

## Proceedings

### Abstracts of the Scientific Meeting of the Hellenic Osteoporosis Foundation

# Clinical Guidelines on Calcium and Vitamin D supplementation Certainties and concerns on the osteoporosis treatment

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## DIAGNOSIS AND CLINICAL SIGNIFICANCE OF OSTEOPOROTIC VERTEBRAL FRACTURES

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Vertebral fractures of the thoracic and lumbar spine are considered the most common type of fracture in patients with osteoporosis. They may present as early as the sixth decade of life and their prevalence increases with age. They are usually attributed to low energy falls (i.e fall from a standing height), but can also occur without falling, most often while bending or trying to lift a heavy object. In such cases, pain may be acute and vertebral fractures are thus termed as clinical. However, in many cases, vertebral fractures remain asymptomatic and are usually diagnosed on routine X-rays of the spine or chest, thereby called morphometric or radiological fractures. Morphometric fractures are usually underestimated from radiologists or clinicians worldwide who fail to acknowledge their clinical significance, and in many occasions may not even be reported in the diagnosis. Clinical signs of previous vertebral fractures may include a marked kyphosis of the thoracic spine and/or loss of height of >2-3 cm. Diagnostic tools include lateral x-rays of the thoracic and lumbar spine, vertebral fracture assessment by dual energy X-ray absorptiometry (VFA), computerised tomography (CT) or magnetic resonance imaging (MRI). Grade and severity of vertebral fractures on lateral x-rays may be calculated using various available methods, one of the most common being the Genant semi-quantitative method; a 20-25% decrease in (anterior/central/posterior) vertebral height is considered a Grade 1 fracture, 25-40% a Grade 2 fracture and >40% a Grade 3 fracture. VFA provides an accurate quantitative assessment of a depression of an endplate that is achieved with minimal radiation doses. Computerised tomography may be additionally used

for the differential diagnosis of a bone lesion inside a vertebrae, including primary or metastatic bone tumors. MRI provides evidence of a recent vertebral fracture, which is accompanied by bone marrow oedema, and has no radiation, but is an expensive and not readily available technique. The clinical significance of osteoporotic vertebral fractures in the context of bone strength is that they are indicators of increased fracture risk, especially in untreated individuals. It has been shown that previous vertebral fractures increase about 3-fold the risk of a new vertebral fracture and about 1,5-2-fold of a non vertebral fracture in osteoporotic women. It has also been shown that the number and severity of prevalent vertebral fractures further increases the risk of various osteoporotic fractures. Patients with spinal deformities such as kyphosis due to multiple vertebral fractures, are also most likely to suffer complications of the cardiopulmonary system as well as pain, related disability and decreased physical activity, possibly increasing bed-rest days or requiring hospitalisation. The social and economic burden of osteoporotic vertebral fractures, as well as morbidity and mortality, are increasing in the western world, and it is considered mandatory for health systems to develop improved strategies in order to identify and effectively treat patients with such fractures.

## IS BALLOON KYPHOPLASTY A SAFE AND EFFECTIVE TREATMENT FOR OSTEOPOROTIC VERTEBRAL COMPRESSION FRACTURES?

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Osteoporotic vertebral compression fractures commonly afflict most aged people back pain, functional disability, substantial vertebral deformity, increased adjacent spinal fractures and decreased quality of life.

Percutaneous vertebral augmentation included percutaneous vertebroplasty and percutaneous balloon kyphoplasty are used for the treatment of osteoporotic vertebral compression fractures.

We performed a systematic review of literature, comparing the outcomes of balloon kyphoplasty with conservative treatment. Outcomes included back pain, back disability, new vertebral compression fractures, quality of life and adverse events.

The literature suggests that kyphoplasty is associated with greater improvement in pain, disability quality of life and an increase in risk of early adverse events compared with nonsurgical management.

## THE ROLE OF VITAMIN D IN THE RISK AND PROGRESSION OF PRIMARY OSTEOARTHRITIS

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The low serum level of vitamin D of the patients with osteoarthritis (OA) affects the structure and function increases the risk of involvement. Have been correlated with the pain of the affected joints, the progression of the OA and so the restriction of physical ability and the decrease of the quality of life of the OA patients. Have also been described its relationship with the decrease of muscle power (in particular of the lower limbs). The prevalence of low serum level of vitamin D is high in osteoarthritis patients undergoing of orthopedic joint surgery and may affect its outcomes. The supplementation of vitamin D leads to the improvement of the joints' cartilage architecture, the decrease of the pain of the affected joints as well as the improvement of the physical ability and the quality of life of the OA patients.

## BEYOND DXA: THE DIAGNOSTIC MODALITIES FOR INVESTIGATING MUSCULOSKELETAL DISEASE

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Osteoporosis is a common metabolic disease and is characterized by reduced bone density and microarchitectural deterioration of bone, resulting in increased fracture risk. Therefore appropriate diagnosis and monitoring are required to reduce the burden of osteoporosis-related fractures.

**DXA** currently provides the most widely accepted method for assessment of osteoporosis, used as gold standard in postmenopausal women. However, it still has a number of limitations (e.g. degenerative changes of spine, aortic calcifications, difficulty in positioning the patients, obesity etc.) and may result in inaccuracies in measuring bone changes in the hip and spine.

Despite the advent of newer and highly accurate diagnostic modalities, osteoporosis still is most commonly diagnosed at **conventional radiography**, albeit this modality is able to help detect bone loss only when a substantial amount of such occurs.

**Morphometric methods**, based on vertebral height measurements, are used to identify vertebral fractures. These measurements may be obtained from conventional spine measurements (morphometric x-ray radiology), or absorptiometry images (morphometric x-ray absorptiometry).

**Quantitative US** is used to measure and assess tissue properties, offering quick and simple measurements at low cost without any radiation exposure, but cannot be used as a standard tool in the diagnosis of osteoporosis because of the diversity of the devices and having different levels of validating data for association with DXA measured bone density and fracture risk.

**Quantitative CT** provides separate estimates of trabecular and cortical BMD as a true volumetric mineral density in milligrams per cm<sup>3</sup> and can be performed at axial and peripheral sites. It allows assessment of both volumetric BMD and microarchitecture, thereby providing separate consideration of bone density and bone geometry. Overall, this leads to a more detailed understanding of the changes in the bone. Disadvantages include a considerable radiation dose, high cost, and degree of operator dependence, as well as limited scanner access.

**Peripheral Quantitative CT** allows separate assessment of cortical and trabecular bone and yields direct information on bone geometry at several appendicular sites. It also provides information on the mass and distribution of bone material that can be integrated into indexes of bone stability in response to bending and torsional loads, which are the most important biomechanical measures of susceptibility fractures and may improve accuracy in the prediction of fractures.

Advances in **MRI software** have allowed for substantially enhanced trabecular bone architecture imaging. Lack of radiation makes MR imaging attractive in particular for scientific and clinical studies. The technique has been established mainly for peripheral imaging of the distal radius, tibia, and calcaneus, but recently to femur, as well. Of note, trabecular bone network is revealed indirectly through marrow visualization and appears as a signal void surrounded by high signal intensity fatty bone marrow. Studies have confirmed that the procedure can be used to detect differences in trabecular structure depending on patient age, BMD and osteoporotic status. Its main use lies in the differential diagnosis of osteoporotic spinal fractures and malignancies.

