 **Selección de Resúmenes de Menopausia**

Semana del 27 de Agosto al 2 de Septiembre de 2014

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**Steroids. 2014 Aug 25. pii: S0039-128X(14)00196-2. doi: 10.1016/j.steroids.2014.08.003. [Epub ahead of print]**

**Estrogen metabolites and breast cancer.**

Santen RJ1, Yue W2, Wang JP2.

Epidemiologic studies link several factors related to estrogen production in women to an increased risk of breast cancer. These include early menarche, late menopause, obesity, use of post-menopausal hormone therapy, and plasma estradiol levels. Two possible mechanisms have been proposed to explain the increased risk: (1) estrogen receptor (ER) mediated stimulation of breast cell proliferation with a concomitant enhanced rate of mutations and (2) metabolism of estradiol to genotoxic metabolites with a resulting increase in DNA mutations. The metabolism of estradiol can cause DNA damage in two ways: (a) formation of estradiol-adenine -guanine adducts which are released from the DNA backbone leaving depurinated sites which undergo error prone DNA repair and mutations and (b) generation of oxygen free radicals resulting from redox cycling of 4-OH estradiol to the 3-4 estradiol quinone and back conversion to 4-OH estradiol. If one or both pathways are operative, sufficient numbers of mutations accumulate over a long period of time to induce neoplastic transformation. Our studies are based on the hypothesis that both receptor-mediated and genotoxic pathways contribute to breast cancer. We initially demonstrated that MCF-7 breast cancer cells and normal breast tissue in aromatase transfected mice contain the enzymes necessary to convert estradiol to the estradiol DNA adducts. We then utilized a highly reductionist model to separately analyze the effect of estrogen receptor alpha (ER) on tumor formation and the effects of estrogen depletion by castration in ER knock out /Wnt-1 (ERKO/Wnt) transgenic animals to assess the effects of estradiol in the absence of an ER. Estradiol was added back in castrate ERKO/Wnt animals to determine if Koch's postulates could be fulfilled to increase the incidence of cancer with administration of exogenous estradiol. Finally, we assessed the effects of an aromatase inhibitor on tumor incidence in non-castrate, ERKO/Wnt animals. The studies demonstrated the conversion of estadiol to genotoxic metabolites in breast tissue. In addition, knockout of ERα caused a reduction in incidence of tumor formation and a delay in the occurrence of those that formed. Oophorectomy further reduced the incidence of tumors and delayed their onset whereas estradiol add-back returned the incidence rate to that observed before oophorectomy. The aromatase inhibitor, letrozole, delayed the onset of tumor formation. Taken together, these data support a role for estradiol metabolism as one of the components in the development of experimental breast cancer.

**Arq Bras Endocrinol Metabol. 2014 Jul;58(5):523-9.**

**Long-term risks of bisphosphonate therapy.**

Watts NB.

The objective this study was to summarize long-term risks associated with bisphosphonate therapy. Search of relevant medical publications for data from clinical trials, trial extensions, observational studies and post-marketing reports. Trial extensions and modifications did not reveal significant long-term safety issues. Observational data suggest at least as many benefits as risks. Post-marketing reports of musculoskeletal pain, osteonecrosis of the jaw and atypical femur fractures have been widely circulated in the lay press. Most focus on long-terms risks has been on osteonecrosis of the jaw and atypical femur fractures which occur in patients who have not received bisphosphonate therapy but may be more frequent (though still uncommon) in patients who have been on treatment for 5 years or longer. Lower-risk patients may be able to stop treatment after 3-5 years for a "drug holiday," which mitigates these long-term risks; for higher risk patients, therapy through 6-10 years appears to be advisable and offers more benefits than risks.

**Arq Bras Endocrinol Metabol. 2014 Jul;58(5):470-7.**

**Obesity and fractures.**

Premaor MO1, Comim FV1, Compston JE2.

Until recently obesity was believed to be protective against fractures. However, a report from a Fracture Liaison Clinic in the UK (2010) reported a surprisingly high proportion of obese postmenopausal women attending the clinic with fractures, and in the GLOW study (2011), a similar prevalence and incidence of fractures in obese and non-obese postmenopausal women was observed. Subsequently, other studies have demonstrated the importance of obesity in the epidemiology of fractures. Obese women are at increased risk of fracture in ankle, leg, humerus, and vertebral column and at lower risk of wrist, hip and pelvis fracture when compared to non-obese women. In men, it has been reported that multiple rib fractures are associated with obesity. Furthermore, falls appear to play an important role in the pathogenesis of fractures in obese subjects. Regarding hip fracture and major fractures, the FRAX algorithm has proven to be a useful predictor in obese individuals. Obese people are less likely to receive bone protective treatment; they have a longer hospital stay and a lower quality of life both before and after fracture. Moreover, the efficacy of antiresorptive therapies is not well established in obese people. The latter is a field for future research.

**J Clin Endocrinol Metab. 2014 Aug 27:jc20141415. [Epub ahead of print]**

**Current Issues in the Presentation of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop.**

Silverberg SJ1, Clarke BL, Peacock M, Bandeira F, Boutroy S, Cusano NE, Dempster D, Lewiecki EM, Jian-Min L, Minisola S, Rejnmark L, Silva BC, Walker MD, Bilezikian JP.

