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BONE MODELING AND BONE FRAGILITY

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Key-words: Bone modeling, Remodeling, Bone fragility, Peak bone mass, Fractures

The cellular activities of bone modeling and remodeling determine the material composition and structure of bone. Bone modeling refers to the deposition of new bone without prior bone resorption. Bone remodeling is characterized by the appearance of focally and temporally distinct regions of resorption followed by bone formation that constitutes the basic multicellular units (BMUs).The purpose of bone modeling and remodeling during growth is to build peak bone strength. After the completion of growth, bone modeling continues in adulthood modestly to increase bone size further, whereas bone remodeling maintains bone strength by removal of microdamage.

The concept of peak bone mass more broadly captures peak bone strength, which is characterized by mass, density, microarchitecture, microrepair mechanisms and the geometric properties that provide structural strength. If the magnitude of peak bone mass attained in young adulthood is an important predictor of osteoporosis later in life, then the timing of peak bone mass is also important because it defines the lifecycle phase during which peak bone mass can be optimized

Although bone mineral density (BMD) is among the strongest risk factors for fracture, a number of clinical studies have demonstrated the limitations of bone mineral density measurements in assessing fracture risk and monitoring the response to the therapy. These observations have brought renewed attention to the broader array of factors that influence skeletal fragility, including bone size, shape, micro-architecture and bone quality. Bone fragility can be defined by biomechanical parameters, including ultimate force, ultimate displacement and energy absorption.

The biomechanical definition of bone fragility includes at least three components: strength, brittleness and work to failure. A fourth biomechanical measure, stiffness, also is used to assess mechanical integrity of bones, but is not a direct measure of fragility. There are at least three ways to make the skeleton stronger. First, increase bone mass-larger bones can carry more load. Second, distribute bone mass effectively, i.e. put bone tissue where the mechanical demand are greatest. Third, improve the material properties of bone tissue such that the bone is stronger at a tissue-level.

The causes of bone fragility are: abnormal collagen (Osteogenesis imperfecta, Paget's disease of bone), mineralization defect (osteomalacia), abnormal remodeling rate and balance (turnover) [A. High bone turnover with negative BMU balance- postmenopausal osteoporosis, hyperparathyroidism, B. Other abnormalities of bone turnover with negative BMU balance- osteoporosis in men, corticosteroid-induced osteoporosis]

The genetic basis of osteoporosis has been difficult to identify. Nevertheless, several approaches have been undertaken in the past decades in order to identify candidate genes for bone fragility, including the study of rare monogenic syndromes with striking phenotypes (Osteogenesis imperfecta and osteopetrosis), the analysis of individuals or families with extreme osteoporotic phenotypes (idiopathic juvenile and pregnancy-related osteoporosis) and chiefly, genome-wide association studies.

A better Knowledge of the relative importance of the different determinants of the bone "quality" (intrinsic properties of bone matrix, bone architecture and turnover) in the determination of skeletal strength and fragility will improve the understanding of the pathogenesis of bone fragility in metabolic bone diseases.

References

1. Leali Paolo Tranquilli, Doria Carlo, Zachos Alexandros, Ruggiu Adriano, Milia Fabio, Barca Francesca. Bone Fragility: current reviews and clinical features. Clinical cases in Mineral and Bone Metabolism 2009; 6(2):109-113.

2. Leali Paolo Tranquilli, Muresu Francesco, Melis Alesandro, Ruggiu Adriano, Zachos Alexandros, Doria Carlo. Skeletal fragility definition. Clinical cases in Mineral and Bone Metabolism 2011; 8(2):11-13.
3. Rocha-Braz Manuela GM, Ferraz-de-Souza Bruno. Genetics of osteoporosis: searching for candidate genes for bone fragility. Arch Endocrinol Metab 2016; 60(4):391-401.
4. Turner CH. Determinants of skeletal fragility and bone quality. J Musculoskel Neuron Interact 2002; 2(6):527-528.
5. Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, Karma MO, Wallace TC, Zemel BS. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. Osteoporos Int 2016; 27:1281-1386.

BONE QUANTITY AND SKELETAL FRAGILITY

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Keywords: Bone strength, Fragility, Bone quantity, Bone quality, Bone mineral density

Osteoporosis is defined as "a skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture". This definition underscores the role of bone strength and implies that understanding bone strength is the key to understanding fracture risk. Bone fragility is determined by bone quantity and bone quality, defined broadly as all geometric, microarchitectural, and material factors (e.g., trabecular architecture, collagen crosslinking, mineralization, microcracks) that contribute to whole-bone fracture resistance. Also bone fragility can be defined by biomechanical parameters, including ultimate force, ultimate displacement and energy absorption. Factors that influence skeletal fragility, include bone size, shape, micro-architecture and bone quality. The deterioration of bone with age has focused on bone quantity as a predictor of such fracture risk, where quantity is described by the bone mass or bone mineral density (BMD), defined as the amount of bone mineral per unit cross-sectional area. Bone strength depends on the structural and material properties of bone, both of which are influenced by the rate of bone turnover. Not all determinants of bone strength are well represented by a BMD measurement. Greater understanding of the concept of bone quality will ultimately help improve the assessment of fracture risk and monitoring of patients receiving treatment for osteoporosis. Bone mineral density (BMD, g/cm^2), provides a combined measure of quantity and quality, because areal BMD (aBMD) cannot distinguish between thicker bones (greater quantity) and more highly mineralized bones (altered quality). BMD assessed by DXA has moderate ability to predict fracture risk in untreated patients and to predict the reduction in risk in patients treated with antiresorptive therapies. Although low BMD is among the strongest risk factors for fracture, a number of clinical studies have demonstrated the limitations of BMD measurements in assessing fracture risk and monitoring the response to therapy. One of the keys to redefining osteoporosis is new technology to better identify the risk of fractures. High-resolution peripheral quantitative computed tomography (HRpQCT) is such a technology that allows the measurement of trabecular and compact bone and the repetitive 3D assessment and computation of microstructural and micromechanical properties in patients. The procedure can help improve predictions of fracture risk, clarify the pathophysiology of skeletal diseases, and define the response to therapy. Microarchitectural bone imaging in combination with computational approaches are well suited to investigate structure-function relationships and failure mechanisms in normal, osteoporotic, and treated bone. Furthermore, it may provide a new clinically accessible methodology to assess implant stability and monitor fracture healing.

References

1. Leali PT, Muresu F, Melis A, Ruggiu A, Zachos A, Doria C. Skeletal fragility definition. Clin Cases Miner Bone Metab 2011; 8(2):11-3.
2. Seeman E. Pathogenesis of bone fragility in women and men. Lancet 2002; 359:1841-50.
3. Donnelly E, Lane JM, Boskey AL. Research perspectives: The 2013 AAOS/ORS research symposium on Bone Quality and Fracture Prevention. J Orthop Res 2014; 32(7):855-64.
4. Bouxsein ML, Seeman E. Quantifying the material and structural determinants of bone strength. Best Pract Res Clin Rheumatol 2009; 23:741-753.
5. Ritchie RO. How does human bone resist fracture? Ann N Y Acad Sci. 2010; 1192:72-80.
6. Roux C, Briot K. Current role for bone absorptiometry. Joint Bone Spine. 2016. pii: S1297-319X(16)30067-7. doi: 10.1016/j.jbspin.2016.02.032. [Epub ahead of print]

HOW DO BONES SENSE AND RESPOND TO MECHANICAL STIMULI?

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Key words: Osteocytes, Mechanotransduction, Mechanostat, Bone remodeling

Bone is a dynamic tissue that responds to external stressors in order to maintain a steady state. Whilst gravity is one of the main factors influencing bone growth, there are several other mechanical stimuli of great importance. When force is applied onto bone, the mechanical signal is transduced to intracellular signals that determine bone metabolism. In this way, bone can grow and remodel appropriately, to respond to the external stressor.

The cells involved in orchestrating bone remodeling are the osteocytes. They are specialized cells able to form gap junctions for inter-cellular communication. They possess integrins, ion channels and primary cilia, all of which are essential for the process of mechanotransduction, the translation of a physical (mechanical) stimulus into a biochemical one that is compatible with cells. Examples of signals which can trigger such a response in osteocytes are, but not limited to: electromagnetic fields, vibration and centrifugation. After sensing the signal, focal adhesions can form between integrins to facilitate bone formation. Ion channels are particularly relevant for the movement of Ca^{2+}, which drives intracellular responses. Signaling through primary cilia can result in increased COX-2 expression, increased osteoprotegerin to receptor activator of nuclear factor κB ratio (OPG:NFκB) and release of prostaglandin E2 (PGE2). The osteocytes are capable of sensing tension, fluid flow shear stress (the movement of fluid in the canaliculi), piezoelectricity (temporarily negatively or positively charged areas due to compression or tension, respectively) and streaming potentials. The process of reception of mechanical stimuli by the osteocytes is influenced by genetic factors, age and hormonal background, but not by nutritional status.

