

## Proceedings Article

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## Basic Knowledge of biological responses to musculoskeletal trauma

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### SYSTEMIC INFLAMMATORY RESPONSE TO MUSCULOSKELETAL INJURY (SIRS)

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The Systemic Inflammatory Response Syndrome (SIRS) represents the generalized response of the host to a variety of significant clinical insults, such as infection and trauma. There are specific criteria in the definition, such as: a) hyper- or hypothermia, b) heart rate >90/min, c) respirations >20/minute or PaCO<sub>2</sub> <32 mmHg and d) WBC >12,000/mm<sup>3</sup> or <4,000/mm<sup>3</sup> or >10% immature form, with ≥2 of these criteria being necessary.

Trauma is one of the more common causes of mortality worldwide. Death is the result of a chain of events starting with the “first hit”, which includes severe organ trauma, hypovolemia, hypoxemia or head injury among others. These can lead to the activation of the immune system and the initial inflammatory immune response after trauma can lead to SIRS. If more insults follow, they become the “second hit”, which can include infection, ischemia/reperfusion or surgical operations, then the inflammatory response is augmented, together with the mortality of the patient. Musculoskeletal injury through the activation of SIRS can lead to multi-organ failure with the loss of organ systems that were not directly involved by the initial trauma. The result is the activation of various parts/subsets of the immune system, including the neuroendocrine system, and the involvement of hormones or molecules such as ACTH, catecholamines, corticosteroids, cytokines and chemokines. The goal of this presentation is to stress the fact the musculoskeletal trauma is not an isolated injury, as it can lead to the activation of a mechanism meant to protect the organism; however, if it goes “unchecked” then it can easily lead to death.

### ENDOCRINE AND METABOLIC RESPONSE TO MUSCULOSKELETAL TRAUMA

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Musculoskeletal trauma leads to a cascade of metabolic, endocrine and immunological events, the magnitude of which is proportional to the severity of the trauma. The major stimulator for this response is the activation of the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis, modulated mainly by afferent nerve input. This leads to increased mobilization of substrates from carbohydrate, protein and lipid stores. In particular, the increased secretion of catabolic hormones, such as cortisol, catecholamines and glucagon, results in hyperglycaemia (via increased gluconeogenesis and glycogenolysis), increased protein catabolism coupled with decreased protein anabolism and increased lipolysis and ketone body production. The purpose of protein degradation is to release essential amino-acids, to be used as substrates for gluconeogenesis. This process and its transition to anabolic state are dependent on the extent of the trauma and the nutritional supply, as well as the body core temperature and heart rate. It usually takes a few weeks to a few months and is also induced by cytokine production, such as interleukines (IL) 1-17 (with IL-6 being the major contributor), interferons and tumor necrosis factor alpha. Increased catecholamine, cortisol and glucagon levels in conjunction with decreased insulin sensitivity lead to increased catabolism of triglycerides to free fatty acids and increased oxidation of the latter. Activation of the sympathetic nervous system also leads to increased renin production and concomitant angiotensin II and aldosterone production. The latter plays a major role in sodium and water retention from distal renal tubules, exerting also a negative feedback action on the anterior pituitary. Except for increased adrenocorticotrophic hormone (ACTH), triggered by hypothalamic releasing factors [such as the corticotroph

releasing factor (CRF) and anti-diuretic hormone (arginine-vasopressin)], growth hormone (GH) is also increasingly secreted after musculoskeletal trauma, leading to increased glucogenolysis and lipolysis. The other anterior pituitary hormones (except for prolactin) are relatively unaffected. The secretion of insulin, the main anabolic hormone, by beta-pancreatic cells is also reduced due to the inhibitory effect of catecholamines, creating a state of "insulin resistance". Thyroid hormone production is also reduced by the increased post-traumatic sympathetic activity, as well as that of other steroids such as estrogen and testosterone. Factors affecting metabolic and endocrine response to musculoskeletal trauma are patient's age, nutritional status, type of anaesthesia and surgery, infection, synchronous anti-inflammatory or immunosuppressive therapy, coexisting diseases and genetic predisposition. The main strategies to modify this response are agents such as opioids and anaesthetic drugs (e.g. etomidate), regional (epidural/spinal) anaesthesia, less invasive surgery, maintenance of adequate nutritional status, anabolic therapy (using GH and anabolic steroids) and normothermia.

