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Satellite Symposia Abstracts

Protecting Osteoporosis Patients With Bisphosphonates: Examining Sustained Fracture Efficacy
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Sharing Insights on Musculoskeletal Health
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Plant-based Nutrition and Bone Health
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SY1 - THE IMPACT OF NUTRITION ON BONE HEALTH

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Abstract: Osteoporosis is an ancient disease but has only been recently defined. Osteoporosis is now considered, in most developed countries, as a major public health problem. Every 30 seconds, someone in the European Union has a fracture, as a result of osteoporosis. The incidence of hip fracture in the EU is expected to more than double, from approximately 500,000 to 1 million, over the next 50 years. The risk for women of dying from hip fracture complications equals risk of dying from breast cancer and more women over 45 years are hospitalized by osteoporotic fractures than by heart attack or breast cancer. In Europe and in the USA, the combined annual cost of treating fractures caused by osteoporosis is estimated to be 42 million Euros. Therefore it is important to optimize peak bone mass and to minimize bone loss later in life. Adequate nutrition can play an important role in maintaining an optimal bone health. The presentation will cover the impact of protein, calcium and vitamin D on bone health.

Dietary protein has opposing effects on Ca balance and its net effect on bone is not well established. Several studies have demonstrated that a high protein intake increases urinary Ca excretion and that on average 1 mg Ca is lost in urine for every 1 g rise in dietary protein. This is mainly due to S amino acids present in animal and some vegetable proteins, resulting in a greater acid load and buffering response by the skeleton. The effects of protein on bone may also depend on intake of Ca- and alkali-rich foods, such as fruit and vegetables.

Ca intake, Ca absorption and excretion rates determine the availability of Ca for bone growth and development. Rates of urinary Ca excretion vary with age and pubertal status: during infancy and adolescence, the need for Ca and the rate of absorption are higher than during other ages. Several other factors play a role: Ca absorption is modulated by food source, form of the Ca salt, vitamin D status, whereas urinary Ca losses are modified by the potential renal acid load of the diet, total dietary protein, dietary sodium and potassium content.

Vitamin D is essential for Ca uptake and bone development and remodelling. Growing evidence shows the benefits of vitamin D in fracture prevention. A recent analysis (68,500 patients) revealed that combined supplementation of Ca (1000 mg/d) and vitamin D (10-20 µg/d) is effective in reducing fractures irrespective of age, gender or previous fractures.

Disclosure of Interest: None Declared

SY2 - IMPORTANCE OF NUTRITION FOR OPTIMAL BONE DEVELOPMENT DURING CHILDHOOD AND ADOLESCENCE

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Abstract: Bone mass and strength acquired by the end of growth, the so-called peak bone mass (PBM) is a major determinant of fragility fracture risk in later life. Many interrelated factors can influence the accumulation of bone from fetal life to PBM attainment. Severe nutrient deficiencies such as energy, proteins, vitamin D, whenever sun exposure is insufficient, can impair bone growth and/or mineralization of its organic matrix (rickets). Despite prevention of such severe nutritional deficiencies, PBM variance, as precisely determined in healthy young adults by measuring areal (a) and volumetric (v) bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) and high-resolution

peripheral quantitative computerized tomography (HR-pQCT), remains very wide, even after adjustment for body weight and standing height. This finding prompted us and others to explore the possibility of increasing bone accrual by modifying nutrition and-or physical activity during infancy, childhood and adolescence. Abundant literature has been recently produced regarding what kind of foods could be, more or less beneficial to the general population for optimal bone acquisition. For adequate human bone development no specific foods, but only some nutrients they encompass are essential. Among those, calcium and proteins are two nutrients that have been demonstrated, both experimentally and clinically, to interact with specific endocrine and paracrine systems influencing bone mineral economy. As expected, their influence on aBMD and vBMD is "dose"-dependant. This notion implies that the bone effect size observed in supplemental trials is markedly reliant on spontaneous, i.e., baseline, consumption of the tested nutrient. It can also be skeletal site specific. Furthermore, enhancement in bone gain induced by selective nutrients appears to be modulated by genetic, endocrine (including pubertal maturation stage) and mechanical factors, as it can be analyzed from randomized control trials designed to test the effects of calcium supplements in healthy children and adolescents. Such a complex interactivity may explain, at least in part, the difficulty to achieve a worldwide consensus defining the amount of dietary calcium to be recommended for optimal bone acquisition during childhood and adolescence. Although recommendations may quantitatively differ, there is agreement that foods containing calcium and proteins are required to achieve optimal peak bone mass.

Disclosure of Interest: None Declared

SY3 - NUTRITIONAL ASSOCIATION WITH BONE LOSS DURING THE MENOPAUSAL TRANSITION

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Abstract: It is important to minimize the dramatic musculoskeletal losses that occur during the menopause transition in order to reduce risk of falls and fractures in old age.

Calcium is the main mineral of bone and adequate Ca intake is essential for bone development and preservation. Studies of the effect of added Ca in early postmenopausal women have had mixed results. Several found that Ca in doses of 1000 to 2000 can retard bone loss from the radius. In contrast, supplemental Ca has little effect on bone loss from the spine, even in women with very low usual Ca intakes (<400 mg/d). These findings were confirmed in the WHI. The Ca need may be dependent in part upon the vitamin D status. Cross-sectional studies indicate that among individuals with 25OHD levels <25 to 50 nmol/L, a higher Ca intake is associated with lower serum PTH levels and higher BMD. At higher 25OHD levels, however, Ca intake does not appear to influence PTH or BMD. NAS recommends 1200mg/d of Ca for women age 50+.

VitD insufficiency leads to reduced Ca absorption, higher PTH levels and bone-remodelling rates, and increased bone loss. In older adults, vitD insufficiency has also been linked to poor muscle performance and increased risk of falling. Recent meta-analyses have indicated that supplementing with vitD in amounts needed to raise 25OHD levels to 75 nmol/L or higher reduces risk of falls and fractures by ± 20%. The impact of vitD during the menopause transition has not been studied extensively. In view of recent widespread associations of vitD insufficiency with many diseases that do affect women around menopause, however, including type 2DM, autoimmune diseases, cardiovascular disease, infections, and colon cancer, it seems prudent to maintain a 25OHD level ≥75 nmol/L during the menopause transition and beyond.

With aging, humans develop a mild and progressive metabolic acidosis that results from declining renal function and ingestion of acid-producing diets (= intake of alkali-producing fruits and vegetables is inadequate to neutralize the intake of acid-producing cereals and animal protein). Acid-producing diets are commonly used (in a recent study, 96% consumed an acid load). An acidic environment increases bone turnover and nitrogen wasting and treatment with alkali over a 3-month period significantly reduces bone turnover, decreases nitrogen excretion, and improves muscle performance in healthy postmenopausal women age 50+. The long-term benefits remain to be determined.