Mechanical use is crucial for modeling of bone. Inadequate use can result in loss of bone mass. Physiological use comes with controlled modeling and, overuse results in increased formation of bone. However, pathological overload leads to microdamage, as the repair phase of the remodeling fails to meet the increased demand[1]. Accumulation of microdamage can eventually lead to fracture. This relationship was best framed by H.M. Frost, who proposed the theory of the mechanostat: bone adapts to mechanical stimuli and in order to maintain a healthy state, coordination between modeling and remodeling is required[2]. If the balance is disrupted severely in either side –shifting the system outside of the "useful window"- pathology is established. Factors influencing bone strain are the size, the frequency and the duration of the applied load[3]. The importance of constant bone resorption and formation is seen in targeted remodeling of big bones. Without the ability to restore healthy bone in places of microdamage, weight bearing bones such as tibia are estimated to fracture after 3 years of routine use[4].

In conclusion, mechanical stimuli influence bone metabolism. The signals are received and translated through the osteocytes, which can then stimulate bone formation through release of NO and PGE2. Disuse or excessive overloading can disturb the homeostasis in bone remodeling and lead to fracturing or loss of bone mass. Finally, both low frequency with high tension, and high frequency with low tension stimulate bone formation[3].

References

1. Rosa N, Simoes R, Magalhaes FD, Marques AT. From mechanical stimulus to bone formation: A review. Med Eng Phys. 2015; 37(8):719-728.
2. Tyrovola JB. The "Mechanostat Theory" of Frost and the OPG/RANKL/RANK system. J Cell Biochem 2015;116(12):2724-2729.
3. Carlos Vinicius Buargue de Gusmao, William Dias Belangero. How do bones sense mechanical loading. 2009 Sociedade Brasileira de Orthopedia e Traumatologia.
4. Hughes JM, Petit MA. Biological underpinnings of Frost's mechanostat thresholds: the important role of osteocytes. J Musculoskelet Neuronal Interact. 2010;10(2):128-135.
5. Santos A, Baker AD, Klein-Nulend J. The role of osteocytes in bone mechanotransduction. Osteoporos Int 2009; 20:1027-1031.

IS THERE A ROLE OF OSTEOBLASTS AND OSTEOCLASTS IN BONE MECHANOSENSING AND MECHANOTRASDUCTION?

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Keywords: Osteoblasts, Osteoclasts, Osteocytes, Mechanosensing

Mechanical loading is a criticial regulator of bone function and integrity. Upon loading specialized bone cells sense those changes and convert mechanical signals to biological ones tranducting the information across the skeleton. Cells of the osteoblastic lineage (osteoblasts, lining cells and osteocytes) are the main cells for sensing external loads and adapting to the everchanging bone microenviroment.

The role of the osteocyte as the mechanosensory cell in bone has long been postulated based on the fact that is the most abundant and long-lived cell in bone and is ideally situated to perceive changes in external forces. Osteocytes create a complex network with other osteocytes even at long distance and with cells at the surface, thereby orchestrating bone remodeling through paracrine factors and cell-cell interactions.

The identity of mechanoreceptors is manifold and concerns ion channels, integrins and cell membranes. Integrins are heterodimeric protein complexes that connect the cell to the pericellular environment by spanning the plasma membrane and forming adhesions with the adjacent tissues or cells. The binding of ligands to the extracellular domain of integrins transmits signals activating intracellular signaling, while modification of intracellular domains also regulates the binding affinity of extracellular molecules. Primary cilia, is also one of the most revisited candidates for mechanosensing and consists of a central axis composed of nine microtubules surrounded by a specialized membrane. However, the number of primary cilia found within the bone cells and in the bone marrow is small (<5% and 1% respectively) and thus these structures cannot be the primary mechanosensor. Other

mechanosensing candidates include gap junctions that are created by connexins, pores formed by connexons within the plasma membrane and tethering elements that are transverse and elongated proteoglycan molecules that extend across the pericellular space of the osteocyte.

Similar multiplicity characterizes the intracellular molecular pathways that are activated during mechanical loading with ERK kinases, MAPK kinases, prostaglandins and Wnt signaling contributing the most. In a recent study that compared the mechanosensing abilities of osteoblasts versus osteocytes it has been shown that both cell types activate the same molecular pathways when stressed but with significant differences in the sensitivity and kinetics of the response mechanisms.

Osteoclasts derived from the hemapopetic/macrophage lineage and are the shortest-lived cells in bone tissue. Its function as the bone-resorbing cell of the skeleton is very targeted and osteoclastogenesis takes place almost exclusively in the sites where bone resorption is indicated, as directed by the osteocytes with the secretion of the major osteoclastogenic cytokine RANKL. Due to their short lifespan (approximately 7-14 days) and their proteolytic nature, mature osteoclasts do not hold any kind of mechanosensing property.

References

1. Kamel MA1, Picconi JL, Lara-Castillo N, Johnson ML. Activation of β-catenin signaling in MLO-Y4 osteocytic cells versus 2T3 osteoblastic cells by fluid flow shear stress and PGE2: Implications for the study of mechanosensation in bone. Bone 2010; 47(5):872-81.
2. Yavropoulou MP, Yovos JG. The molecular basis of bone mechanotransduction. J Musculoskelet Neuronal Interact 2016; 16(3):221-3.
3. Chen JC, Hoey DA, Chua M, Bellon R, Jacobs CR. Mechanical signals promote osteogenic fate through a primary cilia-mediated mechanism. FASEB J 2016; 30(4):1504-11. doi: 10.1096/fj.15-276402.
4. Tsuchiya N, Kodama D, Goto S, Togari A. Shear stress-induced Ca(2+) elevation is mediated by autocrine-acting glutamate in osteoblastic MC3T3-E1 cells. J Pharmacol Sci 2015; 127(3):311-8.
5. Capulli M, Paone R, Rucci N. Osteoblast and osteocyte: games without frontiers. Arch Biochem Biophys 2014; 561:3-12.

BIOMECHANICS OF FRACTURE HEALING

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Keywords: Fracture healing, Biomechanics, Mechanobiology, Inter-fragmentary micromotion, Mechanical stability

The biological process of bone fracture healing consists of two types. Primary one, which occurs with absolute stability constructs via intramembranous healing and secondary bone healing which occurs with non-rigid fixation via enchondral healing. The biomechanical process of both primary and secondary bone fracture healing is explained by Perren's inter-fragmentary strain theory. Mechanical stability at the fracture site relates mechanical strain with the type of healing that will occur[1]. Thus, when the strain is above 100% would lead to non-union, when between 10% and 100% would lead to granulation tissue formation, when between 2% and 10% would lead to fibrocartilage formation and when less than 2% would lead to bone formation[2]. Bone contact healing, in case of anatomical reduction and absolute construct stability, ensures that inter-fragmentary strain is less than 2%, leading to primary bone healing. On the other hand, in case of non rigid fixation and relative construct stability, the inter-fragmentary strain should be between 2% and 10%, leading to secondary bone healing. In other words, this means that an initial minimum fracture gap cannot tolerate even minimum micromotion in order to heal, thus requiring rigid fixation to prevent significant motion. On the contrary, an initial wider gap can tolerate some controlled motion at the fracture site, thus requiring relative stability in order to maintain inter fragmentary strain between 2% and 10%. In addition, according to the principles of moment of inertia, callus formation significantly increases stiffness at the fracture site and therefore secondary healing can be considered as stronger fixation than primary one. inter-fragmentary movement, in combination with the fixator type that is used to stabilize the fracture site, plays a crucial role concerning to how loading effects fracture healing outcome. These types of movement are inter-fragmentary axial compression and tension, shear movement in the plane of the defect, axial rotation and bending[3]. Several studies have shown the positive effect of compression on the fracture healing process. Goodship and Kenwright back in 1985 were the first to underline this fact. On the other hand, high tension movement causes an increase in gap size inhibiting callus formation. The role of inter-fragmentary shear and torsion on bone regeneration process remains a debate. Most of the studies indicate a negative effect and only few show the opposite outcome. Bending forces have been slightly investigated and therefore no safe conclusion can be derived. Different theories for tissue differentiation through fracture healing process have been described. The first one was that of Pauwel's in 1960 who distinguished which hydrostatic pressure and shear strain titles lead the mesenchymal stem cells to differentiate into osteoblasts and fibroblasts respectively[4]. In 1998 Claes et al. revisited the theory of Pauwels and determined the exact values of hydrostatic pressure and axial strains which caused differing tissue differentiation[5]. All these mechanoregulation theories of tissue differentiation have been incorporated into mathematical models that can simulate the biological process of fracture healing. The comparison between these models and in vivo studies would allow the mechanobiology of tissue differentiation during fracture healing to be defined.