## THE ROLE OF IMMUNE MECHANISMS IN THE PATHOGENESIS OF DUPUYTREN'S DISEASE

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Dupuytren's disease (DD) is characterized by the progressive development of a scar-like collagen-rich cord that affects the palmar fascia of the hand leading to digital flexion contractures. Nodules due to proliferation of fibroblasts in the superficial palmar fascia histologically are composed of fibroblasts, myofibroblasts and type III collagen. It is not clear whether its pathogenesis is of mechanical or biochemical nature but the net result is the same: excess production of matrix proteins and excessive accumulation of extracellular matrix (scarring) which changes tissue architecture and causes digital contraction.

- Laboratory studies suggesting that fibroblasts and myoblasts are upregulated by mechanical tension potentially leading to worsening of contractures (the incidence of DD is higher among workers exposed to repetitive handling tasks or vibration as compared with those not exposed such trauma).
- The accumulation of immune cells, expression of leukocyte adhesion molecules, as well as pro-inflammatory and pro-fibrotic cytokines near markedly narrowed vessels supports that the abnormal proliferation of fibroblasts and production of extracellular matrix proteins in DD seems to be related to immune-mediated microvascular damage.
- The restricted T-cell receptor repertoire of intra-lesional T-cells points to an antigen-driven process supports that T-cells play an important role in the development of DD.
- It was showed altered expression of extracellular

matrix-degrading proteases (matrix metalloproteases, and 'a disintegrin and metalloprotease domain with thrombospondin motifs', ADAMTS, proteases) in palmar fascia from DD patients compared to control.

- In palmar fascia of the hand of patients with DD in comparison with normal fascia tissue an increase in the number of mast cells was observed.
- Important seems to be also the role of Transforming Growth Factor- $\beta$  (TGF- $\beta$ ) by stimulating Dupuytren's fibroblasts to produce excessive levels of extracellular matrix proteins and promoting their contractile phenotype.
- A significant genome-wide association between DD and loci contain genes known to be involved in the Wnt-signaling pathway, as well as extensive dysregulation of Wnt signalling in DD affected tissue was also reported.
- Finally in DD palmar fascia tissue has been identified the presence of resident MSCs (mesenchymal stem/stromal cells) or adipose stem cells which may differentiate into highly specified fibroblastic populations such as inflammatory fibroblasts or myeloid fibroblasts. Cell-cell contact of DD myofibroblasts with adipose stem cells resulted in inhibition of contractility and smooth muscle actin expression of myofibroblasts.

## OSTEOINTEGRATION OF THE IMPLANTS

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It is well known that the successful survivorship of Orthopaedic implants like plates, screws and mainly prostheses (arthroplasties) greatly depend on primary osseointegration. Osseointegration or osseointegration refers to a direct bone-to-metal interface without interposition of non-bone tissue. This concept has been described by Branemark (1959), as consisting of a highly differentiated tissue making "a direct structural and functional connection between of living bone and the surface of a load-carrying implant".

From this first experimental study, osseointegration, gradually became a realised phenomenon of great importance for the everyday surgical orthopaedic practice. Recently, a lot of literature with clinical and experimental studies, osseointegration has been defined at multiple levels such as clinically, anatomically, histologically and ultrastructurally. The aim of the research was to evaluate the biology of the healing response to the implant surface and how the material's characteristics, such as surface preparations chemical composition, coatings and sterilization procedures, material's shape, size etc may affect the stability of the metallo-biological interface and therefore, implants' survivorship.

The main topics of Biology of implant osseointegration are the **tissue response to implantation** (hematoma, wovenbone and lamellar bone formation), the **peri-implant osteogenesis** (in distance and in contact) with increase the

osteogenic cells and decrease the osteoclastic cells and the formation of osteocontactive and osteoinductive bone tissue. Other topics of research are the **peri-implant bone remodeling** a wonderful phenomenon unique for the bone tissue and of course **the factors affecting osseointegration** internal or external like implant design factors, coating, use of adjuvant treatments etc.

