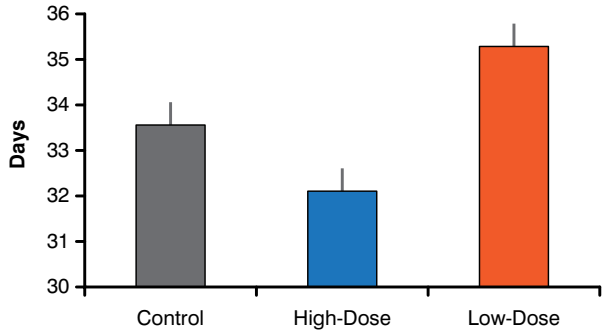
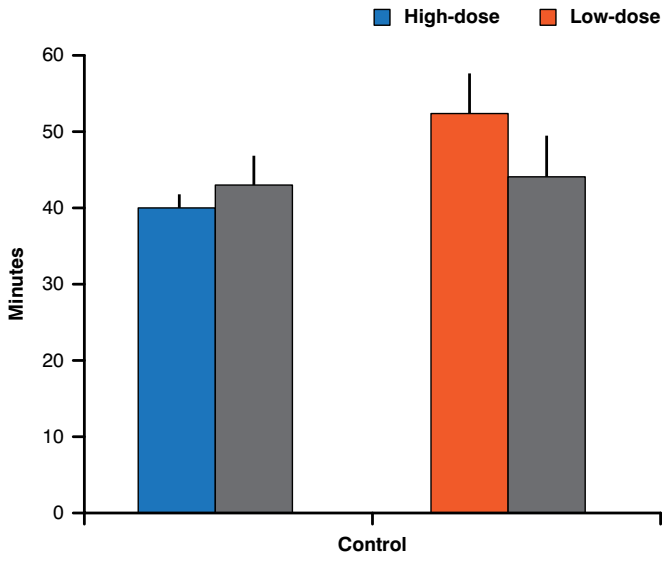
Figure 1. Median Age at Vaginal Opening After High and Low Doses of BPA



BPA=bisphenol A.

Figure 2. GnRH Interpulse Interval After Exposure to High and Low Doses of BPA



BPA=bisphenol A; GnRH=gonadotropin-releasing hormone.

RNA expression of 10 genes showed significant opposing changes in the high- versus low-dose groups at PND 20. The dose of 25 ng/kg affected expression of 14 genes, while 5 mg/kg modified the expression of 472 genes versus controls. A significant difference in levels of RNA expression was observed for 1407 genes when the 2 BPA dose conditions were compared.

Neonatal exposure to a very low dose of BPA delayed pubertal onset, slowed GnRH secretion, and changed hypothalamic RNA expression. Changed hypothalamic RNA expression confirmed the neuroendocrine effects of the 2 BPA doses, with opposing changes of similar genes in relation to BPA dose and with alteration of distinct genes by each dose.

While these data add to the large body of evidence in animal models concerning the effects of BPA on the female reproductive tract [Caserta et al. *Reprod Biol Endocrinol* 2014], the influence of BPA on the pathogenesis of premature puberty in girls has not been confirmed. Some have found a correlation between pubertal stages and BPA serum or urinary levels [Qiao et al. *Wei Sheng Yan Jiu* 2010; Durmaz et al. *J Clin Res Pediatr Endocrinol* 2014], while others have found conflicting data [Wolff et al. *Environ Res* 2008; Yum et al. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2013] perhaps due to confounding variables, such as body mass index and race [Wolff et al. *Environ Health Perspect* 2007]. More studies need to be conducted in humans.

ALN Reduces Bone Turnover in Perimenopausal Women With Low BMD

Written by Emma Hitt Nichols, PhD

Alendronate plus cholecalciferol treatment improved bone mineral density (BMD) at the lumbar spine and reduced bone turnover in perimenopausal women with low BMD. Aliya Khan, MD, McMaster University, Hamilton, Ontario, Canada, presented data in a poster from the Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of Alendronate (ALN) on Bone Mineral Density (BMD) and Bone Turnover in Perimenopausal Women With Low BMD [ICE/ENDO 2014. Poster LBSA-0269].

Menopause-associated bone loss begins during perimenopause, ~2 years before the last menstrual period. The purpose of this study was to determine if treatment with alendronate (ALN), an antiresorptive agent, can prevent bone loss in women who are perimenopausal and have low BMD. This is the first study to evaluate the efficacy of an antiresorptive agent on maintaining BMD in perimenopausal women.