During the past decade, a number of publications focused on osteoporotic insufficiency fractures (femoral condyle of the knee, femoral head, and sacrum), which have been misinterpreted as neoplastic lesions. MRI and bone scanning

have helped to correctly diagnose these fractures, avoiding misguiding patient management, which may render the need for dangerous and costly interventional procedures.

A correct diagnosis of osteoporosis is fundamental for identification of persons who need treatment and are at risk for complications thus, advanced technologies are being developed in an attempt to help diagnose osteoporosis in early stages, reducing the social and economic burden of the disease and preventing patient suffering.

## THE MEASUREMENT OF VITAMIN D METABOLITES IN CLINICAL PRACTICE AND RESEARCH

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It has been more than 80 years since the discovery of vitamin D and its ability to cure rickets in children. Vitamin D is a secosteroid and comes in two distinct forms: Vitamin D<sub>2</sub> which is a 28-carbon molecule and derives from the plant sterol ergosterol and Vitamin D<sub>3</sub> which is 27 carbon molecule and derives from cholesterol. During the last 40 years, the synthesis and metabolism of vitamin D were elucidated and more than 50 metabolites of vitamin D have been discovered (but measurement procedures have been developed for only a few of them).

The clinical significance of vitamin D in calcium and phosphorus homeostasis is well appreciated. It stimulates intestinal calcium and phosphate absorption thus maintaining adequate levels for bone mineralization. However recent epidemiological data indicated that it has several extra-skeletal physiologic actions (for example it is involved in cell growth, proliferation and apoptosis, it modulates the immune system and its chronic deficiency may be related with diseases such as diabetes, cancer, hypertension, and cardiovascular diseases) which are still a matter of scientific debate.

Both research findings and the debate around the interpretation of the research results, created an increased interest for more measurements of vitamin D. With the ever growing family of measurable vitamin D metabolites and the measuring techniques, comes a question: What metabolic product will provide the right answers and what is the best way to measure it.

Until today we have been able to develop methods to measure several metabolites of vitamin D with several analytical techniques. These metabolites are 25-hydroxy-vitamin D [25(OH)D], 1,25-dihydroxy-vitamin D [1,25(OH)<sub>2</sub>D], 24,25-dihydroxy-vitamin D [24,25(OH)<sub>2</sub>D], the epimer [epi-25(OH)D], the free-25(OH)D and finally the vitamin D binding protein (VDBP). The analytical techniques include: radioimmunoassay (RIA), manual and automated non-radioisotopic immunoassays (ELISA, CLIA or ECLIA), and finally more sophisticated analytical techniques based on the principles of Liquid Chromatography either stand-alone

(HPLC) or coupled with Mass Spectrometry (LC-MS/MS). The right choice of analytical technique is connected with the question which metabolite we aim to measure what its serum concentration, and of course what is the purpose of the measurement.

The Hellenic Osteoporosis Foundation (HELIOS) recently published clinical guidelines for routine clinical use it is recommended that the serum levels of total 25(OH)D, the sum of 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub>, is the biomarker of choice since it reflects the vitamin D status in human body. This is the main circulating metabolite of vitamin D in high concentration (ng/mL) and with long half-life (approx. 15 days). These two characteristics make this metabolite easy to measure and several commercial automated assays are in the market. However, all assays are not free from analytical problems with the major being the significant variability between assays. The vitamin D Standardization Program (VDSP) has defined certain criteria for accuracy and reproducibility and recommends that all labs involved in the measurement of 25(OH)D to participate in the international external quality assessment scheme for vitamin D (DEQAS) which can verify the accuracy of the measurements.

The measurement of the rest metabolites is recommended only in special clinical scenarios and for research use. In all cases, the method of choice is recommended the LC-MS/MS

## CLINICAL GUIDELINES FOR THE RIGHT USE OF CALCIUM AND VITAMIN D FOR THE SKELETON

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Calcium, a key component of bone, is obtained through diet or supplements, or both, and vitamin D is necessary for normal calcium absorption. Controversy exists as to the efficacy and even the safety of calcium. Our opinion, backed by studies and guidelines, is that adequate amounts of calcium are a must for patients concerned about bone health, and cardiovascular safety is not a concern. We advise modest targets for total calcium intake, maximizing dietary calcium intake and making up the deficit with calcium supplements. Gastrointestinal complaints are common with calcium supplements and can be mitigated taking the tablets after meal or with dose adjustment. High dietary calcium intake has not been shown to increase the risk of kidney stones but there is a modest increase in renal stones in those who did use personal supplements.

On the basis of the current evidence, we recommend the use of calcium in combination with vitamin D supplementation rather than as the sole agent for reduction of fracture risk, but with the magnitude of effect being modest. However, efficacy has not been demonstrated for all individual fracture types, or for calcium supplementation alone. Intervention is probably best directed, therefore at those judged to be at high risk of calcium/vitamin D deficiency (although how this

high-risk population may be defined is much debated) and in those who are receiving treatment for osteoporosis. The role of routine calcium and vitamin D supplementation as a population health strategy for fracture prevention is not robustly supported.

## CLINICAL PRACTICE GUIDELINES FOR THE USE OF CALCIUM AND VITAMIN D IN PREGNANCY AND LACTATION

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During pregnancy and lactation the mother provides a substantial amount of minerals to the developing fetus and neonate. It is estimated that the mother transfers to the fetus, especially during the third trimester, about 300 mg of calcium per day, while the same amount of calcium is transferred daily to the breast milk, an average total loss that is about four times that of pregnancy. During pregnancy the major mechanism responsible for this adaptation is increased intestinal calcium absorption mediated by the doubling of calcitriol levels, while during lactation, PTHrp produced by the breast, results in calcium mobilization from the maternal skeleton. Vitamin D plays an important role, especially during pregnancy and in the first months of infancy, by supporting active intestinal calcium absorption. Furthermore low vitamin D levels, especially during pregnancy, are associated with several adverse maternal and infant skeletal and non-skeletal outcomes, while randomized intervention studies reported conflicting results.

### Recommendations

#### Calcium

1. The recommended calcium intake in pregnancy and lactation is 1 gr of calcium per day for the ages 19-50 years. In adolescence the recommended daily calcium intake is higher and up to 1.3 gr/ day (A1).
2. In pregnant women with low calcium intake (less than 1 gr/day) at high risk for preeclampsia and arterial hypertension during pregnancy we recommend daily calcium intake of 1.5-2.0 gr/ day from the 20<sup>th</sup> week of gestation (A1).

#### Vitamin D

1. The minimum recommended vitamin D intake during pregnancy and lactation is 600 IU/ day through diet, sun exposure and/or supplements (A1).
2. The desirable range of 25(OH)D during pregnancy and lactation is 20-50 ng/ml (B2).
3. We recommend screening for vitamin D deficiency/insufficiency only in cases at high risk for low 25(OH)D levels, such as obesity, increase in body weight during pregnancy, low sun exposure, black race, special minorities, low compliance with vitamin D supplements

and birth at winter months (A1).

