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Summary Annual Congress of American Society for Bone and Mineral Research 2015. A subjective overview

Introduction

This past October 2015, the annual congress of the American Society for Bone and Mineral Research (ASBMR) was held in Seattle, USA.

Those in attendance observed a constant through all the conference sessions: research aimed at finding new interrelationships in bone mineral metabolism beyond the bone itself or to better understand the patho-physiology or obtain new therapeutic resources.

SEIOMM and the Journal of Osteoporosis and Mineral Metabolism consider it interesting to provide our readers with a personal overview of the proceedings with a summary of the issues that seem most relevant and representative of current research trends in bone metabolism, as I explain below.

Keynote Speakers

Bruce Spiegelman: Bone, Fat and Energy Regulation

In this lecture, the author emphasized the various types of adipocytes: white, brown and beige adipocytes, focusing mainly on their different functions, which are often opposed. So whereas the white adipocyte stores energy and is a "pro-obesity" cell, the brown eliminates energy and would be an "anti-obesity" cell. After a detailed review of the pathophysiology, he concluded by venturing a hypothesis about how we could mobilize fat from white to brown adipocyte, and how it could be handled in the dietary sense. Finally, he posited if this might be possible in humans.

Forum Discussions

ASBMR/ECTS Symposium: skeletal consequences of diabetes and obesity

Serge Ferrari began reviewing the pathophysiology of type 2 diabetes and its relation to bone fragility, highlighting the recognized factors of lower bone turnover and decreased PTH along with microstructural alterations that lead diabetic patients have more bone mineral density but also more fractures, especially those related to the cortical bone. He also recognized that urinary pentosidine seems to increase in those diabetic patients at increased risk of fracture, as well as levels of sclerostin, which have been linked to the risk of vertebral fracture. Thus, metformin and sulfonylurea use appears to decrease the risk of fracture, while treatment with rosiglitazone and other thiazolidinediones increased this risk. Some studies have even reported that insulin treatment increases the risk of non-vertebral fracture, which needs to be confirmed.

Juliet Compston then discussed obesity and bone health, indicating that weight gain decreased risk of fracture, but if this risk is adjusted by BMI itself, the morbidly obese and extremely obese are more likely to suffer fractures. She said that 80% of obese women with fractures have normal bone mineral density and that the obese with non-vertebral fractures have less bone mineral density at three key sites: the spine, hip and forearm.

THE CONSTANT THROUGHOUT THE CONFERENCE WAS RESEARCH AIMED AT FINDING NEW INTERRELATIONSHIPS IN BONE MINERAL METABOLISM BEYOND THE BONE ITSELF OR TO BETTER UNDERSTAND OF THE PATHO-PHYSIOLOGY OR OBTAIN NEW THERAPEUTIC RESOURCES

Finally, William Leslie spoke about diabetes, obesity and the risk of fracture, commenting the contradictory data and the progress made in recent years. He indicated that fractures in the obese are significant, that BMI in the fractures has a site-specific effect and that obesity and diabetes have a detrimental effect on bone tissue as well as that of adipose and muscle. He concluded that there is a need to develop joint strategies for treating these problems.

Proceedings

Clinical debate. Should the diagnosis of osteoporosis be altered to include patients at high risk of fracture rather than relying on the T-score?

In favor of the motion: Nelson Watts. Against: John Kanis

This was one of the most interesting topics of the congress and had raised great expectations, which, at least in my opinion, were not fulfilled (due, in large measure, to many technical difficulties).

Watts defended the need to change the definition of osteoporosis to include fracture risk. He proposed defining osteoporosis as "a disease with a high risk of fracture due in part to increased bone fragility". For this, it relied on the position paper for the clinical diagnosis of osteoporosis "The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group" signed by Ethel Siris and other authors, including Watts himself.

Kanis defended the position of the T-score below -2.5, arguing that, as Voltaire put it, "the best was the enemy of the good," indicating that diagnosis of osteoporosis based on this criterion was adequate, completing it with other criteria such as a fragility fracture or T-score combined with fracture risk values to 10 years over 20% for any fracture or 3% for hip fracture calculated by FRAX scale ®.

In my opinion, Watts won the debate "on points". His arguments were more convincing clinically and perhaps favored by the fact that he was "playing on home turf". Regrettably, all the technological uncertainties marred the discussion.

Meetings with the expert

Michael Lewicki: Communication of benefits and risks of osteoporosis treatment

Lewicki presented the potential risks associated with treating osteoporosis using bisphosphonates. The short-term side effects such as (frequently by parenteral route) acute gastrointestinal upset, hypocalcemia, "fever" reaction, and long term effects, such as osteonecrosis of the jaw and shaft fractures. He also reviewed the questionable side effects, such as atrial fibrillation, esophageal cancer or alteration in the repair of fractures, to finish listing the possible beneficial effects such as reducing the risk of cancer (breast, colorectal, gastric) of stroke, diabetes mellitus and reduced mortality. Later he coordinated a debate about the possible appropriateness of "therapeutic holidays".

