

Proceedings

Abstracts of the Panhellenic Conference of the Hellenic Osteoporosis Foundation

13th-15th September 2019, Volos, Greece

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SARCOPENIA-FALLS AND HIP FRACTURES

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Sarcopenia is the degenerative loss of skeletal muscle mass, quality, strength and functionality associated with aging. It is a component of the frailty syndrome. Severity of sarcopenia is associated with postural balance and falls especially among community older people. Falls of elderly people cause severe injuries such as femoral neck fracture and can lead the patient to become bed-ridden. Frailty, sarcopenia and falls are strongly correlated and both are predictors of negative health outcomes such as falls, disability, hospitalization and death. Multiple factors contribute collectively to frailty, sarcopenia and falls, which include cellular and tissue changes, as well as environmental and behavioral factors. Potentially treatable social factors are alcoholism, inability to shop, prepare and cook meals or to feed self, poverty, social isolation etc. Common medical factors are sensory impairment - vision/hearing, poorly managed pain, especially lower limb pain, thyroid disease, cardiac failure, gastrointestinal disease affecting absorption, poorer BMD and bone architecture, lack of vitamin D. More difficult to treat are cognition - dementia, catabolism, gastritis, cancer, mood- depression, paranoia, medications/polypharmacy. Measures of muscle strength and physical function may help discriminate the risk of falls-related hospitalization. For patient assessment muscle mass (BIA, DXA, anthropometry), muscle strength (handgrip strength, knee flexion/ extension, peak expiratory flow) and physical performance (Short Physical Performance Battery, usual gait speed, timed get up and go test) can be used. As the number of older people increases, their needs will become an increasingly important health

issue. Reduction in physical function can lead to loss of independence, need for hospital and long-term nursing home care and premature death. Prevention of sarcopenia and falls includes exercises, cognitive and physical training, dietary and psychological support. Additional research, preferably by means of controlled randomized trials, is needed to confirm these findings.

A COMPREHENSIVE MANAGEMENT OF SARCOPENIA AND BONE LOSS - OSTEOSARCOPENIA SCHOOL

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In older persons, the combination of osteopenia/osteoporosis and sarcopenia - known as osteosarcopenia - has been proposed as a subset of frailer individuals at higher risk of institutionalization, falls, and fractures. Osteosarcopenic patients have very particular clinical, biochemical, diagnostic, and functional characteristics that could be identified in clinical practice. In addition, new therapies targeting both muscle and bone are being developed. In this session, a clinical definition of osteosarcopenia aiming to describe the clinical, functional, and biochemical features that are unique to these patients will be presented. The use of imaging combined with functional assessments for the diagnosis of osteosarcopenia will be discussed. In addition, we will analyze preventive measures and therapeutic interventions that can benefit both muscle and bone simultaneously. We intend to go over the translational aspects of sarcopenia and osteoporosis research and highlight expected outcomes from different interventions for both conditions. Finally, the new holistic concept called Osteosarcopenia school will be presented.

ETIOPATHOGENESIS OF OSTEOARTHRITIS

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In the etiopathogenesis of osteoarthritis (OA) participate factors genetics, demographics (the increase of age, the female sex), the heavy professional or athletic activities and the trauma of musculoskeletal system, the smoking, the diet (the Mediterranean diet is related with the low risk as well as the better outcome of the disease) and the low levels of vitamin D of the serum (with higher risk and the worse progress of the disease). Important is the role of the increase secretion of the proinflammatory cytokines (as IL-1 β , IL-6, IL-15, IL-17, IL-18, TNF α , etc.) and the oxidative stress. The disturbance of the diversity of the enteric microbiota (dysbiosis) is also related with the high risk and the worse outcome of the OA. Also the use of probiotics and prebiotics can lead to decrease of the inflammation and the symptoms with amelioration of the functional ability of the patients.

SURGICAL ALGORITHM FOR THE TREATMENT OF ARTHRITIS KNEE IN YOUNG ADULTS

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Knee Osteoarthritis is a very common condition that occurs in the middle age mainly in women. When the condition progresses towards then the only therapeutic approach is the total knee replacement.

But when the condition occurs in young adults after an injury or pathological condition, the data changes and the therapeutic strategies include a multitude of interventions to which we will refer to this article.

Causes of cartilage injury are

- a. High-speed sports
- b. RTA
- c. Osteochondritis dissecans
- d. Other conditions

Arthroscopic classification by ICRS

- a. Grade 0: normal cartilage
- b. Grade I: Surface lesions
- c. Grade II: The depth of lesions reaches half of the thickness of the cartilage
- d. Grade III: The depth of lesions is more than half the thickness of the cartilage but does not reach the subchondral bone
- e. Grade IV: Lesions reach a subchondral plaque

Pathology

- a. The lesion of the articular cartilage is a permanent lesion
- b. The cartilage has no vascularity and no prospect of healing.
- c. Adult chondrocytes cells do not reproduce and migrate.

- d. The injury begins a cascade of events leading to degenerative joint disease.

- e. Accelerated in the end stage arthritis

Surgical intervention

It was launched with the application of arthroscopic techniques.

The invasive treatment include:

- a. Debridement
- b. Microfractures
- c. Subchondral drilling
- d. Osteochondral autografts
- e. Osteochondral allografts
- f. ACI
- g. Mosaicplasty
- h. Bio-Materials

Surgical interventions in the early stages have some position most involve removal of mechanical symptoms. All this performs a repair on the fibrous cartilage and may affect the integrity of the subchondral plate.

Cartilage Damage Treatment algorithm

- a. Grade I: Conservative treatment
- b. Grade II:
 1. Debridement
 2. Extensive rehabilitation program
- c. Grade III & Grade IV:
 1. Lesion < 1 cm: Monitoring or Microfractures
 2. Lesion 1-2 cm: Microfractures
 3. Lesion 1.5-4 cm: Mosaicplasty
 4. Lesion 3-10 cm: Autologous bone marrow transplantation (ACI, MACI), Osteochondral allografts.

Analysis of arthroscopic techniques

1. Arthroscopic Cleansing

Arthroscopic cleansing of the includes:

- a. Rinsing
- b. Partial meniscectomy
- c. Synovectomy
- d. Removal of the osteophytes or free loose bodies
- e. Shaving
- f. Chondroplasty

The objectives of arthroscopy are:

- a. The reduction of pain and symptoms
- b. The delay of partial or total arthroplasty

2. Advanced Techniques

- a. Marrow Stimulation Techniques (MST)
- b. Autologous Chondrocyte Implantation (ACI)
- c. Matrix induced Autologous Chondrocyte Implantation (MACI)
- d. Osteochondral Autografts Transplantation (OATS) - (Mosaicplast)
- e. Osteochondral Allograft Transplantation (cadaveric)

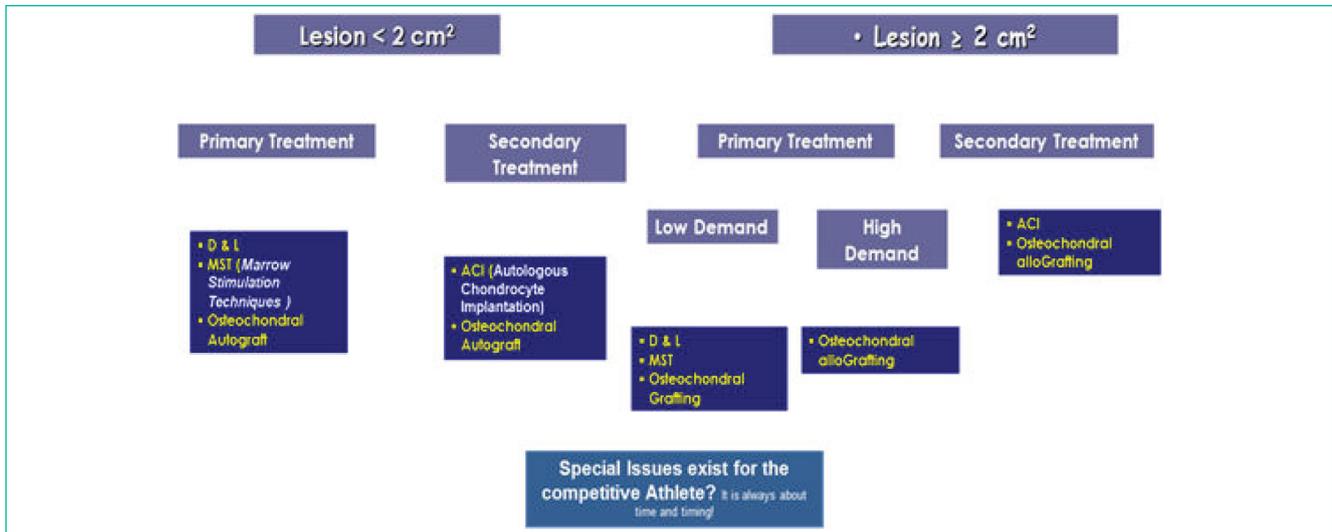


Figure. Cartilage lesions treatment algorithm in young adults.

Osteotomies

The treatment of choice of OA lesions of the knee with shaft deformities in young adults is the HTO. Coventry and Insall, refined and popularized the lateral closed wedge (HTO) in the high osteotomy of the tibia.