Disclosure of Interest: None Declared

SY4 - ARE SOY FOODS USEFUL FOR OPTIMAL BONE HEALTH?

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Abstract: Most epidemiologic studies of soy foods consumption suggest a beneficial effect of soy foods on markers of bone health especially among Asian women. Cross sectional studies showing no benefit have generally been conducted in populations with much lower mean soy food intakes as typically found in the U.S. and Europe. To date, two longitudinal prospective studies have investigated the relationship between soy foods intake and fracture risk. Both found a reduction in fracture risk for Chinese women, but a similar result was not observed in Chinese men. In addition, among pre- and peri-menopausal Chinese women (who all have relatively high soy intakes) soy food intake was found to be a significant positive predictor of total body bone mineral content in a longitudinal study investigating determinants of bone change. The numerous clinical trials investigating the effects of soy protein or soy isoflavones on bone mineral density and bone turnover have observed conflicting results with the majority demonstrating beneficial effects, some inconclusive, and some demonstrating no effect. Potential mechanisms have been identified for soy isoflavone effects on bone. Soy foods intake may also indirectly enhance bone strength by replacing animal protein in the diet. Diets high in animal protein have been found to increase calcium excretion. Soy protein intake has been shown to decrease calcium excretion in comparison with meat and dairy protein. In addition, a higher ratio of foods from plant sources compared with foods from animal sources has been linked to better bone outcomes. In epidemiologic comparisons, people in Asian coun-

tries tend to have 50-70% lower osteoporotic fracture risk than individuals in North America and Europe although calcium intake is much higher in these countries. Reviews of the research on the relationship between calcium from foods and supplements show that higher calcium intake does not reliably decrease fracture risk. Both the research on soy isoflavones and on calcium indicate that overall dietary patterns may be more important to bone health and fracture risk reduction than the individual factors – soy isoflavones and calcium – alone. Therefore, soy foods as an integral part of an overall dietary pattern that is built largely from whole plant foods and limited in foods from animal sources are likely to be useful for optimal bone health.

Disclosure of Interest: None Declared

SY5 - DO VEGETARIANS HAVE A NORMAL BONE MASS?

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Abstract: With the recognition in the 1960s of the potential criticality of acid-base balance to skeletal integrity, it was considered that long-term ingestion of 'vegetable-based' diets may have a beneficial effect on indices of bone health. There is evidence that diet and the ageing process affect systemic acidity and there is evidence at the human and cellular level that metabolic acidosis stimulates bone resorption.

Review of the evidence: Early studies (pre-1990) comparing indices of bone health between lacto-ovo-vegetarians and omnivores found bone mass to be higher in the vegetarian groups but more recently published research (post-1990) have found no differences. The discrepancy between these results may be explained, in part, by the use of older techniques for bone health assessment and the inclusion of Seventh Day Adventists who followed a particularly healthy lifestyle and hence may have biased the results. The most recent Bayesian meta-analysis which included 2749 individuals showed that overall, bone density was lower in those subjects who adhered to a vegetarian/vegan diet than in those who consumed an omnivorous one but at a level that is unlikely to be of clinical relevance[1]. Vegetable-based proteins generate a large amount of acid in the urine and have been shown to have a high potential renal acid load (PRAL). The crucial dietary component concerning acid-base homeostasis is the specific intake of alkali-forming foods (i.e., fruit and vegetables). In the last decade, a number of clinical, observational and intervention studies have demonstrated a beneficial effect of fruit and vegetable intake on bone health. The mechanisms behind a fruit and vegetable link to the skeleton remain to be fully determined, since these foods provide not only a source of dietary alkali but also a variety of micronutrients, (e.g., vitamin K), which have plausible workings for an effect on bone.

Conclusion: Dietary protein is essential for skeletal integrity[2,3]. Vegetarianism is not a serious risk factor for osteoporotic fracture and future research should focus on the important dietary components in a vegetarian diet that may yield specific benefits to the skeleton[4].

[1]Ho-Pharm Lt et al Am J Clin Nutr 2009;90:943.
[2]Darling AL et al Am J Clin Nutr 2009;90:1674.
[3]Kerstetter JE Am J Clin Nutr 2009;90:1451.
[4]Lanham-New SA Am J Clin Nutr 2009;90:910.

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Superior Antifracture Efficacy From Improved Bone Quality

Sponsor: SERVIER

SY6 - ASSESSMENT OF BONE QUALITY: METHODS AND IMPLICATIONS FOR TREATMENT

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Abstract: Previously the diagnosis of osteoporosis was based on DXA-BMD measurement exclusively. With this method only bone mass can be measured, not physical density. The calculation of bone strength requires different structural and material parameters. Measurement devices have therefore been developed to assess bone density and bone structure in vivo, such as micro-computed tomography (μCT). With μCT measurements, bone geometry and trabecular structure can be depicted in vivo with an image resolution of 82 μ. Parameters like cortical density, cortical porosity, cortical thickness, trabecular numbers, trabecular thickness, trabecular separation, and bone volume/tissue volume can be calculated to estimate the strength of the bones. Additionally, physical density can be measured. Some recent studies have demonstrated that the effect of osteoporosis treatment will be clearly evident in cortical density. It is possible that these cortical parameters are mainly responsible for the reduction in risk of peripheral fractures.

In addition to bone structure and bone geometry, mineralization can influence the strength of the bones as illustrated in osteogenesis imperfecta and osteomalacia. High mineralization seen in osteogenesis imperfecta generates stiff bones with low toughness and high risk of fracture. Conversely, less mineralized bone, as in the case of vitamin D deficiency, is very elastic and many deformities generate fatigue fractures. Bone mineralization can be measured in vitro by determination of bone mineral density distribution, which will characterize the material properties of the bone .

Preclinical and clinical trials have shown that strontium ranelate improves bone microarchitecture, by increasing cortical thickness, cortical density, trabecular density, BV/TV, and the number of the structural elements, without altering the normal degree of mineralization of the bone. The improvement of bone microarchitecture by strontium ranelate on both cortical and trabecular bone accounts for the anti-fracture efficacy of this agent at the vertebral and hip level.

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SY7 - IMPROVEMENT IN BONE MICROSTRUCTURE: AN ACHIEVABLE TARGET

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Abstract: Bone strength is determined by its microstructure (trabecular volume, connectivity, thickness), geometry (outer diameter, cortical thickness), and mechanical quality (mineralization, porosity). These determinants should be considered when assessing the efficacy of osteoporosis drugs. Preclinical studies have shown that strontium ranelate (SrRan) increases bone strength through the improvement of microstructure and subsequent increase in plastic energy, thereby improving fracture resistance.

