Bisphosphonates have been in use since the middle of the 19th century in the textile, fertilizer and oil industries, with the first synthesis dating back to 1865 in Germany.

The first clinical trial on Bisphosphonates was in 1971, 2 years after the first publication on their biological effects. However, their mechanism of action was not elucidated until the 1990’s, by Professor Mike Rogers, more than 20 years after their clinical use.

The discovery that bisphosphonates can inhibit bone resorption led very quickly to their clinical use in Paget’s disease and in patients with skeletal complications of cancer and later in the treatment of osteoporosis.

Some of the newly elucidated benefits of bisphosphonates include:
- Increased survival in critical care patients
- Inhibition of numerous protozoal parasites
- Decreased progression and improved survival of patients with breast cancer

The Calcium Metabolism and Osteoporosis Program Bone Mineral Density Unit at AUB-MC recently became the 1st accredited Facility outside the United States!

EXCITING NEWS!
BONE HEALTH TELEECCHO
TO LAUNCH AT AUBMC 2020!!!

But WHAT is it? Bone health Tele-Extension for Community Healthcare Outcomes is an ongoing live interactive case-based learning network for healthcare professionals (e.g., practicing physicians, physicians-in-training, advanced practice providers) to share knowledge on the care of patients with osteoporosis and metabolic bone diseases. STAY TUNED!
Dr. Ghada El-Hajj Fuleihan speaks at the ASBMR 2019 annual meeting in Orlando, USA, at the “Challenge the Experts: Parathyroid Disorders” session. The panelists discussed clinical cases including hypoparathyroidism, parathyroid carcinoma and familial hypocalciuric hypercalcemia.

AUB graduates, faculty, SHARP trainees and CaMOP research fellows: Drs. Marlene Chakhtoura, Randa Saad, Vanessa Akiki and Aya Bassatne presented posters on their ongoing research.

**ASBMR 2019 HIGHLIGHTS**

**Effect of Calcium Supplementation on Cardiovascular Health**

Great controversy exists with regards to the effect of calcium supplementation on the risk of cardiovascular events. Suzanne N. Morin, MD, MSc, from McGill University, presented results of a 1-y randomized control trial (RCT), in which 121 healthy postmenopausal women were randomized to daily 1,200 mg of dietary calcium or 750 mg calcium supplement + 450 mg dietary calcium (total 1,200 mg/d) or no intervention. There was no difference in carotid femoral pulse wave velocity (indicator of arterial stiffness), carotid intima-media thickness (indicator of subclinical atherosclerosis), serum total cholesterol or high-sensitivity C-Reactive Protein (CRP), between the three groups at the end of the study. To note, this data only reflects short term effect of calcium supplementation and the study might have been under-powered. (Abstract #1075)

**Effect of Calcium Supplementation on Risk of Abdominal Aortic Calcification**

A 5-y double blinded placebo controlled RCT of 1,200mg elemental calcium (carbonate) in 1,460 elderly women (aged >70 y) showed no evidence of increased risk for development or progression of abdominal aortic calcification with long term use of calcium supplements. (Abstract #LB1168)

**Loss in DXA-Estimated Total Body Lean Mass Predicts Fracture Risk**

In a registry based Canadian study, William Leslie, MD, MSc, from the university of Manitoba, presented data on 9,694 individuals (mean age 67 ± 10 y, 95% women). Loss in total body lean mass, but not fat mass, was associated with significantly higher risk of fracture, especially at the hip at a median follow up of 6 y. A 10-13% increased risk of major osteoporotic fractures and 29-38% increased risk of hip fractures was seen with every standard deviation loss in lean mass, even after adjustment for height loss, FRAX scores ± bone density, and competing mortality. (Abstract #1061)

**Subsequent Fracture Risk Post Traumatic vs. Non-Traumatic Fractures**

In a BMD registry-based cohort study from Canada, including 80,242 individuals (mean age 64 ± 11 y, 90% women), prior traumatic fractures (which were not originally included as a risk factor for future fractures) were associated with low BMD and increased future fracture risk to the same extent as non-traumatic fractures. (Abstract #1154)
Recombinant Human Parathyroid Hormone for Treatment of Hypoparathyroidism