## IMPLANTS IN ORTHOPAEDIC SURGERY: BIOMATERIALS

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Implants are widely used medical devices for the structural support or replacement of bones, especially following a fracture. Their use started very early in the 20<sup>th</sup> century, with documented discoveries dating back to the 19<sup>th</sup> century, as well. Although the practice of using foreign materials to treat human injuries sparked disbelief in its infancy, surgeons and inventors of that era are still highly regarded pioneers (e.g. Hoffman, Kirschner, Lambotte and Smith-Petersen). Nowadays, a plethora of biomaterials is available, covering a wide range of indications.

Biomaterials can be classified into three generations, based on the effects they exert to the host. First generation biomaterials (1980) are inert and offer a supportive role. Consequently, they are associated with minimal toxicity and do not trigger an immune response *in vivo*. Second generation biomaterials (1990s), though, are bioactive and biodegradable. They affect biological responses further to providing support in the tissue of interest. Whilst many are well absorbed in the tissue and degrade *in situ* parallel with the healing process, they are associated with higher immunogenicity rates compared to their first generation counterparts. Lastly, third generation materials (2002) are tailored to stimulate only some responses but not others, depending on the individual case. The specificity of targeting at the cellular level, using these materials, comes at the cost of potential immune-mediated complications.

The biomaterials most commonly used in orthopaedics, fall under three broad categories: metal alloys, ceramics and polymers (including carbon composites). All the aforementioned have clinical value, as shown by osteosynthesis and in joint replacement. Metal alloys (e.g. stainless steel, cobalt-chrome alloys and titanium alloys) are often used for external fixation and bearing surfaces owing to their strength. However, they fail to resist wear effectively and can lead to bone resorption due to excessive stress. Ceramics demonstrate various favourable properties (e.g. electro-thermal insulators and high compressive strength) and are used for knee prosthesis and femoral head replacement, amongst other operations. Depending on the ceramic, they can be bioinert ( $\text{Al}_2\text{O}_3$ ), bioactive (bioglass -  $\text{SiO}_2$ ) or biodegradable ( $\text{Ca}_3[\text{PO}_4]_2$ ). Despite being

very biocompatible, ceramics come at a high cost and their resistance to cracks as well as tensile strength is limited. Ultimately, polymers such as polymethylmethacrylate (PMMA) are tough materials resistant to wear, used in primary fixation, yet cannot withstand tension as effectively as bone and are thermoplastic. Other polymers (e.g. polylactate or polyglycolate) and carbon fibres are also available, but do not differ significantly from PMMA.

In summary, constant advances in biomaterials improve outcomes in patients after implants. The “ideal” material is chemically inert, strong, scores low in elastic modulus, fatigue resistant, non-toxic and all that at a low cost. However, response to implants depends on the age of the patient, amount of motion, mechanical load and composition of the implant, as well. Common complications include aseptic loosening, stress shielding, corrosion and infection. Therefore, the search for the “ideal” implant continues; perhaps, a material with the strength of metals and biocompatibility of ceramics may yield better results in the absence of severe complications.

## BEARING SURFACES IN TOTAL HIP REPLACEMENT

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Choosing the optimal combination of bearing surfaces in total hip replacement has been an area of debate since the first popular total hip replacement by Sir J. Charnley who used a metal head with a polyethylene acetabular cup. Ever since, various combinations have been tested and used, in an effort to identify the optimal one. Ideally it should combine low friction, low wear rate and high biocompatibility. These combinations fall into two major categories: hard on soft surface and hard on hard. Metal and ceramic bearing represent harder surfaces and polyethylene the softer ones. Each combination has its own advantages and disadvantages. First generation of polyethylene lost its popularity in the 2000's when it was replaced by hard on hard combinations. However its mechanical characteristics were improved in the latest ultra-high molecular weight polyethylene and it has once become the gold standard in most of the cases.