Histomorphometry of 141 transiliac bone biopsies performed in a subset of women enrolled in Phase II and III trials provided 2D demonstration of the safety of SrRan, and a significantly higher mineral apposition rate in cancellous bone (+9% vs. control, P=0.019). Osteoblast surface area was significantly higher (+38% vs. control, P=0.047). 3-D microcomputed tomography of 3-year biopsies showed significant microarchitectural changes in the SrRan group: greater cortical thickness (+18%, P=0.008), trabecular number (+14%, P=0.05), trabecular separation (-16%, P=0.04), with no change in cortical porosity. A lower structure model index (-22%, P=0.01) in SrRan-treated patients reflected a shift from rod-like to plate-like structure, highlighting the capability of SrRan to improve bone structure. SrRan simultaneously increases bone formation and decreases bone resorption, as demonstrated in numerous in vitro and in vivo experiments and confirmed by bone biomarkers in clinical trials.

The link between improved bone architecture and greater bone strength was demonstrated in a recent analysis of hip DXA scans of 483 women enrolled for 5 years in the TROPOS trial. SrRan showed positive effects on all analyzed parameters of bone geometry: at the femoral neck, cortical thickness increased by 5.2% (P<0.001), cross-sectional area by 5.8% (P<0.001), and bending strength (section modulus) by 8.6% (P<0.001). These improvements were also observed at the intertrochanteric region and at the femoral shaft. Furthermore, these results were still statistically significant after adjustment for BMD.

In a head-to-head, multicenter, longitudinal study, we compared effects of SrRan and alendronate on bone microarchitecture in 88 postmenopausal osteoporotic women. HR-pQCT of microstructure parameters of the distal tibia after one- and two-year treatment suggest that SrRan has greater effects than alendronate on both cortical and trabecular microstructure in women with postmenopausal osteoporosis.

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SY8 - STRONTIUM RANELATE: CLINICAL PROOF OF SUPERIOR ANTIFRACTURE EFFICACY

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Abstract: Head-to-head studies of osteoporosis treatment with antifracture efficacy as a primary goal are very scarce. Efficacy can be examined in a wide range of situations using placebo-controlled studies or using absolute fracture risk reduction (fracture incidence in placebo group – fracture incidence in treated group). While not a true comparison between two or more drugs, this is a rational way to show whether or not a treatment is useful in a given situation.

Clinical efficacy of strontium ranelate in a wide range of situations: Two major randomized, double-blind, placebo-controlled, phase III studies have investigated the efficacy of strontium ranelate. In the Spinal Osteoporosis Therapeutic Intervention (SOTI), vertebral fracture risk was reduced by 33% and symptomatic vertebral fracture risk by 36% over four years. In the TReatment Of Peripheral Osteoporosis Study, the risk reduction was 15% in non-vertebral fractures and 43% in hip fractures in high-risk patients over five years. Strontium ranelate is the only osteoporosis drug proven to be effective over 4-5 years on vertebral and nonvertebral fractures in a randomized clinical trial.

Strontium ranelate reduces the risk of both vertebral and major nonvertebral fractures by 32% and 37%, respectively, in elderly women (≥80 years), and in younger osteoporotic women (50-65), by preventing vertebral and symptomatic vertebral fractures. Clinical efficacy is seen whatever the disease severity, from osteopenia (with and without prevalent vertebral fracture) to multiple prevalent fractures or additional risk factors.

A valuable approach: absolute fracture risk reduction: Absolute risk reduction depends on the fracture risk in the placebo group, which may vary between studies. The highest risk and the highest absolute risk reduction were seen with strontium ranelate and risedronate, in the SOTI and VERT-MN studies, respectively. Randomized clinical trials show that the absolute risk reduction with strontium ranelate is double that with other osteoporosis treatments (e.g., 12% vs. 5% with ibandronate for vertebral fractures). Literature data are scarcer for hip fracture: absolute risk reduction is highest for strontium ranelate (2.1%), low for zoledronate, risedronate, and alendronate (1.1%), and cannot be calculated for ibandronate, which has no proven efficacy on hip fractures.

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SY9 - PATIENT BENEFITS WITH STRONTIUM RANELATE

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Abstract: Osteoporosis is characterized by an increase in bone fragility due to low bone mass and deterioration of bone quality, occurring during aging and after menopause, and leading

to an increase in the risk of fractures. Osteoporosis is currently managed with a range of therapies that decrease bone resorption or increase bone formation. For an anti-osteoporotic drug to be beneficial in reducing the burden of fractures it needs to be effective against all types of fracture in all age groups of postmenopausal women. The response to treatment depends on a patient's characteristics, such as age, bone mineral density (BMD), and prevalent fractures.

With its dual mode of action, strontium ranelate has been shown to have early and sustained antifracture efficacy in all age groups including young postmenopausal women and those over 80 years of age with and without prevalent fractures.

Recently, a preplanned analysis of the grouped data of two international, randomised, double blind vs. placebo studies, SOTI and TROPOS, concerning 1488 women aged 80-100 years, showed that strontium ranelate significantly reduced the risks of vertebral and nonvertebral fractures by 59% and 41%, respectively, from the first year, by 32% and 31% over three years, and by 31% and 27% over 5 years.

Strontium ranelate was also observed to decrease the risk of vertebral fractures over 3 years even in the most severe patients such as those with more than 2 prevalent fractures. The risk of vertebral fracture in patients without prevalent vertebral fracture was reduced by 48%, in patients with one prevalent vertebral fracture by 45%, and in patients with more than two prevalent fractures by 33%.

Evidence is therefore now available to show that all women, including the elderly and severe osteoporotic, can benefit from treatment with strontium ranelate to improve bone architecture and to decrease the risk of further fractures.

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Optimising Patient Care in Osteoporotic Vertebral Compression Fractures: The Role of Minimally Invasive Therapies
Sponsor: MEDTRONIC

Abstracts not available.