4. In cases of vitamin D insufficiency [(25(OH) D<20 ng/ml)] or deficiency [(25(OH) D<10 ng/ml)] we recommend treatment with vitamin D up to a dose of 4000 IU/ day. The safety of higher doses of vitamin D is not adequately studied (A1).
5. The positive effects of systemic vitamin D administration during pregnancy and lactation on maternal outcomes (preeclampsia, gestational hypertension, gestational diabetes, preterm labor, etc.) or neonatal/infant outcomes (low birth weight, small for gestational age, bone mineral content, etc.) are not adequately established.

## CALCIUM AND VITAMIN D IN PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD)

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Calcium and vitamin D play a central role in skeletal health of patients with chronic kidney disease, as well as in the general population. Main indications of Ca and vitamin D chronic administration are so far: secondary hyperparathyroidism suppression, treatment of hypocalcemia, management of osteoporosis along with anti-osteoporotic agents in CKD stage I-IIIb and hyperphosphoremia (calcium alone taken during meals as phosphate binder).

Vitamin D deficiency is prevalent in CKD patients. It is related to bone demineralization, hyperparathyroidism and increased osteoclastic activity. Utility of vitamin D for secondary hyperparathyroidism suppression is controversial. Failure of conversion into its active form, calcitriol, due to lack of 1 $\alpha$  hydroxylase and extremely low activation of VDR are the main drawbacks. As a matter of fact, recent meta-analysis showed that, although vitamin D administration can achieve 25(OH)D repletion, is ineffective in PTH-lowering.

Vitamin D deficiency is also related to high cardiovascular morbidity and mortality, immune dysfunction and predisposition to infection, reduced muscle strength, high arterial stiffness, left ventricular hypertrophy and anemia. However, recent interventional randomized trials are negative. No single prospective study has shown positive result in hard (survival and hospitalization) and in surrogate outcomes.

This lack of effectiveness can be ascribed to the fact that entry levels of 25(OH)D were not low enough, short follow up for so long-standing conditions, such as cardiovascular disease and the need for higher dose of vitamin D in order to overcome 1- $\alpha$  hydroxylation deficiency.

Once thought negative calcium balance and phosphate retention lead to widespread use of calcium, as a phosphate binder. In addition, it was believed that could safely suppress secondary hyperparathyroidism.

On the contrary, recent studies revealed that calcium

balance is usually neutral and can be positive with even modest use of calcium in CKD patients. Extra calcium is toxic and could lead to detrimental consequences, as low bone turn over and extraskeletal calcifications. The latter can be manifested as increased coronary calcium score, arteriosclerosis, increased arterial stiffness and calciphylaxis. Calcium toxicity is common both in low and in high rate of bone metabolism.

Taken the above into consideration, recent KDIGO (Kidney Disease: Improving Global Outcomes) guidelines suggested, among others:

1. nutritional D supplementation in CKD patients as in general population but vitamin D administration solely for suppression of secondary hyperparathyroidism is discouraged,
2. avoiding hypercalcemia and correction of hypocalcemia close to low normal values and use of calcium containing phosphate binder only in persistent hyperphosphoremia,
3. suppression of secondary hyperparathyroidism only if it is severe and in latest stages, because it is considered as compensatory.

## CERTAINTIES AND DOUBTS FOR BIPHOSPHONATES DRUG HOLIDAYS

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Osteoporosis treatments reduce the risk of fractures by 30-50%. Drug holiday, a period with no active treatment, is part of routine management. The pharmacological properties of bisphosphonates, which are considered the mainstay of anti-resorptive treatment for osteoporosis, due to their high binding affinity to bone mineral, and long retention in the skeleton provide unique opportunities unlike all the other drugs used to treat osteoporosis, since the effects of bisphosphonates on bone remodeling persist after stopping therapy.

Fracture protection starts within the first few months after initiating treatment with osteoporosis and persist throughout the treatment period. Uninterrupted treatment with bisphosphonates for 3-5 years should be strongly encouraged for the majority of osteoporotic patients in the absence of intolerance or side effects, since the risk of debilitating complications of long term treatment such as atypical femoral fractures and osteonecrosis of the jaw, are very low during the first 5 years of treatment. After that period of 3-5 years, the decision about whether to continue or to temporarily discontinue bisphosphonates can be re-addressed depending on the severity of osteoporosis and the presence of fragility fractures.

There are few data available for assessing the efficacy of long-term bisphosphonate use (>5 years) in reducing the risk

of fractures. The bulk of the evidence regarding continuing treatment beyond 5 years derives from the Fracture Intervention Trial Long-Term Extension (FLEX), which randomly assigned 1099 postmenopausal women who had previously received an average of 5 years of daily alendronate therapy to continued alendronate treatment or placebo for an additional 5 years. The other relevant randomized trial, the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Extension trial, used a similar design with a shorter treatment period (3 years of treatment followed by 3 years of placebo or active extension). Both studies showed significant reductions in the risk of vertebral fracture with continuation of bisphosphonate treatment and neither of them showed significant reductions in non-vertebral fractures.

However, not all bisphosphonates are alike, so recommendations for discontinuation of bisphosphonates need to be drug-specific.

## UNCERTAINTIES REGARDING DENOSUMAB DISCONTINUATION IN PATIENTS WITH OSTEOPOROSIS

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In contrast to bisphosphonates, denosumab, a human RANKL monoclonal antibody approved for the treatment of osteoporosis, is not incorporated into the skeleton, and thus its pronounced effects on the osteoclastic activity do not extend beyond six months. At this time-point, bone remodeling appears to resume, as evidenced in the bone turnover markers (BTM). In specific, not only BTMs do increase, they are reported to be at even higher levels than baseline. This is at least the case for bone-specific alkaline phosphatase and carboxy-terminal collagen crosslinks (CTX) levels, with the latter reported to be a >50% from baseline at six months after discontinuation and considered to be a result of synchronous, concurrent activation of bone modeling units (BMU) associated with a lack of microcracking repair, as opposed to the asynchronous BMU activity reported in osteoporosis. This state of accelerated bone turnover after denosumab discontinuation may result in net bone loss, reflected in (both lumbar spine and total hip) bone mineral density decrease to the baseline.

Apart from urging persistence and adherence to treatment recommendations when denosumab is prescribed, this bone loss following denosumab discontinuation is an alarming observation, since it might be associated with a parallel increase in the risk of osteoporotic fractures. In fact, several independent reports of spontaneous osteoporotic fractures following denosumab discontinuation are evidenced in the literature from early 2016. Notably, in a small case-series, three cases of women with postmenopausal osteoporosis

and no previous fractures were reported to suffer from spontaneous vertebral fractures following denosumab discontinuation. Another women with postmenopausal osteoporosis and no previous fractures, outlined in an independent report, suffered multiple vertebral fractures following denosumab discontinuation. Two additional cases of clinical vertebral fractures following denosumab discontinuation were reported, followed by a case-series of nine women with similar clinical course. In the latter case-series, an early pattern of multiple vertebral fractures (mean: 5.5 fractures) began to emerge, fractures observed shortly after treatment discontinuation (9-16 months) in patients at presumably low risk for fractures. These findings were corroborated in a multicenter study from Israel, in which 36 clinical fractures in nine patients were reported. In a systematic review in 2017, a total of 112 fractures (mainly in twelfth thoracic and first lumbar vertebrae) were described in 24 cases with postmenopausal osteoporosis, a quarter of whom were on aromatase inhibitor therapy. In an extension study of a phase 2 trial, a total of 10% of patients experienced multiple fractures after denosumab discontinuation and in a post-hoc analysis of the FREEDOM trial, the rate was estimated to be 7.0 per person-years and even greater in those with a history of fracture. Several attempts to identify those at rebound-associated risk have been proposed, yet a universally recommended strategy is still lacking. However, a rapid transition to an alternative antiresorptive treatment is advocated and BTM change may provide a safe monitoring tool to individualize intervention.