## BONE GRAFTS

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Bone graft is a material with either osteoinductive, osteoconductive or/and osteogenic properties and it is mainly used for the treatment of delayed union or non-union, for fusion procedures, after osteotomies, for reconstruction of bone defects secondary to trauma, tumor or infection

and as bone block. Since 1668 and Van Meekeren's first recorded bone transplant, bone grafting has been evolved significantly and nowadays over one million bone grafting procedures performed in US each year.

In order to achieve uneventful fracture healing four parameters (osteogenic cells, osteoconductive scaffold, growth factor and a stable mechanical environment) are mandatory, the so called 'Diamond Concept'. Later vascularity at the defect site is added as an important factor in the fracture healing process.

Bone grafting materials can be classified in autografts, allografts and synthetics. Though autografts considered gold standard, limitations do exist regarding donor side morbidity and graft availability. Iliac crest bone graft (ICBG) is by far the most commonly used autologous bone graft compared to other alternative donor sites.

Allogenic bone is available in many forms: demineralized bone matrix (DBM), morselized and cancellous chips, corticocancellous and cortical grafts, and osteochondral and whole-bone segments.

Demineralized Bone Matrix (DMB) is probably the most common form of allograft used nowadays.

Synthetics, like Calcium hydroxyapatite (HAp), Tricalcium phosphate (TCP) or Calcium phosphate cement (CpC), are used for their osteoconductive properties. Their basic function is to provide a matrix to support the attachment and colonization of bone-forming cells for subsequent bone formation. Can also be used as a vehicle for local growth factor or antibiotic delivery.

Also Osteogenic proteins (OP) are elements of a class of natural growth factors called bone morphogenic proteins (BMP). The isolation of the genes coding these proteins from human DNA has identified a family of proteins from BMP 2 to BMP 6 and from OP 1 to OP 3.

In addition, as investigators continue to find new materials and biologic approaches to bone repair, the future of bone graft substitutes continues to be an expanding topic.

Control of bone regeneration with strategies that mimic the normal cascade of bone formation will offer successful management of conditions requiring enhancement of bone regeneration, and reduce their morbidity and cost in the long term.

## DRUGS AND IMPLANT 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. Currently, an implant is considered as osseointegrated when there is no progressive relative movement between the implant and the bone with which it has direct contact.

Low-molecular weight heparin (LMWH) is routinely used to

prevent thromboembolism in orthopaedic surgery, especially on the treatment of fractures or after joint-replacement. Impairment of fracture healing due to increased bone resorption, delayed remodeling and lower calcification caused by direct osteoclast stimulation is a well-known side-effect of unfractionated heparin. 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. Further large clinical studies to compare different types of LMWHs, in different dosages and in different patient or animal models are needed for exploring the effects of LMWH on fracture healing process and implant osseointegration.

Moreover, enoxaparin, as early as the first week of treatment, increases mesenchymal stem cells (MSCs) potential to migrate to the trauma site and proliferate, however, enoxaparin also inhibits MSCs 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.

Furthermore, even low dose methotrexate acts as a potent inhibitor of osteoblast's proliferation and mitochondrial metabolism in vitro. These results suggest possible negative effects of disease modifying antirheumatic drugs (DMARDs) concerning bone healing and implant osseointegration. Finally, cyclosporine A therapy negatively affects the bone healing around osseointegrated implants due to the significant lower values for bone to implant contact and bone density.

On the other hand, in rats losing bone rapidly after ovariectomy, systemic administration of zoledronic acid (ZOL), alendronate (ALN) and strontium ranelate (SR) causes better bone-implant osseointegration; ALN and SR have similar positive effects on osseointegration, while ZOL, that was given in a dose with more positive bone mineral density (BMD) effect than that of ALN or SR, causes better osseointegration than either ALN or SR. Simultaneously, ibandronate accelerates osseointegration of hydroxyapatite-coated cementless implants in an animal model while teriparatide enhances titanium implant anchorage in low-density trabecular bone.

Implants loaded with simvastatin by an electrochemical process improved implant osseointegration in osteoporotic rats. Furthermore, the increased concentration of simvastatin could affect the osseointegration, but the dose effects also need further investigation. Moreover, the efficacy of vitamin D3 supplementation on osseointegration of implants remains controversial and requires further investigation.

