Selección de Resúmenes de Menopausia

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Bisphosphonates Inhibit Pain, Bone Loss, and Inflammation in a Rat Tibia Fracture Model of Complex Regional Pain Syndrome.

Wang L, Guo TZ, Wei T, Li WW, Shi X, Clark JD, Kingery WS.

BACKGROUND: Bisphosphonates are used to prevent the bone loss and fractures associated with osteoporosis, bone metastases, multiple myeloma, and osteogenesis deformans. Distal limb fractures cause regional bone loss with cutaneous inflammation and pain in the injured limb that can develop into complex regional pain syndrome (CRPS). Clinical trials have reported that antiresorptive bisphosphonates can prevent fracture-induced bone loss, inhibit serum inflammatory cytokine levels, and alleviate CRPS pain. Previously, we observed that the inhibition of inflammatory cytokines or adaptive immune responses attenuated the development of pain behavior in a rat fracture model of CRPS, and we hypothesized that bisphosphonates could prevent pain behavior, trabecular bone loss, postfracture cutaneous cytokine upregulation, and adaptive immune responses in this CRPS model. METHODS: Rats underwent tibia fracture and cast immobilization for 4 weeks and were chronically administered either subcutaneously perfused alendronate or oral zoledronate. Behavioral measurements included hindpaw von Frey allodynia, unweighting, warmth, and edema. Bone microarchitecture was measured by microcomputed tomography, and bone cellular activity was evaluated by static and dynamic histomorphometry. Spinal cord Fos immunostaining was performed, and skin cytokine (tumor necrosis factor, interleukin [IL]-1, IL-6) and nerve growth factor (NGF) levels were determined by enzyme immunoassay. Skin and sciatic nerve immunoglobulin levels were determined by enzyme immunoassay. RESULTS: Rats with tibia fractures developed hindpaw allodynia, unweighting, warmth, and edema, increased spinal Fos expression and trabecular bone loss in the lumbar vertebra and bilateral distal femurs as measured by microcomputed tomography, increased trabecular bone resorption and osteoclast surface with decreased bone formation rates, increased cutaneous inflammatory cytokine and NGF expression, and elevated immunocomplex deposition in skin and nerve. Alendronate (60 μg/kg/d subcutaneously [s.c.]) or zoledronate (3 mg/kg/d orally) treatment for 28 days, started at the time of fracture, completely inhibited the development of hindpaw allodynia and reduced hindpaw unweighting by 44% ± 13% and 58% ± 5%, respectively. Orally administered zoledronate (3 mg/kg/d for 21 days) treatment also completely reversed established allodynia and unweighting when started at 4 weeks postfracture. Histomorphometric and microcomputed tomography analysis demonstrated that both the 3 and 60 μg/kg/d alendronate treatments reversed trabecular bone loss (an 88% ± 25% and 188% ± 39% increase in the ipsilateral distal femur BV/TV, respectively) and blocked the increase in osteoclast numbers and erosion surface observed in bilateral distal femurs and in L5 vertebra of the fracture rats. Alendronate treatment inhibited fracture-induced increases in hindpaw inflammatory mediators, reducing postfracture levels of tumor necrosis factor by 43% ± 9%, IL-1 by 60% ± 9%, IL-6 by 56% ± 14%, and NGF by 37% ± 14%, but had no effect on increased spinal cord Fos expression, or skin and sciatic nerve immunocomplex deposition. CONCLUSIONS: Collectively, these results indicate that bisphosphonate therapy inhibits pain, osteoclast activation, trabecular bone loss, and cutaneous inflammation in the rat fracture model of CRPS, data supporting the hypothesis that bisphosphonate therapy can provide effective multimodal treatment for CRPS.

Age (Dordr). 2016 Sep 14. [Epub ahead of print]

Age at menarche and age at natural menopause in East Asian women: a genome-wide association study.

Shi J, Zhang B, Choi JY, Gao YT, Li H, Lu W, Long J, Kang D, Xiang YB, Wen W, Park SK, Ye X, Noh DY, et al.