RACE is an open-label study of recombinant human parathyroid hormone (rhPTH 1-84) for the treatment of hypoparathyroidism. 49 patients received 25-100 mcg/d of subcutaneous rhPTH to maintain an albumin corrected calcium (Ca) level of 8-9 mg/dl. 38 patients completed the 72 month study. Serum Ca levels were maintained within target range, and urinary Ca excretion, serum phosphorus levels and Ca-phosphorus product levels declined to within normal range. Bone turnover markers peaked at 1 y of treatment, then slowly declined to a stable plateau that was higher than baseline, but within or close to normal range. BMD was stable, except for a decline within the normal range at the forearm. Continuous use of rhPTH over 6 y resulted in a safety profile consistent with other studies, and no cases of osteosarcoma were observed. (Abstract #1019)

Effect of Denosumab on Falls, Muscle Function and Strength

In an interventional study, 79 older community-dwelling adults (age >65 y), at high risk of fall and fracture, were prescribed either Denosumab or Zoledronic Acid. At 6 months, the Denosumab group showed improvement in gait speed, timed up-and-go, four square step test, and fear of falling. This may explain its anti-fall efficacy, which adds to its direct beneficial bone effect. (Abstract #LB-1170)

Total Hip BMD as a Surrogate for Fracture Risk Reduction

A meta-regression of 22 osteoporosis trials (61,495 total participants from the FNIH cohort), using baseline and follow-up BMD results and incident fractures from each study, assessed the relationship between treatment related difference in total hip BMD changes to observed fracture risk reduction. The surrogate thresholds for vertebral, hip and non-vertebral fractures were 1.7%, 4.6% and 3.2% change in the total hip BMD, respectively, at 24 months. Total hip BMD may be used as a surrogate to assess fracture risk reduction in future osteoporosis treatment trials. This however, is based on mean data and might not apply to individual patients. (Abstract #1090)

Predicting Fracture Risk During Bisphosphonate Holiday

FLEX was a placebo controlled RCT of drug holiday after 5 y of Alendronate (ALN) treatment (FIT trial). Patients who continued on ALN had reduced clinical spine fractures. Therefore, the investigators based their model, to quantify fracture risk following bisphosphonate discontinuation, on predicting risk of clinical spine fractures. The resulting risk model was then applied to predict non-vertebral and hip fractures. Significant predictors in the final FLEX multivariate model included BMD, age and vertebral fracture status measured at baseline of FLEX. FRAX major osteoporotic fracture (MOF) was equal or superior to the FLEX equation for predicting risk for clinical vertebral as well as non-spine and hip fractures. After 5 y of ALN, FRAX 10-y MOF risk above 23% identifies a high risk group that will likely benefit from an additional 5 y of ALN. (Abstract #1089)

Efficacy of Romosozumab Among Patients with Chronic Kidney Disease

The FRAME study included 7,180 postmenopausal women, randomized to Romosozumab (Romo) 210 mg/month or placebo for 12 months. At baseline, 88% had mild or moderate renal insufficiency and 0.3% had severe renal insufficiency. Romo increased BMD and reduced the incidence of new vertebral fractures irrespective of eGFR level compared to placebo. Safety was also generally comparable among eGFR subgroups. (Abstract #1085)
Increased Risk of Atypical Femoral Fractures in Asian Women
In a study of 197,103 women (aged > 50 y) who had at least one prescription for any osteoporosis medication, those of an Asian descent had a ~5-fold greater risk for atypical femoral fracture (AFF) when compared to women with Caucasian ancestry, with no significant difference seen between ethnic subgroups. No confounding factors, including duration of bisphosphonate use, age, smoking, initial BMD or fracture history explained the increase in AFF risk. (Abstract #FRI-631)

Patient Characteristics Do Not Predict BMD Response to Bisphosphonates After Denosumab Cessation
Denosumab Adherence Preference Satisfaction (DAPS) study was a 2-y open-label randomized crossover study of postmenopausal, treatment-naive women with T-scores between -4.0 and -2.0 randomly assigned to Denosumab (60 mg once every 6 months) or Alendronate (70 mg once weekly). Of those randomized to Denosumab, 115 were switched to Alendronate at 12 months, and most showed maintained or increased BMD at 24 months. Those who showed BMD loss at 24 months, had previously shown greater BMD gain on Denosumab. Baseline characteristics, BMD at 12 months and adherence to oral Alendronate showed no trend with the BMD change from 12 to 24 months. (Abstract #1047)

Effect of Parathyroidectomy on Quality of Life
A 10-y Scandinavian RCT on mild primary hyperparathyroidism randomized 191 patients to parathyroidectomy or observation. The psychological and mental domains were more affected than physical domains and patients randomized to surgery scored better on psychological scales. To note, psychological complaints are not a criteria for parathyroidectomy. (Abstract #1018)