Objective: This report summarizes data on traditional and nontraditional manifestations of primary hyperparathyroidism (PHPT) that have been published since the last International Workshop on PHPT. Participants: This subgroup was constituted by the Steering Committee to address key questions related to the presentation of PHPT. Consensus was established at a closed meeting of the Expert Panel that followed. Evidence: Data from the 5-year period between 2008 and 2013 were presented and discussed to determine whether they support changes in recommendations for surgery or nonsurgical follow-up. Consensus Process: Questions were developed by the International Task Force on PHPT. A comprehensive literature search for relevant studies was undertaken. After extensive review and discussion, the subgroup came to agreement on what changes in the recommendations for surgery or nonsurgical follow-up of asymptomatic PHPT should be made to the Expert Panel. Conclusions: 1) There are limited new data available on the natural history of asymptomatic PHPT. Although recognition of normocalcemic PHPT (normal serum calcium with elevated PTH concentrations; no secondary cause for hyperparathyroidism)is increasing,data on the clinical presentation and natural history of this phenotypeare limited. 2) Although there are geographic differences in the predominant phenotypes of PHPT (symptomatic, asymptomatic, normocalcemic), they do not justify geography-specific management guidelines. 3) Recent data using newer, higher resolution imaging and analytic methods have revealed that in asymptomatic PHPT, both trabecular bone and cortical bone are affected. 4) Clinically silent nephrolithiasis and nephrocalcinosis can be detected by renal imaging and should be listed as a new criterion for surgery. 5) Current datadonot support a cardiovascular evaluation or surgery for the purpose of improving cardiovascular markers, anatomicalor functional abnormalities. 6) Some patients with mildPHPT have neuropsychological complaints and cognitive abnormalities, and some of these patients may benefit from surgical intervention. However, it is not possible at this time to predict which patients with neuropsychological complaints or cognitive issues will improve after successful parathyroid surgery.

**Menopause. 2014 Aug 26. [Epub ahead of print]**

**Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society.**

Portman DJ1, Gass Ncmp ML; on behalf of the Vulvovaginal Atrophy Terminology Consensus Conference Panel.

BACKGROUND: In 2012, the Board of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the Board of Trustees of The North American Menopause Society (NAMS) acknowledged the need to review current terminology associated with genitourinary tract symptoms related to menopause. METHODS: The 2 societies cosponsored a terminology consensus conference, which was held in May 2013. RESULTS AND CONCLUSIONS: Members of the consensus conference agreed that the term genitourinary syndrome of menopause (GSM) is a medically more accurate, all-encompassing, and publicly acceptable term than vulvovaginal atrophy. GSM is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder. The syndrome may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent urinary tract infections. Women may present with some or all of the signs and symptoms, which must be bothersome and should not be better accounted for by another diagnosis. The term was presented and discussed at the annual meeting of each society. The respective Boards of NAMS and ISSWSH formally endorsed the new terminology-genitourinary syndrome of menopause (GSM)-in 2014.

**J Alzheimers Dis. 2014 Aug 26. [Epub ahead of print]**

**Update on the Neuroprotective Effect of Estrogen Receptor Alpha Against Alzheimer's Disease.**

Lan YL1, Zhao J2, Li S1.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss and disordered cognition. Women have a higher AD incidence than men, indicating that the declining estrogen levels during menopause may influence AD pathogenesis. However, the mechanism underlying estrogen's neuroprotective effect is not fully clarified and is complicated by the presence of several distinct estrogen receptor (ER) types and the identification of a growing number of ER splice variants. Thus, a deeper analysis of ERs could elucidate the role of estrogen in age-related cognitive changes. Intracellular calcium signaling cascades play a pivotal role in ERα neuroprotection against AD. The ERα-mediated inhibition of Death domain-associated protein (Daxx) translocation and the combination of membrane ERα and caveolin in caveolae may protect against AD. Moreover, the voltage-dependent anion channel (VDAC)/ERα association may be important for maintaining channel inactivation and may be relevant in neuronal preservation against Aβ injury. Additionally, ERα may prevent glutamate excitotoxic injury by Aβ through estrogen signaling mechanisms. ERα and IGF-IR co-activation may mediate neuroprotection, and many other growth factors and intracellular signaling responses triggered by ERα may also play important roles in this process. Furthermore, details regarding the genes and mRNA variants of ERα that are expressed in different parts of the human organs have been clarified recently. Therefore, here we review the literature to clarify the neuroprotective role of ERα. This review focuses on the potential mechanisms mediated by ERα in the intracellular signaling events in nervous system cells, thereby clarifying ERα-mediated protections against AD.

**Int J Urol. 2014 Aug 29. doi: 10.1111/iju.12610. [Epub ahead of print]**

**Association of urinary incontinence and sexual function in women.**

Su CC1, Sun BY, Jiann BP.

OBJECTIVES: To investigate the association between urinary incontinence and female sexual function in a non-clinical population. METHODS: A self-administered questionnaire was distributed to 2159 female employees of two hospitals. RESULTS: Of the 883 sexually active participants, pure stress urinary incontinence was reported in 18.3%, pure urge urinary incontinence in 6.8%, mixed urinary incontinence in 15.1% and no urinary incontinence in 59.8%. The prevalence of female sexual difficulty, defined by the Female Sexual Function Index total score ≤26.55, was 52.0%, 56.1%, 54.3% and 42.2%, respectively (P < 0.05). After adjustment of age, menstrual status, length of marriage, having children and relationship with the partner, all types of urinary incontinence showed a significant association with female sexual difficulty with an odds ratio of 1.6-1.8. Taking into consideration the individual domains, pure urge urinary incontinence was a risk factor for decreased sexual lubrication and more sexual pain, and mixed urinary incontinence was a risk factor for less sexual satisfaction, whereas pure stress urinary incontinence was not related to a difficulty in individual domains. CONCLUSIONS: Stress urinary incontinence and urge urinary incontinence are associated with general impairment of female sexual function to a mild degree. Only urge urinary incontinence is related to sexual difficulty in specific domains including sexual lubrication and sexual pain.