## ANABOLIC TREATMENT OF OSTEOPOROSIS TODAY

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Teriparatide is the only available anabolic treatment for osteoporosis in Greece, for the moment. It is approved for the treatment of established postmenopausal osteoporosis since 2003, for male osteoporosis also since 2007, for the treatment of osteoporosis due to corticosteroids since 2008, as of duration of treatment for up to 24 months since 2009.

Two more anabolic drugs are expected: The first is abaloparatide (a PTHrP peptide with 34 amino acids, 13 of them common with teriparatide), already approved by FDA since April 2017, but with negative trend vote from the CHMP of EMA in July '18. The second is romosozumab (humanized monoclonal antibody targeting sclerostin), with a still pending application to FDA since July 2016.

Results of scientific research are getting richer as time goes by, about teriparatide, especially concerning real-world effectiveness. Having treated more than a million females over 65 years old for two years, teriparatide succeeded to

reduce clinical vertebral fractures by 72%, while zoledronic acid 50%, denosumab 45% and oral BPs 24%. (Arch Osteopor 2018, 13:33).

It is well known that non-vertebral fractures are the most difficult target of every antiosteoporotic treatment. Especially hip fracture, a global "killer", was not possible to be proven less frequent with teriparatide in the original trial (Neer RM., N Engl J Med 2001), due to the small number of patients. Real-world clinical practice (8828 patients) proved high effectiveness of teriparatide in reducing hip fractures after the first 18 months of treatment (85.2%) comparing with the first 6 months of treatment (Calcif Tis Int, on line 20 Oct. 2018). Similar results are available in another study (Bone 120, 2019, 1-8), a systematic review and meta-analysis, showing a 56% reduction of hip fractures with teriparatide treatment. Statistical significance of reducing upper limb fractures, in the same study, was not achieved by little.

Teriparatide is a "worth-paying-for" drug in patients with T-score < -2.5 and at least 1 fracture (established osteoporosis) in different ages in proportion with the "worth to pay per QALY gained" amount of money. In Greece, were the "worth to pay per QALY gained" is 30.000 €, this age is >73.

Large meta-analysis of the literature (1996-2014) is published (Menopause 2015, 22 (9):1021-1025), trying to compare (indirectly) the prevention of vertebral and non-vertebral fractures achieved with teriparatide, denosumab and oral BPs. Higher reduction of vertebral fractures was seen with denosumab (66%) close only with teriparatide (64%) but not with BPs (52% to 45%), while for nonvertebral fractures teriparatide being far ahead with 36% reduction and every other drug achieving reductions less than half (18%).

Direct comparison of teriparatide with a potent oral bisphosphonate (risedronate) was made in VERO study. The 2-year, randomized, double-blind, active-controlled fracture endpoint VERO study included postmenopausal women with established osteoporosis, who had at least 2 moderate or 1 severe baseline vertebral fractures (VFX), and bone mineral density (BMD) T-score -1.5. A total of 1360 women were randomized and treated (680 per group). Mean age was 72.1 years. After two years of treatment, comparing to risedronate group, teriparatide group had a 56% reduction of new vertebral fractures.

Since both antiresorptive and anabolic drugs are disposed, sequential and combined use of them must be tested. This was the purpose of D ATA-Switch study (Lancet, 2015). In this study three groups of patients were treated in three different ways: The first took teriparatide for two years, followed by two years of denosumab. The second group made the opposite and the third group took both drugs for two years followed by two years of denosumab alone. BMD of the spine, hip and radius was followed every 6 months. As a result, teriparatide does not adequately prevent bone loss after denosumab, whereas denosumab stabilizes and

further increases bone mineral density when used after teriparatide or combination therapy. In the discussion of the study, the authors pointed out: These results should influence the approach to the initial and sequential treatment of osteoporotic women, particularly those with established disease who are at an acutely high risk of fragility fracture. Comparing indirectly, efficacy, safety and tolerability of the above mentioned osteoanabolic drugs, we can point out in a recent study (JEndo Soc 2018, 2 (8) 922-932): Teriparatide (65%), abaloparatide (86%) and romosozumab (75%) reduced vertebral fractures, whereas teriparatide (53%) and abaloparatide (43%) reduced non-vertebral fractures, according to their basic trials (FPT, ACTIVE and FRAME).

Concerning teriparatide, as it is the only anabolic drug in use for now, safety and tolerability were checked: In the 2001 Fracture Prevention Trial, teriparatide compared with placebo resulted in greater dizziness (9% vs 6%), leg cramps (3% vs 1%), and hypercalcemia (11% vs 2%). The majority of incidences of hypercalcemia were <1 mg/dL above the laboratory's reference range. Women who did not develop hypercalcemia within the first 6 months of teriparatide seldom developed hypercalcemia thereafter. Orthostatic hypotension rarely occurred after the initial dose. There have only been three reported cases of osteosarcoma among the more than one million worldwide patients who have received teriparatide, a rate that does not exceed the expected incidence of osteosarcoma in the general population.

Given that use of anabolic treatment is limited to 2 years, it should always be followed by antiresorptive treatment. Emerging research suggests a potential role of anabolic agents in the treatment of delayed fracture healing, although more randomized, placebo-controlled studies are needed. In general, teriparatide patients never had life threatening events due to the use of the drug, unlike other drugs used in osteoporosis (Reumatismo, 2013, 65 (4), 143-166).

Deep inspection of the literature is driving to the conclusion of the authors of a recent study (JBMR, 32, 2, 2017, 198-202): "In cases where patients are treatment naive, initiation of anabolic therapy first is suggested, followed by potent antiresorptive therapy whenever possible". In the same study, the authors also concluded that: "An extremely important clinical issue is the patient who is currently being treated with a bisphosphonate or denosumab who sustains a hip fracture. The transition to TPTD might in fact lead to a transient loss of strength in cortical sites, including the other hip. This is critically important in patients with a recent fracture where we know the risk of a second imminent fracture is extremely high (10% in the following year). In cases such as these, we suggest consideration of combination treatment with utilization of potent antiresorptive therapy and addition of TPTD, for up to 2 years, to improve skeletal strength during this critical period".

Hellenic Society for the Study of Bone Metabolism formulated and published "Guidelines for the diagnosis and treatment of osteoporosis 2018", approved by the Central Council

of Health and used by the Ministry of Health to update the electronic recipe-writing algorithm. In this guidelines is defined the patient to start treatment with teriparatide, if possible: T-score < -3.0 after a hip or vertebral or two other fractures.