References

1. Malik Sheraz S, Malik Shahbaz S. Biomechanical process of bone fracture healing. In: Malik Sheraz S, Malik Shahbaz S, editors. Orthopaedic Biomechanics Made Easy. Cambridge, United Kingdom: Cambridge University Press (2015). p. 78-79.
2. Perren SM, Cordey J. The concept of interfragmentary strain. In: Uhthoff HK, Stahl E, editors. Current Concepts of Internal Fixation of Fractures. New York, NY: Springer (1980). p. 63–77.
3. Betts DC, Müller R. Mechanical regulation of bone regeneration: theories, models, and experiments. Front Endocrinol (Lausanne). 2014; 5:211
4. Pauwels F. Eine neue Theorie über den Einfluß mechanischer Reize auf die Differenzierung der Stützgewebe. Zeitschrift für Anatomie und Entwicklungs-Geschichte 1960; 121(6):478-515.
5. Claes LE, Heigele CA, Neidlinger-Wilke C, Kaspar D, Seidl W, Margevicius KJ, et al. Effects of mechanical factors on the fracture healing process. Clin Orthop Relat Res 1998;355:S132-47.

THE ROLE OF MECHANICAL FACTORS ON BONE DELAYED UNION

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Keywords: Bone healing, Delayed union, Mechanical, Micro-movement, Bone stimulators

Bone healing is a natural and physiological process which is initiated at the time of a fracture. The time period between bone trauma and bone healing may vary. An estimation of the expected time until bone union is succeeded can be made depending on the fracture type and location. Delayed union is the situation in which a fracture has not united in what is considered a reasonable amount of time for a fracture of that type in that location to heal.

Development of delayed union is multifactor, with mechanical factors being of key importance in the majority of the cases. Type of the fracture, method of stabilization, bone gap at fracture site and micro-movement at fracture site are recognized as significant mechanical factors[1]. The more unstable the fracture pattern is and the largest the bone gaps are, the more possible bone healing will be compromised. The method of stabilization and fixation also is of key role, since methods that induce callus formation instead of direct contact or gap healing seem to have better chance to succeed mechanically thus avoiding delayed union. Moreover, it has been shown that micro-movement within certain limits, in certain intensity and parallel to bone axis can have a significant beneficial effect on bone formation[2]. Excessive movement or shear forces on the other hand may lead to unsatisfactory results.

There is evidence that mechanical stimuli have a direct impact on bone metabolism, with osteoblasts being able to detect changes of the mechanical environment and respond adequately. Controlled movement at fracture site and axial forces of compression and tension induce bone morphogenetic protein production and osteoblast activation[3].

It is common clinical practice to use mechanical stimuli to achieve bone healing in cases of delayed union. Dynamic splinting and weight bearing, use of external fixators that are not completely rigid, intramedullary nailing with locking screws in dynamic position or locking screw removal, are all methods of allowing micro-movement on fracture site in order to stimulate healthy bone tissue formation.

Bone stimulators using electric currents, electromagnetic fields and various ultrasound frequencies have also been used the last decades in cases of delayed union and acute fractures. Many studies imply a positive effect of bone stimulation with financial and functional benefits[4]. Careful meta-analysis of the current literature, however, suggests that there is only low recommendation of those techniques, since the quality and quantity of those studies are limited[5]. Further multicenter randomized control trials need to be planned in order to assess bone stimulator efficiency before accepting such modalities in standard clinical practice.

References

1. Augat P, Simon U, Liedert A, Claes L. Mechanics and mechano-biology of fracture healing in normal and osteoporotic bone. Osteoporos Int 2005; 16 Suppl 2:S36-43.
2. Kenwright J, Richardson JB, Cunningham JL, White SH, Goodship AE, Adams MA, Magnussen PA, Newman JH.Axial movement and tibial fractures. A controlled randomised trial of treatment. J Bone Joint Surg Br 1991; 73(4):654-9.
3. Nomura S, Takano-Yamamoto T. Molecular events caused by mechanical stress in bone. Matrix Biol 2000; 19(2):91-6.
4. Hannemann P, Göttgens KW, van Wely BJ, Kolkman KA, Werre AJ, Poeze M, Brink PR. Pulsed Electromagnetic Fields in the treatment of fresh scaphoid fractures. A multicenter, prospective, double blind, placebo controlled, randomized trial. BMC Musculoskelet Disord 2011; 12:90.
5. Griffin XL, Smith N, Parsons N, Costa ML. Ultrasound and shockwave therapy for acute fractures in adults. Cochrane Database Syst Rev 2012; 2:CD008579.

CONTROLLED DYNAMIC BIOLOGICAL FIXATION

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Keywords: Controlled dynamic biological fixation, Micromotion, Bridging plates

Although rigid plate osteosynthesis and primary bone healing was for many years the mainstream in fracture management, the development of novel theories concerning the biology and mechanoregulation of fracture repair

brought new aspects into the operative management of long bone fractures. Controlled dynamic biological fixation takes advantage of secondary bone healing principles as developed and described by Peren, and introduce a new, more flexible mode of internal fixation. Controlled Dynamic Biological fixation takes advantage of the fracture site micromotion to form bone via tissues which undergo change in material structure until skeletal continuity is restored (indirect healing).

The indications for dynamic biological plating include metaphyseal long bone fractures, comminuted midshaft fractures where the blood supply is good, or can be restored within bridges between the soft tissues and bone, and adolescent tibial and femoral fractures with no fully closed growth plates.

Additionally over the last decades it became clear that the effective treatment of fractures depends upon good soft tissue management. Biological fixation where soft tissue envelope and perfusion of the bone is left intact, is widely accepted.

Following the development of more flexible biological fixation, new implants promoting the use of minimal invasion techniques (MIPO) like locking plates and improved conventional have been introduced. In order to gain full advantage of biological internal fixation and of MIPO some simple rules have to be applied by the surgeon:

1. For bones such as the femur and tibia that are exposed to large bending forces, long plates (bridging plates) with a small number of screws should be considered. Two or three holes at the fracture site should be omitted.
2. Because torsional strength is mainly restricted by the number of screws, fractures of the humerus and radius, which are exposed to large torsional forces, should be stabilized with a plate with a high number of screws on either side of the fracture line.
3. Oblique screws at the plate ends increase the pull out strength.
4. Lag screws, especially through the plates must be avoided
5. Compression is not desirable.

Dynamic plate osteosynthesis is a demanding surgical procedure with a high learning curve, but when respecting the above basic concepts, it is a safe procedure with a high healing and a low complication rate.

References

1. Perren Stephan M. Physical and Biological aspects of fracture healing with special reference to internal fixation. Clin Orthop Relat Res 1979; (138):175-96.
2. Sonderegger Juerg, Grob Karl R, Kuster Markus S. Dynamic plate osteosynthesis for fracture stabilization: how to do it. Orthopedic Reviews 2010; 2(1):e4.
3. Perren Stephan M. Evolution of the internal fixation of long bone fractures. The scientific basis of biological internal fixation: choosing a new balance between stability and biology. J Bone Joint Surg [Br] 2002; 84-B:1093-110.
4. Stoffel K, Forster T, Stachowiak G.W, Gächter A, Kuster MS. Oblique screws at the plate ends increases the fixation strength in synthetic bone test medium. Journal of Orthopaedic Trauma. 2004; 18(9):611-6.
5. Stoffel K, Ulrich D, Stachowiak G, Gächter A, Kuster M.S. Biomechanical testing of the LCP- How can stability in internal fixators be controlled? Injury. Int. J. Care Injured 2003; 34 (Supplement 2):11-19.

