

Selección de Resúmenes de Menopausia

Semana del 7 al 13 de agosto de 2019

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Manipulation of ovarian function influenced glucose metabolism in CBA/J mice.

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Menopause is associated with a decline in overall health in women. One health aspect impacted is glucose metabolism. As women experience menopause, their metabolism declines dramatically. The current study addressed the influence of ovarian somatic cells on the improvement of metabolic health through transplantations of young, germ cell-depleted ovaries. The purpose of this study is to expand the understanding of female reproductive health on metabolism. Control mice were grouped by age and treatment mice were age-matched. Treatment mice were placed into one of three groups: 1) mice received germ cell-depleted ovaries, 2) mice received germ cell-containing ovaries, and 3) mice received ovarian somatic cells via injection directly to their original ovary. All mice were subject to a glucose tolerance test, during which a bolus of dextrose was administered, and blood glucose levels were collected and recorded. Mice were euthanized between 680 and 700 days. Metabolic results showed an improvement of glucose metabolism in both germ cell-depleted and germ cell-containing groups compared to controls. No significance difference was noted between the germ cell-containing and germ cell-depleted groups. Somatic cell injection groups also showed improved glucose metabolism compared to controls. This experiment has shown that post-reproductive health is positively influenced by reproductive status. Additionally, somatic cells play an important role in the restoration of health to post-reproductive mice.

JAMA Netw Open. 2019 Aug 2;2(8):e198420. doi: 10.1001/jamanetworkopen.2019.8420.

Changes in Bone Mineral Density After Prophylactic Bilateral Salpingo-Oophorectomy in Carriers of a BRCA Mutation.

Kotsopoulos J1,2, Hall E1, Finch A1, Hu H3, Murphy J4, Rosen B3, Narod SA1,2, Cheung AM3.

IMPORTANCE: Preventive surgery is strongly recommended for individuals with a BRCA mutation at a young age to prevent ovarian cancer and improve overall survival. The overall effect of early surgical menopause on various health outcomes, including bone health, has not been clearly elucidated. **OBJECTIVE:** To evaluate the association of prophylactic bilateral salpingo-oophorectomy with bone mineral density (BMD) loss among individuals with a BRCA mutation. **DESIGN, SETTING, AND PARTICIPANTS:** This retrospective cohort study of participants with a BRCA mutation who underwent oophorectomy through the University Health Network, Toronto, Ontario, Canada, recruited participants from January 2000 to May 2013. Eligibility criteria included having a BRCA mutation, at least 1 ovary intact prior to surgery, and no history of any cancer other than breast cancer. Bone mineral density was measured using dual-energy x-ray absorptiometry before and after surgery. Data analysis began in December 2018 and finished in January 2019. **MAIN OUTCOMES AND MEASURES:** The annual change in BMD from baseline to follow-up was calculated for the following 3 anatomical locations: (1) lumbar spine, (2) femoral neck, and (3) total hip. **RESULTS:** A total of 95 women had both a baseline and postsurgery BMD measurement with a mean (SD) follow-up period of 22.0 (12.7) months. The mean (SD) age at oophorectomy was 48.0 (7.4) years. Among women who were premenopausal at time of surgery (50 [53%]), there was a decrease in BMD from baseline to follow-up across the lumbar spine (annual change, -3.45%; 95% CI, -4.61% to -2.29%), femoral neck (annual change, -2.85%; 95% CI, -3.79% to -1.91%), and total hip (annual change, -2.24%; 95% CI, -3.11% to -1.38%). Self-reported hormone therapy use was associated with significantly less bone loss at the lumbar spine (-2.00% vs -4.69%; $P = .02$) and total hip (-1.38% vs -3.21%; $P = .04$) compared with no hormone therapy use. Among postmenopausal women at time of surgery (45 [47%]), there was also a significant decrease in BMD across the lumbar spine (annual change, -0.82%; 95% CI, -1.42% to -0.23%) and femoral neck (annual change, -0.68%; 95% CI, -1.33% to -0.04%) but not total hip (annual change, -0.18%; 95% CI, -0.82% to 0.46%). **CONCLUSIONS AND RELEVANCE:** This study found that oophorectomy was associated with postoperative bone loss, especially among women who were premenopausal at the time of surgery. Targeted management strategies should include routine BMD assessment and hormone therapy use to improve management of bone health in this population.

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Long-term outcome of postmenopausal women with non-atypical endometrial hyperplasia on endometrial sampling.

Rotenberg O1, Fridman D2, Doulavaris G1, Renz M3, Kaplan J1, Gebb J4, Xie X5, Goldberg GL6, Dar P1.