Age at menarche (AM) and age at natural menopause (ANM) are complex traits with a high heritability. Abnormal timing of menarche or menopause is associated with a reduced span of fertility and risk for several age-related diseases including breast, endometrial and ovarian cancer, cardiovascular disease, and osteoporosis. To identify novel genetic loci for AM or ANM in East Asian women and to replicate previously identified loci primarily in women of European ancestry by genome-wide association studies (GWASs), we conducted a two-stage GWAS. Stage I aimed to discover promising novel AM and ANM loci using GWAS data of 8073 women from Shanghai,

China. The Stage II replication study used the data from another Chinese GWAS (n = 1230 for AM and n = 1458 for ANM), a Korean GWAS (n = 4215 for AM and n = 1739 for ANM), and de novo genotyping of 2877 additional Chinese women. Previous GWAS-identified loci for AM and ANM were also evaluated. We identified two suggestive menarcheal age loci tagged by rs79195475 at 10q21.3 (beta = -0.118 years, P = 3.4 × 10-6) and rs1023935 at 4p15.1 (beta = -0.145 years, P = 4.9 × 10-6) and one menopausal age locus tagged by rs3818134 at 22q12.2 (beta = -0.276 years, P = 8.8 × 10-6). These suggestive loci warrant a further validation in independent populations. Although limited by low statistical power, we replicated 19 of the 98 menarche loci and 5 of the 20 menopause loci previously identified in women of European ancestry in East Asian women, suggesting a shared genetic architecture for these two traits across populations.

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Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis.

Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH.

Importance: As many as 10% of women experience natural menopause by the age of 45 years. If confirmed, an increased risk of cardiovascular disease (CVD) and all-cause mortality associated with premature and early-onset menopause could be an important factor affecting risk of disease and mortality among middle-aged and older women. Objective: To systematically review and meta-analyze studies evaluating the effect of age at onset of menopause and duration since onset of menopause on intermediate CVD end points, CVD outcomes, and all-cause mortality. Data Sources: Medical databases (ie, Medline, EMBASE, and Web of Science) until March 2015. Study Selection: Studies (ie, observational cohort, case-control, or cross-sectional) that assessed age at onset of menopause and/or time since onset of menopause as exposures as well as risk of cardiovascular outcomes and intermediate CVD end points in perimenopausal, menopausal, or postmenopausal women. Data Extraction and Synthesis: Studies were sought if they were observational cohort, case-control, or cross-sectional studies; reported on age at onset of menopause and/or time since onset of menopause as exposures; and assessed associations with risk of CVD-related outcomes, all-cause mortality, or intermediate CVD end points. Data were extracted by 2 independent reviewers using a predesigned data collection form. The inverse-variance weighted method was used to combine relative risks to produce a pooled relative risk using random-effects models to allow for between-study heterogeneity. Main Outcomes and Measures: Cardiovascular disease outcomes (ie, composite CVD, fatal and nonfatal coronary heart disease [CHD], and overall stroke and stroke mortality), CVD mortality, all-cause mortality, and intermediate CVD end points. Results: Of the initially identified references, 32 studies were selected that included 310 329 nonoverlapping women. Outcomes were compared between women who experienced menopause younger than 45 years and women 45 years or older at onset; the relative risks (95% CIs) were 1.50 (1.28-1.76) for overall CHD, 1.11 (1.03-1.20) for fatal CHD, 1.23 (0.98-1.53) for overall stroke, 0.99 (0.92-1.07) for stroke mortality, 1.19 (1.08-1.31) for CVD mortality, and 1.12 (1.03-1.21) for all-cause mortality. Outcomes were also compared between women between 50 and 54 years at onset of menopause and women younger than 50 years at onset; there was a decreased risk of fatal CHD (relative risk, 0.87; 95% CI, 0.80-0.96) and no effect on stroke. Time since onset of menopause in relation to risk of developing intermediate cardiovascular traits or CVD outcomes was reported in 4 observational studies with inconsistent results. Conclusions and Relevance: The findings of this review indicate a higher risk of CHD, CVD mortality, and overall mortality in women who experience premature or early-onset menopause.