The concept of drugs and biology of implants osseointegration is complicated and larger and more sophisticated in vitro and in vivo studies are needed in the future, in order to confirm the effect of drugs on this.



## STEM CELLS IN THE TREATMENT OF FRAILITY AND SARCOPENIA

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Frailty is a syndrome of old age characterized by increased mortality and poor muscle strength and regarded as an end stage consequence of the biological processes of aging. Underlying pathobiology includes cellular senescence, mitochondrial dysfunction, increased oxidative stress, dysregulation of inflammatory processes and genomic instability. Therapies proposed up to date have little success and include exercise, vitamins, special diet and hormone supplementation. Impaired muscle regeneration might contribute to loss of muscle mass and increased lipid content, both characteristic of aged muscle and the process of sarcopenia. Muscle side population (SP) cells are rare multipotent stem cells that can participate in myogenesis and muscle regeneration upon transplantation. Muscle SP cells that express the hematopoietic stem cell markers Sca-1 and CD45 can differentiate not only in skeletal muscle but also in cells into hematopoietic cells. On the other hand bone marrow-derived hematopoietic stem cells have abundantly found in regenerating muscle areas of both young and old rats. An age-related decrease in the number of these cells in regenerating areas of old rat muscle has been reported coinciding with the reduction in muscle SP cell number with age related impaired muscle regeneration. It has been observed that depletion of stem cells conserving motor neurons sped up muscle decline. On the contrary no evidence of motor neuron loss, contributing to muscle loss has been observed in old age. It has been reported that mesenchymal stem cells (MSCs) home to sites of inflammation and injury; differentiate into various cell types; secrete growth factors and suppress inflammation being immunomodulatory. Hundreds of clinical trials for many disorders including osteoarthritis, trauma, stroke, autoimmune disease, heart infarct and , graft-versus-host disease have been reported. The safety of these therapies has been proven, while the best conditions to improve efficacy are a matter of continuing investigation. MSC can be harvested from the patients themselves (autologous) or from a donor (allogeneic), with autologous cells being preferable. It has been observed that stem cells harvested from younger donors are more potent in those therapies since age-related changes in stem cells impair their differentiation and multiplication ability. The possibility that young stem cells may become in the future “vehicles for youthful regeneration of aged tissues” is well known. Hematopoietic and Mesenchymal stem cells from young mice infused into old mice reversed the effects of aging and increased life span, improving cardiac and reproductive function. An alternative therapeutic approach is to rejuvenate endogenous stem cells inducing “Yamanaka factors”, as shown in a progeria mouse model. Frailty is

associated with reduced circulating MSC, and therefore could become an ideal target for clinical trials of MSC therapies. Recently the results of two early phase clinical trials considering MSC administration in frail patients have been published, indicating the safety and possible efficacy of these treatments. Larger clinical trials are expected in the near future to corroborate the usefulness of such interventions. A disadvantage in these treatments, is that autologous stem cells cannot be used, since no one of these patients has stored stem cells upon birth.

## LEGAL STATUS OF STEM CELLS IN GREECE: BIOETHICAL ISSUES

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Stem cells have attracted significant international interest over the last decades. Various controversial issues have arisen, concerning a variety of fields, such as medical practice and research, public health policy, bioethics, and, of course, law. The legal regulation of stem cells cuts across many areas of law, as diverse as constitutional law and human rights, administrative law, medical law, data protection and bioethics, contract law, family law and company law. The presentation provides an overview of the legal framework of stem cells in Greece. In particular, it discusses the legal status of stem cells, and the rights and obligations arising thereof. Focusing mainly on the legal treatment of umbilical-cord-blood-derived stem cells, the presentation analyses the legal provisions for collection, processing and cryopreservation of stem cells, and the regulatory framework of stem-cell banking and research.

## SPINAL CORD INJURY AND CELLULAR THERAPIES

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Spinal cord injury is a devastating disease resulting in loss of motor, sensory and sphincter function. The prognosis for substantial and lasting neurological recovery after complete lesions remains dismal. From the pathophysiological point of view, one can discern the primary injury, which is the result of the immediate impact and the secondary one, which is the most detrimental and results from reduced blood flow, breakdown of blood-brain barrier and various metabolic derangements.

