Selección de Resúmenes de Menopausia

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Metformin; an old antidiabetic drug with new potentials in bone disorders.

Bahrambeigi S, Yousefi B, Rahimi M, Shafiei-Irannejad V.

The prevalence of diabetes mellitus especially type 2 diabetes mellitus is increasing all over the world. In addition to cardiomyopathy and nephropathy, diabetics are at higher risk of mortality and morbidity due to greater risk of bone fractures and skeletal abnormalities. Patients with diabetes mellitus have lower bone quality in comparison to their non-diabetic counterparts mainly because of hyperglycemia, toxic effects of advanced glycosylation end-products (AGEs) on bone tissue, and impaired bone microvascular system. AGEs may also contribute to the development of osteoarthritis further to osteoporosis. Therefore, glycemic control in diabetic patients is vital for bone health. Metformin, a widely used antidiabetic drug, has been shown to improve bone quality and decrease the risk of fractures in patients with diabetes in addition to glycemic control and improving insulin sensitivity. AMP activated protein kinase (AMPK), the key molecule in metformin antidiabetic mechanism of action, is also effective in signaling pathways involved in bone physiology. This review, discusses the molecules linking diabetes and bone turnover, role of AMPK in bone metabolism, and the effect of metformin as an activator of AMPK on bone disorders and malignancies.

PLoS One. 2018 Dec 12;13(12):e0207885. doi: 10.1371/journal.pone.0207885. eCollection 2018.

Increased Alzheimer's risk during the menopause transition: A 3-year longitudinal brain imaging study.

Mosconi L, Rahman A, Diaz I, Wu X, Scheyer O, Hristov H, Vallabhajosula S, Isaacson R, de Leon M, Brinton RD.

Two thirds of all persons with late-onset Alzheimer's disease (AD) are women. Identification of sex-based molecular mechanisms underpinning the female-based prevalence of AD would advance development of therapeutic targets during the prodromal AD phase when prevention or delay in progression is most likely to be effective. This 3-year brain imaging study examines the impact of the menopausal transition on Alzheimer's disease (AD) biomarker changes [brain β-amyloid load via 11C-PiB PET, and neurodegeneration via 18F-FDG PET and structural MRI] and cognitive performance in midlife. Fifty-nine 40-60 year-old cognitively normal participants with clinical, neuropsychological, and brain imaging exams at least 2 years apart were examined. These included 41 women [15 premenopausal controls (PRE), 14 perimenopausal (PERI), and 12 postmenopausal women (MENO)] and 18 men. We used targeted minimum loss-based estimation to evaluate AD biomarker and cognitive changes. Older age was associated with baseline Aβ and neurodegeneration markers, but not with rates of change in these biomarkers. APOE4 status influenced change in Aβ load, but not neurodegenerative changes. Longitudinally, MENO and PERI groups showed declines in estrogen-dependent memory tests as compared to men ($p < .04$). Adjusting for age, APOE4 status, and vascular risk confounds, the MENO and PERI groups exhibited higher rates of CMRglc decline as compared to males ($p \leq .015$). The MENO group exhibited the highest rate of hippocampal volume loss (p's $\leq .001$), and higher rates of Aβ deposition than males ($p < .01$). CMRglc decline exceeded Aβ and atrophy changes in all female groups vs. men. These findings indicate emergence and progression of a female-specific hypometabolic AD-endophenotype during the menopausal transition. These findings suggest that the optimal window of opportunity for therapeutic intervention to prevent or delay progression of AD endophenotype in women is early in the endocrine aging process.

Osteoporos Int. 2018 Dec 11. doi: 10.1007/s00198-018-4790-4. [Epub ahead of print]

Combination therapy with parathyroid hormone analogs and antiresorptive agents for osteoporosis: a systematic review and meta-analysis of randomized controlled trials.

Lou S, Lv H, Yin P, Li Z, Tang P, Wang Y.