THE ROLE OF BIOMECHANICS IN OSTEOARTHRITIS

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Keywords: Biomechanics, Biomechanical, Osteoarthritis, Obesity, Mechanical axis

Osteoarthritis is a debilitating disease of the joints which was estimated to affect 27 million people in the USA alone in 2005 and is likely to have increased since then. The prevalence increases with age, with radiographic findings of arthritis in more than 70% of the general population over the age of 65[1]. The disease is characterized by pain, dysfunction and in the advanced stages limb deformity. It affects the whole joint, including tendons, ligaments, muscle, synovium, articular cartilage and the bone. The etiology of osteoarthritis is multifactorial and is not fully understood. It occurs when the dynamic state between destructive forces on one hand and repair mechanisms on the other, tends to destabilize the joint. There are two ways this imbalance works. The first mode is where the joint is exposed to normal stresses but there is some sort of underlying abnormal physiology. This can be inflammation, sepsis, aging, genetic factors or an immune response. The second mode is where the physiology of the joint is normal but it sustains abnormal stresses. This is characteristic in obesity, trauma, malalignment, instability and abnormal anatomy[1]. Obesity is the one reversible cause of osteoarthritis. Apart from excessive loading of the joint, obesity is linked to systemic inflammation linked to other conditions like cancer, cardiovascular conditions and diabetes[2,3]. Obesity and arthritis is directly linked and loss of 5 kg decreases the risk of arthritis by 50%[3]. Furthermore a loss of 3 kg of body weight is linked to a decrease of systemic inflammation markers like IL-6[4]. Trauma is also linked to arthritis with an impact on normal anatomy and change of the loading axis[5]. Deviation of the mechanical axis of a joint causes an increase of the adduction moment and leads to the destruction of the part of the joint which receives the biggest load. It has also been shown that insufficiency of the soft tissues

supporting a joint, leads to degenerative changes. This is particularly the case with the knee, where meniscal tears, ligament ruptures and osteochondral lesions are directly related to arthritis. Treatment of osteoarthritis involves non-surgical options where reversible causes like obesity and muscle weakening are balanced by diet and exercise. Surgical options mainly involve osteotomies of the acetabulum, the femur and the tibia in order to correct mechanical axis deviations and arthroplasty, where the joint is replaced with metallic alloys and polyethylene[5].

References

1. Guilak F. Biomechanical factors in osteoarthritis. Best Pract Res Clin Rheumatol 2011; 25(6):815-23.
2. Buckwalter JA. Osteoarthritis and articular cartilage use, disuse, and abuse: experimental studies. J Rheumatol Suppl 1995; 43:13-5.
3. Felson DT. Obesity and osteoarthritis of the knee. Bull Rheum Dis 1992; 41(2):6-7.
4. Bastard JP, Jardel C, Bruckert E, Vidal H, Hainque B. Variations in plasma soluble tumour necrosis factor receptors after diet-induced weight loss in obesity. Diabetes Obes Metab 2000; 2(5):323-5.
5. Egloff C, Hugle T, Valderrabano V. Biomechanics and pathomechanisms of osteoarthritis. Swiss Med Wkly 2012; 142:w13583.

PATHOGENESIS OF OSTEOARTHRITIS

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Keywords: Osteoarthritis, Inflammation, Cartilage

In the pathogenesis of osteoarthritis (OA) important is the role of a number of risk factors as:

- The mechanical stress as it in physiologic spectrum leads in the normal function of the chondrocytes and the synthesis of the proteins of the matrix of the cartilage of the joints. On the contrary the high mechanical stress is correlated with cartilage damage and it's absence or very low value in cartilage atrophy.
- The inflammation as a great number of proinflammatory cytokines as IL-1, IL-6, IL-15, IL-17, IL-18, TNFα, which are found in a high level in synovial fluid, synovium and cartilage and are correlated with a high rate of chondrocytes apoptosis, the production of metalloproteins with role in cartilage deterioration and the reduction of the synthesis of the proteins of the matrix of the cartilage.
- A number of genetic factors as certain polymorphisms of the gene of the asporin, the growth and differentiation factor 5, the bone morphogenic protein 5, the IL-1β and the antagonist of IL-1, etc.
- The oxidant stress seems to have a role in the increase of chondrocytes apoptosis and an impact on cartilage.
- Role in the cartilage damage have also epidemiologic factors as the high body weight (the obesity), the trauma of the joints, some professional and sports activities, the meniscal damage the high age as well as the gender (female>male).

References

1. Felson DT, Hodgson R. Identifying and treating preclinical and early osteoarthritis. Rheum Dis Clin North Am 2014; 40(4):699-710.
2. Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. Nat Rev Rheumatol 2015; 11:35.
3. Man GS, Mologhianu G. Osteoarthritis pathogenesis - a complex process that involves the entire joint. J Med Life 2014; 7(1):37-41.
4. Hwang HS, Kim HA. Chondrocyte Apoptosis in the Pathogenesis of Osteoarthritis. Int J Mol Sci 2015; 16(11):26035-54.
5. Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. Nat Rev Rheumatol 2015; 11:35.

THE BIOMECHANICAL IMPORTANCE OF SUBCHONDRAL BONE IN THE PHYSIOLOGY OF THE JOINT AND IN THE PATHOGENESIS OF OSTEOARTHRITIS

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Keywords: Osteoarthritis, Subchondral bone, Crosstalk between articular and Subchondral bone, Osteoarthritis etiological treatment

Osteoarthritis is a slowly progressing joint degeneration which is characterized by cartilage damage, subchondral bone alterations, osteophyte formation and synovial tissue inflammation. Specific anatomical regions have been described in joint underlying cartilage bone, including the subchondral cortical plate, subchondral trabecular bone and sub-articular bone. Subchondral bone refers to the bony components lying under calcified cartilage and comprising of subchondral bone plate and trabecular bone. Subchondral bone plate consists of relatively nonporous and poorly vascularized cortical bone. It is separated from the overlying articular cartilage by zone of calcified cartilage. Subchondral bone has two essential functions: stress absorption and maintenance of cartilage nutrient supply. Animal models show that changes in the subchondral bone go parallel to cartilage degradation. There are changes observed in both articular cartilage and subchondral bone in osteoarthritis. Changes in the bone include sclerotic changes, thinning of articular cartilage, Thickening of the subchondral plate and subchondral cortical thickness, osteophyte formation, advancement of tidemark associated with vascular invasion of the calcified cartilage and the development of bone marrow lesions and bone cysts in the subchondral compartment. Although

subchondral cortical plate is not very porous or vascular in nature subchondral compartment has a rich nervous and vascular supply. The distribution and intensity of these channels depends on age and compressive forces transmitting through cartilage and subchondral bone. Mechanical effects of loading on bone remodelling not only affect bone mass but also produce alterations in the contour and shape of the subchondral bone. The subchondral bone explants from osteoarthritis patients, secrete high levels of alkaline phosphatase, osteocalcin, osteopontin, Interleukin-6 (IL-6), Interleukin-8 (IL-8), and progressive ankylosis protein homolog (ANKH), urokinase plasminogen activator, prostaglandin and insulin growthfactor-1 compared to normal bone explants. Many trials demonstrated that the presences of bone marrow lesions (BMLs) are related to structural deterioration in knee osteoarthritis. There is attribution of subchondral bone attrition and BMLs. BMLs adjacent to the subchondral plate have been shown to have increased bone volume fraction and increased trabecular thickness, but reduced tissue mineral density, meaning that osteoarthritis is associated to increased bone turnover. Both subchondral bone abnormalities are associated to cartilage loss. In animal studies, was demonstrated that as antiresorptive treatment biphosphonate therapy suppress bone resorption and development of osteoarthritis is postponed. The microarchitecture of subchondral bone is associated with aging. It was shown that subchondral trabecular bone thickness and bone volume decrease, connectivity between trabecular bone and calcified cartilage becomes slower by age. In other studies, it was indicated that increased biomechanical loads in obese patients lead to subchondral bone stiffness. Subchondral bone responds to stress of physical activity by increasing bone formation and density. Joint malalignment and microfractures result in ligament injuries affecting subchondral bone. There has been reported that venous drainage of subchondral bone is defective. Necrosis of bone trabeculae and bone marrow is early manifestations of both osteoarthritis and ischemic necrosis and hypertension in subchondral bone decreases its nourishment. Judging from the fact of various such as biochemical, hormonal, paracrinical, signaling, vascular and mechanical crosstalk between articular cartilage and Subchondral bone there may be in combination with biomarkers development part of etiological treatment for the majority of the forms of osteoarthritis.

