

## Selección de Resúmenes de Menopausia

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### **RANKL inhibition improves muscle strength and insulin sensitivity and restores bone mass.**

Bonnet N, Bourgoin L, Biver E, Douni E, Ferrari S.

Receptor activator of Nfkb ligand (RANKL) activates, while osteoprotegerin (OPG) inhibits, osteoclastogenesis. In turn a neutralizing Ab against RANKL, denosumab improves bone strength in osteoporosis. OPG also improves muscle strength in mouse models of Duchenne's muscular dystrophy (mdx) and denervation-induced atrophy, but its role and mechanisms of action on muscle weakness in other conditions remains to be investigated. We investigated the effects of RANKL inhibitors on muscle in osteoporotic women and mice that either overexpress RANKL (HuRANKL-Tg+), or lack Pparb and concomitantly develop sarcopenia (Pparb-/-). In women, denosumab over 3 years improved appendicular lean mass and handgrip strength compared to no treatment, whereas bisphosphonate did not. HuRANKL-Tg+ mice displayed lower limb force and maximal speed, while their leg muscle mass was diminished, with a lower number of type I and II fibers. Both OPG and denosumab increased limb force proportionally to the increase in muscle mass. They markedly improved muscle insulin sensitivity and glucose uptake, and decrease anti-myogenic and inflammatory gene expression in muscle, such as myostatin and protein tyrosine phosphatase receptor- $\gamma$ . Similarly, in Pparb-/-, OPG increased muscle volume and force, while also normalizing their insulin signaling and higher expression of inflammatory genes in skeletal muscle. In conclusions, RANKL deteriorates, while its inhibitor improves, muscle strength and insulin sensitivity in osteoporotic mice and humans. Hence denosumab could represent a novel therapeutic approach for sarcopenia.

**Clin Interv Aging. 2019 Apr 29;14:743-752. doi: 10.2147/CIA.S195498. eCollection 2019.**

### **The potential role of testosterone in hypertension and target organ damage in hypertensive postmenopausal women.**

Li N1, Ma R1, Wang S1, Zhao Y1, Wang P1, Yang Z1, Jin L1, Zhang P1, Ding H1, Bai F1, Yu J1.

Objective: The aim of this study was to confirm the potential role of testosterone in hypertension and target organ damage (TOD) in hypertensive postmenopausal women. Methods: A matched group study was conducted. One hundred sixty-one hypertensive postmenopausal women between 45 and 65 years of age were enrolled as group 1. Another 161 age-matched hypertensive men were enrolled as group 2. Ambulatory blood pressure monitoring, echocardiographic imaging, vascular function, sex hormones and clinical characteristics were evaluated. Quantitative data were analyzed using independent Student's t-test and multiple regression analysis. Results: The mean and load level of blood pressure were lower in women than in men ( $P < 0.05$ ), except for the mean level and load of the nocturnal systolic blood pressure (SBP) ( $123.77 \pm 15.72$  mmHg vs  $126.35 \pm 15.64$  mmHg, and  $50.43 \pm 30.31\%$  vs  $55.35 \pm 28.51\%$ ,  $P > 0.05$ ). However, the carotid-femoral pulse wave velocity (cf-PWV) in women was higher than that in men ( $9.68 \pm 2.23$  m/s vs  $8.03 \pm 2.82$  m/s,  $P < 0.05$ ). The ratio of the early diastolic mitral peak flow velocity to early diastolic mitral annular velocity (E/Em) was obviously impaired ( $13.06 \pm 3.53$  vs  $12.05 \pm 3.68$ ,  $P < 0.05$ ) in women. Furthermore, in women, a positive correlation was found between testosterone and cf-PWV ( $\gamma = 0.157$ ,  $P = 0.046$ ), and Cf-PWV was positively related to the mean level of nighttime SBP ( $\gamma = 0.210$ ,  $P = 0.008$ ). Moreover, nocturnal SBP was a risk factor for E/Em ( $\gamma = 0.156$ ,  $P = 0.048$ ,  $P < 0.05$ ). Conclusion: Testosterone may play a role in the correlation between hypertension and TOD in hypertensive postmenopausal women.

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### **Long-Term Effects of Teriparatide Followed by Antiresorptive Therapy on Clinical Outcomes in Patients with Severe Spinal Osteoporosis.**

Oswald AJ1, Berg K1, Ralston SH1, Riches PL2.