At present, patients are treated surgically, provided there is an indication for decompression and stabilization, as soon as possible (according to STACIS) and follow intensive rehabilitation protocols. Although a modest level of quality of life and interdependence is achieved in a lot of cases, the functionality of the nervous tissue is not yet restored.

Current research in spinal cord injury focuses on three distinct orientations, namely neuroprotection (Rescue neurons), regeneration (Rewiring) and reactivation of the intact circuits (Reactivation), commonly known as the 3Rs in the literature. Neuroprotection entails various pharmaceutical substances and surgical techniques (hypothermia, duroplasty) aiming at rescuing neurons at a critical situation. Even though numerous drugs have been used, no clear beneficial effect has been characterized so far and the initial enthusiasm for corticosteroids has been abandoned. Reactivation of the circuits of the central pattern generator is a very promising domain. Implantation of spinal cord stimulators has begun, and very optimistic results have been published.

The most exciting, challenging and rewarding target, however, is the restoration of the damaged neural circuits. Central nervous system, in contrast with the peripheral one, lacks the ability of regeneration. Various factors, most of them related to myelin, have been implicated for this difference. A substantial number of studies have been performed towards the creation of a more permissive environment for the induction of regeneration, albeit with limited results.

Cellular therapy is undoubtedly the mainstay for inducing regeneration. Cell transplantation confers several advantages for laboratory and clinical trials. Although intuitively, one should expect lost neuronal cell replacement by the transplanted cells, the beneficial effect is mainly indirect, by providing a scaffold for trophic support, neurotrophin production, neovascularization, scar tissue minimization.

In laboratory animals, several studies have clearly shown that cellular transplantation improves neurological recovery, in behavioral, electrophysiological and neuroanatomical aspect. It is very difficult to extrapolate these results in human patients but cell types which have been used comprise:

- **Schwann cells:** to take advantage of the inherent regenerative capacity of the peripheral nervous system.
- **Mesenchymal cells:** collected from bone marrow stroma, adipose tissue, periosteum, placenta. Present two basic advantages, firstly they are abundant and secondly, they are autologous, obviating the need for immunological suppression.
- **Olfactory ensheathing glial cells:** differentiated nervous system cells capable of multiplication. Easily obtained.
- **Embryonic stem cells:** present the most intriguing advantages and have the greater potential for nerve tissue repair.
- **Induced pluripotent stem cells:** the most recently discovered cell type which has opened new horizons into cellular therapy. Somatic cells of any individual may be converted to stem cells and then become reimplanted into the same individual. No clinical application has been reported, but at least theoretically, it would be an ideal option. A lot of issues remain to be resolved.

Recapitulating the recent findings, there is considerable hope that spinal cord injury will not be irreversible in the nearby future. Cellular therapy is one of the most optimistic

approaches for nerve tissue regeneration and functionality restoration and will be probably implemented combined with the other available techniques.

## CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS

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Chronic recurrent multifocal osteomyelitis (CRMO) is an idiopathic inflammatory disorder of bone, characterized by multifocal nonpyogenic inflammatory bone lesions, a course of exacerbations and remissions, and an association with other inflammatory disorders (palmoplantar pustulosis, psoriasis vulgaris, Sweet syndrome, and pyoderma gangrenosum). Patients typically present with nonspecific complaints such as pain, tenderness, swelling, or limited range of motion at one or more sites. Systemic manifestations such as fever, weight loss, and lethargy may be present. The duration of symptoms can vary from days to several years. At histologic evaluation, CRMO bone lesions show nonspecific inflammatory changes with granulocytic infiltration. Laboratory findings at initial presentation are essentially nonspecific, with the most common findings being mildly elevated erythrocyte sedimentation rate and C-reactive protein level with a normal white blood cell count. The imaging evaluation of CRMO should start with radiographic evaluation of the symptomatic sites. In the early stages, plain radiographs typically demonstrate an osteolytic lesion but with time, progressive sclerosis is seen around the lytic lesion, so that chronic lesions may be predominantly sclerotic with associated hyperostosis. MR imaging is useful both for determining the extent of disease and for follow up. During the active phase of the disease, MR imaging shows typical findings of marrow edema, which appears hypointense on T1-weighted images and hyperintense on T2-weighted images. When a diagnosis of CRMO is considered on the basis of clinical findings and initial imaging evaluation, further evaluation of the whole body is suggested to identify multifocal lesions that may be clinically asymptomatic. Whole-body evaluation has traditionally been performed with <sup>99m</sup>Tc bone scintigraphy, although whole-body MR imaging is being increasingly used for evaluation of multifocal bone lesions. Diffusion-weighted imaging (DWI) helps to gain information about tissue cellularity. Treatment generally involves antiinflammatory agents targeting symptomatic relief. NSAIDs are usually effective in symptomatic relief. Other pharmaceutical agents that have been tried include corticosteroids, bisphosphonate, sulfasalazine, methotrexate, colchicines, interferon- $\alpha$  and interferon- $\gamma$ , and  $\gamma$ -globulin. Recently, biologic therapy as