References

1. Burr DB, Gallant MA. Bone Remodelling in Osteoarthritis. Nature Reviews Rheumatology 2012; 8:665-673. http://dx.doi.org/10.1038/nrrheum.2012.130.
2. Goldring MB, Goldring SR. Articular Cartilage and Subchondral Bone in the Pathogenesis of Osteoarthritis. Annals of the New York Academy of Sciences. 2010; 1192:230-237. http://dx.doi.Org/10.1111/j.17496632.2Q09.05240.x.
3. Li G, Yin J, Gao J, Cheng TS, Pavlos NJ, Zhang C, Ming H Zheng. Subchondral Bone in Osteoarthritis: Insight into Risk Factors and Microstructural Changes. Arthritis Research & Therapy 2013; 15:223. http://dx.doi.org/10.1186/ar4405.
4. Madry H, van Dijk CN, Mueller-Gerbl M. The Basic Science of the Subchondral Bone. Knee Surgery, Sports Traumatology, Arthroscopy 2010; 18:419-433. http://dx.doi.org/10.1007/s00 167-010-1054-z.
5. Sharma AR, Supriya Jagga, Sang-Soo Lee, Ju-Suk Nam. Interplay between Cartilage and Subchondral Bone Contributing to Pathogenesis of Osteoarthritis. Int J Mol Sci 2013; 14:19805-19830. doi:10.3390/ijms141019805.

REHABILITATION AFTER TOTAL KNEE REPLACEMENT

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Keywords: Total knee replacement, CPM, Rehabilitation, Central sensitization, Gait disturbances

Osteoarthritis is a major cause for total joint replacement. Total knee arthroplasty (TKA) surgery is a common orthopedic surgery performed to reduce pain and improve function in degenerative knee joints. Recent studies have reported that 15-20% of patients are not satisfied after TKA without evident clinical or radiological reasons[1]. Pain is the main reason of dissatisfaction for most of these patients[2].

It is known that 6-10% of patients with TKA may have moderate to severe pain that continues for at least 3 months post-operatively and this is defined as chronic post-surgical pain (CPSP)[3], approximately 30% the origin of CPSP might be neuropathic[4]. It is recognized that constant intense nociceptive sensory information, generated by painful and inflamed deep somatic structures, produces significant neurochemical and metabolic changes, as well as neurologic reorganization within spinal cord segments[5]. Increased excitability of dorsal horn neurons produces pain hypersensitivity in a segmental distribution[6] which is known as central sensitization. The desensitization of the central nervous system before or after the TKA is mandatory for patients with long lasting osteoarthritis pain.

Patients with long standing osteoarthritis of the knee present different pattern of recruiting muscles (shorter stride length, longer stance phases, reduced speed, longer stride time and increased double support)[7]. These gait abnormalities are obvious up to 24 months after TKA even in patients with excellent functional score. Muscle activation becomes normal but not when high demand

motor tasks are required[8]. Reduced knee flexion during load absorption phase, propulsion and swing phase, associated with reduced external extension moment[9] and prolonged co-contraction of rectus femoris-harmstrings and gastro-tibialis anterior[10] are also characteristics of gait. Different patterns of external flexion-extension joint moments are associated with abnormal phasing of quadriceps and hamstrings[11] and might have implications in long-term prosthesis failure. Prolonged activity in knee muscles found by means of dynamic EMG, seems to be a peculiar feature of TKA gait, persistent throughout follow up associated with 'stiff-knee pattern'[12].

The main goals of rehabilitation in acute care are the management of pain and the improvement of the range of motion. The use of continuous passive motion (CPM) has been resulted in contradictory findings[13]. CPM did not affect the long-term knee ROM attained by 6 months[14] or a year[15] after the operation. Some studies have shown that early pro-operative knee range of motion (ROM) improves the functional results where as other studies have demonstrated no difference[16].

After discharge from acute unit the rehabilitation continues on an outpatient basis. The main goals of rehabilitation are full normal ROM, management of pain and improvement of proprioception. Exercise should aim the static and dynamic equilibrium and train the new patterns of activation. Also occupational therapy is mandatory for the proper and safe function for activities of daily living (bath, grooming, toilet e.t.c). The equipment that might be needed at home and exercises for the upper limbs are also offered by the occupational therapist. The role of social worker is essential in some countries to contact the insurance companies.

Rehabilitation after TKR is a long and persistent procedure, in an outpatient basis. Safety in the activities of daily living, management of pain, and improvement ROM and proprioception are the main goals. These goals make mandatory the presence of a multidisciplinary team to take over after (and sometimes before) the major operation.

References

1. Wylde V, Bruce J,Beswick A, Elvers K, Gooberman-Hill R Assessment of chronic postsurgical pain after knee replacement: a systematic review. Arthritis CareRes (Hoboken) 2013; 65:1795-1803.
2. Lewis GN, Rice DA, McNair PJ, Kluger M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. Br J Anaesth 2015; 114:551-561.
3. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. Pain 2015; 156:1003-1007.
4. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain 2013; 154:95-102.
5. Zimmermann M. Pain mechanisms and mediators in osteoarthritis. Semin Arthritis Rheum 1989; 18:22-29.
6. J, Neto FL, Ableitner A, Castro-Lopes JM, Willoch F, Bartenstein P, et al. Metabolic activity changes in the rat spinal cord during adjuvant monoarthritis. Schadrack. Neuroscience 1999; 94:595-605.
7. Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ. Biomechanical changes at the hip, knee, and ankle joints during gait are associated with knee osteoarthritis severity, J Orthop Res 2008; 26(3):332-341.
8. Severijns P, Vanslembrouck M, Vermulst J, et al. High-demand motor tasks are more sensitive to detect persisting alterations in muscle activation following total knee replacement. Gait and Posture 2016; 50:151-158.
9. Benedetti MG, Catani F, Bilotta TW, Marcacci M, Marian E, Giannin S. Muscle activation pattern and gait biomechanics after total knee replacement Clinical Biomechanics 2003; 18:871-876
10. Wilson SA, McCann PD, Gotlin RS, Ramakrishnan HK, Wootten ME, Insall JN. Comprehensive gait analysis in posterior-stabilized knee arthroplasty. J Arthrop 1996; 11:167-359.
11. Andriacchi T. Functional analysis of pre and post knee surgery, total knee arthroplasty and ACL reconstruction. J Biomech Eng 1993; 115:575-581.
12. Dorr LD, Ochsner JL, Gronley J, Perry J. Functional comparison of posterior cruciate-retained versus cruciate-sacrificed total knee arthroplasty. Clin. Orthop 1988; 236:36-43.
13. Beaupré LA1, Davies DM, Jones CA, Cinats JG. Exercise combined with continuous passive motion or slider board therapy compared with exercise only: a randomized controlled trial of patients following total knee arthroplasty. Randomized controlled trial. Phys Ther 2001; 81(4):1029-37.
14. Maloney WJ, Schurman DJ, Hangen D, et al. The influence of continuous passive motion on outcome in total knee arthroplasty. Clin Orthop 1990; 256:162-168.
15. Ververeli PA, Sutton DC, Hearn SL, et al. Continuous passive motion after total knee arthroplasty: analysis of cost and benefits. Clin Orthop 1995; 321:208-215.
16. Nadler SF, Malanga GA, Zimmerman JR. Continuous passive motion in the rehabilitation setting: a retrospective study. Am J Phys Med Rehabil 1993; 72:162-165.

FRAGILITY OF BONES IN CHILDREN WITH MOTOR DEFICIENCY

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Keywords: Osteoporosis, Fractures, Children

Fractures are common in the pediatric population. Distinguishing a traumatic from pathological fracture is often **difficult** because it is not clearly defined what constitutes a **fragility** fracture. We investigate children with fractures of long bones, with absence of significant trauma. **Osteoporosis** in children may be primary, due to an intrinsic bone abnormality or secondary, due to an underlying medical condition.

Primary osteoporosis is mainly found in **Osteogenesis imperfecta** and **secondary osteoporosis** in **cerebral palsy children**. Identification of the underlying pathology

is the most important in the evaluation of children with fractures. A comprehensive pediatric reference database for Hologic densitometers is available. 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 decision to perform screening densitometry in a child 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.

Children affected from **Cerebral Palsy** are the main population of children with motor deficit. 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. The diagnosis is delayed or missed in those patients who cannot communicate. The most common site of fractures was the lower limb, almost 80% of fractures occurring around the knee and being metaphyseal fractures.