Teriparatide (TPTD) is the most widely used anabolic agent in the treatment of patients with osteoporosis although its use is restricted in many countries. A recent randomised trial confirmed that TPTD was superior to risedronate at preventing vertebral fractures over a 2-year period. There is limited information on the relative effectiveness of TPTD compared with standard care in routine clinical practice. In this paper, we report the results of an extended observational study of 724 women referred to a specialist clinic with severe osteoporosis over an 11.5-year period, who were considered for TPTD therapy. Of these patients, 496 (68.5%) were treated with TPTD, whereas the remaining 228 (31.5%) received other treatments. This was either because they were unwilling or unable to self-inject (52.6%), because they had already been established on oral bisphosphonates (31.1%) or because of contraindications (12.7%). The TPTD group were younger than the standard care group (69.6 vs. 74.1 years) and had a lower 10-year fracture risk (25.7% vs. 28.6%). Those treated with TPTD had a greater increase in BMD at the lumbar spine compared with standard care (13.3% vs. 8.2%,  $p < 0.001$ ) after approximately 2 years and had a lower incidence of vertebral fractures (4.8% vs. 10.1%,  $p = 0.01$ ) over the course of our observation. There was no difference between groups with respect to either BMD change at the femoral neck or incidence of non-vertebral fractures. This study confirms that TPTD is superior to standard care at reducing the risk of vertebral fracture in patients with severe osteoporosis.

**Prz Menopausalny. 2019 Apr;18(1):57-62. doi: 10.5114/pm.2019.84159. Epub 2019 Apr 9.**

### **Therapeutic regimens for vitamin D deficiency in postmenopausal women: a systematic review.**

Tayem Y1, Alotaibi R2, Hozayen R2, Hassan A3.

**Introduction:** We reviewed the most effective vitamin D3 regimen for vitamin D deficiency in postmenopausal women. **Material and methods:** We searched for studies and clinical trials conducted on healthy postmenopausal women published on PubMed from 2000 to 2018 using the term "Vitamin D deficiency" combined with the following terms: "dose", "supplement", "supplementation", "cholecalciferol" or "cholecalciferol dose". We identified 1376 articles which matched the search criteria. Based on reviewing the title and abstract, 17 articles were eligible for a full-text review. Of those, 12 manuscripts were ultimately included. **Results:** A majority of the studies (75%) reported using daily maintenance doses which were predominantly administered orally (83.3%). Two studies reported favorable results following therapy with a single oral dose of 300,000 IU. After one month, however, 25-hydroxy vitamin D [25(OH)D] was satisfactory; both studies failed to maintain adequate responses after 60 and 90 days. One study found that loading oral doses of 50,000 IU/day for 2 weeks followed by the same doses every 2 weeks for one year were effective. Five studies employed oral doses of 800 IU/day but none of them reported that this dose was adequate. Three studies used doses of 1000 IU/day but only two of them reported positive results. Three trials examined oral doses of 2000 IU/day and another 3 studies tested oral doses of 4000-4800 IU/day. All of them reported acceptable responses that lasted with continued treatment. **Conclusions:** Oral maintenance doses of 2000-4800 IU/day satisfactorily corrected vitamin D deficiency and maintained 25(OH)D levels in postmenopausal women with continuous therapy.

**Reumatol Clin. 2019 May 18. pii: S1699-258X(19)30078-6. doi: 10.1016/j.reuma.2019.04.001. [Epub ahead of print]**

### **Severe osteoporosis: Principles for pharmacological therapy in Mexico.**

Clark P1, Carlos Rivera F2, Méndez Sánchez L3, Mendoza Gutiérrez CF4, Vargas Neri JL3, Carrillo Vázquez SM5, Xibillé Friedmann DX6, Alvarado Ceballos A7, Aguilera Zepeda JM8, Mercado Cárdenas V9, Ávila Armengol H10. **BACKGROUND:** This article presents evidence and recommendations regarding the efficacy and safety of the approved and available therapies in Mexico to treat severe or established osteoporosis with the aim of developing a position regarding therapeutics in this stage of the disease, according to the descriptive cards of the National Drug Formulary of the National General Health Council of Mexico. **METHODS:** We performed a systematic and narrative review of the evidence of teriparatide and denosumab, from their pharmacological profile, effectiveness, and safety derived from clinical trials, as well as an analysis of the general recommendations of the national and international clinical practice guidelines. **RESULTS:** The evidence establishes that teriparatide and denosumab belong to different therapeutic classes, with biologically opposed mechanisms of action and indications of use, which are clearly differentiated in their respective national codes, therefore these drugs cannot be substitutable or interchangeable in severe osteoporosis therapy. Both represent the best options currently available for this stage of the disease; being similar in their efficacy in preventing new vertebral fragility fractures, with an RR of .35 (CI 95%; .22-.55) for teriparatide, and .32 (CI 95%; .26-.41) for denosumab. The absolute risk reduction is higher with teriparatide 9.3% (21 months) compared with denosumab at 4.8% (36 months). **CONCLUSIONS:** Our results agree with the

recommendations available in national and international clinical practice guidelines, with both therapies proposed as a sequential, but not a substitute, treatment.

**J Clin Densitom. 2019 Apr 26. pii: S1094-6950(19)30054-X. [Epub ahead of print]**

### **Does the Severity of Obesity Influence Bone Mineral Density Values in Premenopausal Women?**

Hammoud E1, Toumi H2, Jacob C3, Pinti A2, Lespessailles E2, Hage RE4.