Anabolic treatment today remains a valuable tool to treat severe osteoporosis, only because its high cost, otherwise should be first choice for most of the patients.

## THE MOST INTERESTING ARTICLES OF 2018 REGARDING OSTEOPOROSIS TREATMENT

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**Vitamin D supplements:** Bolland et al., aimed to clarify the effects of vitamin D supplementation on musculoskeletal health by conducting a systematic review, random-effects meta-analysis, and trial sequential analysis of published randomized controlled trials (RCTs), thus providing the highest level of medical evidence in this regard<sup>1</sup>. Authors found that vitamin D supplementation did not prevent total or hip fractures [relative risk (RR) 1.00, 95% CI 0.93-1.07 and 1.11, 0.97-1.26, respectively], or falls (RR 0.97, 0.93-1.02), or have had a significant effect on bone mineral density (BMD) at any site. Furthermore, they found no differences between higher (>800 IU) and lower doses of vitamin D. Authors propose that clinical guidelines should be modified in light of these results.

**Currently available agents:** In the ACTIVEExtend trial, treatment with alendronate for 24 months following 18 months of abaloparatide or placebo in women with postmenopausal osteoporosis further increased BMD at all measured sites and resulted in a cumulative reduction in the risk of new vertebral fractures by 84%, non-vertebral fractures by 39%, clinical fractures by 34%, and major osteoporotic fractures by 50%<sup>2</sup>.

In an RCT comparing the 12-month skeletal effects of denosumab versus risedronate in patients with glucocorticoid-induced osteoporosis<sup>3</sup>, denosumab achieved larger BTM suppression and greater BMD increases at the LS and the TH of both patients initiating glucocorticoids (3.8 vs. 0.8% and 1.7 vs. 0.2%, respectively) and patients on glucocorticoids (4.4 vs. 2.3% and 2.1 vs. 0.6%, respectively).

A recent RCT from Australia challenges current guidelines on who should be treated for fracture prevention<sup>4</sup>. The researchers administered zoledronic acid or placebo every 18 months for a study period of six years in postmenopausal women older than 65 years of age with hip osteopenia and a FRAX score below the current thresholds for treatment initiation. Zoledronic acid was proved beneficial for the studied population, achieving a significant reduction in the risk of both vertebral [Hazard Ratio (HR) 0.45, 95% CI 0.27-0.73] and non-vertebral fractures (HR 0.66, 0.51-0.85),

despite the longer than usual interval between infusions (18 instead of 12 months) and the non-administration of calcium supplements. Of note, safety data suggested a reduced incidence of cancer, coronary heart disease, and death.

**Agents pending approval:** McClung et al., published the results of a phase 2 RCT on the effects of 24 months of romosozumab or placebo or 12 months of alendronate followed by another 12 months of romosozumab, followed by 12 months of denosumab or placebo on lumbar spine (LS) and total hip (TH) BMD of postmenopausal women with low bone mass<sup>5</sup>. Romosozumab achieved remarkable increases of BMD at the LS and TH during the 1<sup>st</sup> year of treatment (11.3% and 4.1%, respectively), more modest increases during the 2<sup>nd</sup> year (3.8% and 1.3%, respectively) while sequential treatment with denosumab during the 3<sup>rd</sup> year resulted in additional increases (2.6% and 1.9%, respectively). In the subgroup treated with alendronate for the 1<sup>st</sup> year, sequential treatment with romosozumab during the 2<sup>nd</sup> year resulted in additional increases at the LS and TH (5.0% and 0.7%, respectively). BMD gains were rapidly lost in the group transitioning to placebo during the 3<sup>rd</sup> year of the study (losses of 9.3% at the LS and 5.4% at the TH). Bone turnover markers (BTM) remained below baseline levels during the 2<sup>nd</sup> year of romosozumab treatment indicating a sustained antiresorptive effect.

Similar results were obtained from the phase 3 RCT evaluating the effect of 12 months of romosozumab or placebo in men with osteoporosis<sup>6</sup>. BMD increased by 12.1% at the LS and 2.5% at the TH irrespectively of baseline testosterone levels, T-score, age or the 10-year fracture risk. A numerical imbalance in cardiovascular serious adverse events was also reported.

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## IS THERE ANY CORRELATION BETWEEN OSTEOPOROSIS AND CARDIOVASCULAR DISEASE?

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Osteoporotic fractures and cardiovascular disease (CVD) are important causes of morbidity, mortality and disability among the elderly. These two conditions were considered unrelated and their coexistence has been attributed to independent processes exclusively related to age. However there is an increasing number of evidence supporting the link between these two conditions that cannot be explained by age alone. Many epidemiological studies have indicated an association between osteoporosis and CVD. Prevalent CVD and atherosclerosis have been found to be related to low bone mass and increased fracture risk. Similarly, low BMD (Bone Mineral Density) has been related to increased cardiovascular risk. Recent evidence suggests a direct association, independent of age and inactivity, between Osteoporosis and CVD. Several hypotheses have been proposed to explain the link between these two degenerative processes, Atherosclerosis (CVD) and Osteoporosis (Osteoporotic Fractures). They have causal association, they share common pathophysiological mechanisms and common risk and genetic factors.

Vascular calcification and bone mineralization share a number of interesting anatomical and pathophysiological common features. The calcification of the arterial tissue is highly organized and regulated by mechanisms similar to those involved in bone mineralization. Vascular calcification is an active process, regulated by factors involved in the process of osteogenesis e.g Bone Morphogenetic Protein, Alkaline Phosphatase, Osteopontin etc. Osteoporosis and CVD share common etiologic factors besides age, such as Smoking, Physical activity, Alcohol consumption, Estrogen deficiency, Hypertension, Vitamin K deficiency, Vitamin D metabolism, Hyperparathyroidism, Homocysteine etc., which can simultaneously promote or inhibit atherosclerosis and bone demineralization. Oxidative stress is associated with decrease of  $\beta$ -cell mass and glucose handling and increase of gluconeogenesis, LDL cholesterol, atherosclerosis and blood pressure. On the other hand oxidative stress is associated with decrease of osteoblastogenesis and increase of osteoclastogenesis and apoptosis of osteoblasts resulting in reduce bone mass and osteoporosis.

Atherogenesis and bone loss have in common genetic factors such as mutations in genes related to the osteoprotegerin,



the Gla protein of matrix, the apolipoprotein E, the LRP6 or LRP5. For example, the LRP6 or LRP5 mutations are associated with early CAD, hypertension, hyperlipidemia (LDL and TGs), diabetes mellitus, and osteoporosis.

Finally evidence that some medications such as statins, insulin, antihypertensives, raloxifene and bisphosphonates are effective on both osteoporosis and cardiovascular disease, suggests a common pathophysiological basis. Experimental studies in mice have shown that bisphosphonates, widely used as treatment of osteoporosis and prevention of risk of fracture, also inhibit the atherosclerotic process, acting on blood pressure and ventricular hypertrophy. Oral bisphosphonates are also associated with a reduction in the risk of death in the elderly men and women, and were found to reduce all-cause and post-fracture mortality risk (CaMos study).