drugs blocking the tumor necrosis factor- $\alpha$  (infliximab, etanercept) or the receptor of interleukin-6 (tocilizumab) has shown successful symptomatic relief and decrease or disappearance of the MRI findings.

## BIPHOSPHONATE-RELATED ADVERSE EVENTS

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Bisphosphonates are considered the mainstay of anti-osteoporosis treatment. Their antifracture efficacy has been demonstrated in numerous studies in the last decades and the use of bisphosphonates has been growing steadily with the introduction of simpler dosing regimes and availability of lower-priced generics. Although bisphosphonates have a relatively good safety record and are tolerated well by the majority of patients, serious adverse events have been associated with their use, even when prescribed and used correctly. However, only the most common of adverse effects are robustly observable in clinical trials.

The most common acute adverse events reported during the use of bisphosphonates for osteoporosis are gastrointestinal discomfort and acute influenza-like syndrome. Renal complications are very rare with oral bisphosphonates and rare with i.v. bisphosphonates when used appropriately. Based on our current knowledge, skeletal events in the form of osteonecrosis of the jaw and atypical fragility fractures are rare compared with the risk of osteoporotic fractures, at least in patients with the same risk of fractures. From a biological point of view atypical fragility fractures could follow from suppression of bone remodeling, but high-quality studies proving causality are lacking.

Other less common bisphosphonate-related adverse events include: bone, muscle, and joint pain, atrial fibrillation, ocular adverse events such as uveitis, periscleritis, and scleritis, severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, which are very rare, hypocalcemia and hepatotoxicity. Physicians are advised to critically reassess BMD and risk profile after 3-5 years of therapy to avoid treatment in patients at low risk.

## DISCONTINUATION OF ANTI-OSTEOPOROTIC TREATMENT: IN WHOM AND FOR HOW LONG?

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Osteoporosis is a chronic disease, thus a long-term treatment seems rational to protect the affected individuals from low-energy fractures. However, owing to uncertainty about the long-term use and effectiveness of existing anti-osteoporotic medications, their discontinuation (or drug holiday) has been

proposed. Given the pharmacologic differences of available anti-osteoporotic medications, they should be separately evaluated.

Bisphosphonate (BP) treatment partly preserves its benefits after their discontinuation, because they are retained in the skeleton for long after their use. A drug holiday should be considered after a 5-year treatment, especially in patients on risedronate, alendronate or zoledronic acid, since more data exist for these BPs. If the patient sufficiently responded to BP treatment (a bone mineral density [BMD] T-score  $>-2.5$  is regarded as the cut-off by most authors), did not experience a new low-energy fracture during treatment and remains at low risk of fracture, the BP treatment could be discontinued. Follow-up of 1-2 years is recommended. Although directly comparative data are missing, drug holiday may be longer after zoledronic acid rather than alendronate or risedronate discontinuation. Treatment with BP or another anti-osteoporotic medication should be restarted, if the patient experiences a new low-energy fracture or T-score becomes  $\leq -2.5$  or the fracture risk is increased during follow-up.