Zoledronic Acid 5 mg – Optimizing Fracture Protection in Osteoporosis Treatment
Sponsor: NOVARTIS

SY10 - THE MATERIAL AND STRUCTURAL BASIS OF BONE FRAGILITY: INSIGHTS INTO THE ANTIFRACTURE EFFICACY OF ZOLEDRONIC ACID

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Abstract: Four age-related abnormalities in the cellular machinery of bone modelling and remodelling produce structural decay and bone fragility predisposing to vertebral, hip and nonvertebral fractures. (i) Periosteal bone formation decreases precipitously after completion of growth, (ii) bone formation by the osteoblasts of the basic multicellular unit (BMU) decreases in early adulthood, (iii) at menopause, bone resorption by osteoclasts of the BMU transiently increases, and (iv) remodelling intensity on bone's intracortical, endocortical and trabecular surfaces increases. The driving force responsible for the structural decay is the intensity of bone remodelling. Zoledronic acid 5 mg is a potent suppressant of bone remodelling. It (i) reduces the appearance of new excavation sites on the inner surfaces of bone allowing completion of remodelling by bone formation in sites excavated before treatment was started, (ii) reduces the appearance of new resorption cavities, which likely reduces the appearance of stress concentrators, slows progression of cortical porosity and thinning, and reduces trabecular thinning and perforation. These changes partly reverse fragility and slow its progression. Whether any antiresorptive treatment reduces the volume of bone resorbed by the osteoclasts of a BMU or increases the volume of bone formed by the osteoblasts of individual BMUs is uncertain, but it is likely. There is some evidence for the latter for zoledronic acid; an effect that would reduce the negative BMU balance in the BMUs that continue to remodel bone slowly. With continued remodelling suppression, secondary mineralization of existing osteons goes to completion so tissue mineral density increases. Increasing tissue mineralization increases tissue stiffness but reduces ductility predisposing to microdamage. Studies in animals suggest microdamage accumulates with prolonged therapy with potent bisphosphonates, but the benefit of preservation of structure appears to outweigh any increase in material stiffness. Zoledronic acid 5 mg is a safe and effective approach to the prevention and partial reversal of bone fragility in women and in men.

Disclosure of Interest: None Declared

SY11 - OSTEOPOROSIS MANAGEMENT ACROSS THE PATIENT SPECTRUM

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Abstract: Bisphosphonates, acting at the bone surface, reduce the rate of bone remodelling, increase BMD, maintain or improve structural and material properties of bone and, thereby, decrease the risk of osteoporotic fractures. Among them, zoledronate 5 mg (ZOL) given once-yearly has been extensively evaluated in a clinical programme involving thousands of patients across a broad spectrum of osteoporosis indications.

In the HORIZON Pivotal Fracture Trial (HORIZON-PFT), ZOL demonstrated significant, sustained fracture protection at all key sites in women with postmenopausal osteoporosis (relative risk reduction [RRR] at 3 years 70%, 41% and 25% for vertebral, hip and nonvertebral fractures, respectively). In the HORIZON Recurrent Fracture Trial (HORIZON-RFT) of low-trauma hip fracture patients, ZOL significantly decreased the incidence of clinical fractures (RRR=35%; $p<0.01$ vs. placebo), and reduced all-cause mortality (28%; $p<0.01$ vs. placebo; median follow-up 1.9 years). A subgroup analysis of male patients in this trial showed that ZOL reduced clinical fracture risk by 15% vs. place-

bo (hazard ratio 0.85, 95% CI 0.44-1.65), while in a noninferiority study of male patients with osteoporosis, ZOL was noninferior to weekly alendronate in increasing LS BMD (p=0.7935). These trials have further enabled numerous subanalyses of the efficacy and safety of ZOL in patient groups with different fracture risk profiles.

Finally, ZOL was more efficacious than daily oral risedronate (RIS) in the prevention and treatment of glucocorticoid-induced osteoporosis (GIO). Bone mineral density (BMD) was significantly increased at the lumbar spine (LS) with ZOL vs. RIS in both the treatment (ZOL 4.1%, RIS 2.7%; p=0.0001) and prevention groups (ZOL 2.6%, RIS 0.6%; p<0.0001) at 12 months.

The results of these studies led to the approval of ZOL in the EU for the treatment of osteoporosis in men and postmenopausal women, including recent low-trauma hip fracture patients, and those with GIO. Furthermore, ZOL was shown to effectively prevent bone loss in postmenopausal women with low bone mass and was approved also for this indication in the US. In addition, it has potential as an adjunct to PTH therapy. For example, recently obtained data showed that ZOL plus daily PTH 20 µg does not blunt the PTH effect on LS BMD, and results in significantly greater increases in total hip BMD than PTH alone.

Disclosure of Interest: None Declared

Strategies and Tactics For the Management of Severe Osteoporosis
Sponsor: ELI LILLY

Abstracts not available.

The Long Road Towards Disease Modification in Osteoarthritis: Current Perspectives
Sponsor: ROTTAPHARM | MADAUS

SY12 - PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS ON THE CLINICAL USE OF GLUCOSAMINE IN OSTEOARTHRITIS

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Abstract: Glucosamine is a natural amino-monosaccharide, structurally incorporated in glycosaminoglycans as a SO_4 ester. In contrast to glucosamine salts, this sulfated intermediate has not been used in pharmacological studies. Glucosamine HCl is a readily available salt commonly used in dietary supplements and generic pharmaceuticals. There is a unique patented form of glucosamine SO_4 that is a prescription pharmaceutical. This stabilized crystalline salt of glucosamine SO_4 includes glucosamine, SO_4, Na and Cl ions in a stoichiometric ratio of 2:1:2:2.

Previously, exogenously administered glucosamine was believed to be incorporated in proteoglycans thereby stimulating their production; however, studies now suggest that its putative anabolic effects may be mediated by upregulation of TGF-ß (Varghese, 2007). In addition, studies have supported an anti-catabolic role of glucosamine through the inhibition of IL-1-stimulated gene expression by blockade of its cytokine intracellular signalling pathway (Largo, 2003). These findings support both the symptom- and the structure-modifying activities of the crystalline glucosamine SO_4 in clinical trials. These effects were observed in vitro with glucosamine concentrations in the 10 µM range, consistent with the plasma levels observed after oral administration of crystalline glucosamine SO_4 1500 mg once daily.

Persiani et al (2005, 2007) explored the pharmacokinetics of glucosamine (assayed by HPLC with mass spectrometry detection) at steady state with orally administered crystalline glucosamine SO_4. The compound was rapidly absorbed and the pharmacokinetics were linear up to 1500 mg once daily, with a C_{max} of around 10 µM. In patients with knee osteoarthritis, peak plasma and synovial fluid levels were highly correlated with both in the 10 µM range. Benefit of this dosing was demonstrated in several long-term trials (Reginster, 2001; Pavelka, 2002; Herrero-Beaumont, 2007).

In contrast, glucosamine HCl 500 mg t.i.d., as used in the GAIT study (Clegg, 2006; Sawitzke, 2008) demonstrated peak plasma concentrations 50% lower than that reported above, possibly explaining the different treatment effects between the studies. This latter study also demonstrated that concomitant glucosamine HCl with chondroitin SO_4 further decreased glucosamine bioavailability.

Finally, glucosamine does not bind to plasma proteins and excreted in the urine. Its metabolism is independent of the CYP450 system, making drug interactions unlikely.