In conclusion, the association between osteoporosis and cardiovascular disease could allow an early identification of patients at high risk and may set the stage for dual-purpose preventive and therapeutic interventions aimed at reducing bone loss - Osteoporosis and the progression of atherosclerosis - CVD.

## DRUGS OF CARDIOVASCULAR SYSTEM AND BONE METABOLISM

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Bone metabolism is closely regulated by hormones and cytokines, which have effects on both bone resorption and deposition. Renin-angiotensin system (RAS) has been known to play an important role in bone metabolism. Especially, angiotensin II induces the differentiation and activation of osteoclasts (which are responsible for bone resorption) and the expression of RANKL (receptor activator of NF-kappa ligand) in osteoblasts, leading to the activation of osteoclasts. These effects of angiotensin II are completely blocked by an angiotensin II type 1 receptor blockade. Finally, the use of angiotensin-converting enzyme inhibitors might have a small but significant risk effect on fractures, especially for the over 65-year-old users.

Statin treatment may be associated with a decreased risk of overall fractures and hip fractures, an increased BMD at the total hip, BMD at the lumbar spine, and osteocalcin. Moreover, statin use may have a greater effect on male patients than on female patients. The osteoprotective effect of statins seemed to be more prominent with a dependency on the cumulative dosage and statin intensity.

Beta-blockers are associated with a reduction in fracture risk and higher BMD. Despite of them the inconsistency of the available clinical data means that the effects of b-blockers on bone in humans remains an open question. These data do not provide support for concluding that b-blocker use

is an important factor to be considered when assessing an individual's future fracture risk nor that they should be deployed at this time as therapeutic agents.

Moreover, cardiac arrhythmias and osteoporotic fractures are common in the elderly. Special attention should be paid to patients on treatment with amiodarone and/or a diagnosis of atrial fibrillation as they may have an increased risk of fracture. Conversely, treatment with digoxin may reduce fracture risk.

Treatment with nitrates is associated with a decreased risk of fracture. The risk of a hip fracture was significantly lower among users of as-needed organic nitrates, when compared with users of maintenance medication. Further studies should determine whether a causal relationship exists.

Treatment with diuretics may affect calcium homeostasis and bone metabolism. On one hand, thiazide diuretics reduce, whereas loop diuretics (LDs) increase, renal calcium excretion, decrease BMD and are associated with a higher risk of hip fracture. Several studies have indicated that treatment with thiazides may exert positive effects on bone with an increased BMD and a decreased fracture risk. The protective effect disappears within 4 months after use is discontinued.

Osteopenia is a major concern of long-term heparin therapy. Long-term heparin treatment during pregnancy is associated with a small but significant decrease in BMD at the lumbar spine and neck of femur. Moreover, long-term use of warfarin was associated with osteoporotic fractures, at least in men with atrial fibrillation. Furthermore, switching to rivaroxaban from warfarin in patients with atrial fibrillation was associated with an increase of bone formation markers and a decrease of bone resorption markers.

## CURRENT ADVANCES IN PHOSPHATE METABOLISM

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Phosphorus plays an important role in growth, development, and maintenance of skeletal integrity. It plays also critical role in acid-base regulation and cellular metabolism. Inorganic phosphorus exists primarily as structural ion, phosphate (PO<sub>4</sub>), which serves as a constituent of hydroxyapatite, the mineral basis of the skeleton, while at the molecular level provides the molecular axis of DNA.

It is now clear that the skeleton, the kidney, and the intestine co-operate to maintain proper serum phosphate concentrations, with the kidney being the main site for minute-to-minute regulation. Several hormones are able to modulate phosphate reabsorption by the kidney. Among these FGF23, PTH, PTHrP, calcitonin, atrial natriuretic peptide, acidosis, TGFβ, glucocorticoids, hypercalcemia, and phosphate loading. In contrast, IGF-1, growth hormone,

insulin, thyroid hormone, EGF, alkalosis, hypocalcaemia, and phosphate depletion stimulate renal phosphate reabsorption. Genetic studies in primary disorders of phosphate metabolism have led to the isolation of novel genes and new roles for existing proteins in the control of renal phosphate handling, such as fibroblast growth factor-23 (FGF23) and its processing systems, the co-receptor  $\alpha$ -Klotho and phosphate transporters. Traditionally, the parathyroid hormone (PTH)/vitamin D axis provided the conceptual framework to understand mineral metabolism. Fibroblast growth factor 23 (FGF23) is a circulating protein secreted by osteocytes/osteoblasts that is essential for phosphate homeostasis. Interestingly, many of the proteins involved in phosphate regulation are secreted by the osteocyte, including: 1) PHEX, which regulates FGF23 secretion, with loss-of-function resulting in elevated circulating FGF23; 2) DMP1, a SIBLING protein, in which loss-of-function also results in elevated circulating FGF23; 3) FGF23 itself, and 4) FGFR1 which appears to be activated in osteocytes resulting in elevated FGF23 expression. FGF23 inhibits renal tubular phosphate reabsorption and suppress circulating  $1,25(\text{OH})_2\text{-D}$  levels by decreasing Cyp27b1-mediated formation and stimulating Cyp24-mediated catabolism of  $1,25(\text{OH})_2\text{-D}$ . Excess production of FGF23 cause renal phosphate wasting and suppression of circulating  $1,25(\text{OH})_2\text{D}_3$  and are associated with several hereditary hypophosphatemic disorders with skeletal abnormalities, including X-linked hypophosphatemic rickets (XLH) and autosomal recessive hypophosphatemic rickets (ARHR).

Until recently, therapeutic approaches to these diseases were limited to treatment with active vitamin D analogues and phosphate supplementation, often merely resulting in partial correction of the skeletal aberrations. Recent studies, using of FGFR inhibitors for the treatment of FGF23-mediated hypophosphatemic disorders showed, in two different hypophosphatemic mouse models, Hyp and Dmp1-null mice, resembling the human diseases XLH and ARHR, that pharmacological inhibition of FGFRs efficiently abrogates aberrant FGF23 signalling and normalizes the hypophosphatemic and hypercalcaemic conditions of these mice. Correspondingly, long-term FGFR inhibition in Hyp mice leads to enhanced bone growth, increased mineralization, and reorganization of the disturbed growth plate structure. In addition, several additional clinical trials indicated that a humanized anti-FGF23 antibody increased serum phosphate and improved quality of life in patients with XLH. Furthermore, circulatory FGF23 is high in patients with chronic kidney disease (CKD). Many epidemiological studies indicated the association between high FGF23 levels and various adverse events especially in patients with CKD. However, it is not yet known whether the inhibition of FGF23 activity in patients with CKD is beneficial for these patients.

## NONALCOHOLIC FATTY LIVER DISEASE AND BONE METABOLISM

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Nonalcoholic fatty liver disease (NAFLD) is a global public health concern, affecting approximately 25-30% of the general population. NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), characterized by inflammation and fibrosis, and may progress to NASH-related cirrhosis and hepatocellular carcinoma. Since insulin resistance (IR) is a key contributor to the pathogenesis of NAFLD, NAFLD prevalence increases in parallel with the epidemics of obesity and type 2 diabetes mellitus (T2DM) and is associated with cardiovascular disease. NAFLD has also been linked to impaired bone metabolism, although data remain controversial and the mechanisms linking them are still poorly understood.