Indications

- a. Patients With Varus Limb Alignment
- b. Patients With Valgus Limb Alignment
- c. Osteochondritis Dissecans
- d. Medial compartment overload following meniscectomy
- e. Osteonecrosis
- f. Posterolateral Instability
- g. Osteochondral defects

Osteotomy Techniques are:

- a. Lateral closing wedge osteotomy
- b. Medial opening wedge osteotomy
- c. Dome osteotomy

Coventry report Outcome

- a. 5-year survival of 87%
- b. 10-year survival 66%
- c. However the 5-year survival was reduced down to 38% when valgus angulations was less than 8°

Outcome

- a. Obesity and inadequate correction are negative factors.
- b. Age < 50 years is a positive factor predictor
- c. Joint line preservation is the key to success.

Complications

- a. Inadequate valgus correction
- b. Overcorrection - PFJ derangement
- c. Alteration in patella height
- d. Intra-articular fracture
- e. Osteonecrosis of tibial plateau

- f. Vascular lesions - anterior tibial artery, perineal artery
- g. Peroneal nerve palsy
- h. Delayed or non-union
- i. Compartment syndrome
- j. TKR more difficult
- k. Varus laxity (loose LCL)

Epilogue

“From the time of Hippocrates to the present, it is universally permissible that cartilage ulcers are a problem and that something that was once destroyed, not repaired” HUNTER 1743.

THE ROLE AND RESPONSIBILITY OF ORTHOPAEDIC SURGEONS IN MANAGING OSTEOPOROSIS

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Osteoporosis has been recognized as a serious public health problem for the last 30 years. However, the push for orthopaedic surgeons to take an active role in the diagnosis and treatment of patients with osteoporotic fractures has been relatively recent. These patients are not seeking medical attention and therefore are not treated adequately, because there is little awareness among physicians and patients, insufficient rates of diagnosis and poor adherence to prescribed doses. Usually these patients present after they suffered a fracture, rendering secondary prevention the area in which orthopaedics exerts the greatest influence on patient care.

Although these fractures are associated with increased morbidity and mortality and their number is expected to increase dramatically over the next years, the majority

of patients are discharged without adequate evaluation of osteoporosis. Even though a prior fracture is one of the strongest risk factors for future fractures, most orthopaedic surgeons are afraid to take the responsibility for the treatment as they consider themselves acute care physicians and assume that the hospital or primary care physicians will, probably because they feel uncomfortable with medical management and the basics on bone metabolism.

As an orthopaedic surgeon is usually the first and only doctor the patient sees, he/she has certain responsibilities:

- To inform the patient for the need of an osteoporosis evaluation,
- To investigate whether osteoporosis is the underlying cause of the fracture,
- To ensure that appropriate intervention is started.

Proper education from the beginning of specialist training on bone metabolism is essential in the form of follow up with seminars for retention and application of knowledge. Unless treatment is contraindicated, any patient with fragility fracture and osteoporosis should be treated to reduce the risk of new fractures.

The underdiagnosis of fractures, delayed initiation of medical treatment, and the controversy as to which specialty should manage and monitor patients with osteoporosis, begs for implementation of the Fracture Liaison Service (FLS), involving a multidisciplinary team of healthcare professionals. A recent retrospective systematic review of 159 studies over the course of 15 years, comparing patients managed using the FLS to those managed without access to this service, found that FLS is superior in monitoring patients with DXA (48%-FLS group, 23.5%-controls), timely inception of medical therapy (38%-FLS group, 17.2%-controls), refracture rates (6.4%-FLS group, 13.4%-controls) and overall mortality (10.8%-FLS group, 15.8%-controls), hence reducing the number needed to treat (NNT) for the prevent refracture from 33 to 20.

MUSCULOSKELETAL INVOLVEMENT IN HAEMATOLOGICAL DISORDERS

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Various haematological diseases and their treatment modalities may result in musculoskeletal manifestations. Sometimes musculoskeletal (MS) symptoms (such as pain, swelling around a specific area: knee, hip, thigh or calf, etc) may be first appearance of underlying haematological disease.

Both benign and malign haematological disorders may have MS manifestations. The most common benign haematological

disorders having MS manifestations are haemophilia, sickle cell disease and thalasseмииs.

Haemophilia is the prototype disease of this group. It's an X-linked hereditary hematological disease related to the insufficiency of clotting factor VIII (Haemophilia A) or IX (Haemophilia B) and characterized by frequent bleeding episodes. More than 80% of bleeding episodes occur into joint cavities and 10% into fascial compartments. If the serum factor level is less than 1% of normal, patients may have spontaneous intra-articular or intra-muscular bleedings. Knee is the joint where intra-articular bleedings are most commonly seen. Ankle and elbow joints follow it. Hip and shoulder joints bleed less frequently. The reason why some particular joints bleed more frequently is not clear. However, some factors such as amount of synovial tissue (which is the most vascular tissue around any joint), volume of the joint cavity and biomechanical loads on the joint have been all proposed as possible reasons.

There are three stages in the evolution of hemophilic joint deterioration: acute frequent bleeding episodes, chronic hemophilic synovitis and chronic haemophilic arthropathy. Timely and effective intervention during first two stages may prevent the progression to last stage which leads to painful and functionally impaired joint(s).

Sickle cell disease is a group of hemoglobinopathies and its homozygous forms have more severe clinical appearance. Red blood cells with abnormal hemoglobin undergo sickling under hypoxia and (or stress. These sickled cells occlude small vessels and result in painful vaso-occlusive crises. In bone tissue avascular necrosis may develop among up to 50% of the patients. In advanced stages of AVN of femoral head, hip replacement surgery may be required. This surgery is highly complicated (both medical and surgical cx) and must be executed in close collaboration with hematology team.

Finally, thalassaemia is also a group of genetic blood disorder related to the mutation or deletion of hemoglobin gene. Skeletal changes in thalasseмииs are mainly caused by ineffective erythropoiesis. Bone marrow undergoes to hyperplasia, expands and results in cortical thinning. Weakened bone breaks easily, osteopenia and osteoporosis may develop. The iron overload caused by frequent transfusion to treat anemia also affects MS system and synovial and/or cartilage changes in large joints may develop.

In conclusion, both benign and malign haematological disorders may require orthopaedic surgical intervention related to the progressive bone and joint involvement. These are risky, highly complicated surgeries. The close collaboration with hematology team is of paramount importance. Patients and relatives should be informed during all the course of treatment. These surgeries must stay exclusive to the centers where multi-disciplinary team work on haematological disorders is available.

ART AND BONES. STUNNING CONTRIBUTION TO ART

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Throughout history, art in all its forms has been shaped by numerous and varied ideas, emotions, situations and notions. Art, which is inspired by, influenced by and deals with different objects (such as bones) and to which different social groups are drawn, has guided humankind towards lofty intellectual heights.

The difficult and time-consuming process of analysing emotions, ideas and thoughts requires communication, achieved through speech and writing. For our ancestors, this was a vital obligation and duty. Out of fear, insecurity, ignorance and the innate tendency to hope, they came up with religion. Thus, being naturally drawn to beauty, and spending time contemplating what made something beautiful, while also trying to better convey and depict their environment, they conceived Art and, through it, Image.

Speech, writing, religion, images and art (elements of philosophical inquiry) led to a “cultural revolution” (I’m not laying claim to the term!!)

Attending a lecture suggests that there is a speaker and audience, whereas attending a presentation includes an additional element, the symbols (images-data).

Sources confirm that artists have always excited using bones, due to the variety of shapes available and their negative emotional content (feelings of disquiet - metabolic acidosis, cortisol [stress hormone]).

Connecting terms such as symbolisation, symbolic, symbol, symbolise and symbolism with elements such as bones, skulls and skeletons, new “key words” are introduced that allude to a certain era, culture or object of study.

In the past and present, bones have represented eternal truth, strength, unpleasant notions, poison, a warning, and so on. For instance, in the past, bones symbolised an idea or state, such as mortality. They served as a reminder of passing time and a motivation to enjoy life. Today, they also symbolise mortality, in addition to eternity, earth, truth, bodily support, hearth and shelter.

In art works Spine and skeleton symbolize pain, endurance, mortality and infinity. They also represent skeletal beauty and aesthetics, the axis of our personal world, individual consciousness, equality and death.

Pelvis symbolises a vessel that holds the magic of the creation of life; it represents something sacred, reproduction, fertility, rebirth.

Bones as a whole symbolise endurance, toughness and innocence (being white in colour).

Without a doubt, art is inspired by life and influenced by science. This is why artists - possessed with inspiration and motive, expressing growth and individual artistic promotion and seeking to give shape to the inspiration they have drawn from bones - make use of the natural, congenital and acquired

properties of bones and their diseases and deformities.

The 19th century symbols and symbolisms fostered the spread of art using bones, which had always represented truth. The durability of bones after death imbued them with the symbolism of “eternal truth”.

Is artistic inspiration a conscious, unconscious or subconscious process? This is a question which the artists such as Henry Moore answered directly, saying that “... though the non-logical, instinctive, subconscious part of the mind must play its part in [the artist’s] work, he also has a conscious mind which is not inactive.”

Artist physicians, who deal with diseases of the skeleton, form a group of doctors who - bearing the enormous responsibility to prevent such diseases - need specialised knowledge to be able to treat metabolic bone diseases and gain scientific recognition.