Disclosure of Interest: None Declared

SY13 - STRUCTURE-MODIFYING STUDIES OF GLUCOSAMINE SULFATE IN OSTEOARTHRITIS: THE PROBLEM, THE DATA AND FUTURE PERSPECTIVES

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Abstract: Pain in patients with Osteoarthritis (OA) is a consequence, in part, of the pathologic changes in joint structures; hence, the interest in developing potential Disease Modifying OA Drugs (DMOADs). Presently, registration of such agents is dependent on demonstrating slowing of the rate of decline in joint space width (JSW) assessed on plain radiographs. While new imaging modalities, including magnetic resonance imaging (MRI), are being developed, conventional radiography yields images that only provide estimates of the actual cartilage thickness and no information on other structural parameters associated with pain such as bone marrow lesions or synovitis. Different drugs have been studied for their DMOAD effects in clinical trials, mainly in knee OA. While risedronate failed to show relevant effects, there are single promising studies with the metalloproteinase (MMP) inhibitors doxycycline and diacerein, and two positive studies with chondroitin sulfate. Similarly, two placebo-controlled trials of prescription glucosamine sulfate 1500 mg once-a-day both showed positive results in slowing the rate of decline in JSW and improving symptoms over 3 years in patients with knee OA (Re-

ginster, 2001; Pavelka, 2002). These trials have been critiqued for using the conventional standing antero-posterior view instead of semi-flexed views, but post hoc analyses excluded evidence of bias and confirmed the results (Pavelka, 2003). Furthermore, pooled post-hoc analyses in patients who were in the trials for at least 12 months, indicated a 57% reduction in rate of undergoing total knee replacement during a mean follow-up of 5 years after termination of the 3-year trials and drug discontinuation (Bruyere, 2008).

The GAIT ancillary study failed to show significant structure-modifying effects after 2 years of glucosamine hydrochloride 500 mg t.i.d., chondroitin sulfate alone or combined with glucosamine, or with celecoxib (Sawitzke, 2008). GAIT has been recently criticized for being underpowered (Brandt, 2009). A study of another uncharacterised formulation of glucosamine sulfate did not prevent JSN in hip OA (Rozendaal, 2008); whether this is due to differences in the formulation or in response between hip and knee, is not known. Finally, a systematic review and economic evaluation conducted in the UK confirmed the statistically significant improvement in decline in JSW with glucosamine sulfate (Black, 2009).

Disclosure of Interest: None Declared

SY14 - INTERPRETING THE CURRENT EVIDENCE ON GLUCOSAMINE SULFATE EFFECTS AS A SYMPTOM-MODIFYING DRUG IN KNEE OSTEOARTHRITIS

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Abstract: Current global international (OARSI, 2008) or European (EULAR, 2003) practice guidelines recommend glucosamine sulfate for the treatment of knee osteoarthritis symptoms. These recommendations are based on the clinical evidence, which has recently been assessed in a Cochrane Review (Towheed, 2009) including 25 trials with 4963 patients. The efficacy is apparently restricted to glucosamine sulfate, while glucosamine hydrochloride was never shown to be effective. In particular, only the patented, prescription formulation of crystalline glucosamine sulfate has shown efficacy in clinical studies, while the data for other glucosamine sulfate formulations are at best conflicting. Indeed, a complete pharmaceutical package and pharmacokinetic studies characterize the prescription product, at the standard oral dosage of 1500 mg once daily, for which 3 pivotal clinical trials exist (Reginster, 2001; Pavelka, 2002; Herrero-Beaumont, 2007). These are large, high quality, randomised, placebo-controlled, double-blind, long-term trials from a minimum of 6 months to 3 years of continuous treatment. A recent meta-analysis (Reginster, 2007) of these trials showed an effect size of 0.27 on knee pain and of 0.33 on function, i.e., a small to moderate effect in line with that of available treatments for osteoarthritis, but with the advantage of the long-term application and the excellent tolerability.

The GUIDE trial by Herrero-Beaumont (2007) provides exploratory comparison with the pure analgesic paracetamol, with a trend for higher efficacy with glucosamine sulfate. These data confirm those from previous comparative studies with NSAIDs, showing at least comparable short-term efficacy with significantly better safety.

American or British national guidelines (e.g., the AAOS and the NICE guidelines) do not distinguish between the original prescription product and the numerous dietary supplements or generics. NICE acknowledges that glucosamine sulfate 1500 mg once daily may be cost effective, as we recently confirmed (Scholtissen, 2010), while AAOS relies mainly on the US trial experience, based on glucosamine hydrochloride at a different regimen (500 mg t.i.d.). The NIH-sponsored trial GAIT failed to show efficacy of this formulation, although the huge placebo effect (60%), the minor efficacy of the reference drug (celecoxib) and the inexplicable major efficacy of glucosamine combination with chondroitin sulfate in the severe patient subset, poses questions on this trial design.

Disclosure of Interest: None Declared

Challenges and Advances in the Treatment of Osteoporosis

Sponsor: AMGEN in collaboration with **GSK**

SY15 - COST OF FRACTURES: THE BURDEN AND COST OF OSTEOPOROSIS-RELATED FRACTURES

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Abstract: Osteoporosis is a common skeletal disease, particularly in postmenopausal women, and is characterized by low bone mass, microarchitectural deterioration of bone tissue and increased bone fragility.1 Whereas diagnosis is by quantitative assessment of bone mineral density (BMD), the clinical significance of this disease lies in the increased propensity for bone fractures. The major sites for osteoporotic fracture sites are spine, hip, forearm and humerus. In women from western Europe aged 50 years, the remaining lifetime likelihood of fractures at these sites is 46%.2 About 2.7 million osteoporotic fractures occur every year in men and women in Europe.3

Osteoporosis is associated with a substantial burden of morbidity and mortality, as osteoporotic fractures can lead to acut e pain and often loss of function, hospitalization, incomplete recovery, long-term nursing care and premature mortality.[1,4] Hip fractures are the cause of death in 1.5% of people in Sweden – an incidence similar to death from breast cancer (1.7%) or pancreatic cancer (1.4%).[4] The burden of osteoporosis in Europe – as estimated by disability-associated life years (DALYs) – is greater than for any cancer (except lung cancer), or chronic diseases such as rheumatoid arthritis, asthma or hypertensive disease.[1,5]

Hospitalization, outpatient care, long-term care, disability and premature death account for the substantial economic cost of osteoporotic fractures.[6] The direct annual cost of osteoporotic fractures is €36 billion in Europe[3]. Ageing populations mean that the annual number of fractures and associated costs are expected to increase by 50% between 2005 and 2025.[7] Despite the high economic cost to society and the personal cost to affected individuals and their families, osteoporosis prevention remains suboptimal, because many patients do not receive treatment and therapy is

often associated with poor adherence.[7] Thus, a significant opportunity to improve osteoporosis outcomes remains.