There are many risk factors associated with fractures in children with CP. The severity of neurological involvement is an important factor. Contractures and stiffness of the major joints create long lever arms, also predispose to fracture. The fracture rate increase more than threefold, after a previous fracture. Prolonged immobilization with or without surgery can predispose to fracture. Malnutrition, low body weight (z-score) and use of AEDs are associated with an increased fracture risk.

Prevention of bone fragility and fractures in CP children can be done with physical activity and standing weight-bearing. Proper physiotherapy is essential. Stable internal fixation of any osteotomy, will minimize the postoperative duration of cast immobilization. Operations to correct lower limb joint deformities, to provide plantigrade feet and straight knees will allow standing weight-bearing and physical exercise in children with severe CP. The use of DXA BMD requires adjustments for body size, pubertal status and skeletal maturity.

The primary cause of osteoporosis is found in **osteogenesis imperfecta**. It is a rare disease, characterized from excessive fragility of bones. Prevention of fractures with appropriate bracing and education of the parents and children is encouraged. 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.

References

1. Boyce A M. and Gafni RI. Approach to the Child with Fractures. J Clin Endocrinol Metab 2011; 96(7):1943-1952.
2. Bianchi ML, Baim S, Bishop NJ, Gordon CM, Hans DB, Langman CB, Leonard MB, Kalkwarf HJ. Official positions of the International Society for Clinical Densitometry (ISCD) on DXA evaluation in children and adolescents. Pediatr Nephrol 2010; 25:37-47.
3. Chad KE, Bailey DA, McKay HA, Zello GA, Snyder RE. The effect of a weight-bearing physical activity program on bone mineral content and estimated volumetric density in children with spastic cerebral palsy. J Pediatr 1999; 135:115-117.
4. Caulton JM, Ward KA, Alsop CW,Dunn G, Adams JE, Mughal MZ. A randomised controlled trial of standing programme on bone mineral density in non-ambulant children with cerebral palsy. Arch Dis Child 2004; 89:131-135.
5. Szalay EA, Harriman D. Adapting pediatric DXA scanning to clinical orthopaedics. J Pediatr Orthop 2006;26:686e90.
6. Bachrach SJ, Kecskemethy HH, Harcke HT, Hossain J. Decreased fracture incidence after 1 year of pamidronate treatment in children with spastic quadriplegic cerebral palsy. Dev Med Child Neurol 2010; 52:837.

HOW DOES EXERCISE AFFECT BONE DEVELOPMENT DURING GROWTH?

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Keywords: Bone growth, Exercise, Physical activity, Skeletal development, Mechanostat

It is increasingly accepted that osteoporosis is a paediatric issue. The prepubertal human skeleton is quite sensitive to the mechanical stimulation elicited by physical activity. To achieve the benefits for bone deriving from physical activity, it is not necessary to perform high volumes of exercise, since a notable osteogenic effect may be achieved with just 3 hours of participation in sports.

Physical activity or participation in sport should start at prepubertal ages and should be maintained through the pubertal development to obtain the maximal peak bone mass potentially achievable. Starting physical activity prior to the pubertal growth spurt stimulates both bone and skeletal muscle hypertrophy to a greater degree than observed with normal growth in non-physically active children.

High strain-eliciting sport like gymnastics, or participation in sports or weight-bearing physical activities like football or handball, are strongly recommended to increase the peak bone mass. Moreover, the increase in lean mass is the most important predictor for bone mineral mass accrual during prepubertal growth throughout the population.

Since skeletal muscle is the primary component of lean mass, participation in sport could have not only a direct osteogenic effect, but also an indirect effect by increasing muscle mass and hence the tensions generated on bones during prepubertal years.

References

1. Bergmann P, Body JJ, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, Kaufman J, Reginster JY, Rozenberg S. Loading and Skeletal Development and Maintenance. Research Journal of Osteoporosis. 2010; 2011:786752. doi:10.4061/2011/786752.
2. Morseth Bente, Emaus Nina, Jørgensen Lone. Physical activity and bone: The importance of the various mechanical stimuli for bone mineral density. A review. Norsk Epidemiologi 2011; 20(2):173-178.
3. Maffulli N, Pintori E. Intensive training in young athletes. The orthopaedic surgeon's viewpoint. Br J Sp Med 1990; 9(4):229-43.
4. Nordström Anna, Tervo Taru, Högström Magnus. The Effect of Physical Activity on Bone Accrual, Osteoporosis and Fracture Prevention. The Open Bone Journal 2011; 3:11-21.

ALTERATIONS OF THE MECHANOSTAT THEORY IN SPINAL CORD INJURY (SCI)

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Keywords: Mechanostat theory, Utah paradigm of physiology, Spinal cord injury, Muscle, Bone

The mechanostat theory describes a system in which a minimum effective strain, is essential for maintaining bone. Frost H. described the above theory which was developed to the Utah paradigm of Physiology, which seems valid in SCI. Unloading reduces mechanical strains leading to increased remodelling in favor of bone resorption. In SCI disuse may have a role, but factors independent of mechanical loading of the skeleton also appear to be important. Possible influential non-mechanical factors may include poor nutritional status, disordered vasoregulation, hypercortisolism, alterations in gonadal function, endocrine disorders and neural factors.

Under physiological conditions, the largest forces arise from muscle contractions. After SCI, sensory and motor functions are disrupted, depending on the completeness of injury, due to damage of the neural tissue within the spinal canal. However, in most cases this does not imply a complete loss of muscle contractions.

It could be argued that the reduction in muscle strength would not be the cause, but rather a parallel to the reduction in bone strength after SCI, as there is accumulating direct evidence for an involvement of the central nervous system in bone metabolism. Such nervous influence is probably best understood for the sympathetic nervous system, which is thought to hamper bone formation and stimulate bone resorption. However, sympathetic nerve activity is decreased after SCI, and, accordingly one should expect increases in bone mass and strength via this pathway, which is not the case in SCI.

Disuse was thought to be also the mechanism responsible for the skeletal muscle atrophy in paraplegics. After the first months, muscular atrophy reaches a steady state, which is likely to maintained by reflexing activity of lower motoneuron (muscle spasms). However, the effect of spasticity on bone and muscle is controversial because the myopathic muscle may not accept stimuli because of its degeneration or recognizes them wrongly. Although in bone after a period of 16-24 months during injury the metabolic process tends towards a new steady bone state, bone mineral density at different regions continues to decrease and is inversely associated with the time of injury, which means continuous bone loss beyond the first 2 years after injury, reaching a new steady state at 4 (femur) to 7 (tibia) years. Bone loss is an ongoing biological phenomenon during the years of paralysis required to reach the new steady state according to the *paraplegic mechanostat* when bone impairment is complete, meaning also geometrical property alterations and not only volumetric bone mineral density losses. SCI groups loose more muscle than bone per unit bone/muscle area after injury, meaning that bone loss follows muscle loss.

We could interfere in the *paraplegic mechanostat* process either on bone (mostly by giving drugs) or on muscles launching a rehabilitation program using exercise protocols or physical and mechanical means. The most important is the optimal timing of this intervention. Because of the higher bone area/muscle area ratio in paraplegics the intervention should be started early to protect muscle loss, which tends to start sooner and is leading the bone-muscle relationship.

References

1. Frost HM. The mechanostat: a proposed pathogenic mechanism of osteoporoses and the bone mass effects of mechanical and nonmechanical agents. Bone Miner 1987; 2:73-85.
2. Jee WS, Tian XY. The benefit of combining non-mechanical agents with mechanical loading: a perspective based on the Utah Paradigm of Skeletal Physiology. J Musculoskelet Neuronal Interact 2005; 5:110-8.
3. Rittweger J, Gerrits K, Altenburg T, et al. Bone adaptation to altered loading after spinal cord injury: a study of bone and muscle strength. J Musculoskelet Neuronal Interact 2006; 6:269-76.
4. Dionyssiotis Y, Stathopoulos K, Trovas G, Papaioannou N, Skarantavos G, Papagelopoulos P. Impact on bone and muscle area after spinal cord injury. Bonekey Rep 2015;28;4:633.
5. Castro MJ, Apple DF Jr, Staron RS, Campos GE, Dudley GA. Influence of complete spinal cord injury on skeletal muscle within 6 mo of injury. J Appl Physiol 1999; 86:350-8.

HORMONAL REGULATION OF THE MECHANOSTAT

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Keywords: Estrogen, Hormone, Mechanostat, Leptin

Our skeleton has the unique ability to continuously reform himself according to the routinely applied mechanical forces

in order to perform optimally during the expected everyday demands. The positive feedback system that controls this adaptation has been named "the mechanostat". The main forces that "drive" the mechanostat are considered to be muscle contractions, which induce tension in the bones, thereby activating bone modeling in both the periosteal and the endocortical surface of the cortex via mechano-receptors on the osteocytes[1]. Therefore, factors, including hormones, could affect the mechanostat performance either directly through actions in the bone or indirectly through effects on the muscle.

