or 13, when 97% of participants were post-menopausal. Adipokines were assayed from serum specimens obtained concurrently at these visits. Linear and logistic

regression models were used to evaluate adiponectin or leptin, both log-transformed attributable to skewness, in relationship to carotid artery intima-media thickness, adventitial diameter, baPWV, and presence of carotid plaque. Covariates included age, race, study site, smoking, alcohol use, obesity, cardiovascular disease risk factors, and menopausal status. Lower levels of adiponectin were related to greater carotid artery intima-media thickness, wider adventitial diameter, and faster baPWV; associations were attenuated after adjusting for cardiovascular disease risk factors. Higher levels of leptin were associated with greater carotid artery intima-media thickness and wider adventitial diameter in minimally and fully adjusted models, and contrary to expectation, with slower baPWV, particularly among women with diabetes mellitus or obesity. Conclusions Adiponectin and leptin are 2 important inflammatory pathways that may contribute to adverse subclinical cardiovascular disease risk profiles in women at midlife.

Circ Heart Fail. 2021 Mar 29;doi: 10.1161/CIRCHEARTFAILURE.120.007297.

Metabolically Healthy/Unhealthy Overweight/Obesity Associations With Incident Heart Failure in Postmenopausal Women: The Women's Health Initiative

Amber R Cordola Hsu 1 2 , Bin Xie, Darleen V Peterson, Michael J LaMonte, et al, Short List of WHI Investigators
Background: Obesity is associated with an increased risk of heart failure (HF); however, how metabolic weight groups relate to HF risk, especially in postmenopausal women, has not been demonstrated. Methods: We included 19 412 postmenopausal women ages 50 to 79 without cardiovascular disease from the Women's Health Initiative. Normal weight was defined as a body mass index ≥18.5 and <25 kg/m2 and waist circumference <88 cm and overweight/obesity as a body mass index ≥25 kg/m2 or waist circumference ≥88 cm. Metabolically healthy was based on <2 and unhealthy ≥2 cardiometabolic traits: triglycerides ≥150 mg/dL, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or blood pressure medication, fasting glucose ≥100 mg/dL or diabetes medication, and HDL-C (high-density lipoprotein cholesterol) <50 mg/dL. Risk factor-adjusted Cox regression examined the hazard ratios (HRs) for incident hospitalized HF among metabolically healthy normal weight (reference), metabolically unhealthy normal weight, metabolically healthy overweight/obese, and metabolically unhealthy overweight/obese. Results: Among our sample, 455 (2.34%) participants experienced HF hospitalizations over a mean follow-up time of 11.3±1.1 years. Compared with metabolically healthy normal weight individuals, HF risk was greater in metabolically unhealthy normal weight (HR, 1.66 [95% CI, 1.01-2.72], P=0.045) and metabolically unhealthy overweight/obese individuals (HR, 1.95 [95% CI, 1.35-2.80], P=0.0004), but not metabolically healthy overweight/obese individuals (HR, 1.15 [95% CI, 0.78-1.71], P=0.48). Subdividing the overweight/obese into separate groups showed HRs for metabolically unhealthy obese of 2.62 (95% CI, 1.80-3.83; P<0.0001) and metabolically healthy obese of 1.52 (95% CI, 0.98-2.35; P=0.06). Conclusions: Metabolically unhealthy overweight/obese and metabolically unhealthy normal weight are associated with an increased risk of HF in postmenopausal women.

Metabolism. 2021 Mar 24;154753.doi: 10.1016/j.metabol.2021.154753. Online ahead of print.

The link between COVID-19 and VItamin D (VIVID): a systematic review and meta-analysis

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Background: Disease severity and mortality rates due to COVID-19 infection are greater in the elderly and chronically ill patients, populations at high risk for vitamin D deficiency. Vitamin D plays an important role in immune function and inflammation. This systematic review and meta-analysis assesses the impact of vitamin D status and supplementation on COVID-19 related mortality and health outcomes. Methods: We searched four databases until December 18th 2020, and trial registries until January 20th 2021. Two reviewers screened the studies, collected data, assessed the risk of bias, and graded the evidence for each outcome across studies, independently and in duplicate. Pre-specified outcomes of interest were mortality, ICU admission, invasive and non-invasive ventilation, hospitalization, time of hospital stay, disease severity and SARS-CoV-2 positivity. We only included data from peer-reviewed articles in our primary analyses. Results: We identified 31 peer-reviewed observational studies. In our primary analysis, there was a positive trend between serum 25(OH)D level < 20 ng/ml and an increased risk of mortality, ICU admission, invasive ventilation, non-invasive ventilation or SARS-CoV-2 positivity. However, these associations were not statistically significant. Mean 25(OH)D levels was 5.9 ng/ml (95%CI [-9.5, -2.3]) significantly lower in COVID-19 positive, compared to negative patients. The certainty of the evidence was very low. We identified 32 clinical trial protocols, but only three have published results to-date. The trials administer vitamin D doses of 357 to 60,000 IU/d,

from one week to 12 months. Eight megatrials investigate the efficacy of vitamin D in outpatient populations. A pilot trial revealed a significant decrease in ICU admission with calcifediol, compared to placebo (OR = 0.003), but the certainty of the evidence was unclear. Another small trial showed that supplementation with cholecalciferol, 60,000 IU/d, decreased fibrinogen levels, but did not have an effect on D-dimer, procalcitonin and CRP levels, compared to placebo. The third trial did not find any effect of vitamin D supplementation on COVID-19 related health outcomes. Conclusion: While the available evidence to-date, from largely poor-quality observational studies, may be viewed as showing a trend for an association between low serum 25(OH)D levels and COVID-19 related health outcomes, this relationship was not found to be statistically significant. Calcifediol supplementation may have a protective effect on COVID-19 related ICU admissions. The current use of high doses of vitamin D in COVID-19 patients is not based on solid evidence. It awaits results from ongoing trials to determine the efficacy, desirable doses, and safety, of vitamin D supplementation to prevent and treat COVID-19 related health outcomes.