[1]Kanis JA et al. Osteoporos Int 2008;19:399.
[2]Kanis JA et al. Osteoporos Int 2000;11:669.
[3]Kanis JA et al. Osteoporos Int 2005;16:220.
[4]Kanis JA et al. Bone 2003;32:468.
[5]Johnell O et al. Osteoporos Int 2006;17:1726.
[6]Ben Sedrine W et al. Rheumatology 2001;40:7.
[7]Seeman E. Osteoporos Int 2007;18:569.

Disclosure of Interest: None Declared

SY16 - EFFECTS OF DENOSUMAB ON BONE'S STRUCTURAL PROPERTIES

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Abstract: Advancing age is associated with abnormalities in bone modelling and remodelling that compromise bone's material and structural strength. These abnormalities are rational targets for drug development, particularly the birth rate of new basic multicellular units (BMUs) which drives structural decay. After menopause, increased signalling from matrix (whatever its nature) increases RANKL-mediated osteoclastogenesis and the number of BMUs. Osteoclasts excavate bone on the intracortical, endocortical and trabecular surfaces removing a larger volume of matrix than osteoblasts subsequently deposit producing stress concentrators, cortical porosity and thinning, loss of trabeculae and so, bone fragility.

Denosumab (DMAb) binds RANKL, inhibiting osteoclastogenesis and so the birth of BMUs on the three internal surfaces. Remodelling is suppressed very rapidly and by 80-90% preventing progression of structural decay. BMUs in the excavation, reversal or formation phases when treatment is started complete remodelling but with concurrent appearance of only 10-20% of the new BMUs (that would have appeared without treatment). The net effect is partial reversal of fragility as existing porosity decreases and excavated sites on the endocortical and trabecular surfaces partly refill (unless bone formation by existing BMUs is abbreviated).

As DMAb also rapidly reduces the function and survival of existing osteoclasts, the volume of bone resorbed by BMUs present when treatment began and by the fewer BMUs arising during treatment might also be reduced. Moreover, if this rapid and marked suppression of resorption is also accompanied by endogenous PTH secretion and reduced osteoblast apoptosis, the volume of bone deposited in the smaller resorption site may increase, both further reducing progression of structural decay.

Evidence for several, but not all, of these notions is available. During 12 months, DMAb reduced cortical porosity (rib, tibial diaphysis) and increased compressive strength (vertebral trabecular cores) in adult ovariectomized monkeys. In a double-blind study of 247 postmenopausal women with low bone mass, DMAb increased distal radial cortical vBMD (a surrogate of porosity) assessed using high-resolution peripheral quantitative computed tomography and increased the calculated polar moment of inertia at the ultradistal radius. DMAb is a rational approach to preventing and partly reversing bone fragility.

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SY17 - NEW EVIDENCE IN THE TREATMENT OF OSTEOPOROSIS WITH DENOSUMAB

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Abstract: The purpose of anti-osteoporotic drug therapy is to reduce the risk of fractures. Factors that should determine the choice of a specific therapy include evidence for antifracture efficacy, safety, tolerability, and patient preference and adherence. Denosumab (DMAb) is a potential new treatment option for fracture prevention. Evidence for the reduction in fracture risk observed with DMAb comes from the international, randomized, double-blind, placebo-controlled FREEDOM trial (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months).1

FREEDOM enrolled 7868 women aged 60-90 years with osteoporosis (BMD T-score <−2.5 at the lumbar spine or total hip and not <−4.0 at either site). Subjects were randomized to receive DMAb 60 mg subcutaneously or placebo every 6 months for 3 years. Subjects also received daily calcium and vitamin D supplements. Compared with placebo, DMAb reduced the risk of new vertebral fracture by 68% (95% CI: 59%, 74%; P<0.001), the risk of hip fracture by 40% (95% CI: 3%, 63%; P=0.04), the risk of nonvertebral fracture by 20% (95% CI: 5%, 33%; P=0.01), and the risk of major osteoporotic fracture by 35% (95% CI: 22%, 45%; P<0.001). The frequency and severity of adverse events was similar between DMAb and placebo-treated women.[1]

Post hoc analyses examined the risks of new vertebral and hip fractures in women at increased risk of fracture, and found that the relative risk reductions were consistent with those seen in the overall study population. Compared with placebo, DMAb significantly reduced the risk of new vertebral fracture by 64% in women aged ≥75 years (prespecified analysis) and by 55% in women with two or more prevalent vertebral fractures or a moderate or severe prevalent vertebral fracture. Compared with placebo, DMAb also significantly reduced the risk of hip fracture by 62% in women aged ≥75 years and by 47% in women with a femoral neck BMD T-score of ≤−2.5. Women from the FREEDOM trial are continuing to receive DMAb to provide longer-term efficacy and safety evidence.

[1] Cummings SR et al. N Engl J Med 2009;361:756.

Disclosure of Interest: None Declared

How, When and Why: Different Approaches For a Common Disease

Sponsor: IBSA-GENEVRIER

Abstracts not available.

Osteoporosis Management: What Have We Learned From the Past Decade?
Sponsor: THE ALLIANCE FOR BETTER BONE HEALTH

SY18 - MANAGEMENT OF FRACTURES AND INTERNATIONAL COMPARISON OF TREATMENT PATTERNS FOR WOMEN AT RISK OF FRACTURE: THE GLOBAL LONGITUDINAL STUDY OF OSTEOPOROSIS IN WOMEN (GLOW)

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Abstract:
Aim: To assess, on an international level, who receives treatment for osteoporosis, if those at greatest risk are treated, and to what degree there is variation in treatment practice between different geographic regions.
Methods: In two separate analyses, we examined the proportion of women treated with anti-osteoporosis medications (AOM) in GLOW study sites in five regions of the world, the United States, Canada, Australia, Northern Europe and Southern Europe. In the first, we compare rates of treatment for osteoporosis according to region and to risk factors for fracture. In the second, we assess the frequency of treatment among women with incident fractures, and the characteristics of those treated vs. those not treated.
Results: Current use of an AOM was the lowest (13%) in Northern Europe and the highest 32% in the U.S. and Australia. Among women diagnosed with osteoporosis the percentage of treated cases was lowest in Europe (45-52%) compared to the other regions (62-65%). A similar regional relationship was found for those previously diagnosed with osteopenia and no other risk factors (31% for U.S. and Canada and 12-16% in Europe and Australia). In both the U.S and Southern Europe, 52% of subjects age 65 or older with prior hip or spine fractures were treated. Treatment for this group was least common in Northern Europe (42%). After adjusting for risk factors, women in the U.S. were almost 3 times as likely to be treated as women in Northern Europe, (OR=2.8, 95% CI = 2.5- 3.1) but only 1.5 times as likely to be treated as Southern European women (OR=1.5, 95% CI = 1.4- 1.6).