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Analysis of Patients with Helicobacter pylori Infection and the Subsequent Risk of Developing Osteoporosis after Eradication Therapy: A Nationwide Population-Based Cohort Study.

Shih HM, Hsu TY, Chen CY, Lin CL, Kao CH, Chen CH, Yang TY, Chen WK.

PURPOSE: Previous studies have reported conflicting results on the association between Helicobacter pylori infection and osteoporosis. A few studies have discussed the influence of H. pylori eradication therapy on bone mineral density.

METHODS: We assessed the prevalence of osteoporosis among the H. pylori-infected population in Taiwan and the influence of early and late H. pylori eradication therapy on bone mineral density. RESULTS: Using data from

Taiwan's National Health Insurance Research Database, we identified 5,447 patients who received H. pylori eradication therapy from 2000 to 2010 and 21,788 controls, frequency-matched according to age, sex, and year of receiving H. pylori eradication therapy. Those who received H. pylori eradication therapy were divided into two groups based on the time interval between the diagnosis of a peptic ulcer and commencement of eradication therapy. The risk of developing osteoporosis was higher in the early H. pylori treatment cohort (hazard ratio [HR] = 1.52, 95% confidence interval [CI] = 1.23-1.89) and late H. pylori treatment cohort (HR = 1.69, 95% CI = 1.39-2.05), compared with the risk in the control cohort. When followed for less than 5 years, both the early and late cohorts had a higher risk of developing osteoporosis (HR = 1.69, 95% CI = 1.32-2.16 and HR = 1.72, 95% CI = 1.38-2.14). However, when the follow-up period was over 5 years, only the late eradication group exhibited a higher incidence of osteoporosis (HR = 1.62, 95% CI = 1.06-2.47).
CONCLUSION: The development of osteoporosis is complex and multi-factorial. Via this population-based cohort study and adjustment of possible confounding variables, we found H. pylori infection may be associated with an increased risk of developing osteoporosis in Taiwan. Early eradication could reduce the influence of H. pylori infection on osteoporosis when the follow-up period is greater than 5 years. Further prospective studies are necessary to discover the connection of H. pylori and osteoporosis.

Psychoneuroendocrinology. 2016 Sep 5. doi: 10.1016/j.psyneuen.2016.08.026. [Epub ahead of print]

Metabolic and hormone influences on emotion processing during menopause.

Berent-Spillson A, Marsh C, Persad C, Randolph J, Zubieta JK, Smith Y.

Disturbances of emotion regulation and depressive symptoms are common during the menopause transition. Reproductive hormone levels are not directly correlated with depressive symptoms, and other factors may influence mood symptoms during menopause. In this study, we sought to determine the role of metabolic function in mood symptoms during menopause, hypothesizing an association with menopause status and long-term glucose load. We studied 54 women across three menopause transition stages (15 premenopause, 11 perimenopause, and 28 postmenopause), examining effects of age, hormones, and metabolism on mood and neural activation during emotional discrimination. We assessed participants using behavioral and functional MRI measures of negative emotion and emotion discrimination, and glycated hemoglobin A1c, to assess long-term glucose load. We found that emotionally unpleasant images activated emotion regulation (amygdala) and cognitive association brain regions (prefrontal cortex, posterior cingulate, temporal-parietal-occipital (TPO) junction, hippocampus). Cognitive association region activity increased with menopause stage. Perimenopausal women had left TPO junction activation, and postmenopausal women had prefrontal cortex, posterior cingulate, and TPO junction activation. Negative affect was associated with decreased amygdala activation, while depression symptoms and negative mood were associated with increased TPO junction activation. Hemoglobin A1c was associated with negative interpretation bias of neutral images and cognitive region recruitment during emotion discrimination. FSH levels, indicating menopause stage, were associated with negative mood. Age was not associated with any behavioral measures or activation patterns during the emotion task. Our results suggest that an interaction between metabolic and hormonal factors may influence emotion regulation, leading to increased risk for depression during menopause.

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Preparation and in vivo evaluation of an orally available enteric-microencapsulated parathyroid hormone (1-34)-deoxycholic acid nanocomplex.

Hwang SR, Seo DH, Byun Y, Park JW.