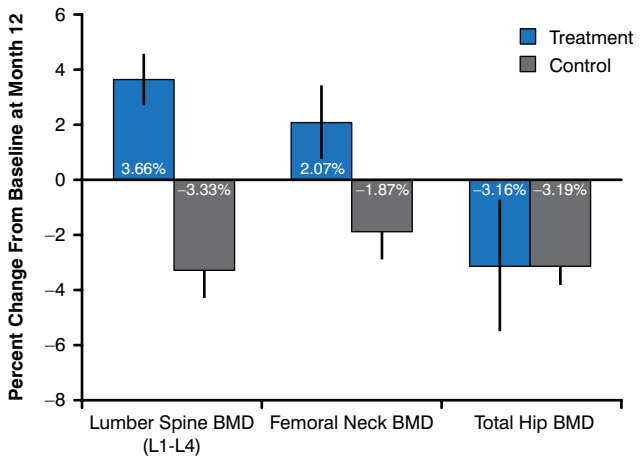
In this double-blind trial, women aged 40 to 55 years with reduced bone density (T-score < –1.0) of the lumbar spine, total hip, or femoral neck were randomly assigned to receive 70 mg of ALN plus 2800 IU of cholecalciferol (vitamin D3) once weekly or placebo for 1 year. In addition, all patients received 500 mg of calcium carbonate once daily. Patients were eligible if they had at least 5 menstrual periods per year and had follicle-stimulating hormone (FSH) levels > 20 IU/L but < 40 IU/L on 2 independent occasions. Patients were excluded if they had

hyperthyroidism, hyperparathyroidism, liver disease, acromegaly, Cushing syndrome, rheumatoid arthritis, myeloma, Paget disease, renal osteodystrophy, osteomalacia, or polycystic ovarian disease. Other exclusion criteria included treatment during the past 6 months with androgens, calcitonin, systemic corticosteroids, fluoride, parathyroid hormone, selective estrogen receptor modulators, estrogen, oral contraceptives, bisphosphates, vitamin D > 2000 IU per day, or vitamin D metabolites. In addition, patients with esophageal abnormalities, including stricture or achalasia, were excluded from the study.

At 12 months, there was a significant increase in BMD at the lumbar spine (L1 to L4; 3.66%; $p < .01$) and a trend of increased BMD at the femoral neck (2.07%; $p = .14$) from baseline among patients who received ALN plus cholecalciferol compared with placebo (Figure 1). In addition, there was a significant decrease in bone-specific alkaline phosphatase (–37.8%; $p < .01$) and N-telopeptide in the urine (27.2%; $p = .03$) and an increase in FSH (101.13%; $p < .01$), as well as a trend of decreased N-telopeptide in the serum (–27.6%; $p = .23$), from baseline in the ALN arm compared with the placebo arm. Treatment with ALN plus cholecalciferol resulted in no significant difference from baseline compared with placebo in albumin, calcium, phosphate, magnesium, estradiol, or urine creatinine.

In conclusion, treatment of perimenopausal women with low BMD with ALN plus cholecalciferol reduced bone turnover and improved BMD in the lumbar spine over 12 months. Prof. Khan indicated that the data from this study suggest that providing early intervention with a bisphosphonate during the menopausal transition may limit BMD loss.

Figure 1. Effect of Alendronate on BMD in Perimenopausal Women



BMD=bone mineral density.

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Elevated Stress Hormones Related to Worse 1-Year Outcome Following Severe Brain Injury

Written by Brian Hoyle

Endocrine alterations that occur soon after severe brain injury are an indication of prolonged stress, rather than brain damage, and are important in predicting the 1-year functional outcome of the injury. The routine use of pituitary assessment soon after traumatic brain injury (TBI) is not recommended, and instead it should be reserved for patients suspected of hypopituitarism. Djordje Marina, MD, Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark, presented a poster with the conclusions from a study conducted by Danish researchers to assess pituitary hormone alterations after TBI.

The study involved 163 patients aged ≥15 years who had suffered TBI (n = 111) or nontraumatic brain injury (non-TBI; n = 52) and who were receiving neurorehabilitation. Pituitary assessment at baseline and a median of 3.3 months (range, 2.1 to 4.9 months) post injury included gonadal and thyroid hormones, stress-related hormones (cortisol, prolactin, and insulin-like growth factor 1), and adrenal function. The primary outcomes at the time of referral, discharge, and the 1-year follow-up were daily functioning as assessed by the Functional Independence Measure (FIM), which covers 18 items of activities of daily living, with score-related outcomes ranging from total assistance to full independence, and ability measured by the Extended Glasgow Outcome Scale (GOS-E), a ranking of independence at and outside the home, and social and work capability. The characteristics of the TBI and non-TBI groups at the time of admission to rehabilitation are summarized in Table 1.

FIM scores were similar in the TBI and non-TBI groups at admission, discharge, and follow-up concerning complete dependency (TBI: 90%, 40%, and 25% of patients, respectively; non-TBI: 90%, 50%, and 25% of patients, respectively), moderate dependency (TBI: 3%, 5%, and 4% of patients, respectively; non-TBI: not applicable, 4%, and 5% of patients, respectively), and low-to-absent dependency (TBI: 3%, 50%, and 70% of patients, respectively; non-TBI: 10%, 50%, and 70% of patients, respectively). The data indicated improvements in activities of daily living during follow-up. At