Of the 51,491 for whom one year follow-up data was available, 1075 who were not taking AOM the previous year had an incident fracture during the follow-up period. Only 17% of those women were taking an AOM after the fracture.
Conclusion: Across GLOW study sites in 5 regions of the world, approximately half to two-thirds of women reporting previous hip or spine fracture after age 45 do not receive treatment. Only 17% of women in this study with incident fractures were treated with an AOM. Twice as many women at low risk were treated in the U.S. as in Europe. This is the first study to show, on an international basis, that treatment for osteoporosis is poorly targeted to those at highest risk of fracture.

Disclosure of Interest: None Declared

SY19 - SAFETY OF BISPHOSPHONATES IN THE TREATMENTS OF OSTEOPOROSIS

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Abstract: Bisphosphonates are the most widely used drugs to treat osteoporosis due to their efficacy to reduce the risk of osteoporotic fractures and their safety profile.
Adverse events attributed to any drug, including bisphosphonates, are identified from different sources (clinical trials, post-marketing reporting, epidemiological studies, case reports or case series) that provide different levels of evidence for an association between drug use and safety.

The tolerability and safety profile of bisphosphonates has been established in clinical trials of 60,000 patients studied for 3 years or longer representing the best evidence-based data linked to drug effect. Nevertheless, osteoporotic patients often undergo long-term therapy and have concomitant medical conditions that must be considered when choosing a treatment. Recently, unexpected adverse events such as osteonecrosis of the jaw (ONJ), atrial fibrillation (AF), subtrochanteric/diaphyseal (ST/SF) fractures and esophageal cancer have been reported with the use of bisphosphonates but a causal association has not yet been established. No cases of ONJ have been reported in clinical trials of alendronate, risedronate and ibandronate. In the major zoledronate clinical trial one case was reported in a zoledronate-treated patient and one in a placebo-treated patient. To date, no causal association has been shown between AF and risedronate or ibandronate. Furthermore, definitive evidence to support claims of a potential increased risk of AF with zoledronate and alendronate is still missing. Case series and case reports suggest that ST/SF fractures having unique clinical and radiographic features might occur in patients treated with long-term bisphosphonates. On the other hand, analysis of clinical trial data with alendronate, ibandronate, risedronate and zoledronate and a large cohort analysis with alendronate failed to show an association between these fractures and bisphosphonate use. Extensive post-marketing surveillance data are being collected and are currently analyzed. In osteoporotic patients with a high risk of fracture, the evaluation of the benefit-risk ratio for long term bisphosphonate use should be assessed based on patients' characteristics and therapeutics' profile.

Disclosure of Interest: None Declared

SY20
A DECADE OF EXPERIENCE IN OSTEOPOROSIS MANAGEMENT WITH RISEDRONATE

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Abstract: Osteoporosis is a chronic disease in which the density and quality of bone is reduced. As bones become more porous and fragile, there is an increased risk of fracture. Major risk factors related to increased fracture risk have been identified and new tools for the clinical management of osteoporosis have been developed. It is estimated that one out of every three women over the age of 50 will sustain an osteoporotic fracture. A high rate of morbidity

and mortality is associated with both vertebral and non vertebral fracture, in particular with those of the hip. Over the last decade, results of randomized clinical trials of several therapies have proven their efficacy to reduce fracture risk in osteoporotic women and men and in patients suffering from secondary osteoporosis including glucocorticoid-induced osteoporosis. Bisphosphonates, inhibitors of bone resorption, are the frontline regimens to treat osteoporosis and have demonstrated consistent efficacy in the reduction of vertebral fracture risk; conversely the treatments' effect on non-vertebral fractures have varied significantly. Once the first fracture occurs, the risk for further fractures increases dramatically, consequently requiring a prompt treatment for these high-risk patients. Efficacy onset is, therefore, an important marker in treatment outcomes; risedronate has been shown to significantly reduce clinical vertebral and non-vertebral fractures incidence within 6 months. Other studies have focused on potential mechanisms that might influence fracture protection, in particular the interactions of bisphosphonates with the skeleton. Bisphosphonates bind to the mineral component of bone with a range of binding affinities and cellular enzymatic interactions. While there are still uncertainties, it is clear that each bisphosphonate has a unique pattern of effects on both mineral and enzyme activity.

For these treatments to be effective, they need to be taken long term, frequently associated with calcium and vitamin D. New bisphosphonates dosing regimen (weekly, monthly) have been developed to help patients' adherence. The lack of understanding of patients' personal risks long term and discernible symptoms of osteoporosis, confer to the treating physicians the critical role to help patients stay on treatment to achieve a favorable outcome.

Disclosure of Interest: None Declared

SY21 - LONGITUDINAL CHANGE IN CLINICAL FRACTURE INCIDENCE IN DAILY PRACTICE: AN INNOVATIVE METHODOLOGY

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Abstract: The assessment of drug efficacy relies on randomised placebo-controlled clinical trials which must comply with strict regulatory criteria and therefore have narrowly defined study populations. Consequently, in the real world, about 80% of osteoporosis patients cannot be recruited into clinical trials because of their multiple comorbidities, their use of concomitant medications and the presence of other conditions. Thus, the demonstrated efficacy of a specific therapy in a randomized clinical trial may not predict its actual effectiveness in real world clinical practice.

Many recent observational studies have examined the effectiveness of oral bisphosphonates to reduce clinical fractures using data on large numbers of patients from health care plans in the US. The design of these observational studies has included comparisons between patient populations with or without a fracture/bisphosphonates use, compliant or not compliant, or between patient populations on different bisphosphonates. A key limitation in interpreting these comparisons is the uncertainty as to whether known or unknown differences in baseline fracture risk between patient populations could account the reported results.

A new study used a different method to evaluate treatment effects on fracture risk reduction by comparing fracture incidence in the first three months with that in the subsequent year. This design allowed the effectiveness of a therapy to be evaluated in the actual population in which it was prescribed without prescription bias. In an osteoporotic population of 210,000 patients, the results showed that, relative to the 3-month wash-in period, the following 12-month treatment period reduced the occurrence of clinical fractures, specifically vertebral, nonvertebral and hip fractures, by 57%, 28% and 18% for alendronate, and 54%, 21% and 27% for risedronate, respectively, whereas Ibandronate only decrease clinical vertebral fractures. These results are consistent with the efficacy data from the randomized, placebo controlled clinical trials of each of these drugs. In conclusion, the insights well-designed observational studies provide into bisphosphonate effectiveness may enable physicians to choose the most appropriate treatment in the management of osteoporosis.

Disclosure of Interest: None Declared

Nutrition, Physical Activity and Bone Health: State of the Art and Emerging Trends

Sponsor: DANONE RESEARCH

SY22 - NUTRIENTS, MUSCLE AND BONE: WHERE DO WE STAND?