Robert Josse: Therapeutic Holidays. When and how?

At this meeting the author courageously expressed his dissenting view concerning therapeutic holidays. He believes that osteoporosis is a chronic disease whose treatment does not cure and treatment is stopped when usually the beneficial effect is lost, more or less quickly. Regarding medication holidays but not real discontinuation, he wondered if the "retention of bisphosphonates" that occur in the bone is sufficient to ensure a reduction of fracture risk. He also questioned whether it is appropriate to lose the beneficial side effects, such as reducing mortality, interrupting a treatment that is not harmful.

He said that the incidence of side effects such as diaphyseal humeral fracture is very low, on the order of 1.7 cases per 100,000 treatments per year in the first two years, and 113 cases per 100,000 treatments / year from the 8- 9 years of treatment. He concluded that osteoporosis was the only disease in which treatment was discontinued before the complication appears.

Oral communications and posters

Of the numerous clinical submissions, these ten were selected, as I considered them the most interesting:

1. Reference MO1142. *Eighteen months of treatment followed by abaloparatide with six months of treatment with alendronate in postmenopausal women with osteoporosis – Results of the ACTIVExtend Trial. Felicia Cosman, et al.*

In this work, known as ACTIVE by its authors, the results of phase 3 double-blind randomized study presented abaloparatide compared with teriparatide, in which 2,463 patients (all women with postmenopausal osteoporosis) received 18 months 80 abaloparatide ug sc, or teriparatide 20 mcg sc, or placebo. All the women received calcium and vitamin D. In the branch extension, treatment lasted 24 months, with continuous alendronate. The two treated groups showed abaloparatide and teriparatide increased BMD and reduced fracture risk compared with the control group, but in the (L2-L4) spine obtained with abaloparatide, increase was higher than teriparatide.

2. Reference 1092. *The effects of a longer-term, low-protein diet on calcium absorption*

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and kinetic Measures of bone turnover in young women. Jessica Bihuniak et al.
This study was conducted in 11 premenopausal women who were prescribed a diet low in protein (<0.7 g/kg/day) for 6.5 weeks, carrying out a study of calcium absorption (radioactive) together with the bone turnover markers and PTH. The authors conclude that low protein intake, defined as less than 0.8 g / kg, produces gastric malabsorption, increased PTH and greater loss of urinary excretion of calcium in young women.

3. Reference 1153. *Reduced mortality and subsequent fracture risk with oral bisphosphonate treatment in secondary fracture prevention: an 8-year observational follow-up study. Tineke van Geel, et al.*
The authors analyzed the effect of oral bisphosphonates on the risk of new fragility fractures and mortality after 8 years of follow-up. 9,439 patients of both sexes aged over 50 years who had suffered at least one fracture were reviewed, and after 8 years of follow mortality decreased from 15% to 9% and also observed a reduced risk of new fractures after making adjustments.

4. Reference 1115. *Predicts sarcopenia fracture risk in 65-year old healthy community dwellers. Trombetti Andrea, et al.*
In this paper, the authors studied 930 patients of both sexes in a prospective study with a duration of 3.4 years on average. They found an association between the presence of sarcopenia and risk of fragility fracture in patients over 65 years and independently calculated risk by FRAX®.

5. Reference 1144. *Efficacy of odanacatib in Women with postmenopausal osteoporosis: subgroup analyzes of data from the phase 3 Long-term Odanacatib Fracture Trial (LOFT). Kenneth G. Saag, et al.*
The authors presented the results of a study of the phase 3 odanacatib, called LOFT study, which included 16,713 women over 65 years of age without vertebral fracture and a T-score between -2.5 and -4 , 0, or a vertebral fracture and a T-score between -1.5 and -4.0. They were randomized and classified into 2 groups, one treated with odanacatib (50 mg / week) and another with those receiving placebo. All the women were given calcium and vitamin D. Patients receiving odanacatib showed a reduction of vertebral, non-vertebral morphometric vertebral and hip fractures. Among the results, the authors suggested that studying all cardiovascular events was a higher number of strokes in patients receiving odanacatib.