GLUCOCORTICOIDS AND OSTEOPOROSIS

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Glucocorticoids (GCs) are widely administered to reduce inflammation, to treat various immune-mediated diseases and as an immune-suppressive therapy for organ transplant recipients. The prevalence of use of oral GCs in the community population is between 0.5 and 0.9% (65% women), rising to 2.7% in women aged ≥50 years. However, glucocorticoid use is associated with a range of adverse effects, including glucocorticoid-induced osteoporosis (GIOP). Glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis, and the degree of bone loss is related to the dose of glucocorticoids and the duration of the exposure. Although awareness of the condition has grown in recent years, it remains under-diagnosed and under-treated. GIOP has distinct characteristics; in particular, rapid bone loss and increased fracture risk occur early after therapy is initiated. More than 10% of patients who receive long-term GC treatment are diagnosed with a fracture, and 30-40% have radiographic evidence of vertebral fractures. The highest rate of bone loss occurs within the first 3-6 months of GC treatment, and a slower decline continues with persistent use. Both high daily and high cumulative GC doses increase risk of fracture, particularly vertebral fracture, due to the greater effects of GCs on trabecular bone than on cortical bone. The pathogenesis of GIOP is thought to result from direct effects of exogenous glucocorticoids on bone cells and indirect effects mediated by altered calcium handling by the kidneys and the gut, reduced production of gonadal hormones and detrimental effects on the neuromuscular system. With long-term use, the predominant effect of glucocorticoids on the skeleton is reduced bone formation. The decline in bone formation is mediated by direct inhibition of osteoblast proliferation and differentiation and by an

increase in the apoptosis rates of mature osteoblasts and osteocytes. The reduction in bone formation is associated with a decrease in the mineral apposition rate and in serum and urine biochemical markers of bone formation. Glucocorticoids also decrease gastrointestinal calcium absorption and enhance bone resorption by increasing osteoclastogenesis since they stimulate the expression of receptor activator of NF- κ B ligand and colony stimulating factor-1, and decrease the levels of osteoprotegerin, a soluble decoy receptor for receptor activator of NF- κ B ligand. Glucocorticoids may prolong the life of mature osteoclasts. Numerous medical societies have issued guidelines or other guidance for the management of patients receiving glucocorticoid therapy. Screening for fracture risk should be performed soon after the initiation of glucocorticoid treatment. The recently updated ACR guideline defines three categories of fracture risk; high, moderate and low. In adults aged ≥ 40 years, previous osteoporotic fracture, hip or spine BMD T-score ≤ -2.5 , or 10 year fracture probability of $\geq 20\%$ (major osteoporotic fracture) or $\geq 3\%$ (hip fracture) are the criteria for high risk. Moderate and low risk are defined solely on the basis of FRAX-derived fracture probability (10-19% and >1 to $\leq 3\%$ respectively for moderate risk, $<10\%$ and $\leq 1\%$ respectively for low risk). In adults <40 years old, the criterion for high risk is a previous osteoporotic fracture, whereas moderate and low risk are defined on the basis of BMD. Oral bisphosphonates (alendronate, risedronate) are recommended as the first line drugs for individuals at moderate or high risk, with intravenous bisphosphonates (zoledronic acid), teriparatide, or denosumab in patients who are contraindicated or intolerant to oral bisphosphonates. Also patients who receive glucocorticoids should be intake adequate of calcium and vitamin D, weight-bearing exercise, and to avoidance of smoking and excessive alcohol intake.

THE MOLECULAR BIOLOGY OF FRACTURE HEALING

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Fracture healing is a perfect reparative mechanism having the unique characteristic of complete bone remodeling to normal bone architecture.

There are two types of bone healing. The primary type of bone healing, mainly involving the osteonic osteogenesis at the site of the bone cortex. It is artificial, occurring after internal osteosynthesis. The secondary type of bone healing, mainly involving the endochondral osteogenesis at the sites of surrounding soft tissues and endomembranous osteogenesis at the site of the periosteum. It is a natural process occurring during

conservative treatment of a fracture. The intramedullar osteogenesis at the diaphysial parts of long bones plays a minor role in both types of bone healing. Cancellous bone endomembranous osteogenesis plays a major role in metaphyseal and epiphyseal fractures.

Endomembranous osteogenesis has four consecutive phases, the haematoma formation, the inflammatory reaction, the formation of cartilaginous soft porous, and finally the mineralization of the soft porous and formation of hard porous. After this initial repair that lasts several weeks, a remodeling period of many months occurs until the formation of a porous with normal architecture.

During the inflammatory reaction of osteogenesis, three phases occur and interact to each other: (a) Ischemia of the bone fragments due to traumatic devascularization, (b) Cytokine secretion from the local inflammatory cells, and (c) Neovascularization that helps mesenchymal stem cells accumulation.

TNF- α and IL-1 are the main inflammatory cytokines. IL-6 enhances neovascularization through the activation of VEGF. TGF- β is involved at the local function of mesenchymal stem cells at the sites of endochondral osteogenesis and BMP-5 and -6 at the sites of endomembranous osteogenesis. TNF- α enhances cartilaginous cells apoptosis and the mineralization of soft porous starts. Then, RANK ligand activates pre-osteoclastic macrophages to mature osteoclasts that absorb mineralized woven bone and the osteoblasts replace it with lamellar mature bone. The Wnt signaling pathway is considered as the regulator for mesenchymal stem cells maturation to osteoblasts. At that phase there is local increase of the levels of IL-1, TNF- α and BMPs.

For the final remodeling of immature woven bone into mature lamellar bone, electrochemical reaction occur simultaneously with the biological pathways. Mechanical loading at the concave surface of the bone produces electro-positive loads leading to osteoclastic reaction whereas mechanical loading at the convex surface of the bone produce electro-negative loads leading to osteoblastic activity.

Conclusively, biological pathways and mechanical forces under the conduction of the osteocytes control the repair and remodeling of the fracture bone tissue leading to the formation of a new bone with normal structure and mechanical properties.

BONE LOSS AND RISK OF FRACTURE IN PATIENTS WITH SPONDYLOARTHRITIS

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Spondyloarthritis (SpA) includes several disorders such as psoriatic arthritis (PsA), arthritis related to inflammatory bowel disease (IBD), reactive arthritis and ankylosing spondylitis (AS). The risk of fracture and bone loss in

patients with AS is higher than the general population. The data are limited and less robust in PsA compared to AS. Concerning to arthritis related to IBD, no data exist, but it is well known that IBD is associated with bone loss and fracture risk, induced by both inflammatory and non-inflammatory mechanisms.

Patients with AS have a higher risk of vertebral fractures compared to health controls and patients with rheumatoid arthritis. Higher rates have been reported recently in studies using systematic imaging methods of the spine [either X-rays or the vertebral fracture assessment (VFA) method by DXA]. However, most of vertebral fractures were mild (a decrease in at least one vertebral body height of 20-25%). The use of large databases gives the opportunity to assess the prevalence of VFs in a very large number of patients but with the limits of such method, in particular the absence of the confirmation of the fracture in most of the cases. All the vertebral fractures are those which come to clinical attention, which may represent a minority of them.

Patients with a bamboo spine, hyperkyphosis and difficulties with peripheral vision have potential impairments in balance and coordination and a high risk of falls. Disease duration and wall-occiput distance have been reported as risk factors for vertebral fractures. Furthermore, patients with vertebral fractures have lower BMD than patients without. A low BMD is common in patients with AS with progressive disease. However, increased BMD can be due to artefacts related to the presence of syndesmophytes. Femoral neck is the best site for BMD measurement in this population. Low weight and low body mass index (BMI), old age, long disease duration, male gender, high disease activity and increased inflammatory markers (ESR and CRP) are associated with osteoporosis and low BMD. There is an association between the presence of syndesmophytes and a low hip BMD, suggesting the role of both the severity of the disease and the reduced mobility of the patients. Patients with AS have lower cortical BMD at peripheral sites, a result which is in accordance with the role of systemic inflammation and thus a systemic bone effect in this disease.

Thus, osteoporosis can occur in AS because of reduced physical activity, and decreased functional capacity related to pain, stiffness and ankylosis. However, low BMD is found in patients with early disease, before any structural changes. All these data support the role of inflammation in bone loss in AS, and a beneficial effect of anti-inflammatory drugs on bone is expected, not only through the increased mobility related to pain relief, but also through a direct effect on bone. TNF inhibitors increase the lumbar spine and hip BMD of patients with AS, but there is so far no evidence of an anti-fracture effect. There is no guidelines for osteoporosis in AS. However, in patients with severe osteoporosis and prevalent fractures, available guidelines in osteoporotic participants and male osteoporosis must be applied.

FACTORS AFFECTING IMPLANTS OSSEOINTEGRATION

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Osseointegration refers to a direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant. Osseointegration is not the result of an advantageous biological tissue response but rather the lack of a negative tissue response. Factors affecting osseointegration include:

1) Implant-related factors such as implant design and chemical composition, topography of the implant surface, material, shape, length, diameter, implant surface treatment and coatings. The biocompatibility of the material is of great importance and a predictor of osseointegration, as it is essential to establish stable fixation with direct bone-implant contact and no fibrous tissue at the interface.

2) The status of the host bone bed. A healthy bone bed with minimal surgical trauma is important since it is the source of cells, local regulatory factors, nutrients, and vessels that contribute to the bone healing response. A high-quality bone also seems to be important for the initial implant stability while patients' related factors such as osteoporosis, rheumatoid arthritis, advanced age, nutritional deficiency, smoking and renal insufficiency inhibit osseointegration.