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Abstract: Several nutrients, such as vitamin B12, omega-3 fatty acids and vitamin C have been associated with better bone health, while a higher protein, B-vitamin, and omega-3 fatty acid intake has been associated with benefits on muscle mass or function. However, trial data for these nutrients are limited, and missing for fall and fracture endpoints. Two 2009 meta-analyses of double-blind RCTs suggest a dose-dependent benefit of vitamin D on both fall[2] and fracture prevention[3], supported by mechanistic evidence and epidemiologic studies on bone density and lower extremity function[4]. Based on 12 double-blind RCTs of oral vitamin D supplementation, a minimal received dose (treatment dose*adherence) of more than 400 IU vitamin D per day reduced hip fractures by 18% and any non-vertebral fractures by 20%, while a dose of 400 IU or less did not reduce fractures. At the higher dose of vitamin D, non-vertebral fracture prevention was most pronounced among community-dwelling older individuals (-29%) and those age 65-74 (-33%), and did not depend on additional calcium supplementation. Notably, fracture reduction increased significantly with a higher achieved 25-hydroxyvitamin D level with a threshold of at least 75 nmol/l. These findings were challenged by a 2010 individual data meta-analysis of 7 RCTs suggesting that vitamin D may only reduce fractures if combined with calcium, irrespective of its dose[5]. The differential findings may be explained by trial selection, the inclusion of open design trials and trials with intra-muscular vitamin D in the individual data meta-analysis of 7 RCTs[5], and the consideration of hetero-

geneity by received dose (incorporating adherence) or achieved level of 25 hydroxyvitamin D only in the classic meta-analysis of 12 double-blind RCTs[3]. In the second 2009 meta-analysis of 8 double-blind RCTs, fall prevention increased with a higher treatment dose of vitamin D and higher 25-hydroxyvitamin D levels[2]. Anti-fall efficacy was only observed in trials of at least 700 IU vitamin D per day. The dose-dependent benefit and safety of vitamin D was reviewed recently extending musculoskeletal health to overall health[6].

1.Bischoff-Ferrari HA et al 2007; 2.Bischoff-Ferrari HA et al 2009; 3.Bischoff-Ferrari HA et al 2009; 4.Bouillon R et al 2008; 5.Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. Bmj; 340:b5463; 6.Bischoff-Ferrari HA et al 2009.

Disclosure of Interest: None Declared

SY23 - DAIRY PRODUCTS AND BONE: DEVIL OR ANGELS?

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Abstract: Peak bone mass (PBM) is a significant determinant of fracture risk later in life. Genetics, accounts for more than 70% of PBM variance. Nutritional intakes modulate the genetic effects. Protein intakes are positively correlated to bone growth and bone mass accumulation in children and adolescents. Calcium supplementation favourably influences bone mineral mass accrual, particularly in the peripheral skeleton. There is an interaction between the effects of calcium supplementation on bone in prepubertal girls and the occurrence of menarche. Milk and dairy products provide large amounts of calcium, phosphorus, and other nutrients like proteins. In a balanced diet, about 70% of dietary calcium come from milk and dairy products. In children and adolescents, intervention studies with dairy products show positive effects on bone mass accrual. Dairy products are associated with significantly greater total and cortical areas at the distal third of radius, suggesting a possible effect on bone modelling.

In the elderly, several nutritional insufficiencies contribute to a negative calcium balance, and to bone mass and structure alterations. With ageing, there is a decrease in calcium intake by the reduction in spontaneous dairy products consumption, in the intestinal absorption of calcium, and in the absorptive capacity of the intestine to adapt to a low calcium intake. Slowing down the rate of activation of new remodelling sites should be associated with a decrease in bone fragility. Hence, the calcium effect on bone remodelling is usually ascribed to an inhibition of parathyroid hormone secretion, whose plasma level tends to increase with aging. Sufficient protein intakes are mandatory for maintaining the integrity and function of skeletal muscles and bone. A recent meta-analysis shows that BMD is positively correlated to protein intakes, which explain 2-4% of BMD variance. Correction of poor protein nutrition in patients with a recent hip fracture improves the clinical course by significantly lowering the rate of medical complications. The duration of hospital stay of elderly patients with hip fracture can thus be shortened. Intervention trials with dairy products have shown a decrease in bone turnover and a attenuation of bone loss. By providing both calcium and protein, dairy products may constitute an efficacious nutritional way to maintain bone and muscle health in the oldest old.

Disclosure of Interest: Consultant / Speaker's bureau / Advisory activities with: Amgen, Danone, Eli Lilly, Nycomed, Servier, Roche, Novartis

SY24 - INTERACTION BETWEEN NUTRIENTS AND EXERCISE ON BONE STRENGTH

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Abstract: Weight-bearing exercise (Ex) and adequate nutrition, particularly Ca-vitamin D, are independently recognized as important factors to optimize bone strength. However, the mechanism by which Ex and nutrition influence bone strength is different. Exercise has a site-specific modifying effect that can increase cortical area through periosteal apposition and/or reduce endocortical resorption, particularly during growth. In contrast, nutrition has a permissive, generalized effect that acts systemically to down-regulate bone remodelling to preserve bone mass and cortical thickness by reducing endocortical resorption. Despite this, there is evidence that various nutrients may modulate the skeletal responses to loading. Several factorial (2x2) RCTs in children and elderly women with Ca intakes <1000 mg/d have shown that increasing Ca can enhance the effects of Ex on bone mass at loaded sites. There is also evidence that additional Ca can promote exercise-induced gains in cortical area in young children, but similar findings have not been observed in older adults. Vitamin D and protein are also important for bone health through their actions on calcium absorption (and muscle), but whether these factors act synergistically with Ex to enhance bone strength is not clear. During growth, a high protein diet has been reported to enhance the positive effects of Ex on bone mass, size and trabecular microarchitecture. In contrast, resistance training and/or weight-bearing Ex combined with protein supplementation or a multi-nutrient supplement providing additional Ca, vitamin D and protein does not appear to enhance bone mass or structural properties in either young or older adults, despite positive changes in muscle mass, IGF-1 and bone turnover. However, these findings could be explained by the short intervention period in several of these trials (6 months) and the fact that participants had adequate nutrient intakes at baseline. Finally, there is indirect evidence that a negative energy balance may blunt osteogenesis; bone mass has been reported to be reduced in ballet dancers and amenorrheic runners. Overall, the current evidence indicates that Ex and nutrition may produce synergistic benefits to bone strength, particularly during growth and when correcting states of nutritional inadequacy. However, we must await the outcome of further studies to determine if a threshold for specific nutrients exists to maximise bone strength.

Disclosure of Interest: None Declared