Given that both osteoporosis and NAFLD are highly prevalent diseases, they may coexist by a simple coincidence, or they may have common predisposing factor(s). For example, sarcopenic obesity predisposes to both osteoporosis and NAFLD, as well as the glucocorticoid treatment. However, there is increasing evidence favouring direct bidirectional interplay between hepatic and bone metabolism: hepatic metabolism may affect bone metabolism and vice versa.

Experimental data have shown complex interactions between the liver, adipose tissue and bone, which mutually modulate the function of each other. Dysregulation of liver - adipose tissue - bone interactions may predispose to the development of obesity, T2DM, NAFLD and osteoporosis. IR has been proposed to play a critical role in this cross-talk. Core experimental evidence towards bone-liver interaction has been published by Fulzele et al. who showed that mice harboring selective osteoblast deletion of the insulin receptor developed IR, obesity, NAFLD and osteopenia, alterations that were all reversed by the administration of osteocalcin. Other factors may also lie at the intersection of hepatic and bone metabolism, including the secretion of pro-inflammatory, pro-coagulant and pro-fibrogenic hepatokines, cytokines and interleukins from the inflamed liver, the secretion of bone-specific hormones and myokines from the impaired musculoskeletal system, and vitamin D deficiency.

In clinical terms, some, but not all, observational (cross-sectional and case-control) studies have shown higher rates of low bone mineral density (BMD) in NAFLD patients than controls, in children and adults. More importantly, at least three cohort studies reported inverse association between BMD and NAFLD, although this association was limited to men, but not postmenopausal women. Core clinical evidence towards bone-liver interaction is the paradigm of thiazolidinediones (TZDs). TZDs are beneficial for the treatment of NAFLD, mainly by increasing adiponectin and

decreasing IR. Nonetheless, they have been associated with bone loss and increased risk of fractures in some studies. In conclusion, NAFLD and osteoporosis are highly prevalent chronic diseases, with serious individual and public health consequences and financial burden. Deeper knowledge of their potential mutual interactions may result not only in better understanding of their pathophysiology, but may also render their treatment more efficient and safer. Ideally, common medications may benefit both diseases, but, most importantly, medications used for the treatment of either with a possible adverse effect on the other one may be avoided.

## HORMONE REPLACEMENT THERAPY - THE LATEST DATA

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Hormone therapy was prescribed for prevention of menopause consequences such as osteoporosis, cardiovascular disease, cognitive impairment, some types of cancers and for menopause symptoms (hot flushes and vaginal dryness).

After publication of the women's Health initiative (WHI) in 2002, prescriptions for HRT have decreased.

A review from the US Preventive Services Task Force on the benefits and harmful effects of hormone therapy included 18 trials which provided data on 40058 perimenopausal and postmenopausal women. The duration of follow-up in the trials was 3.5 years and the women's age participating in trials ranged from 53 to 79 years.

Hormone therapy has various forms and doses. Women who have had hysterectomies take only estrogen, whereas women who have not had hysterectomies use a combination of estrogen plus progestin to prevent endometrial hyperplasia and endometrial cancer.

The risks for diabetes, osteoporotic fractures and long-term risk for invasive breast cancer were statistically significantly reduced for women using estrogen only. There is not statistically significant reductions in risks of lung cancer, coronary heart disease, colorectal cancer, dementia. The beneficial effects did not persist after stopping estrogen therapy except of the risk for breast cancer. Estrogen only therapy led to a statistically significant increase in the risk of stroke, venous thromboembolism, gallbladder disease and urinary incontinence.

As far as women using combination therapy (estrogen plus progestin) are concerned, the risks for osteoporotic fractures, diabetes and colorectal cancer were statistically significantly reduced, compared to women on a placebo therapy. No statistically significant differences were found for endometrial cancer, cervical cancer, ovarian cancer and lung cancer.

The harmful effects of combination therapy are the increase

of risks for invasive breast cancer, stroke, gallbladder disease, venous thromboembolism, urinary incontinence.

Observational and randomized controlled trials showed differential effects of HRT on CVD risk. Observational studies suggested benefit whereas randomized studies showed harm particularly in elderly women. A 2015 meta-analysis of 19 trials of oral HT in 40,000 postmenopausal women performed subgroup analyses in women who started HT less than 10 years after menopause. This meta-analysis showed an extremely low risk of CHD and a lower mortality rate. The "timing hypothesis" proposes that HRT started in the perimenopausal or early postmenopausal period is cardioprotective whereas HRT which begun later, thus after menopause increases the CVD risk.

Among healthy women between the ages of 50-59 years taking estrogen only or combined therapy, the only significant side effect is increased incidence of venous thromboembolism in those taking combined HRT. Absolute risk of thromboembolism is very low at 0.5% for a woman taking combined hormone therapy for 5 years whereas for women taking estrogen only for 5 to 6 years, which, on the contrary, appears relatively safe and may offer some benefits. Younger healthy women (<60 years) have favourable risk-benefit profile when use HRT at the onset of menopause. Hormone therapy is not indicated for primary prevention of chronic conditions related to menopause. Treatment of vasomotor menopause symptoms remains the primary indication for hormone therapy.

## ADVANCES IN PAGET'S DISEASE

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Paget disease of bone is a disorder of bone metabolism, characterized by an increase of bone remodeling. Although being the second commoner metabolic bone disease following osteoporosis, its prevalence is approximately 3%, which increases with age. Many genetic factors have been implicated to the pathogenesis of Paget disease. Among them are the TNFRSF11A (RANK-RANKL pathway) and the SQSTM1 genes (ubiquitin binding protein sequestosome-1). Viral infection, such as measles, has been suggested as well. Paget disease's main clinical phenotypes are a) asymptomatic (the majority of the cases), b) pain and arthritis, c) bone deformity. Less common manifestations include fractures, disturbances in calcium and phosphate equilibrium and bone tumors. Paget disease may affect one (monostotic) or many (polyostotic) bones, such as the skull, vertebral spine, pelvis and long bones. The diagnosis depends on the clinical appearance. In asymptomatic cases, the diagnosis is made by a biochemical profile (key finding: increase in alkaline phosphatase) performed as a

routine procedure or by an imaging modality (key finding: characteristic changes in bone morphology) performed for another reason. The classic laboratory profile constitutes of increased concentrations of serum alkaline phosphatase (sAP), procollagen type I N-terminal propeptide (PINP), serum C-telopeptide (CTX), urinary N-telopeptide (NTx), and urinary hydroxyproline. Diagnostic imaging procedures include plain bone X-rays and bone scintigraphy, the latter being more sensitive but less specific compared with the former. The main treatment modality are nitrogen-containing bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid) given either *per os* or parenterally. Adequate supplementation of vitamin D and calcium must be ensured to avoid hypocalcemia. The periodic monitoring of the sAP assesses the response to treatment.