3) Primary mechanical stability of the implant is essential. It consists of rigid fixation between the implant and the host bone cavity with no micro-motion of the implant or minimal distortional strains. Primary stability depends on the surgical technique, implant design, and implantation site. Cortical bone allows a higher mechanical anchorage to the implant than cancellous bone. Primary stability limits micro-motion of the implant in the early phases of tissue healing and favors successful osseointegration.

4) The use of adjuvant treatments and pharmacological agents which enhance or inhibit osseointegration. Especially, bone grafting, growth factors, bone morphogenic proteins (BMPs) and pharmacological agents such as bisphosphonates, teriparatide, simvastatin, angiotensin converting enzyme inhibitors, b-blockers, nitrites and thiazide diuretics enhance early stability of implants and fracture healing. Moreover, the efficacy of vitamin D3 supplementation on osseointegration of implants remains controversial and requires further investigation.

On the other hand, radiation therapy and pharmacological agents such as loop diuretics, cyclosporin A, methotrexate, cisplatin, corticosteroids, non-steroid anti-inflammatory drugs especially selective COX-2 inhibitors, proton pump inhibitors (PPI), warfarin, antiepileptics and selective inhibitors of serotonin inhibit osseointegration and fracture healing.

Furthermore, low-molecular weight heparin (LMWH) is routinely used to prevent thromboembolism in orthopaedic

surgery, especially on the treatment of fractures or after joint-replacement. However, the effect of LMWH is unclear and controversial. Recent studies strongly suggest impairment of bone healing in vitro and in animal models, characterized by a significant decrease in volume and quality of new-formed callus, systemic osteoporosis and poor materials' osseointegration as inhibit mesenchymal stem cells (MCSs) to differentiate into osteoblasts. Rivaroxaban has minimal to no impact on MCS migration, proliferation or mRNA expression of osteogenic markers and seems to be superior to Enoxaparin in early stages of bone healing and osseointegration of implants in vitro.

The concept of factors affecting implants osseointegration is complicated and larger and more sophisticated studies are needed in the future.

SYMPTOMATIC PRIMARY HYPERPARATHYROIDISM: CLASSICAL AND NON CLASSICAL COMPLICATIONS

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Primary Hyperparathyroidism (PHPT) is a common endocrine disorder characterized by incompletely regulated, chronic, excessive secretion of parathyroid hormone from one or more parathyroid glands. A single benign parathyroid adenoma is the cause in most people. However, multiglandular disease is not rare and is typically seen in familial PHPT syndromes. PHPT is associated with hypercalcemia and elevated or inappropriately normal serum levels of parathyroid hormone. The pathophysiology of PHPT relates to the loss of the homeostatic control of PTH synthesis and secretion, leading to increased PTH secretion by individual cells or increased parathyroid cell proliferation. Both conditions give rise to PHPT and can cause hypercalcaemia, the classic disorder, but a normocalcaemic PHPT was recognized recently.

In past decades most patients with PHPT were diagnosed when they had complaints of nephrolithiasis, bone pain, or bone deformity. Now, most patients are asymptomatic, diagnosed when hypercalcemia is incidentally discovered on a chemistry profile. The routinely measured calcium has increased markedly the incidence of PHPT.

The classical complications of the disease, mainly represented by skeletal, kidneys and gastrointestinal involvement. Bone involvement is characterized by pain and other complaints. Radiologically can be found the picture of osteitis fibrosa cystica, characterized by subperiosteal bone resorption, osteolysis of selected bone, such as for example the distal clavicles, a salt and pepper appearance of the skull, bone cysts, brown tumors, peripheral and vertebral fracture and very reduced bone mineral density values. Now, new imaging techniques have highlighted deterioration of skeletal tissue in patients with PHPT not captured by

traditional DXA measurement. The renal involvement includes, hypercalciuria kidney stones and nephrocalcinosis. It has been shown that clinically silent vertebral fractures and kidney stones can be uncovered also in asymptomatic PHPT. Gastrointestinal manifestations include acid-peptic disease, constipation, pancreatitis and gall stone disease.

The PHPT may be also associated with cardiovascular (CV), neuromuscular and articular complications, impaired quality of life and increased cancer risk. Left ventricular hypertrophy is probably the only cardiovascular complications associated with PHPT, which seems to improve after parathyroidectomy.

Both hypercalcemia and PTH could affect the CV system. Data suggest that PTH causes vasodilation, affects blood pressure, has chronotropic and indirect inotropic effects on the heart and may act as a "hypertrophic factor" upon cardiomyocytes. On the other hand, calcium also affects cardiac contractility and vasodilation.

The diagnosis of hyperparathyroidism is usually first suspected because of the finding of an elevated serum calcium concentration. If hypercalcemia is confirmed on a repeat sample, the serum PTH concentration should then be measured. The diagnosis of PHPT is usually made by finding hypercalcemia and frankly elevated levels of PTH, while some will have values that fall within the reference range for the general population (inappropriate normal PTH). PTH levels should be very low in those patients with PTH-independent hypercalcemia. Most patients with malignancy-associated hypercalcemia are known to have cancer and the PTH levels are suppressed.

Surgery remains the definitive treatment for primary hyperparathyroidism, but medical treatment with bisphosphonates or cinacalcet can be useful in selected patients.

NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM (NPHPT)

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Primary hyperparathyroidism (PHPT) represents one of the most common endocrine disorders, affecting up to 3% of the postmenopausal women and characterized by hypercalcemia associated with elevated or inappropriately normal PTH levels. However the increasing use of PTH determination in the diagnostic workup of osteoporosis has identified a distinct form of PHPT, probably an early phase of the disease, characterized by stable elevation of PTH levels, in the absence of known secondary causes (CKD, hypercalciuria, low vitamin D, drugs), along with normal total and ionized calcium levels. The prevalence of NPHPT ranges from 0.4-6%; however the diagnostic

criteria differ between studies, especially concerning ionized calcium levels and UCa. The diagnosis of NPHPT requires rigorous testing for the exclusion of secondary causes of PTH elevation, several tests (thiazide challenge test, calcium loading test, correction of vitamin D deficiency) and long-term follow-up for the confirmation of stable PTH elevation. Concerning bone involvement in patients with NPHPT the true prevalence is unknown and most data suffer from selection bias, as the results come from tertiary bone clinics. Data about kidney disease report prevalence of nephrolithiasis of 14-36%. The management of NPHPT is controversial due to lack of solid data about the natural history as well as the effects of surgical or medical treatments. Nevertheless at least yearly follow-up is recommended for the detection of potential progression. Surgical treatment might be considered in cases of emergence of hypercalcemia or progression of osteoporosis or renal disease. Otherwise medical treatment to prevent progression of bone and/or kidney disease is advisable.

CONSERVATIVE TREATMENT OF PRIMARY HYPERPARATHYROIDISM

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Primary hyperparathyroidism (PHP) is one of the most common endocrinopathies. It is associated with persistent hypercalcemia and hypercalciuria due to excessive excretion of parathyroid hormone from the parathyroid glands. The major cause of PHP is a benign parathyroid adenoma, or hyperplasia, while parathyroid carcinomas are also rarely reported.

The majority of PHP cases occur sporadically, but rarely PHP can manifest in the context of inherited endocrine diseases, such as multiple endocrine neoplasia syndromes 1 and 2a, familial hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism and hyperparathyroidism-jaw tumor syndrome.

Most of the patients with PHP are asymptomatic. Symptomatic hyperparathyroidism, due to prolonged hypercalcemia is characterized by nonspecific symptoms such as generalized weakness, fatigue, poor concentration, and depression.

Since the disease may run an occult course for many years before detection, the initial manifestations in some cases are associated with renal and skeletal complications, such as nephrolithiasis, nephrocalcinosis, osteitis fibrosa cystica, and osteoporosis. Less recognizable and unspecific symptoms are associated with dysfunctions of other organ systems such as the cardiovascular, the gastrointestinal, rheumatic, and neuropsychiatric. Although PHP is a benign disease,

when left untreated for a long time can lead to irreversible changes from the skeletal and the renal system such as severe osteoporosis with fractures and renal insufficiency. Definitive therapy for both symptomatic and asymptomatic PHP is parathyroidectomy.

In cases where parathyroidectomy is contraindicated medical treatment that target the correction of hypercalcemia and hypercalciuria is strongly recommended.

In patients with severe and symptomatic hypercalcemia (serum levels of total calcium >14 mg/dl) intravenous hydration with isotonic sodium chloride solution that reduces calcium levels and restores euvolemia is considered the mainstay of treatment.

Bisphosphonates and selective estrogen modulators (SERMs) in postmenopausal women with PHP have been efficiently used to provide skeletal protection and reduce the PTH-induced bone resorption, but their effect on hypercalcemia is limited.

Denosumab, a monoclonal antibody against RANKL has also been efficiently used in patients with decreased bone mineral density and PTH-induced hypercalcemia. In addition denosumab, unlike bisphosphonates, is not cleared by the kidneys and therefore, there is no restriction of its use in patients with chronic kidney disease, for whom bisphosphonates are used with caution or contraindicated.

Cinacalcet, is a calcimimetic, that reduces both serum calcium and PTH levels and raises serum phosphorus. Its mechanism of action is through reducing PTH secretion by altering the function of parathyroid calcium-sensing receptors. Cinacalcet, however, has no effect on increased bone turnover or low bone mineral density. At present, the use of this agent in PHP is limited to control of serum calcium in patients with symptomatic hypercalcemia who are unable to undergo parathyroidectomy.