Selective estrogen receptor modulators (SERMs) treatment should be re-evaluated after 3-5 years of use. Drug holiday and follow-up may be considered for patients with low fracture risk. However, sequential treatment, usually with BP or denosumab, should be considered for high-risk patients.

Denosumab, an antibody against the receptor activator of nuclear factor kappa-B ligand (RANKL), discontinuation results in a rapid rebound in bone turnover markers followed by a rapid decrease in BMD. This may even lead to multiple vertebral fractures in some patients, especially those with a prior vertebral fracture and/or those without previous BP treatment. Based on these considerations, denosumab must not be discontinued based on BMD. If discontinuation is decided (by the patient or the physician) or the patient completes a 10-year treatment with denosumab, another anti-osteoporotic treatment, preferably a BP, should be immediately administered, so as to prevent the rapid rebound in bone turnover.

The use of teriparatide or recombinant parathyroid hormone, both osteoanabolic medications, is limited to a 24-month duration, partly owing to cost-effectiveness policy. However, sequential treatment with an anti-resorptive medication, preferably BP or denosumab, is considered important to maintain bone mass and improve mineralization. Similarly, limited data on discontinuation of romosozumab, an anti-sclerostin antibody, support that its anabolic effects are limited to the time of administration, so sequential treatment is needed, possibly with BP or denosumab.

Calcium and vitamin levels must not be discontinued together with the aforementioned medications; their levels should be monitored and supplementation should be considered separately, as needed. In conclusion, until well-designed trials provide better clinical answers, it is of importance that the benefits and potential side effects of each medication be weighted in an individual basis.

## UNIQUE PROPERTIES OF THE IMMATURE SKELETON, RESPONDING TO TRAUMA

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Fractures in children are common. Almost 30% of boys have sustained a fracture by the age of 16. Bones have higher elasticity, thick periosteum and active growth plate. There are different types of fractures in children. The remodeling process is active and the management of pediatric fractures is different, regarding deviation and time for healing.

Buckle or torus fractures are found at the junction of metaphyseal to diaphyseal area of long bones. There is deformation of one cortex to complete fracture, with buckle appearance. Green stick fractures appear with complete fracture of one cortex and plastic deformation of the other site, due to the thick and intact periosteum. Plastic deformation, usually affecting the forearm and mainly the ulna, is a type of fracture with angulation, without cortex fracture.

The striking feature of pediatric fractures is the remodeling process. The ability for gradual correction of the angulation is greater the younger the child. The more proximal to the growth plate is the angulation and the level of deformity, the bigger the remodeling. We must carefully estimate the deformity in order to accept it as part of conservative management or proceed to intervention.

Neonatal fractures are rare regarding long bones, most commonly affecting the femur. They pose severe medico legal problems, we must consider pathological fractures as in osteogenesis imperfecta. Often no cause can be detected.

Fractures of the clavicle are consolidated with rapid bone formation, with the membranous bone formation process.

Fractures of the growth plate are unique. Classification of growth plate injuries, commonly with the Salter Harris, enables us to decide the appropriate treatment. We aim for the most accurate reduction but occasionally greater effort may lead to more damage. Intra articular separation requires anatomical reduction. Severe crushing injury may lead to physal arrest and disturbance of the growth of the limb, mainly the lower limb.

Fractures in children with minor violence are sustained when the bone strength is impaired, as in bone cysts. The bone healing is not affected, but the treatment is focused for the management of the underlying pathology that appeared as pathological fracture.

Osteoporotic fractures are found in children with primary osteoporosis (osteogenesis imperfecta) or in secondary osteoporosis, (cerebral palsy). All neuromuscular disorders may present with fractures. Their management is influenced from the underlying disease, as children with muscular dystrophy that we must regain quickly their motor ability. Appropriate antiosteoporotic medication is helpful. In absence of pain (meningocele), fractures are discovered because of deformity.

Fractures in children have different types of management, depending on the anatomical site and the age. Fractures of the upper part of the humerus are more often treated conservatively while fractures of the elbow region are more complicated and require intervention often. In the lower limb, fractures are often treated with intervention, for better quality of daily life of the family, but with the risk of the intervention.