The aim of this study was to compare bone mineral content (BMC), bone mineral density (BMD), and geometric indices of hip bone strength among 3 groups of adult obese premenopausal women (severely obese, morbidly obese, and super morbidly obese). This study included 65 young adult premenopausal women whose body mass index (BMI) > 35 kg/m<sup>2</sup>. They were divided into 3 groups using international cut-offs for BMI. Body composition and bone variables were measured by DXA. DXA measurements were completed for the whole body (WB), lumbar spine, total hip (TH), and femoral neck (FN). Geometric indices of FN strength (cross-sectional area, cross-sectional moment of inertia [CSMI], section modulus [Z], strength index [SI], and buckling ratio) were calculated by DXA. Results showed that age and height were not significantly different among the 3 groups. WB BMC values were higher in super morbidly obese women compared to severely and morbidly obese women. WB BMD, L1-L4 BMD, total hip BMD, FN BMD, cross-sectional area, CSMI, Z, and buckling ratio values were not significantly different among the 3 groups. SI values were lower in super morbidly obese compared to morbidly and severely obese women. In the whole population (n = 65), body weight, BMI, lean mass, fat mass, and trunk fat mass were positively correlated to WB BMC and negatively correlated to SI. Weight and lean mass were positively correlated to WB BMD and CSMI. Our findings suggest that the severity of obesity does not influence BMD values in premenopausal women.

**Gynecol Endocrinol. 2019 May 21:1-4. doi: 10.1080/09513590.2019.1616687. [Epub ahead of print]**

### **Changes in breast density during hormone treatment with transdermal estrogens alone or in combination with progesterone.**

Garcia-Alfaro P1, Rodríguez I1, Tresserra F1, Browne J1.

A retrospective observational study to assess whether hormonal treatment (HT) with transdermal estrogens alone or in combination with micronized progesterone increases breast density and to compare these changes to those of a control group of 4120 patients were not given HT. We included 150 patients whose baseline breast density was assessed with photon-counting spectral mammography and 1 year after hormone treatment. The reduction in breast density was compared using an analysis of covariance. The difference in breast density between mammographies in the HT group was  $-0.40 \pm 5.5$  and  $-0.85 \pm 4.2$  in the control group. The changes in density according to the type of HT, we found that women on treatment with estrogen alone presented a difference of  $0.44 \pm 5.8$ , and  $-1.35 \pm 5$  ( $p = 0.13$ ) in women on combined treatment. After adjusting changes in density for age and average number of days between mammographies, we observed a difference of  $-0.36$  95% confidence intervals (CI)  $[-1.04$  to  $-0.31]$  in the women on HT and  $-0.71$  95% CI  $[-1.65$  to  $-0.21]$  in the control group. No increased breast density was observed in women on HT treatment, nor did we observe an increase according to HT type. The difference in breast density loss was smaller in the HT group versus the control group.

**Exp Ther Med. 2019 Jun;17(6):4417-4420. doi: 10.3892/etm.2019.7518. Epub 2019 Apr 23.**

### **Relationship between senile osteoporosis and cardiovascular and cerebrovascular diseases.**

Hu X1, Ma S1, Yang C1, Wang W1, Chen L1.

The relationship between senile osteoporosis and cardiovascular hypertension, coronary heart disease and cerebral infarction was investigated. A retrospective study on 428 elderly patients hospitalized in Harrison International Peace Hospital from June 2014 to January 2017 was conducted. There were 207 cases of coronary heart disease, 102 cases of hypertension and 119 cases of cerebral infarction. According to bone density measurement results, the subjects were divided into the osteoporosis group and the non-osteoporosis group. Risk factors for osteoporosis were analyzed, and the incidence of osteoporosis in hypertension, coronary heart disease, and cerebral infarction populations of different severity was analyzed. Hypertension, coronary heart disease and cerebral infarction were the main risk factors for osteoporosis in the elderly. Incidence of osteoporosis in the double-vessel disease group and the three-vessel disease

group was significantly higher than that in the single-vessel disease group. Incidence of osteoporosis was significantly higher in the three-vessel disease group than that in the double-vessel disease group ( $P<0.05$ ). Incidence of osteoporosis was significantly higher in the moderate hypertension and severe hypertension groups than that in the mild hypertension group. Incidence of osteoporosis was significantly higher in patients with severe hypertension than that in the moderate hypertension group ( $P<0.05$ ). Incidence of osteoporosis in patients with moderate cerebral infarction and severe cerebral infarction was significantly higher than that in the mild cerebral infarction group ( $P<0.05$ ). Incidence of osteoporosis in patients with severe cerebral infarction was significantly higher than that in the moderate cerebral infarction group ( $P<0.05$ ). The results indicated that there is a close correlation between senile osteoporosis and hypertension, coronary heart disease and cerebral infarction. Osteoporosis can be used as a predictor of early screening for hypertension, coronary heart disease and cerebral infarction in the elderly population.