¹⁸F-SODIUM FLUORIDE PET USE FOR DIAGNOSIS AND MONITORING OF OSTEOPOROSIS: AN INEVITABLE ROUTE FOR THE FUTURE?

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The prevalence of metabolic bone diseases particularly osteoporosis and its precursor, osteopenia, continue to grow as serious global health issues today. Bone mineral density (BMD) assessment using dual-energy X-ray absorptiometry (DXA) scan is the current gold standard test for the diagnosis of osteoporosis. However, about 50% of women who had sustained osteoporotic fracture have BMD above the WHO definition of osteoporosis. Hence, there is a need for developing novel tools which detect the dynamics of bone remodeling with respect to bone formation and resorption. Bone turnover markers (BTM) have an important role in research studying the effect of new treatments for osteoporosis on bone metabolism, since they can respond to

the integrated effects of treatment across the entire skeleton. Positron emission tomography with ^{18}F -sodiumfluoride (^{18}F NaF PET) provides a novel tool for studying bone metabolism that can measure the effects of treatment at specific sites, such as the spine and hip.

Dynamic PET imaging with ^{18}F NaF allows the quantitative assessment of regional bone formation by measuring the plasma clearance of fluoride to bone at any site in the skeleton. A simplified approach to image acquisition and analysis, with little loss of accuracy or precision, enables the same information to be obtained from a single short (3- to 5-minute) static scan acquired 45 to 75 minutes after tracer injection, provided that venous blood samples are taken to estimate the input function. The advantage of the static scan approach is that, with a series of short acquisitions made at different bed positions, quantitative measurements of bone plasma clearance can be made at multiple sites in the skeleton with only a single injection of ^{18}F NaF.

Standardized uptake values (SUV) in bone may also be measured but it has several disadvantages comparing to bone plasma clearance. The main limitation of measuring SUVs is that only a finite amount of tracer is administered to the patient, and this has to be shared out between the various competing tissues. In the case of ^{18}F NaF, these include the kidneys and other regions of the skeleton. If a patient is treated with a potent bone anabolic agent such as teriparatide, or has extensive metastatic bone disease, or a large area of active Paget's disease, the ^{18}F NaF plasma concentration will be reduced by the increased competition for tracer, resulting in a reduced measurement of SUV. Measurements of a change in SUV at a particular site partly reflect the changes in bone formation occurring at other sites in the skeleton. In contrast, plasma clearance measurements are free of this limitation because the uptake is expressed relative to the arterial concentration of tracer actually delivered to tissue rather than the amount of tracer injected. Quantitative ^{18}F NaF PET imaging provides a novel way to study regional bone formation rate that complements conventional measurements with BTM. It has potential as an early biomarker of treatment efficacy at different sites in the skeleton as well as a tool to investigate new treatments for osteoporosis, and for use in future clinical trials.

APPLICATION PROBLEMS OF OSTEOPOROSIS GUIDELINES IN CLINICAL PRACTICE

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The main issue with osteoporosis is that is usually underdiagnosed. More than 50% of total population is never screened for osteoporosis and less than 50% of osteoporotic patients receive treatment. This fact is related to the education and information (guidelines) that

physician should receive from official international or national scientific boards.

Recently, the term prevention is used for fragility fractures. There are three levels of prevention: (1) Primary prevention, any intervention applied to the general population, independently of evaluation of the fracture risk, (2) Secondary prevention, diagnosis in at-risk population through BMD and/or fracture risk algorithms, and (3) Tertiary prevention, treatment of patients who suffered one or more fragility fracture(s).

Another issue is the recognition of the first osteoporotic fracture as indicator of a future fracture. An episode of osteoporotic fx at least doubles the likelihood of further fxs. A past history of at least one vertebral fx leads to a 4-fold increased risk of vertebral fx.

The last few years, the care gap of osteoporosis and fragility fractures is recognized. 80% of fracture patients are not tested or treated for osteoporosis or falls risk. Such fragility fracture patients fail to have risk assessed, remain untreated, lack prescriptions, are not diagnosed and eventually break another bone! There are two main causes for this care gap: (a) the lack of clarity as to whose responsibility it is to provide secondary or tertiary prevention, and (b) there is ambiguity as no single group can manage all aspect of a fracture.

The main barriers contributing to osteoporosis re-fracture prevention care gap are categorized as:

A. Clinician factors:

- Lack of ownership of the problem
- Lack of awareness of increased risk
- Lack of knowledge of treatments and prevention strategies
- Concerns about costs of investigation and treatment
- Concern about treatment side effects
- Lack of awareness of male osteoporotic fracture risk
- Lack of priority to treat this issue in older patients

B. Patient factors:

- Lack of awareness of risk
- Lack of knowledge of possible treatments
- Concern about costs of tests and treatments
- Concern about side effects

C. Health system and social factors:

- Lack of integrated health systems
- Lack of communication between clinical services
- Lack of ICD (International Classification of Diseases) coding for fragility fxs
- Lack of funding and foresight to invest in fragility fracture coordinators

The media seem to contribute to the care gap due to the influence on poorly educated physicians and sciolist readers. The lay press is a messenger of bringing news and opinion from the scientific community, however some or much of them are ill-judged. Potential side effects of anti-osteoporotic treatment such as osteonecrosis of the jaw, atypical femoral fxs, atrial fibrillation, venous thrombosis and thromboembolism are overemphasized making the patients reluctant to any anti-osteoporotic treatment. According to

Dr. Kanis saying, “we confront a paradox: we seek to treat individual patients to the highest standards but at the same time disservice and disadvantage the wider osteoporosis community...”

In clinical practice, one can identify gaps and ambiguities when reading the newly released osteoporosis treatment guidelines, such as:

- A. There are no clear guidelines for pre-menopausal women
- B. There are no evidence based data for male osteoporosis
 - No consensus for the definition of male osteoporosis
 - What is the T-score in young males
 - All data are taken from IOF from limited number of males
- C. FRAX limitations
 - Patients without previous treatment are only included
 - No history of previous falls (and number of falls) predictive to a future fall
 - Does not include all causes of secondary osteoporosis
 - Does not include number of previous fractures
 - Does not include cortisone time intake and dosage
 - Does not include DXA of lumbar spine

Another important issue is the management of anti-osteoporotic drug arsenal. Since there is a limited drug availability (bisphosphonates, denosumab and teriparatide) it is very important to follow special administration criteria related to the age of the patient, the safe administration period of a medication, the drug holiday decision and also the side effects that may occur.

Finally, a fragility fracture network with the co-ordination of health providers from different specialties is imperative for the holistic treatment of osteoporosis and its main complication - the fragility fracture.

SECONDARY RENAL OSTEOPOROSIS

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Chronic Kidney Disease (CKD) patients present with a very high morbidity and mortality which is partly attributed to the development of CKD Bone and Mineral Disease (MBD). CKD-MBD develops early in the course of CKD and affects not only the bones and the mineral parameters but also the vessels and the heart.

Osteoporosis is one aspect of the broad spectrum of bone manifestations of CKD-MBD and it was only recently acknowledged. CKD patients’ osteoporosis is described in the literature as “CKD-associated osteoporosis” or “Renal osteoporosis” or “Kidney induced osteoporosis”. The prevalence of osteoporosis and fractures in patients with GFR<60 ml/min is two-fold that of persons with GFR>60 ml/min. Incidence of fractures in patients with GFR<16 ml/min is 5% and 9.6% compared to 1.6% and 4.3% for persons with GFR>60 ml/min. The diagnosis and treatment of CKD-associated osteoporosis is currently based on the 2017 Kidney Disease Improving Global Outcome

(KDIGO) guidelines. For patients with CKD G1-G3b with osteoporosis and/or high risk of fracture, diagnosis and management follows that for the general population, provided their PTH is in the normal range. In patients with CKD G3a-G5D with evidence of CKD-MBD and/or risk factors for osteoporosis the recommendation is: a) to measure Bone Mineral Density (BMD) in order to assess fracture risk and/or clinical risk factors for osteoporosis, b) to “take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy”.

Apparently the KDIGO guidelines do not provide specific clinically relevant guidelines for CKD 3-5d patients. Moreover, the diagnosis of osteoporosis in CKD stage 3-5d patients is uncertain. The available evidence for interpreting DXA results is very limited and CKD G5d patient comorbidities, such as osteoarthritis of the spine and calcifications, might lower the accuracy of BMD evaluation with DXA. Although DXA is undeniably helpful in assessing areal BMD or bone quantity, it is considered inappropriate to assess bone quality. Quantitative Computed Tomography (QCT) was not found to offer extra diagnostic value compared to DXA. Bone turnover markers are also affected by CKD and considered unreliable for osteoporosis detection and treatment. Bone biopsy is undeniably the gold standard for diagnosis but it is underutilized since it is an invasive procedure requiring expertise in histo-morphometric assessment. The prognostic value of BMD measurement by DXA in CKD patients has been confirmed and the prevalence of fragility fractures was found to be higher in CKD patients, including dialysis patients with low BMD. Based on comparisons by histology, DXA results have been found appropriate for the diagnosis of osteopenia and osteoporosis in patients with CKD-5D.