Combination therapy with parathyroid hormone (PTH) analogs and antiresorptive agents may be more effective than monotherapy for the treatment of osteoporosis. This study aimed to estimate the effectiveness and safety of this

combination therapy for osteoporosis. MEDLINE, EMBASE, and Cochrane Library were searched from inception to May 1, 2018, including randomized controlled trials (RCTs) with a duration of at least 6 months on adults with osteoporosis treated with combination therapy versus monotherapy. Outcomes included fractures, bone mineral density (BMD) changes, and adverse events. A meta-analysis was performed using a random-effect model, to estimate risk ratios (RRs) for fractures, and mean differences (MDs) for BMD changes. A total of 19 RCTs and 2177 patients were included. Compared with monotherapy, combination therapy had an advantage of 36% (RR, 0.64; 95% confidence interval (CI), 0.42-0.98) regarding fracture risk reduction. It also appears to improve lumbar spine BMD by 4.06% (95%CI = 2.60-5.53) and total hip BMD by 1.89% (95%CI = 1.25-2.53). No RCT reported an increased risk of serious adverse events. Among patients with osteoporosis, combination therapy was superior to monotherapy regarding improvement of the lumbar spine and total hip BMD, without risk of serious adverse events. Combination therapy also had an advantage over monotherapy on fracture risk reduction. However, owing to the limited sample size, additional larger studies are required to confirm this benefit.

J Bone Miner Res. 2018 Dec 7. doi: 10.1002/jbmr.3654. [Epub ahead of print]

Comparison of BMD Changes and Bone Formation Marker Levels 3 Years After Bisphosphonate Discontinuation: FLEX and HORIZON-PFT Extension I Trials.

Kim TY, Bauer DC, McNabb BL, Schafer AL, Cosman F, Black DM, Eastell R.

An ASBMR task force recommends a drug holiday for certain women treated for ≥5 years with oral alendronate or ≥3 years with intravenous zoledronic acid, with reassessment 2-3 years later. It is not known whether changes in BMD or bone turnover markers differ after oral or intravenous therapy. Our goal was to compare changes in BMD and procollagen type I N propeptide, PINP, after oral or intravenous bisphosphonate use. In the Fracture Intervention Trial Long-term Extension (FLEX), women who received a mean 5 years of alendronate were randomized to placebo or continued treatment. In the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial Extension I (HORIZON-PFT E1), women who received 3 years of zoledronic acid were randomized to placebo or continued treatment. We examined the proportion of participants with BMD loss or PINP gain ≥least significant change (LSC), and those whose values exceeded a threshold (T score ≤-2.5 or PINP ≥36.0 ng/mL, a premenopausal median value). After 3 years of placebo, the FLEX group had greater mean total hip BMD decreases (-2.3% versus -1.2% in the HORIZON-PFT E1 group, $p < 0.01$), and greater rises in PINP (+11.6 ng/mL versus +6.7 ng/mL, $p < 0.01$). There was a greater proportion of individuals in FLEX with total hip BMD loss and PINP increases that exceeded LSC, and PINP values ≥36.0 ng/mL. In contrast, there were small changes in the proportion of women with femoral neck T scores ≤-2.5 in both groups. In conclusion, 3 years after bisphosphonate discontinuation, a considerable proportion of former alendronate and zoledronic acid users had meaningful declines in total hip BMD and elevations in PINP. Despite a longer treatment course, alendronate may have a more rapid offset of drug effect than zoledronic acid.

J Clin Endocrinol Metab. 2018 Dec 10. doi: 10.1210/jc.2018-02236. [Epub ahead of print]

Comparison of denosumab vs. bisphosphonates in osteoporosis patients: A meta-analysis of randomized controlled trials.

Lyu H, Jundi B, Xu C, Tedeschi SK, Yoshida K, Zhao S, Nigwekar SU, Leder BZ, Solomon DH.

Background: Among the currently available osteoporosis therapeutics, bisphosphonates and denosumab are widely used. However, it remains uncertain which therapy is more effective. Objective: To determine whether the use of denosumab increases bone mineral density (BMD) and reduces the risk of fractures more than bisphosphonates in patients with low BMD or osteoporosis. Data Sources: We searched PubMed, Embase and the Cochrane Library through Nov 2018. Study Selection: Head-to-head randomized controlled trials comparing denosumab versus bisphosphonates among adult patients with low BMD or osteoporosis. Data Extraction and Synthesis: Random-effects models were used. We identified 10 eligible trials including 5361 participants. Denosumab increased BMD more than bisphosphonate at 12 months, with a mean difference of 1.42% (95% CI 0.95-1.89%, p<0.001) at lumbar spine, 1.11% (95% CI 0.91-1.30%; p<0.001) at total hip, and 1.00% (95% CI 0.78-1.22%, p<0.001) at femoral neck. At 24 months, the increase difference was 1.74% (95% CI 1.05-2.43%, p<0.001) at lumbar spine, 1.22% (95% CI 0.66-1.77%, p<0.001) at total hip, and 1.19% (95% CI 0.65-1.72%, p<0.001) at femoral neck. There was no difference in fracture endpoint at 12 months, but denosumab had a lower osteoporotic fracture incidence than alendronate at 24 months (RR

0.51, 95% CI 0.27-0.97). Conclusions: Denosumab improved BMD significantly more than bisphosphonates at the lumbar spine, total hip and femoral neck at 12 and 24 months. There was only one study demonstrating greater osteoporotic fracture reduction using denosumab. Future longitudinal studies with longer follow-up and large sample size are needed to confirm the efficacy difference.