The N-terminal 34-amino-acid peptide fragment of human parathyroid hormone PTH (1-34), is used clinically to treat osteoporosis; however, it is currently administered by a once-daily subcutaneous injection, resulting in poor patient compliance. We have developed enteric microcapsules containing an ionic nanocomplex between PTH (1-34) and lysine-linked deoxycholic acid (LysDOCA) for the oral delivery of PTH (1-34). We measured the particle size of the PTH/LysDOCA complex and assessed its biological activity by determining the cAMP content in MC3T3-E1 cells. We also assessed its permeability across a Caco-2 cell monolayer and the bioavailability of the intrajejunally administered PTH/LysDOCA complex compared with PTH (1-34) in rats. In addition, the antiosteoporotic activity of the PTH/LysDOCA complex, encapsulated in an enteric carrier by coaxial ultrasonic atomization, was evaluated after it was orally administered to ovariectomized (OVX) rats. The formation of an ionic complex between PTH (1-

34) and LysDOCA produced nanoparticles of diameter 33.0±3.36 nm, and the bioactivity of the complex was comparable with that of PTH (1-34). The Caco-2 cell permeability and AUClast value of the PTH/LysDOCA (1:10) nanocomplex increased by 2.87- and 16.3-fold, respectively, compared with PTH (1-34) alone. Furthermore, the OVX rats treated with oral PTH/LysDOCA-loaded enteric microcapsules showed an increase in bone mineral density (159%), bone volume fraction (175%), and trabecular number (174%) compared with those in the OVX control group. Therefore, the PTH/LysDOCA nanocomplex oral delivery system is a promising treatment modality for osteoporosis because it improves osteogenesis and trabecular connectivity.

Maturitas. 2016 Oct;92:15-23. doi: 10.1016/j.maturitas.2016.07.006. Epub 2016 Jul 9.

Menopause: Genome stability as new paradigm.

Laven JS, Visser JA, Uitterlinden AG, Vermeij WP, Hoeijmakers JH.

Menopause is defined as the age-dependent permanent cessation of menstruation and ovulation due to ovarian failure. Menopause occurs on average around the age of 51 years. Recent genome-wide association studies (GWAS) have identified over 44 genetic variants that are associated with age of onset of natural menopause. Genes linked with menopause can be classified into three major groups: genes implicated in genome stability (DNA repair), immune function and mitochondrial biogenesis. Biological and epidemiological data indicate that reproductive performance, age at menopause and longevity are interlinked through common genetic factors, which play a pivotal role in DNA repair and genome maintenance, which has been linked before with the process of ageing. Consequently, ageing of the soma as a result of inefficient DNA repair appears also to be responsible for failure to reproduce and the subsequent occurrence of menopause. In this way reproductive performance may be strongly linked to the physical condition of the soma and may be a very good predictor of general health in later life.

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Three to five years later: long-term effects of prophylactic bilateral salpingectomy on ovarian function.

Venturella R, Lico D, Borelli M, Imbrogno MG, Cevenini G, Zupi E, Zullo F, Morelli M.