The goal of the treatment of “CKD-associated osteoporosis” is the prevention of fractures. The therapeutic challenge lies in the treatment of CKD patients in stages 4 to 5D. The first-line therapy for CKD-associated osteoporosis is the treatment of CKD-MBD and must precede osteoporosis specific medications: treatment of mineral and metabolic abnormalities, management of secondary hyperparathyroidism, treatment of hyperphosphatemia, measures to avoid calcium overload and vascular calcifications. Along with vitamin D receptor activators which are widely used for treating Secondary Hyperparathyroidism, nutritional vitamin D supplementation, cholecalciferol or ergocalciferol, is proposed for symptomatic CKD patients with low BMD. The use of anti-osteoporosis specific treatments, bisphosphonates, denosumab and teriparatide, in CKD stage 3-5d patients is extensively debated. Bisphosphonates are not indicated for use in patients with eGFR<30 ml/min/1.73 m² because they accumulate in bone tissue. Low renal clearance promoting high storage may cause defective bone mineralization and osteomalacia and induce adynamic bone disease (ABD). Before the off-label use of bisphosphonates, risk factors for ABD such as aging, diabetes, calcium overload,

malnutrition, inflammation and relative hypo-parathyroidism should be taken into consideration. In order to avoid adverse effects, low-dose bisphosphonates are proposed for CKD4-5d patients but without clear evidence from clinical trials. Denosumab administration is not contraindicated in CKD patients of all stages, but it should be monitored closely because of possible marked hypocalcemia and increase of PTH. In older studies, alendronate was found to increase BMD and decrease fractures in patients with GFR<45 ml/min but CKD stage 5d patients were not separately identified. Denosumab was recently associated with a reduced risk of vertebral, non-vertebral, and hip fractures in osteoporotic women. However, a recent systematic review provided no clear evidence that any one of the anti-osteoporotic specific drugs could be helpful in CKD.

Clinical trials in osteoporotic CKD-5D patients are ongoing and hopefully will provide answers regarding the effects of anti-osteoporotic drugs in BMD and mineral metabolism. At present, specific anti-osteoporotic therapy should be probably initiated only in CKD-5D patients with fragility fractures. Most importantly, further trials are awaited to test the effect of anti-osteoporotic therapy on fracture risk.

OSTEOPOROSIS IN CHILDREN

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Diagnosis of osteoporosis in children requires the presence of significant fracture history and low bone mineral density. Distinguishing a traumatic from pathological fracture is often difficult because it is not clearly defined what constitutes a fragility fracture. Fragility fractures include fractures of long bones with absence of significant trauma, repeated minor metaphyseal fractures in the distal femur, compression fractures of the spine usually as atypical finding in an X-ray. Vertebral fractures without high-energy injury in children are usually indicative of increased bone fragility. In chronically ill children, vertebral fractures are surprisingly common and often asymptomatic

Osteoporosis in children may be primary, due to an intrinsic bone abnormality or secondary, due to an underlying medical condition. Primary osteoporosis is found in hereditary bone fragility disorders, mainly in osteogenesis imperfecta. Secondary osteoporosis in glucocorticosteroids treated conditions, in cerebral palsy (CP), in mobility disorders that affect weight bearing.

The diagnosis and management of osteoporosis in the pediatric patient must be based on a combination of clinical and radiographic findings, rather than relying upon bone densitometry alone. We denote osteoporosis in children when we have a BMD Z-score threshold -2.0 or worse, with long bone fractures, defined as ≥ 2 long bone fractures by age 10 and ≥ 3 long bone fractures by age 18.

DXA measurements are performed in the axial or the

appendicular skeleton. Z-scores should be calculated as SD scores compared with age-, sex-, and ethnicity-matched controls. The diagnosis of low BMD in a child should never be made on the basis of T-score.

The fracture incidence in CP children is much higher than that in the general pediatric population. These fractures occur with minimal trauma or are 'spontaneous' with no apparent history of injury.

Malnutrition, low body weight (z-score) and use of AEDs are associated with an increased fracture risk. More severely affected children have higher incidence of fragility fractures. Prevention of bone fragility and fractures in CP children can be achieved with physical activity and standing weight-bearing. Nutrition supplements and vitamin D are essential. The primary cause of osteoporosis is found in osteogenesis imperfecta. It is a rare disease, characterized from excessive fragility of bones. The use of pamidronate today has reduced the incidence of fractures in these children.

Appropriate treatment for realignment of deformed and contoured long bones and use of expanding telescoping rods have significantly improved the life of the children.

Fragility fractures in children may be due to a wide variety of genetic, medical, or nutritional disorders. The decision to perform screening densitometry in a child or adolescent must be made on an individual basis, taking into account fracture history and risk factors.

The clinical implications of low BMD in the pediatric population have not been well-established, and the diagnosis of osteoporosis must be made in association with clinical history rather than relying upon bone densitometry alone.

The use of bisphosphonates in children and adolescents is controversial due to lack of long-term efficacy and safety data and should be limited to clinical trials and as compassionate therapy in children with significantly compromised quality of life.

"DRUG HOLIDAYS" IN OSTEOPOROSIS: WHEN AND FOR HOW LONG?

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Bisphosphonates and denosumab are the most widely used anti-resorptive drug categories with well-established efficacy regarding vertebral, non-vertebral and hip fracture risk reduction. Nevertheless, their long-term use has been associated with an increased risk of adverse effects (AE), such as atypical femoral fractures (AFF) and osteonecrosis

of the jaw (ONJ). In fact, the absolute risk associated with these AE is very low, compared with the overall anti-fracture efficacy, and increases with the duration of the use of anti-resorptive therapy. In detail, the incidence of AFF ranges from 3.2 to 50 cases per 100,000 person-years, whereas ONJ has been reported in 0.001-0.04% of cases with osteoporosis (1-15% in oncological patients receiving intravenous bisphosphonates on the purpose of reducing the risk of bone metastases). Due to the possibility of these AE and the long period of retention to bone, the idea of a “drug holiday” after long-term of bisphosphonate use, has emerged. Existing data show that the use of alendronate, zoledronic acid and risedronate may be suspended for five, three and three years respectively, provided that the patient remains at low risk (defined as femoral neck T-score >-2.5 , age <70 years, no prevalent fractures and absence of a disease or medication associated with increased fracture risk) before drug discontinuation. However, the evidence for the effectiveness of this approach on reducing the risk of AFF and ONJ is weak. This “drug holiday” strategy should not be implemented in cases of denosumab or others agents such as estrogen, estrogen-receptor modulators and teriparatide. More specifically, denosumab discontinuation has been associated with increased risk of rebound fractures in both genders and, therefore, its discontinuation should always be followed by another anti-osteoclastic agent, such as bisphosphonates.

KYPHOPLASTY - DIAGNOSTIC AND TECHNICAL PITFALLS

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Kyphoplasty is a well-established minimal invasive treatment in osteoporotic or pathological vertebral compression fracture (VCFs). However, strict inclusion criteria and technical tips may ensure the success of the surgery and avoid complications which may be catastrophic in rare occasions. Best candidates for the operation are those with acute or subacute painful fractures (less than 3 months old and VAS $>5/10$). Although there are published reports for chronic fractures, the results are not going to be as optimal as with fresh VCFs (except from cases of pseudarthrosis/ kummel disease) along with the better chance of restoration of sagittal alignment (unlikely with the old collapsed vertebrae). Same accounts for patients with mild pain less than 4 in a 0-10 scale, since bibliographic data refer to a 4-5 point's reduction in the pain scale. Clinical examination is of paramount importance, since different pain generators may exist (ie. spinal stenosis or spondylarthritis) and therefore if the primary source of pain is not the fracture, kyphoplasty will not ameliorate patient's symptoms. Patients with

unstable fractures or burst fractures with myelopathy are also contraindicated. In cases of multiple fractures (i.e. corticosteroid induced fractures or multiple myeloma) multiple levels may be needed to be augmented. However, one should focus on the most important ones (more edema in MR or hot signal in bone scan, SPECT or low T-Score in DXA) and avoid performing more than 4 spinal levels in a single operative session, since this may predispose to more serious cardiopulmonary complications. Indeed, lengthy operations with the patient in the prone position lead to increased oxygen desaturation from prolonged administration of sedative drugs, decrease functional residual capacity due to thoracic compression and increased chance of fat or cement pulmonary emboli (along with the bigger cement volumes used).

Cement extravasation is often encountered; however in less than 1% this is clinically important. To avoid leakage in the canal or venous plexus special attention to the C-arm image intensifier images must be paid; early recognition of cement extrusion may necessitate halting the operation until the cement hardens, reinserting the cannula in a more appropriate position, or even early termination of the procedure in this level. Extravasation in the disk may also happen and in this occasion prophylactic augmentation of the neighboring vertebrae is advised, since it is shown that cement leakage in the disk may predispose to adjacent segment fracture.