Hormones that have been implicated in the regulation of the mechanostat so far include sex hormones (androgens-estrogens), parathyroid hormone (PTH), the system of growth hormone (GH) – insulin growth factor-1 (IGF1), prostaglandin E_2 (PGE_2), vitamin D, glucocorticoids, and leptin.

Sex hormones. Androgens seem to affect the mechanostat both directly and indirectly[2]. Androgens increase osteoprotegerin (OPG) expression and thus decrease remodeling and maybe direct it towards bone formation. Furthermore, they stimulate bone modeling and increase bone dimensions. Additionally, they maintain a positive calcium balance through stimulation of calcium reabsorption in the distal renal tubules. However, the most significant effect of androgens on the mechanostat is probably exerted indirectly, through stimulation of muscle growth independently of IGF1 and through increased muscle contraction by activating the calcium signal. Androgen-related bone mass accrual is mostly periosteal while endosteal surface is minimally affected. On the contrary, estrogens decrease the set point of the mechanostat in the endocortical surface resulting in increased osteogenic response on mechanical loading and, therefore, increased endocortical bone apposition, while their effect on muscle mass is considerably smaller than androgens. The positive effect of estrogens on the endocortical and trabecular one surfaces is exerted via their type alpha receptor (ERα) while activation of their type beta receptor (ERβ) inhibits the exercise-induced anabolic response at the periosteal surface and retards periosteal bone formation. The lowering of the modeling set-point by the estrogens in adolescent females results in accumulation of bone in quantities higher than mechanically required. This has been proposed to represent a mechanism to get along with the anticipated increased demands of pregnancy and lactation during the forthcoming reproductive period.

Anabolic hormones. GH and IGF1 mostly affect the mechanostat indirectly, through increased protein synthesis and subsequently increased muscle mass which results in an adaptive increase of bone mass until a higher steady state is achieved[3]. Moreover, it has been shown that GH and IGF1 decrease the mechanostat threshold and reinforce the effect of exercise on bone formation. Bone formation is typically observed on cortical bones and mostly in their periosteal surface[2,3]. A synergistic effect of exercise with PTH in increasing bone mass has also been reported while the unloaded vertebral bodies in rats responded poorly to PTH administration[4]. Similarly, PGE_2 administration repeatedly revealed a greater osteogenic response in the more heavily loaded parts of animal skeletons and PGE_2 combined with external loading had a synergistic effect on periosteal and an additive effect on endocortical bone formation[4]. Thus, anabolic agents have been postulated to modulate the responsiveness of bone tissue to mechanical loading by lowering the modeling and raising the remodeling set points. The net effects are synergistic increases in modeling-dependent bone mass (increased periosteal bone gain), additive increase in endosteal bone mass and decrease of the remodeling and the resorption drifts[4].

Vitamin D – myokines. Through its receptor VDR on the bone regulates the response of the skeleton to growth factors while through its receptors on the muscle increases protein synthesis and activates transcriptional factors, thereby promoting muocyte growth and function. Besides vitamin D, the bone-muscle unit might also be affected by several newly identified hormones secreted by the skeletal muscle, the myokines (irisin, follistatin, activin, myostatin) that regulate muscle growth and functionality.

Glucocorticoids. Glucocorticoids adversely affect the skeleton though various mechanisms: reduced protein synthesis by the osteoblasts, negative regulation of several genes of the osteoblasts, premature apoptosis of the osteocytes, decrease of GH-IGF1 and levels, hypogonadal effect (decrease of androgen/estrogen secretion) and muscle weakening/myopathy.

Leptin – adipokines. During the previous decade, adipose tissue has been identified as an endocrine organ secreting hormones called adipokines. The best studied adipokine is leptin, which regulates energy homeostasis and body mass by controlling appetite and energy expenditure. The role of leptin in bone mass regulation was identified in a study where the positive correlation between body mass and bone mass observed in normal mice was lost in leptin deficient mice, while leptin administration in humans maintained bone mass despite inducing weight loss[5]. Leptin exerts both direct and indirect effects on the skeleton. Leptin dramatically sensitizes the skeletal response to increased body weight by modulating mechanosensitivity of the skeleton. Indirect actions include modification of the levels of other hormones: leptin deficiency results in hypogonadism, elevated corticosteroid levels and impaired growth hormone signaling.

References

1. Frost HM. Bone's mechanostat: a 2003 update. Anat Rec A Discov Mol Cell Evol Biol 2003; 275:1081-101.

2. Zofkova I. Hormonal aspects of the muscle-bone unit. Physiol Res 2008; 57(Suppl 1):S159-69.
3. Rittweger J. Ten years muscle-bone hypothesis: What have we learned so far? -Almost a Festschrift-. J Musculoskelet Neuronal Interact 2008; 8:174-8.
4. Jee WSS, Tian XY. The benefit of combining non-mechanical agents with mechanical loading: a perspective based on the Utah Paradigm of Skeletal Physiology. J Musculoskelet Neuronal Interact 2005; 5:110-8.
5. Iwaniec UT, Turner RT. Influence of body weight on bone mass, architecture and turnover. Journal of Endocrinology 2016; 230:R115-30.

ANABOLIC AGENTS AND MECHANOSTAT

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Keywords: Osteocytes, Anabolic treatment, Mechanostat

The central role of osteocytes in bone homeostasis has long been envisioned by pioneers in the field, who proposed potential mechanisms by which these cells could contribute to the functions of the skeleton.

Gastone Marotti and colleagues found by microscopic examination of human bone that osteocytes within lacunae have multiple cytoplasmic projections that reach neighbouring osteocytes and cells on bone surfaces. Marotti proposed that osteocytes are key participants in this cellular network in which cells, connected via gap junctions, are able to sense mechanical and biochemical signals[1].

In ground-breaking studies, Harold Frost demonstrated that the viability of osteocytes decreases with age proposed that osteocytes regulate water and calcium flow from the canaliculi to the blood compartment, and developed the 'mechanostat' theory, which proposes that the magnitude of the mechanical stimulation applied to bone dictates whether bone will be increased (by increasing bone formation) or decreased (by increasing bone resorption).In this model, osteocytes sense the load imposed on bone and respond by signalling to osteoblasts and osteoclasts to adapt to mechanical changes[2].

Seminal work by A. Michael Parfitt in the 1970s postulated that osteocytes are involved in the response of the skeleton to **parathyroid hormone (PTH)**. PTH has profound effects on the skeleton. Recent investigations have markedly advanced our understanding of the cellular and molecular mechanisms of PTH on bone. PTH downregulates Sost/sclerostin expression in osteocytes. PTH/PTH-related peptide (PTHrP) receptor (PPR) activation by PTH elevates cAMP levels and inhibits myocyte enhancer factor (Mef2)-stimulated Sost promoter activity leading to decreased expression of the inhibitor of bone formation sclerostin, and elevated bone formation rate[3]. Similar to PTH, **N-terminal PTHrP** analogs tested so far (PTHrP(1-34), PTHrP(1-36), Abaloparatide, stimulate proliferation of pre-osteoblasts and their differentiation to osteoblasts, and also increase osteoblast survival.

Wnt signaling plays a central role in regulating the development of many tissues and organs, and alterations in the pathway are commonly associated with human disease. Several ways of activating Wnt-βcatenin signalling by blocking antagonists of the pathway through pharmacological interventions have been designed. **A neutralizing antibody directed against sclerostin** has also been developed. Sclerostin expression is restricted to osteocytes among bone cells and increased *SOST* expression leads to a bone-specific phenotype. Sclerostin is, therefore, an excellent target to improve bone health without affecting other tissues. Preclinical studies have shown that inhibition of sclerostin using the antibody prevents the decrease in bone mass induced by ovariectomy, excess glucocorticoid administration, ulcerative colitis, immobilization and ageing. Phase II/III studies with the anti-sclerostin antibody have been carried out in postmenopausal women and increased BMD, increased bone formation and inhibited bone resorption and decreased fractures[4]. Studies using humanized neutralizing anti-DKK1 antibodies increase bone mass in growing female mice and in ovariectomized adult rhesus monkeys. However, since the Wnt pathway is active in numerous tissues and DKK1 and is widely expressed, use of these inhibitors might need to be restricted to local bone applications to avoid unwanted effects in other organs. Nevertheless, anti-DKK1 antibodies are currently being tested for the treatment of skeletal complications in multiple myeloma[5]. PGE2 has an anabolic effect in bone when administered intermittently165. However, owing to the widespread systemic distribution and the adverse effects associated with PGE2 administration, this agent is not currently used in the clinic. To avoid the systemic effects of activation of this receptor, a bisphosphonate-conjugated agonist was developed for bone targeting[6].