## THE EFFECT OF GUT MICROBIOTA ON BONE METABOLISM

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Gut microbiota refers to a cluster of 1000-5000 different species of bacteria, exceeding a number of  $10^{12}$ , located within the intestinal tract lumen. It is being developed since the endometrial life, under the influence of the maternal microbiota, and interacts with the human body, by affecting digestion of nutrients and protecting against infectious bacteria. Many factors contribute to its composition in later life, such as host's age, diet, genetics, status of the immune system, travelling, geography and medication. Gut microbiota has attracted interest during the last decade, since it has been implicated in the pathogenesis of a variety of human diseases, such as obesity, type 2 diabetes mellitus, rheumatoid arthritis and colorectal cancer. Accumulating data from experimental and human studies suggest also a potential pathogenetic role in metabolic bone diseases, such as osteoporosis. In particular, specific gut bacteria induce osteoclastogenesis by increasing the number of CD4<sup>+</sup> T-cells, which leads to increased production of inflammatory cytokines, such as tumor-necrosis factor alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6). Studies with germ-free animals (which are raised in a sterilized environment) have shown increased cortical and trabecular bone mass compared with those raised in conventional environments. However, others have not replicated these results. The main mechanisms of the effect of gut microbiota on bone metabolism include malabsorption of nutrients that are essential for bone mass (such as calcium, carbohydrates and vitamin K), through the disruption of intestinal mucosal barrier, and dysregulated immune response, either at a local or systematic level (characterized by increased production of TNF- $\alpha$ , IL-6 and neurotransmitters such as serotonin). Increased production of

TNF- $\alpha$  and IL-6 may also impair skeletal muscle performance and strength. Some gut bacteria, such as *Bifidobacterium* and *Lactobacillus reuteri* positively affect bone mass, by increasing calcium, phosphate and magnesium absorption and by secreting short-chain fatty acids, such as butyric acid, which stimulate bone formation. Interventional studies using probiotics mainly consisting of these two species, have shown an increase in bone mineral density (BMD) and protection from ovariectomy-induced bone loss in mice. Limited data from human studies supports a potentially beneficial role in bone metabolism, by reducing bone loss. However, inconsistency exists with regard to their effect on BMD in humans. Further studies of gut microgenome may elucidate its exact effect in bone metabolism and enhance its role in diagnosis and treatment of osteoporosis.

## EXTRA-SKELETAL ACTIONS OF VITAMIN D

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**Vitamin D** is a group of fat-soluble secosteroids that play a crucial role in calcium homeostasis and bone metabolism. However, they also have a number of extra-skeletal actions. Newer data and knowledge on vitamin D and its active metabolite 1,25(OH)<sub>2</sub>D<sub>3</sub>, known as calcitriol, have shown that it mediates its biological effects by binding to the vitamin D receptor (VDR). VDRs are expressed by at least 36 different type of cells in most organs, including the brain, heart, skin, gonads, prostate, and breast. These observations have led to the conclusion that Vitamin D exerts a number of other important actions apart from its vital role in bone remodelling. Furthermore, in addition to the endocrine production of calcitriol from the kidneys, it has been found that there is paracrine production of calcitriol in at least ten extra-renal loci. The currently accepted actions of vitamin D include immune effects, reduction of oxidative stress, neuro-protective actions, antimicrobial effects, anti-inflammatory and anti-neoplastic properties and cardiovascular benefits. More recent epidemiological studies have demonstrated the connection between low Vitamin D levels and a number of diseases, including total and cardiovascular mortality, various cancers and autoimmune conditions. Finally, low Vitamin D has a direct effect on falls and frailty on top of its indirect relevant effect linked to its role on bone metabolism. **Vitamin D and cancer:** Associations have been shown in observational studies between low vitamin D levels and the risk of development of certain cancers (mainly bowel, breast, prostate, lung and lymphomas). Vitamin D exerts its anticancer properties at various stages of cancer pathogenesis including proliferation, cells apoptosis, angiogenesis and metastases. However, the current evidence is not conclusive with regards to the optimal vitamin D levels in patients with cancer.

**Vitamin D and cardiovascular disease:** Vitamin D deficiency has been proven to contribute to endothelial inflammation and platelet dysfunction. Additionally, the VDRs are expressed directly at the myocardial cells and Vitamin D contributes to the blood pressure regulation through its effect on the renin - aldosterone system. All the above explain the hypothesis that low vitamin D is associated with a number of cardiovascular conditions including hypertension, ischaemic heart disease, cardiomyopathy and cardiac failure. Most of the available evidence at this stage points towards maintaining normal vitamin D levels in these patients, but it less clear if there is a meaningful reduce the risk of stroke, cerebrovascular disease, cardiac infarction, or ischaemic heart disease.

**Vitamin D, infection, autoimmunity and inflammation:** Vitamin D functions to activate the innate and dampen the adaptive immune systems. Deficiency has been linked to increased risk or severity of infections, including HIV, tuberculosis and respiratory tract infections. Tentative data link low levels of vitamin D to asthma, multiple sclerosis and inflammatory bowel disease.

**Vitamin D and other conditions:** Vitamin D deficiency has been linked with increased incidence or severity of type 1 diabetes, type 2 diabetes metabolic syndrome, renal disease and cognitive decline or dementia. However, it is less clear at this stage the extent of beneficial effect of vitamin D replacement therapy in these conditions.

In summary, it is clear that vitamin D receptors are expressed in many organs and tissues facilitating its extra-skeletal functions. Furthermore, there are several epidemiological studies linking vitamin D deficiency with a number of conditions. However, there are very few randomised controlled studies looking into the potential benefits of vitamin D replacement in the prevention of these conditions therefore further research is required.

## VITAMIN D AND MUSCULOSKELETAL SYSTEM

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The importance of vitamin D for musculoskeletal health is known. Several cases of young and older adults have been described in which prolonged vitamin D deficiency has been associated with severe muscle weakness, often resulting in a disability which improved after several weeks of vitamin D supplementation.

Vitamin D can act on the muscles in two ways, either through long-acting (classical or genomic action, including intracellular receptor binding and target gene activation), or through short-acting (non-genomic, the direct activation of signaling paths). Vitamin D status is estimated by measuring levels of 25 (OH) D (25-hydroxyvitamin D in plasma.) As evidenced by studies, the ideal concentration of 25 (OH) D is from 80 nmol/l and above. Values below 50 nmol/l indicate insufficiency and below 25 nmol/l severe deficiency. Risk for osteomalacia and severe proximal myopathy occur below 12 nmol/l.

Overall, seven studies showed positive correlation of vitamin D supplementation with muscle strength, body oscillation and/or body performance, while in nine studies the vitamin D levels had no effect on the assessed parameters. Since all studies evaluating the effect of vitamin D formulations on body oscillation and the TUG test had low plasma 25 (OH) D as inclusion criteria for subjects, the benefit of supplemental vitamin D was most apparent in people with vitamin D deficiency. However, it should be noted that many of the studies that failed to show a benefit included subjects with low plasma levels of 25 (OH) D, making it difficult to deduce clear conclusions on this issue. Overall, data from the RCT and meta-analyses support a positive effect of daily vitamin D supplementation on muscle function, especially in elderly subjects with vitamin D deficiency at baseline.