OBJECTIVE: To assess the long-term outcome of post-menopausal women diagnosed with non-atypical endometrial hyperplasia (NEH). **METHODS:** It is a retrospective study of women aged 55 and older who underwent endometrial sampling in our large academic medical center between 1997 and 2008. Women diagnosed with NEH were included in the study group and were compared to women diagnosed with atrophic endometrium on endometrial sampling. Outcome data was obtained through February 2018. The main outcomes were the risk of progression to endometrial carcinoma and the risk of persistent endometrial hyperplasia (EH). Logistic regression was used to identify covariates that remained significant risk factors for cancer progression. **RESULTS:** 1808 women aged 55 and older underwent endometrial sampling during the study period. The median surveillance time was 10.0 years. 73 women were found to have NEH and they were compared to 742 women with atrophic endometrium (AE). When compared to women with AE, women with NEH had a significantly higher BMI (33.9 vs. 30.6, $p=0.01$), a higher rate of progression to type 1 endometrial cancer and persistent endometrial hyperplasia (8.2% vs. 0.8%, $p<0.0001$ and 21.9% vs 0.7% respectively, $p<0.0001$). They also had a higher rate of progression to all types of uterine cancer or persistent hyperplasia (32.9% vs 3.4%, $p<0.0001$). Women with NEH also had significantly higher rate of future surgical intervention (50.7% vs 15.4%, $p<0.0001$) and future hysterectomy (34.3% vs. 9.6%, $p<0.0001$). On logistic regression analysis, NEH, BMI>35, thick endometrium on ultrasound and diabetes remained significant risk factors for progression to cancer. **CONCLUSIONS:** Postmenopausal women with NEH are at significant risk for persistent endometrial hyperplasia (EH) and progression to uterine cancer, at higher rates than rates previously reported. Guidelines for the appropriate management of postmenopausal women with NEH are needed to decrease the rate of persistent disease or progression to cancer.

J Endocr Soc. 2019 Jun 6;3(8):1583-1594. doi: 10.1210/js.2019-00074. eCollection 2019 Aug 1.

Conjugated Estrogens and Bazedoxifene Improve β Cell Function in Obese Menopausal Women.

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CONTEXT: Studies suggest that menopausal hormone therapy (MHT) prevents type 2 diabetes (T2D). The combination of conjugated estrogens (CE) with the selective estrogen receptor modulator bazedoxifene (BZA) is an MHT that improves obesity and T2D in preclinical models of menopausal metabolic syndrome. The effect of CE/BZA on adiposity and glucose homeostasis in obese postmenopausal women is unknown. **OBJECTIVE:** To investigate the effect of CE/BZA on body composition, glucose homeostasis, and markers of inflammation in obese postmenopausal women. **RESEARCH DESIGN INTERVENTION AND PARTICIPANTS:** Randomized, double-blind, placebo-controlled pilot trial of 12 obese menopausal women assigned to 12-week treatment with CE 0.45 mg/BZA 20 mg ($n = 7$) or placebo ($n = 5$). At baseline and after 12 weeks, we assessed body composition (dual-energy X-ray absorptiometry), glucose homeostasis (IV glucose tolerance test), and inflammation biomarkers. **RESULTS:** Women treated with CE/BZA exhibited increased β cell function using homeostatic model assessment-B [median (interquartile range) CE/BZA vs placebo: 18.5 (-0.9 to 320.6) $\mu\text{U}/\text{mM}$ vs -25.5 (-39.9 to -0.1) $\mu\text{U}/\text{mM}$; $P = 0.045$], and decreased basal glucose concentrations (Gb) [-5.2 (-9.2 to -1.7) mg/dL vs 2.7 (0.9 to 4.9) mg/dL; $P = 0.029$]. Insulin sensitivity was higher in the placebo arm [1.35 (1.12 to 1.82) ($\mu\text{U}/\text{mL}$) min^{-1} vs -0.24 (-1.50 to 0.19) ($\mu\text{U}/\text{mL}$) min^{-1} ; $P = 0.029$]. No changes between treatment groups were observed for the acute insulin response to glucose (AIRg), the disposition index (DI), body composition, and inflammatory biomarkers. **CONCLUSIONS:** A 12-week treatment of obese postmenopausal women with CEs/BZA improves fasting β cell function and glucose concentrations without change in AIRg, HOMA-IR, DI, body composition, or markers of inflammation.

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Gut microbiota alterations associated with reduced bone mineral density in older adults.

Das M1,2, Cronin O3,4, Keohane DM3, Cormac EM1,2, Nugent H3, Nugent M3, Molloy C3, et al.

OBJECTIVE: To investigate compositional differences in the gut microbiota associated with bone homeostasis and fractures in a cohort of older adults. **METHODS:** Faecal microbiota profiles were determined from 181 individuals

with osteopenia (n = 61) or osteoporosis (n = 60), and an age- and gender-matched group with normal BMD (n = 60). Analysis of the 16S (V3-V4 region) amplicon dataset classified to the genus level was used to identify significantly differentially abundant taxa. Adjustments were made for potential confounding variables identified from the literature using several statistical models. **RESULTS:** We identified six genera that were significantly altered in abundance in the osteoporosis or osteopenic groups compared with age- and gender-matched controls. A detailed study of microbiota associations with meta-data variables that included BMI, health status, diet and medication revealed that these meta-data explained 15-17% of the variance within the microbiota dataset. BMD measurements were significantly associated with alterations in the microbiota. After controlling for known biological confounders, five of the six taxa remained significant. Overall microbiota alpha diversity did not correlate to BMD in this study. **CONCLUSION:** Reduced BMD in osteopenia and osteoporosis is associated with an altered microbiota. These alterations may be useful as biomarkers or therapeutic targets in individuals at high risk of reductions in BMD. These observations will lead to a better understanding of the relationship between the microbiota and bone homeostasis.