6. Reference SA 0328. *Longitudinal cohort study of once weekly in glucocorticoid- induced osteoporosis teriparatide in Japanese patients. Ikuko Tanaka, et al.*
In this paper the authors present the results obtained using teriparatide administered weekly to patients with steroid osteoporosis. 87% of patients treated with bisphosphonates and teriparatide 13% weekly and were monitored for 1 year. a statistically significant risk reduction of new vertebral fractures, which was 16% in patients receiving bisphosphonates and 10% in those with teriparatide weekly decline was observed. What was not clear from the presentation and I could not ask the author not agree with him on the poster, is whether teriparatide was the same as is commonly used or if it is a different gelenic formulation.

7. Reference SA 337. *Bone mineral density with response rates teriparatide, denosumab, or both: to respond DATA analysis of the Study. Paul Wallace, et al.*
In my opinion, one of the most interesting papers of the congress. The authors studied 94 women at high risk of fracture, randomizing them in 3 treatment groups: only teriparatide, only denosumab or both drugs combined. They followed up for 24 months. The results showed that patients receiving the combination therapy had a statistically significant increase in bone mineral density than the other 2 groups in all anatomical locations in which it was determined: Total lumbar spine, femoral neck and hip. The sample size did not yield results on reducing the risk of fracture, but still worth continuing with this type of studies that looks very promising for severe of patients with severe osteoporosis.

8. Reference 1143. *Romosozumab improves strength at the lumbar spine and hip in postmenopausal women with low bone mass compared with teriparatide. Keaveny TM, et al.*
Work done on a small number of patients, but with very interesting results. In one group (n=28) received teriparatide 20 mcg/day, in another (n=24) romosozumab, 210 mg/month (both subcutaneous), and the third group (n=27) received placebo. Efficacy on bone strength in the spine and hip was evaluated used a finite element analysis performed on scans obtained. The observed increase in resistance with rosomozumab column was 27.3% per year, whereas teriparatide the increase was 18.5%; in the placebo group a decrease of 3.9% was observed. In the femur, romosozumab only showed an increase, which was 3.6%. By increasing the resistance in the trabecular and cortical compartments, the overall strength of the bone increased significantly, and this augurs romosozumab excellent results in reducing long-term risk of fracture.

ABOUT THE THERAPEUTIC VACATION ROBERT JOSSE BELIEVES THAT OSTEOPOROSIS IS A CHRONIC DISEASE WHOSE TREATMENT DOES NOT CURE AND TREATMENT IS STOPPED WHEN USUALLY THE BENEFICIAL EFFECT IS LOST, MORE OR LESS QUICKLY

9. Reference 1067. *Vertebral fracture risk in elderly diabetic*

men: The MrOS Study. Nicola Napoli, et al.
One result over MrOS study conducted in men in recent years. In it, the authors studied the possible association between type 2 diabetes mellitus and the incidence of vertebral fracture in a population of 5,994 men over 65 years, of which 875 were diabetic and 80 used insulin for treatment. BMD DXA and QCT was determined. After an average of 4.6 years, a side column radiography control was carried out.

No increased incidence of vertebral fractures among diabetics, or incident or prevalent was found. Conversely, they obtained an association with patients who had lower bone mineral density.

10. Reference 1073. *Change in fracture risk after bariatric surgery from a pattern Associated with obesity to a typical pattern of osteoporosis: A study using healthcare administrative databases. Catherine Rousseau, et al.*
The authors studied a total of 10,662 patients who received bariatric surgery between 2001 and 2012 and compared the results with other 2 groups: one formed by 31,986 obese who were not operated on and another, a group of 31,986 age-matched non-obese. The risk of fracture comparing the 3 groups with a mean of 4.2 years were analyzed. After surgery, the risk of fracture in the lower extremities decreased by 33% in the group which underwent surgery, but the risk of upper limb fracture increased by two and by three the risk of this fracture would occur in pelvis or hip. In the other 2 groups (obese and non-obese intervention) the risk remained stable. The authors conclude that after bariatric surgery pattern changes fracture risk in these patients, from the typical pattern of postmenopausal women.

Others

There was a very limited number of papers on odanacatib in this conference as opposed to ASBMR last year in Houston, where many were presented. This makes me suspect that they will abandon the research and sale of this drug. The number of strokes described the previous year must have caused alarm and a reconsideration of the strategy. There is no official information or any other data. This is an assumption.

Moreover, I noted that an engineered PTH molecule, abaloparatide, cropped up in several aforementioned oral communications and posters. It presents exceptionally good results in both increased bone mineral density and reduction of fracture risk, which suggests that the next drugs in the therapeutic panorama of osteoporosis will be rosomozumab and abaloparatide.

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Many tables, meetings with the expert and various communications were related to metabolic issues including obesity, diabetes and nutrition, in an effort perhaps, as I indicated at the outset, to open new physio-pathogenic bone-related lines and also to find new potential therapeutic targets.