OFF-LABEL USE OF ANTI-OSTEOPOROTIC AGENTS IN PATIENTS UNDERGOING SPINAL FUSION

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Osteoporosis is a chronic disease, characterised by reduced bone strength and increased risk of fracture. Current pharmacological treatment in various countries all over the world may include anti-resorptive (bisphosphonates, denosumab, SERMs) or bone anabolic agents (teriparatide in Europe and also abaloparatide and romosozumab in the US). The possible effects of these agents in patients undergoing spine surgery has been investigated in only a few studies. Spinal fusion is advocated in patients with spine instability of numerous aetiologies and presents difficulties especially in patients with compromised bone micro-architecture. Use of anti-osteoporotic agents after spinal fusion has shown some promising results in such patients. Most studies have been performed with teriparatide alone versus placebo or oral bisphosphonates. Thus, a small number of retrospective studies (Ohtori et al, Inoue et al, Kaliya-Perumal et al) suggest that teriparatide 20 μg daily for up to 6 months is superior in promoting earlier bone fusion. In a prospective randomised clinical trial by Ebata et al, a weekly dose of teriparatide has been shown to significantly

increase fusion rates versus placebo at four and six months post-operatively. In another prospective study, Ohtori et al reported that daily subcutaneous teriparatide administered for 10 months was more effective for achieving bone union than oral bisphosphonates (time to radiographic fusion 8 months versus 10 months respectively). Other studies have looked at the results of alternating daily teriparatide 20 µg with bisphosphonates (i.e alendronate 70mg per week per os) for 3- month cycles for a total of 12 months vs only oral alendronate (Zanchetta et al). The authors report earlier fusion in the teriparatide group (6.0 ± 4.8 months in the teriparatide group versus 10.4 ± 7.2 months in the alendronate group), with higher fusion rate at 6 months, but no differences between groups at 12 and 24 months after surgery. Seki et al reported that 2 years post surgery, patients who received alendronate 3 months pre-operatively and 21 months post-operatively had more adjacent vertebral fractures, implant failure and pain as opposed to those who received teriparatide for the same period of time. As far as duration of treatment is concerned, Ohtori et al reported improved outcomes of spinal fusion in patients receiving average 13 months of teriparatide versus patients receiving average 5.5 months of teriparatide in terms of fusion rates and average time to fusion. In terms of safety, Schnell et al reported no evidence of increased risk of spinal stenosis with teriparatide as assessed with computed tomography (CT). Finally, Chao-Wei Tu et al recently reported that zoledronic acid 5 mg given intravenously once yearly may be associated with better fusion rates versus placebo at 2 years post operatively, with lower rates of adjacent vertebral compression fractures and pedicle screw loosening, with a positive effect on pain.

WHEN OSTEOPOROSIS TREATMENT IS INDICATED?

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Several agents are available for osteoporosis treatment and their anti-fracture efficacy has been tested in numerous randomized control trials and meta-analyses. However, as osteoporosis treatment is probably the only chronic therapy with a time limitation, the decision for the initiation of treatment is quite crucial and needs critical thinking in order for the patients to receive treatment when the risk of a fragility fracture is real and high enough. In Greece, the recommended strategy for the initiation of osteoporosis treatment is deployed in two therapeutic options based on the BMD values, the FRAX derived fracture risk, and the presence of fragility fractures.

In specific, per os and i.v. bisphosphonates, denosumab, and SERMs (for females) are recommended for patients with at least one vertebral and/or hip fragility fracture, and/or with at least two non-vertebral fragility fractures

regardless of their BMD values, and those with a BMD value ≤ -2.5 at any skeletal site with or without a fragility fracture. This is also the case among patients up to 75 years old with osteopenia and a FRAX score $\geq 10\%$ for major osteoporotic fracture and/or $\geq 2.5\%$ for hip fracture or $\geq 15\%$ for major fracture and/or $\geq 5\%$ for hip fracture among subjects older than 75 years. These are the specific for the Greek population treatment thresholds that came up following a cost-effectiveness analysis.

The second therapeutic option allows treatment with per os and i.v. bisphosphonates, denosumab, SERMs (females), and teriparatide among patients with a BMD ≤ -3.0 at any skeletal site and an additional history of a low-energy vertebral fracture and/or a hip fracture and/or two or more non-vertebral fractures. Although the selection of a BMD ≤ -3.0 in combination with the above-mentioned fragility fractures is an arbitrarily set threshold, it describes the cases of severe osteoporosis who will significantly benefit from the use of teriparatide be it as a first-line treatment, and thus it is also included as a therapeutic regimen in this second therapeutic option.

At any case secondary osteoporosis should be carefully sought prior to the initiation of any treatment modality. Collection of information associated with the patient's medical history and lifestyle as well as clinical examination are indispensable for the evaluation of each person and for the differential diagnosis of secondary osteoporosis. At a minimum, the information obtained should at least address the FRAX-related questions regarding personal medical history, including co-morbidities and medication as well as family history of fractures. In addition, the clinical examination should include weight and height measurements as well as evaluation of the patient's posture: kyphosis and/or a decrease in height might indicate presence of vertebral deformities. Additionally, the minimum baseline laboratory assessment should include: serum calcium (corrected for albumin), serum phosphate, complete blood count, erythrocyte sedimentation rate, serum creatinine, serum total alkaline phosphatase, thyroid stimulating hormone, 25 (OH) vitamin D, and 24h urine calcium.

Finally, clinical judgment is very important and needs always to be combined with any existing guidelines, in order to reach the best therapeutic decision for each patient.

WHEN IS THE ANTI-OSTEOPOROTIC TREATMENT DISCONTINUED?

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Long-term anti-osteoporotic treatment seems rational to protect from low-energy fractures, since osteoporosis is a life-long disease. However, the effectiveness and safety of life-long administration of existing anti-osteoporotic

medications has not been evaluated as yet. Furthermore, mainly owing to the “tail-effect” of bisphosphonates (BPs), a general assumption on discontinuation of all anti-osteoporotic medications still exists.

The “tail-effect” of BPs is mainly attributed to their pharmacokinetics, resulting in their long-term retention in the skeleton that prolongs their effects after their discontinuation. Therefore, it has been proposed that discontinuation should be considered after a 5-year treatment for alendronate and risedronate, and a 3-year treatment for zoledronic acid (ZOL), in the case of low-risk patients (i.e., bone mineral density [BMD] T-score >-2.5 at all sites, no low-energy fracture, no secondary osteoporosis from other chronic diseases or medications). Follow-up of 1-2 years is recommended in these patients. On the contrary, high-risk patients may be further benefit from the continuation of BP administration (for a total of 10, 8 and 6 years for alendronate, risedronate and ZOL, respectively).

Contrary to BPs, discontinuation of denosumab, an antibody against the receptor activator of nuclear factor kappa-B ligand (RANKL), results in rapid rebound of bone turnover and rapid decrease in BMD. In clinical terms, this means that the patients rapidly (within 1-2 years) loss BMD gain and, importantly, are exposed to risk of multiple vertebral fractures, observed in a minority of them. Based on these considerations, denosumab should be handled differently than BPs. Its discontinuation may be considered after a 5-year treatment in low-risk patients (as above defined), but without “drug holiday”, meaning that the patients should be administered another anti-osteoclastic medication, preferably a potent BP like ZOL, upon denosumab discontinuation. In high-risk patients, denosumab treatment may be considered for 10 years, but again, another anti-osteoporotic medications should be added immediately after its discontinuation.

Teriparatide, an osteoanabolic medication, could be administered continuously for 2 years and then it should be discontinued, owing to the lack of long-term safety data and cost-effectiveness policy. Progressive loss of BMD gain is observed after teriparatide discontinuation, without being so dramatic as observed upon denosumab discontinuation. However, sequential treatment with an anti-resorptive medication, preferably a BP or denosumab, is suggested to maintain bone mass gain and improve mineralization of newly formed bone.

Romozosumab, an anti-sclerostin antibody, is another osteoanabolic medication approved in the USA, but not in Europe. Romozosumab could be administered for 1 year and it should be then discontinued, mainly because its beneficial effect reaches a plateau at 1 year. However, loss of BMD gain is observed 1 year after its discontinuation, so sequential treatment is needed, possibly with BP or denosumab.

Calcium and vitamin D must not be discontinued together with the above mentioned medications, but they should be

independently monitored and appropriately supplemented. In conclusion, anti-osteoporotic medications should be differently handled and administered based on a long-term plan designed for each individual patient.

VERTEBRAL FRACTURE PREVALENCE AMONG PEOPLE TREATED FOR OSTEOPOROSIS IN GREECE

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VERTEbral INtegrity ASsessment Study - VERTINAS STUDY
by both the*

*- Hellenic Society for The Study of Bone Metabolism and the
- Hellenic Patients Society “Butterfly”*

Objectives:

1. To assess vertebral fracture (T4 - L5) prevalence among people treated for osteoporosis in Greece.
2. To evaluate the degree of accordance in diagnosis of fractures between radiologists and orthopedics

Methods:

Patients receiving medication for osteoporosis were recruited (2016-2017) via announcement by the Greek national media.

Inclusion criteria:

1. Age > 50 (both sexes)
2. Postmenopausal status for females >2 years
3. Current (>1 year) use of medication for osteoporosis
4. Lack of radiological vertebral assessment for >1 year

Exclusion criteria:

1. Bone metabolic disease other than osteoporosis
2. Secondary osteoporosis
3. Inability to stand/walk
4. Previous high energy vertebral fractures

Design:

All patients completed short-form questionnaire indicating:

- Age
- Sex
- Current pharmaceutical treatment for osteoporosis
- History of previous vertebral fractures
- Consensus in performing lateral spine (T4 - L5) x-rays

Radiographs were evaluated for fractures by radiologists as usual and then by 3 orthopedic consultants according to the “Genant semi-quantitative method”, blinded for the patient data.

Results:

1652 patients were recruited with properly filled questionnaires (age 50 - 102, mean 70,4)

1516 women (91,8%, age 50 - 102, mean 70,2)

136 men (8,2%, age 52 - 94, mean 74,8)

Current treatment: SERMS 1%, BPs 85,7%, Denosumab 11,6%, Strontium Ranelate 0,2%, Teriparatide 1,6%.