J Clin Densitom. 2019 Jul 17. pii: S1094-6950(19)30159-3. doi: 10.1016/j.jocd.2019.07.010. [Epub ahead of print] Repeating Measurement of Bone Mineral Density When Monitoring With Dual-Energy X-Ray Absorptiometry: The 2019 ISCD Official Positions.

Kendler DL1, Compston J2, Carey JJ3, Wu CH4, Ibrahim A3, Lewiecki EM5.

Bone mineral density (BMD) can be measured at multiple skeletal sites using various technologies to aid clinical decision-making in bone and mineral disorders. BMD by dual-energy X-ray absorptiometry (DXA) has a critical role in predicting risk of fracture, diagnosis of osteoporosis, and monitoring patients. In clinical practice, DXA remains the most available and best validated tool for monitoring patients. A quality baseline DXA scan is essential for comparison with all subsequent scans. Monitoring patients with serial measurements requires technical expertise and knowledge of the least significant change in order to determine when follow-up scans should be repeated. Prior ISCD Official Positions have clarified how and when repeat DXA is useful as well as the interpretation of results. The 2019 ISCD Official Positions considered new evidence and clarifies if and when BMD should be repeated. There is good evidence showing that repeat BMD measurement can identify people who experience bone loss, which is an independent predictor of fracture risk. There is good evidence showing that the reduction in spine and hip fractures with osteoporosis medication is proportional to the change in BMD with treatment. There is evidence that measuring BMD is useful following discontinuation of osteoporosis treatment. There is less documentation addressing the effectiveness of monitoring BMD to improve medication adherence, whether monitoring of BMD reduces the risk of fracture, or effectively discriminates patients who should and should not recommence treatment following an interruption of medication. Further research is needed in all of these areas.

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Hormone therapy for first-line management of menopausal symptoms: Practical recommendations.

Palacios S1, Stevenson JC2, Schaudig K3, Lukasiewicz M4, Graziottin A5.

Hormone therapy use has undergone dramatic changes over the past 20 years. Widespread use of hormone therapy in the 1980s and 1990s came to an abrupt halt in the early 2000s after initial findings of the Women's Health Initiative trial were published and the study was terminated. Since then, much has been learned about the characteristics of women most likely to benefit from hormone therapy. There is general agreement that women younger than 60 years or who initiate hormone therapy within 10 years of menopause onset gain short-term benefit in terms of symptomatic relief and long-term benefit in terms of protection from chronic diseases that affect postmenopausal women. Despite accumulating evidence in support of hormone therapy for symptomatic menopausal women, the slow response by the medical community has led to a 'large and unnecessary burden of suffering' by women worldwide. Greater efforts are clearly needed to educate physicians and medical students about the pathophysiology of menopause and the role of hormone therapy in supporting women through the transition. This article provides a brief historical perspective of events that led to the backlash against hormone therapy, explores the current position of guideline groups, and provides practical recommendations to guide first-line management of symptomatic menopausal women.

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Vaginal CO₂ laser for the treatment of vulvovaginal atrophy in women with breast cancer: LAAVA pilot study.

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PURPOSE: Vulvovaginal atrophy (VVA) is a commonly reported issue among breast cancer patients, and its aetiology is multifactorial. Treatment is difficult in these women, particularly because the use of oestrogens has traditionally been discouraged. Vaginal laser treatment has been reported to improve symptoms. We aimed to assess the impact on symptoms and sexual function of vaginal laser in women with early breast cancer (EBC). **METHODS:** We performed a single-arm investigator initiated pilot study of female EBC patients with symptomatic VVA. A total of 3 vaginal laser treatments were administered 4 weeks apart. Questionnaires were completed at baseline, 4, 8 and 12 weeks. Our primary endpoint was symptomatic improvement of VVA at 12 weeks on 10 cm visual analogue scales. Our secondary endpoints were improvement in sexual function using the Female Sexual Function Index (FSFI) and patient-reported improvements in symptoms, sexual function and quality of life. Statistical analysis was performed with a Wilcoxon Signed Rank test. **RESULTS:** 26 patients were enrolled between February 2016 and August 2017. All patients were post-menopausal, 25 of whom had received anti-oestrogen therapy for their breast cancer. Questionnaire compliance was high (98%) and all patients received the three pre-planned treatments. There was significant improvement in each of the VVA symptoms: dryness ($p < 0.001$), itch ($p < 0.001$), burning ($p = 0.003$), dysuria ($p < 0.001$) and dyspareunia ($p < 0.001$). Patients also reported improvement in sexual function on the FSFI ($p \leq 0.001$). **CONCLUSIONS:** Patients receiving vaginal laser had improvement in VVA symptoms and sexual function. Further randomised sham-controlled trials are needed to further assess this treatment.