Long-term Safety and Clinical Outcomes of Burosumab
The final data on long-term safety and clinical outcomes with Burosumab treatment of patients with X-linked Hypophosphatemia (XLH) was presented by Karl Insogna, MD, from Yale University. A 96-week double-blinded randomized, placebo controlled trial, showed that in adults with XLH, long-term treatment with Burosumab was associated with sustained improvements in serum phosphorus level, stiffness, physical functioning and pain without increase in adverse events. (Abstract #1077)

Burosumab Superior to Conventional XLH Therapy in Children
In a phase 3 trial, efficacy of Burosumab was compared to conventional therapy (oral phosphate and active vitamin D), in children aged 1-12 y with XLH. Burosumab resulted in greater improvement in phosphate homeostasis, rickets severity, lower limb deformity, and growth. Adverse events identified from previous Burosumab trials were more frequent with Burosumab but were mild to moderate in severity. (Abstract #1036)
**ASBMR RECOMMENDATIONS FOR SECONDARY FRACTURE PREVENTION**

In patients ≥65 y with hip or vertebral fracture:

1. Inform patients that their fracture is due to osteoporosis, and they are at risk for more fractures especially within the next 2 y
2. Inform primary healthcare providers of the fracture
3. Assess risk of fall regularly
4. Offer pharmacologic therapy for osteoporosis, do not delay for BMD testing
5. Initiate vitamin D supplements, at least 800 IU/d
6. Initiate calcium supplements if unable to achieve dietary intake of 1,200 mg/d
7. Follow and re-evaluate patients on osteoporosis treatment routinely
8. Consider referring patients with secondary causes of osteoporosis to a specialist
9. Counsel patients to stop smoking, limit alcohol intake, and exercise regularly
10. Discuss risks/benefits of therapy with patients
11. Refer to a specialist if continue to lose bone or fracture while on treatment
12. 1st line pharmacologic therapy includes: oral or intravenous bisphosphonates or Denosumab. For high risk patients, anabolic agents (e.g. Teriparatide) may be offered
13. Optimal duration of pharmacologic therapy is unknown, but need for therapy should be re-assessed within 3 to 5 y

*Fundamental recommendations are in bold

**Vitamin D Negative Studies**

**Vitamin D Supplementation Does NOT Reduce Cardiovascular Events or Invasive Cancers!**
The **VITAL** study was a 2X2 factorial RCT of 2,000 IU/d vitamin D$_3$ and 1 g/d omega-3 and included 25,871 healthy individuals with a normal baseline 25-hydroxyvitamin D (25OHD) level (mean 30.8 ± 10.0 ng/ml). Compared to placebo, supplementation with either vitamin D$_3$ or omega-3 did not result in a lower incidence of cardiovascular events or invasive cancer.

**Vitamin D Supplementation Does NOT Reduce Risk of Diabetes!**
In a randomized placebo-controlled trial, including 2,423 participants with prediabetes, supplementation with 4000 IU/d of vitamin D$_3$, regardless of baseline serum 25OHD level, did not result in significantly lower risk of new onset diabetes. The findings of this trial were published in _June 2019 in NEJM by Pittas et al._

**Another Negative Trial on High Dose Vitamin D**
The Calgary Vitamin D Study was a 3-y double-blinded RCT of 311 adults, comparing three doses of vitamin D$_3$: 400 IU/d, 4,000 IU/d or 10,000 IU/d. Both the 4,000 IU and the 10,000 IU lowered radial BMD compared to the 400 IU/d dose. However, radial and tibial bone strengths were not affected by the different doses of vitamin D$_3$. This study was published in _JAMA 2019._

Additional results presented at ASBMR 2019: Effect of high dose vitamin D$_3$ on tibial arterial calcification was a secondary outcome of the same trial. In participants with no baseline calcifications, none developed new calcifications. However, in those with baseline calcifications, a progression of calcification was observed, but it was NOT dose dependent. (Abstract #1076)

**TAKE HOME MESSAGES**
- High dose vitamin D supplementation has no benefit if baseline 25OHD levels are normal (> 20 ng/ml)
- Further studies are needed in community dwelling individuals
- Vitamin D protects against hip fracture in institutionalized individuals

**Vitamin D Supplementation in Colon Cancer**
The **SUNSHINE** phase 2 clinical trial randomized 139 patients, with advanced or metastatic colorectal cancer, to either a high dose vitamin D group receiving 8,000 IU/d during the first cycle of chemotherapy followed by 4,000 IU/d during subsequent cycles, or a low dose group receiving 400 IU/d during all cycles. The high dose group had higher median progression free survival (PFS) of 13 months vs. 11 months, that was not statistically significant. However, it did result in a “significantly improved supportive hazard ratio” for PFS or death.

