



## Selección de Resúmenes de Menopausia

Semana del 5 al 11 de Noviembre de 2014

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### Sex hormonal regulation and hormesis in aging and longevity: role of vitagenes.

Calabrese VI, Scapagnini G, Davinelli S, Koverech G, Koverech A, De Pasquale C, Salinaro AT, et al.

Aging process is accompanied by hormonal changes characterized by an imbalance between catabolic hormones, such as cortisol and thyroid hormones which remain stable and hormones with anabolic effects (testosterone, insulin like growth factor-1 (IGF-1) and dehydroepiandrosterone sulphate (DHEAS), that decrease with age. Deficiencies in multiple anabolic hormones have been shown to predict health status and longevity in older persons. Unlike female menopause, which is accompanied by an abrupt and permanent cessation of ovarian function (both folliculogenesis and estradiol production), male aging does not result in either cessation of testosterone production nor infertility. Although the circulating serum testosterone concentration does decline with aging, in most men this decrease is small, resulting in levels that are generally within the normal range. Hormone therapy (HT) trials have caused both apprehension and confusion about the overall risks and benefits associated with HT treatment. Stress-response hormesis from a molecular genetic perspective corresponds to the induction by stressors of an adaptive, defensive response, particularly through alteration of gene expression. Increased longevity can be associated with greater resistance to a range of stressors. During aging, a gradual decline in potency of the heat shock response occur and this may prevent repair of protein damage. Conversely, thermal stress or pharmacological agents capable of inducing stress responses, by promoting increased expression of heat-shock proteins, confer protection against denaturation of proteins and restoration of proteome function. If induction of stress resistance increases life span and hormesis induces stress resistance, hormesis most likely result in increased life span. Hormesis describes an adaptive response to continuous cellular stresses, representing a phenomenon where exposure to a mild stressor confers resistance to subsequent, otherwise harmful, conditions of increased stress. This biphasic dose-response relationship, displaying low-dose stimulation and a high-dose inhibition, as adaptive response to detrimental lifestyle factors determines the extent of protection from progression to metabolic diseases such as diabetes and more in general to hormonal dysregulation and age-related pathologies. Integrated responses exist to detect and control diverse forms of stress. This is accomplished by a complex network of the so-called longevity assurance processes, which are composed of several genes termed vitagenes. Vitagenes encode for heat shock proteins (Hsps), thioredoxin and sirtuin protein systems. Nutritional antioxidants, have recently been demonstrated to be neuroprotective through the activation of hormetic pathways under control of Vitagene protein network. Here we focus on possible signaling mechanisms involved in the activation of vitagenes resulting in enhanced defense against functional defects leading to degeneration and cell death with consequent impact on longevity processes.

**Menopause. 2014 Nov 6. [Epub ahead of print]**

### Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis.

Hodis HN1, Mack WJ, Shoupe D, Azen SP, Stanczyk FZ, Hwang-Levine J, Budoff MJ, Henderson VW.

**OBJECTIVE:** This study aims to present methods and baseline data from the Early versus Late Intervention Trial with Estradiol (ELITE), the only clinical trial designed to specifically test the timing hypothesis of postmenopausal hormone therapy (HT). The timing hypothesis posits that HT effects depend on the temporal initiation of HT relative to time since menopause. **METHODS:** ELITE is a randomized, double-blind, placebo-controlled trial with a  $2 \times 2$  factorial design. Six hundred forty-three healthy postmenopausal women without cardiovascular disease were randomized to oral estradiol or placebo for up to 6 to 7 years according to time since menopause ( $<6$  or  $\geq 10$  y). Carotid artery intima-media thickness (CIMT) and cardiac computed tomography were conducted to determine HT effects on subclinical atherosclerosis across menopause strata. **RESULTS:** Participants in the early and late postmenopausal strata were well-separated by mean age (55.4 vs 65.4 y) and median time since menopause (3.5 vs 14.3 y). Expected risk factors (age, blood pressure, and body mass index) were associated with CIMT at baseline in

both strata. In the early postmenopausal group, but not in the late postmenopausal group, we observed significant associations between CIMT and factors that may play a role in the responsiveness of atherosclerosis progression according to timing of HT initiation. These include low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, sex hormone-binding globulin, and serum total estradiol. CONCLUSIONS: The ELITE randomized controlled trial is timely and unique. Baseline data indicate that ELITE is well-positioned to test the HT timing hypothesis in relation to atherosclerosis progression and coronary artery disease.

**Cancer Manag Res. 2014 Oct 17;6:423-30. doi: 10.2147/CMAR.S55219. eCollection 2014.**

### **Preventative therapies for healthy women at high risk of breast cancer.**

Sestak I.