Menopause. 2018 Dec 10. doi: 10.1097/GME.0000000000001279. [Epub ahead of print]

Can the use of probiotics in association with isoflavone improve the symptoms of genitourinary syndrome of menopause? Results from a randomized controlled trial.

Ribeiro AE, Monteiro NES, Moraes AVG, Costa-Paiva LH, Pedro AO.

OBJECTIVE: To evaluate the effect of isoflavone administration, either in conjunction with probiotic use or not, on the symptoms of genitourinary syndrome of menopause, and compare the effects with those of hormone therapy. METHODS: A randomized clinical trial was conducted on 60 postmenopausal women aged 40 to 60 years, randomly assigned to receive oral isoflavone (150 mg dry extract of glycine max) alone or isoflavone plus probiotic (Lactobacillus acidophilus, Lactobacillus casei, Lactococcus lactis, Bifidobacterium bifidum, and Bifidobacterium lactis) or hormone therapy (1 mg estradiol and 0.5 mg norethisterone acetate). The urogenital symptom subscale of the Menopause Rating Scale and International Consultation on Incontinence Questionnaire-Short Form were used to assess genitourinary symptoms. Vaginal maturation value, pH, vaginal health score, and vaginal flora were used to evaluate vaginal atrophy. Equol, equol intermediate, O-dimethylangolensin, and aglycones were measured using gas chromatography coupled to mass spectrometry. RESULTS: After 16 weeks of treatment, the urogenital symptoms, mainly vaginal dryness and sexual problem complaints, improved significantly in the hormone therapy group. There was a significant increase in the daidzein, glycitein, equol intermediate, and O-dimethylangolensin contents after 16 weeks in the isoflavone plus probiotic group. The maturation value, vaginal pH, and vaginal flora improved in the hormone therapy group. The vaginal health score increased in the isoflavone and hormone therapy groups. CONCLUSIONS: Probiotics improved the metabolism of isoflavones after 16 weeks of treatment. However, the increase in the contents of isoflavones and their metabolites failed to yield an estrogenic effect on the urogenital tract and relieve the vulvovaginal symptoms.

Ups J Med Sci. 2018 Dec 10:1-5. doi: 10.1080/03009734.2018.1544597. [Epub ahead of print]

Gynecologists are afraid of prescribing hormone replacement to endometrial/ovarian cancer survivors despite national guidelines-a survey in Sweden.

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BACKGROUND: Prolonged survival in ovarian and endometrial cancer patients increases the importance of paying attention to quality of life. Hormone replacement therapy (HRT) after gynecologic cancer has been controversial. With this survey, we sought to describe Swedish gynecologists' and gynecologic oncologists' attitudes towards prescribing HRT to these cancer survivors and see if prescribing practice is consistent with the available evidence and national guidelines. MATERIAL AND METHODS: A web-based survey containing three hypothetical cases with a total of 15 questions was distributed to gynecologists and gynecologic oncologists in Sweden. Respondents were asked about their HRT prescription practices in endometrial/ovarian cancer patients with moderate to severe menopausal symptoms. RESULTS: In total 262 gynecologists and 24 gynecologic oncologists answered the survey. In the low-risk endometrial cancer case a majority of the gynecologists (55%) and gynecologic oncologists (66.7%) would prescribe local estrogen. A total of 30% of the gynecologists would prescribe estrogen replacement therapy (ERT) in the high-risk endometrial cancer case compared to 58.3% of the gynecologic oncologists. The gynecologic oncologists felt more comfortable treating patients with endometrial cancer than did gynecologists, and the gynecologists were more likely to read the national guidelines. In the ovarian cancer case, 63.7% of the gynecologists would prescribe HRT compared to 92% of the gynecologic oncologists. CONCLUSION: Swedish gynecologic oncologists have a more favorable attitude towards HRT for endometrial/ovarian cancer patients and feel more comfortable treating their patients than do gynecologists. This study illustrates a need for education in these matters in order not to withhold HRT from women due to doctors' sometimes unjustified anxiety.