However, in the **AMATERASU** double blinded RCT of 417 Japanese patients with digestive tract cancers, vitamin D at a dose of 2,000 IU/d resulted in no significant improvement in relapse-free survival compared to placebo.
Research Looks at Impact of High Dose Teriparatide in Combination with Denosumab (DATA-HD)
In an open label-controlled phase 4 trial, postmenopausal osteoporotic women were randomized to either 20 mcg or 40 mcg of daily Teriparatide. At 3 months, both groups were switched to Denosumab 60 mg every 6 months for 12 months. At 15 months, mean spine, femoral neck and total hip areal BMDs increased significantly more in the 40 mcg group. Combined treatment with high dose Teriparatide and Denosumab might provide additional benefits to women at high risk of fracture.
Additional results presented at ASBMR 2019: The high dose Teriparatide group were found to have significantly higher bone balance between bone formation markers (osteocalcin and P1NP) and bone resorption markers (CrossLaps). Overall bone balance favored bone formation throughout the study. (Abstract #1048)

Study Indicates Cyclic Teriparatide and Denosumab may Benefit Patients at High Risk of Fractures
In a parallel design study, Cosman et al. randomized postmenopausal women with osteoporosis to either 18 months of Teriparatide followed by 18 months of Denosumab, or to three separate 12-month-cycles of 6 months of Teriparatide followed by 6 months of Denosumab. At 36 months, both groups experienced similar BMD gains at the lumbar spine, total hip and femoral neck. However, at 18 months, women randomized to the standard regimen experienced a decline in BMD at the distal radius and in total body BMD, whereas women randomized to the cyclic group did not.

UPDATED 2019 POSITIONS OF THE INTERNATIONAL SOCIETY FOR CLINICAL DENSITOMETRY (ISCD)
Serial BMD Measurements
• ...in combination with clinical assessment of fracture risk, bone turnover markers, and other factors including height loss and trabecular bone score (TBS), can be used to determine whether treatment should be initiated in untreated patients, according to locally applicable guidelines.
• ...should be used to monitor individuals following cessation of osteoporosis therapy.
• ...can detect loss of bone density, indicating the need for assessment of treatment adherence, evaluation of secondary causes of osteoporosis, and re-evaluation of treatment options.
• Follow-up BMD testing should be done when likely to influence management.

Role of TBS, previously deemed not useful for monitoring bisphosphonate treatment, has changed to “Unclear” in monitoring anti-resorptive therapy and potentially useful for monitoring anabolic therapy.

*Changes from 2015 emphasized in bold
**TIPS FOR A BONE-HEALTHY LIFESTYLE**

- Increase your physical activity – aim to exercise for 30-40 minutes, 3-4 times each week with some weight-bearing and resistance exercises
- Ensure a balanced diet which includes enough dietary calcium- use the International Osteoporosis Foundation (IOF) Calcium Calculator to estimate your approximate calcium intake
- Dairy intolerance? Find out about calcium-rich alternatives or explore which dairy products you can enjoy in moderation
- Spend more time outdoors to ensure you are getting enough vitamin D or take supplements if required
- Avoid smoking and drink alcohol only in moderation

* Adapted from IOF Osteoporosis Risk checklist

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**SAVE THE DATE!**

**Nov 7-9, 2019:** International Annual Congress of the Lebanese Society of Obstetrics and Gynecology, Lebanon

**Mar 13-14, 2020:** OSTEOS annual meeting, Lebanon

**Mar 28-31, 2020:** Endocrine Society annual meeting, San Francisco, CA, USA

**Apr 2-5, 2020:** WCO-IOF-ESCEO, Barcelona, Spain

**May 21-22, 2020:** International Conference on Osteoporosis, Osteoarthritis & Musculoskeletal Diseases - London, UK

**Sep 11-14, 2020:** American Society of Bone and Mineral Research, Seattle Washington, USA

**Nov 30-Dec 2, 2020:** Royal Osteoporosis Society, ACC Liverpool, UK

**To-be-announced:** Lebanese Society of Endocrinology Diabetes and Lipids (LSEDL)

**To-be-announced:** Lebanese Society of Rheumatology

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**CALCIUM METABOLISM AND OSTEOPOROSIS PROGRAM 2019 PUBLICATIONS**


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