Vitamin D: 40,6%, Alphacalcidol: 8,1%, Calcium supplements: 38,6%.

History of vertebral fracture(s) before the study: 11,1%

Fractures were diagnosed in the study for the 25,4% of the patients (the prevalence of vertebral fractures among people treated for osteoporosis in Greece).

Among 419 patients actually found with fracture(s) -543 fractures in total-, only 98 (23,4%) knew about the existence of the fracture(s).

On the contrary, among the rest 1233 patients actually found without fracture(s), 86 (7,0%) had declared knowledge about the existence of fracture(s) in their history.

For 1289 patients (78%) out of the total 1652, orthopedics could read the opinion of the radiologist about the existence of fracture(s).

Accordance in diagnosis about the existence of fracture(s) between radiologist and orthopedic was achieved in 1088 patients (84,4%).

Among 310 patients for which the 3 orthopedics had diagnosed existence of fracture(s), radiologists did so previously only for 122 (39,4%) of them.

Conclusions:

Vertebral fracture prevalence among people treated for osteoporosis in Greece is 25,4%.

[Very close to similar publications]

76,6% of people treated for osteoporosis in Greece, think they don't have fracture(s), although they do.

[Never start osteoporosis treatment without spinal X-rays done before]

Less than 50% of patients on treatment for osteoporosis in Greece are taking calcium and vitamin D.

[Caution is needed on behalf of doctors and patients on the Ca-vitamin D status during osteoporosis treatment]

Accordance about the existence of vertebral fractures between radiologists and orthopedics in Greece is not very high (84,4%)

[Consensus is needed with radiologists about vertebral fractures diagnosis]

PAGET'S DISEASE OF BONE: AN UPDATE

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Paget's disease is a localized disturbance of bone architecture, affecting a single or multiple synchronous skeletal sites, characterized by an increase in osteoclastic activity followed by deposition of woven bone, which results in deformity, pain and fracture.

It is the second commonest bone disease, affecting up to 8% of octagenarians of Anglo-Saxon descent. Familial clustering is observed and autosomal dominant inheritance with incomplete penetrance accounts for 30% of familial and 10% of sporadic cases. The P392L mutation of *SQSTM1*, encoding p62 protein, accounts for most familial cases, while over 15 additional susceptibility loci have been identified. p62 is a cargo receptor for ubiquitin-mediated autophagy, involved in many RANKL-activated osteoclast

signaling pathways. In the last 2-3 decades a reduction in the prevalence and disease severity has been documented.

Paget's disease is mediated by the pagetic osteoclast, which exhibits distinct morphologic changes and an altered functional phenotype. Some groups have identified paramyxoviral nucleocapsid proteins and transcripts, in pagetic osteoclasts, but the results have been disputed. Animal models support an important role of the measles virus in conjunction with *SQSTM1* mutation in disease pathogenesis.

Although the disease can be asymptomatic in up to 70%, it causes pain, fracture, hearing loss, headache, vascular steal syndromes, pressure radiculopathy, deformity, hyperuricemia, immobilization hypercalcemia and rarely giant cell tumors and osteosarcoma.

Plain x-ray of the affected bone(s) is the examination of choice, featuring osteolytic lesions, cortical and trabecular thickening, bone expansion and deformity. A bone scan at diagnosis delineates the extent of the disease.

An elevated total alkaline phosphatase (ALP) in a symptomatic patient with characteristic X-ray(s) of affected bone(s) and normal liver biochemistry effectively rules in the disease. ALP is the most useful marker of disease activity, extent and severity, as well as treatment efficacy, although it can sometimes be normal in active disease. In such cases, bone-specific ALP (bALP) or serum PINP may be more sensitive.

Recommended treatments are the oral bisphosphonates risedronate (30 mg daily for 2 months) and alendronate (40 mg daily for 3-6 months) and intravenous zoledronic acid (single infusion of 5mg). The latter is preferred because it has been shown to have the best and most durable response rate (96% response at 6 months and 0.7% relapse at 6.5 years). In particular, the mortality at 10 years far exceeds the risk of biochemical disease relapse following a single IV zoledronate infusion.

Indications of therapy include pain, surgery planned on pagetic bone, active lesions on high risk sites and very high levels of ALP. Overtreatment should be avoided. Alternative explanations for pain should be sought when pain is not bisphosphonate responsive. Despite its benefits, treatment has not been shown to prevent complications.

Ongoing research focuses on the etiology of pain in Paget's, the role of microbiome and the potential of zoledronate for disease prevention in *SQSTM1* mutation carriers.

THE IMPORTANCE OF VITAMIN D ON THE MUSCULOSKELETAL SYSTEM

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Although rickets has been identified as a disease hundreds of years ago, the role of vitamin D in its pathogenesis was

only documented in the early twentieth century. Since then, vitamin D is considered beneficial for skeletal health. The primary role of vitamin D is to maintain normal levels of calcium and phosphate by increasing their intestinal absorption, thus ensuring normal skeletal mineralization. Additionally, vitamin D, via its receptor (VDR) expressed in bone stimulates bone resorption, in order to maintain the circulating calcium levels. This effect is exerted mainly in osteoblasts (by modifying RANKL and osteoprotegerin expression to promote osteoclastogenesis) and osteocytes. Excess of vitamin D (hypervitaminosis) is associated with sustained increase of bone resorption, whereas correction of its levels is associated with increases in BMD. On the other hand, severe impairment of vitamin D signaling results in hypocalcemia and osteomalacia, whereas partial vitamin D deficiency stimulates PTH secretion, resulting in secondary hyperparathyroidism, increased bone resorption and renal retention of calcium, which maintain normal serum calcium levels and bone mineralization at the expense of bone mass.

The rationale of administering vitamin D in the management of osteoporosis is to prevent secondary hyperparathyroidism, especially in vitamin D-deficient older adults. However, there are individuals with markedly low levels of 25(OH)D that do not develop secondary hyperparathyroidism and do not manifest adverse skeletal effects. The 25(OH)D threshold for increase in bone turnover markers and adverse biochemical changes is around 20 ng/mL. Treatment with high doses of vitamin D is imperative in patients with rickets/osteomalacia, as it may increase BMD by 50% in just 12 months. In the setting of osteoporosis, vitamin D supplementation is typically recommended to ensure adequate calcium absorption. Meta-analyses of trials evaluating vitamin D monotherapy found different effects on bone mineral density (BMD) depending on the bone site measured, e.g. modest increases by 0.8% at the femoral neck, but no effect at the lumbar spine and non-significant decrease at total body and forearm BMD. Results were dependent on Vitamin D baseline levels (significant increase in femoral neck BMD was observed only with baseline levels less than 16-20 ng/mL) and on Vitamin D dose (only daily dose of less than 800 units significantly increased both LS and FN BMD). The duration of Vitamin D monotherapy did not affect the between-groups differences (no benefit accumulation over time). The coadministration of calcium to all trial participants did not affect outcomes, implying that high calcium intake can partially compensate for low 25(OH)D levels. A meta-analysis of trials evaluating the role of calcium supplements, either as a monotherapy or with vitamin D, showed that calcium increases BMD, at

least by about 1%, with no further benefit when vitamin D was added.

Regarding the effects of Vitamin D supplementation on fracture prevention, meta-analyses of Vitamin D monotherapy demonstrated no benefits on either total or hip fractures. In agreement with these findings, a recent Cochrane Review concluded that "there is high quality evidence that vitamin D alone is unlikely to be effective in preventing hip or any new fracture." Furthermore, two trials administering annual high-dose vitamin D preparations showed significant increases in hip or total fractures, suggesting that infrequent mega-bolus dosing is unsafe. In the same meta-analyses, the combination of vitamin D with calcium reduced both total and hip fractures.

Besides bone, VDRs are abundant in skeletal muscle cells as well, indicating a direct link between vitamin D and muscle growth and function, via genomic and non-genomic mechanisms. In elderly women, supplementation with vitamin D was associated with increase in intra-myonuclear VDR concentration and in muscle fiber cross-sectional area, especially in type 2 fibers. Observational studies have also reported association between low 25(OH)D levels and poor physical performance and muscle dysfunction. Several meta-analyses show beneficial effects of daily vitamin D supplementation on muscle function, strength, balance and gait, especially in older individuals with low baseline 25(OH)D levels. A daily dose of 1000 IU appears to be enough, whereas, in contrast, large intermittent doses of vitamin D do not appear to improve muscle function and strength. The Endocrine Society Clinical Practice Guidelines recommend vitamin D supplementation depending on age and clinical conditions, in order to prevent falls in people at risk. However, the effects of vitamin D on the prevention of falls are debated, due to conflicting trials results. A relationship between vitamin D level and frailty has been demonstrated. However, it is still unclear whether vitamin D supplementation in frail people may reduce mortality and morbidity.

Overall, given that Vitamin D supplementation is safe and inexpensive, it is worthy to recommend vitamin D in patients at risk for falls (such as elderly or frail patients with gait, balance or visual impairments), and in patients with several chronic diseases. These people are most likely to have low 25(OH)D levels and muscle dysfunction, thus justifying supplementation independent of a putative effect on the prevention of falls or fractures.

In the years to come, we have to define more accurately the 25(OH)D levels that are related with adverse skeletal effects, and to determine its optimal levels for musculoskeletal and extraskelatal health, in order to identify who is truly vitamin D deficient and most likely to benefit from its supplementation.