Tamoxifen has been shown to reduce the risk of developing estrogen receptor (ER)-positive breast cancer by at least 50%, in both pre- and postmenopausal women. The current challenge is to find new agents with fewer side effects and to find agents that are specifically suitable for premenopausal women with ER-negative breast cancer. Other selective estrogen receptor modulators (SERMs), such as raloxifene, arzoxifene, and lasofoxifene, have been shown to reduce the incidence of breast cancer by 50%-80%. SERMs are interesting agents for the prevention of breast cancer, but longer follow-up is needed for some of them for a complete risk-benefit profile of these drugs. Aromatase inhibitors have emerged as new drugs in the prevention setting for postmenopausal women. In the Mammary Prevention 3 (MAP3) trial, a 65% reduction in invasive breast cancer with exemestane was observed, and the Breast Cancer Intervention Study-II trial, which compared anastrozole with placebo, reported a 60% reduction in those cancers. Although SERMs and aromatase inhibitors have been proven to be excellent agents in the preventive setting specifically for postmenopausal women and ER-positive breast cancer, newer agents have to be found specifically for ER-negative breast cancers, which mostly occur in premenopausal women.

**BJOG. 2014 Nov 7. doi: 10.1111/1471-0528.13163. [Epub ahead of print]**

### **Hot flushes and night sweats are associated with coronary heart disease risk in midlife: a longitudinal study.**

Herber-Gast G1, Brown W, Mishra G.

OBJECTIVE: The purpose of this study was to investigate associations between vasomotor menopausal symptoms (VMS), i.e. hot flushes and night sweats, and the incidence of coronary heart disease (CHD). DESIGN: A prospective cohort study. SETTING AND POPULATION: 11 725 women, aged 45-50 years at baseline in 1996, were followed up at 3-year intervals for 14 years. METHODS: Self-reported VMS and incident CHD were measured at each survey. MAIN OUTCOME MEASURE: We determined the association between VMS and CHD at the subsequent survey, using generalised estimating equation analysis, adjusting for time-varying covariates. RESULTS: At baseline, 14% reported rarely, 17% reported sometimes, and 7% reported often having night sweats. During follow-up, 187 CHD events occurred. In the age-adjusted analysis, women who reported their frequency of experiencing hot flushes and night sweats as 'often' had a greater than two-fold increased odds of CHD (OR hot flushes 2.18, 95% CI 1.49-3.18; OR night sweats 2.38, 95% CI 1.62-3.50) compared with women with no symptoms (P trend < 0.001 for frequency of symptoms). Adjustment for menopausal status, lifestyle factors, body mass index, diabetes, and hypertension attenuated the associations (OR hot flushes 1.70, 95% CI 1.16-2.51, P trend = 0.01; OR night sweats 1.84, 95% CI 1.24-2.73), P trend = 0.004). CONCLUSIONS: Women who report having hot flushes or night sweats 'often' have an increased risk of developing CHD over a period of 14 years, even after taking the effects of age, menopause status, lifestyle, and other chronic disease risk factors into account.

**J Menopausal Med. 2013 Dec;19(3):123-9. doi: 10.6118/jmm.2013.19.3.123. Epub 2013 Dec 27.**

### **Effects of menopausal hormone therapy on uterine myoma in menopausal women.**

Chang IJ1, Hong GY2, Oh YL3, Kim BR2, Park SN2, Lee HH4, Na YJ5, Namkung J6.

OBJECTIVES: The aim of the present study is to evaluate the long term effects of estrogen-progestogen therapy (EPT) on uterine myomas volume in postmenopausal women. METHODS: We performed a retrospective analysis on postmenopausal women with asymptomatic uterine myoma during the period between April, 2008 and September, 2012. Postmenopause was defined as amenorrhea for longer than a year or serum follicle stimulating hormone levels

higher than 40 IU/L. The volume of the myoma was assessed by transvaginal ultrasonography for every 6 months after administration of EPT. RESULTS: Thirty-eight women were included in the study, with 32 in the EPT group and 6 in the control group. Overall, uterine myoma volume (mean  $\pm$  standard deviation, cm<sup>3</sup>) in the EPT group was  $19.5 \pm 24.6$  at baseline, and those at 6 and 12 months were  $24.7 \pm 35.1$  and  $28.5 \pm 56.4$ , respectively. Myoma volume did not change significantly with EPT, and these changes were not significantly different from the control group. Myoma volume changes were not significantly different in the subgroups according to the route of estrogen administrations and the method of progestogen administrations. Clinically significant volume increases during one year of EPT was noted in 28.1% (9/32), however, only one showed transient increases. CONCLUSION: Our results suggest that treating postmenopausal woman with EPT on a long-term basis does not increase the volume of uterine myomas.