STUDY OBJECTIVE: Preliminary data on the effects of prophylactic bilateral salpingectomy (PBS) show that postoperative ovarian function is preserved up to 3 months after surgery. The confirmation of PBS safety on ovarian function even many years after surgery is essential to reassure the medical community that this new strategy, recently proposed for the prevention of ovarian cancer, is at least able to avoid the risk of premature surgical menopause. We investigated whether the addition of PBS during total laparoscopic hysterectomy (TLH) causes long-term effects on ovarian function. DESIGN: Observational study DESIGN CLASSIFICATION: Canadian Task Force II-3 SETTING: Department of Obstetrics & Gynecology, "Magna Graecia" University - Catanzaro, Italy. PATIENTS: Seventy-nine patients who underwent TLH plus salpingectomy between September 2010 and September 2012 at our Institution have been recalled to be submitted to ovarian reserve evaluation in February 2015. Eight of 79 women refused to participate in this follow-up study. INTERVENTIONS: The ovarian age of PBS patients has been determined through OvAge®, a statistical model that combines Anti-Müllerian-Hormone (AMH), Follicle-Stimulating-Hormone (FSH), 3D Antral Follicle Count (AFC), Vascular-Index (VI), Flow-Index (FI) and Vascular-Flow-Index (VFI) values. The control group consisted of a large population of 652 healthy women (with intact uterus and adnexa) previously enrolled to build the OvAge® model. Comparisons between ovarian ages of PBS patients and the control group have been assessed by (ANCOVA) linear statistical modeling. MEASUREMENTS AND MAIN RESULTS: The main outcome measurement was the differences in the behavior within OvAge/age relation between PBS and control women. Descriptive statistics of those 71 enrolled PBS patients are the following: age 49.61±2.15 years; OvAge 49.22±2.57 years; FSH 43.02±19.92 mU/mL; AMH 0.12±0.20 ng/mL; 3D AFC 1.91±1.28; VI 2.80±5.32%; FI 19.37±5.88; and VFI 0.56±1.12. ANCOVA analysis disclosed that PBS and control women do not exhibit different behavior ($p = 0.900$) within OvAge/age relation.
CONCLUSION: According to our model, the addition of PBS to TLH in the late reproductive years does not modify the ovarian age of treated women up to 3 to 5 years after surgery.

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Cardiovascular Risk Assessment of Subclinical Hypothyroid Patients by Using Framingham Risk Score.

Sertbas Y, Akcan Y, Yazici M.

Objectives: The aim of this study is to evaluate the variation of cardiovascular risks of subclinical hypothyroid patients with thyroid hormone replacement therapy by using Framingham Risk Scoring system. Materials and methods: In this study 21 subclinical hypothyroid and 22 healthy volunteers, between the ages 37 to 68 were taken as cases and control groups. Subclinical hypothyroid patients were given L-T4 replacement therapy for one-year to keep the thyroid hormone (TSH) values in normal ranges. Before and after the treatment clinical and laboratory parameters compared with each other for case and control groups. Results: When we compared the pre and post treatment values of subclinical hypothyroid patients; The systolic and diastolic blood pressures, total cholesterol, low-density lipoprotein (LDL) cholesterol levels and framingham risk scores obviously decreased ($p < 0.05$). Although, at the begining of the study ten-year cardiovacular risk of the case group was significantly higher than that of control group, after treatment no difference was found between the two groups ($p < 0.05$ vs $p > 0.05$). Conclusion: By using Framingham Risk Score, its obviously seen that in subclinical hypothyroid patients, just by thyroid hormone replacement therapy a marked decrease of cardiovascular risk can be obtained.

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Dietary Associations with a Breast Cancer Risk Biomarker Depend on Menopause Status.

Hidaka BH, Carlson SE, Kimler BF, Fabian CJ.

We investigated how timing influences the role of diet in breast cancer risk with a cross-sectional study of pre-malignant change in breast tissue. Women with an elevated risk of developing breast cancer (33 premenopausal and 32 postmenopausal) completed the National Cancer Institute's food frequency questionnaire and underwent random periareolar fine-needle aspiration for evaluation of cytologic atypia, an established risk biomarker. Fatty acid composition of breast adipose was measured in 32 (49%) subjects. We found that premenopausal and postmenopausal women had similar diets, but the associations between atypia and intake of total n-3 polyunsaturated fatty acids (PUFA) and soy differed by menopause status (both P interaction < 0.001). Total n-3 PUFA intake was inversely associated with atypia among premenopausal women ($P < 0.0001$), but not among postmenopausal women ($P = 0.91$); associations were similar for soy ($P = 0.0003$ and $P = 0.48$, respectively). This pattern of dietary interaction with menopause was mirrored in tissue fatty acids (P interaction < 0.05), wherein 1) higher levels of linolelaidic acid (an industrially-produced trans fat) and 2) lower levels of docosahexaenoic acid (the predominant long-chain n-3 PUFA) in breast adipose were associated with atypia in premenopausal (both $P < 0.05$) but not postmenopausal women (both $P > 0.37$). Dietary associations with breast cancer risk are stronger prior to menopause.