References

1. Marotti G & Palumbo C. The mechanism of transduction of mechanical strains into biological signals at the bone cellular level. Eur. J. Histochem 2007; 51(Suppl. 1):15-19.
2. Frost HM. Bone's mechanostat: a 2003 update. Anat Rec 2003; 275A:1081-1101.
3. Saini V, et al. Parathyroid hormone (PTH)/PTH-related peptide type 1 receptor (PPR) signaling in osteocytes regulates anabolic and catabolic skeletal responses to PTH. J Biol Chem 2013; 288: 20122-20134.
4. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016; 375:1532-43.
5. Jelinek T & Hajek R. Monoclonal antibodies- a new era in the treatment of multiple myeloma. Blood Rev 2015; 30:101-110.

6. Liu C, et al. Novel EP4 receptor agonist-bisphosphonate conjugate drug (C1) promotes bone formation and improves vertebral mechanical properties in the ovariectomized rat model of postmenopausal bone loss. J Bone Miner Res 2015; 30:670-680.

THE CLINICAL UTILITY OF TRABECULAR BONE SCORE (TBS) IN THE IDENTIFICATION AND MANAGEMENT OF HIGH-RISK OSTEOPOROTIC PATIENTS

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Keywords: Osteoporosis, Trabecular Bone Score (TBS), Bone microarchitecture, Bone Mineral Density (BMD), Bone Strength

Osteoporosis is defined as a skeletal disorder characterised by compromised bone strength predisposing to an increased risk for fracture[1]. During the last 15 years, we have come to appreciate that bone strength relies not only on the quantity of bone - estimated by measuring bone mineral mass and/or "density" - but also on another set of properties, usually referred to as "bone quality"[2]. These properties include bone geometry, macro- and microarchitectural elements of trabecular and cortical bone, as well as the material properties of bone tissue per se. Dual-energy X ray Absorptiometry (DXA) is currently the method of choice for the diagnosis of osteoporosis, and low BMD by DXA is a strong predictor of fracture risk. TBS is a novel method based on evaluating pixel gray-level variations in the lumbar spine (LS) DXA image, thus providing an indirect index of trabecular bone architecture. While it is not validated for the diagnosis of osteoporosis, ex vivo studies suggest that TBS significantly correlates with indices of trabecular microarchitecture derived by mCT such as trabecular bone volume to tissue volume (BV/TV), trabecular number (Tb.N), and trabecular separation (Tb.Sp)[3]. Moreover, several studies provide evidence that TBS may predict osteoporotic fractures, such as the Manitoba study that included 29,407 women > 50 years old followed for a mean period of 4.7 years. The age-adjusted hazard ratios (HRs) reported for each SD decline in TBS were 1.45 (95% CI, 1.32-158) for vertebral fracture, and 1.46 (95% CI, 1.30-1.63) for hip fracture[4]. The incorporation of TBS in the FRAX algorithm was based on numerous studies that, as shown by a meta-analysis recently published concluded that TBS provides additional information on the 10-year fracture probabilities as estimated by the standard FRAX variables[5]. As a result, TBS may be useful in the selection of patients with high risk of fracture based on additional data regarding the individual's microarchitecture, that is an important element regarding bone strength. TBS is not currently validated for the monitoring of osteoporosis treatment and it is currently debated whether it may be useful in the identification of patients who respond to treatment, especially with antiresorptive agents such as bisphosphonates.

References

1. Klibanski A, Adams-Campbell L, Bassford T, et al. NIH consensus development panel on osteoporosis prevention, diagnosis and treatment. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001; 285:785-795.
2. Seeman E, Delmas PD. Bone quality: the material and structural basis of bone strength and fragility. N Engl J Med 2006; 354:2250-2261.
3. Hans D, Barthe N, Boutroy S, et al. Correlations between trabecular bone score, measured using anteroposterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae. J Clin Densitom 2011; 14(3):302-12.
4. Hans D, Goertzen AL, Krieg MA, et al. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Miner Res 2011; 26(11):2762-9.
5. McCloskey EV, Oden A, Harvey NC, et al. A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J Bone Miner Res 2016; 31(5):940-8.

VITAMIN D AND FALLS

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Falls are a major health problem in elderly people. Fractures at later ages are closely related to muscle weakness and falling. Over 90% of fractures occur after a fall. Following their first fall, about 30% of persons develop fear of falling resulting in decreased mobility and bone mass. Low 25(OH)D levels (<25 nmol/L) are associated with an increased risk of repeated falling over the subsequent year, particularly in persons over the age of 75 years. For many years, vitamin D has been known to be of importance to musculoskeletal health. Growing interest in vitamin D as a medical therapy has led to many trials. Vitamin D exerts wide-ranging effects, including those that relate to physical function. It is well known that severe deficiency causes rickets (in children) and osteomalacia (in adults). Symptoms include paraesthesia in hands and feet as well as aching muscles and bones. Clinical findings include muscle weakness particularly with proximal myopathy causing difficulty getting up from a chair without using arms and walking up the stairs. Gait disturbance occurs and gait is often characterized as waddling ('penguin gait'). Four lines of evidence support the role of vitamin D in muscle health. Firstly, proximal muscle weakness is a prominent feature

of the clinical syndrome of vitamin D deficiency. The clinical feature of the myopathy associated with severe vitamin D deficiency is supported by findings from in vivo and in vitro experimental studies showing histological and electrophysiological changes in severe vitamin D deficiency. Secondly, the vitamin D receptor (VDR) is expressed in the cell nuclei of muscle cells and vitamin D has been shown to affect muscle cell contractility. The number of VDRs decreases with age, which supposedly is a contributing factor to reduced muscle strength in the elderly. Thirdly, several observational studies suggest a positive correlation between 25(OH)D and muscle strength or lower extremity function in older persons. In a randomized controlled trial, Bischoff et al. showed that treatment with vitamin D 3 and calcium (800 IU and 1200 mg per day) for 3 months reduced the risk of falls by 49% compared to calcium alone. Similarly in an Australian study, treatment with vitamin D 2 (initially 10,000 IU per week then 1000 IU per day) and calcium (600 mg per day) for 2 years reduced the risk of falls in the compliant group by 30% compared to calcium alone. Fourthly, vitamin D supplementation increases muscle strength and balance, and reduces the risk of falling in community- dwelling, as well as in institutionalised individuals. In addition to the direct effect of vitamin D on muscle cells, vitamin D deficiency causes secondary hyperparathyroidism which may also impair muscle function. Given the relationship between 25(OH) D level and physical performance, one would expect a similar link when examining falls risk. The beneficial effect of vitamin D on calcium absorption and bone mineral density may not be the only explanation for its protective effects against fractures. In fact, vitamin D deficiency may cause muscular impairment even before adverse events on bone occur. The observed fracture reduction with vitamin D may be modulated in part by its benefit on the muscle, as supported by the presence of the VDR in human muscle tissue and an early effect of vitamin D on falls. Vitamin D insufficiency is frequent in the general population. Strong evidence is available from clinical trials in the elderly suggesting that vitamin D supplementation at a high enough dose reduces the risk of falling. Supplementation should aim to increase 25 (OH)D levels to between 50-75 nmol/l range. Achieved serum 25(OH)D levels of 60 nmol/l resulted in 23% fall reduction whilst lower levels resulted in no reduction in falls. Several double-blind RCTs have documented fracture prevention with 700-800 IU/day but not with lower doses. The clinical practice guidelines document from the Endocrine Society details the implementation for clinicians and patients.

References

1. Murad MH, Elamin KB, Abu Elnour NO, Elamin MB, Alkatib AA, Fatourechi MM, Almandoz JP, Mullan RJ, Lane MA, Liu H, Erwin PJ, Hensrud DD, Montori VM. The effect of vitamin D on falls: a systematic review and meta-analysis. Journal of Clinical Endocrinology and Metabolism 2011; 96(10):2997-3006.
2. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009; 339:b3692
3. Ceglia L, da Silva MM, Park LK, Morris E, Harris SS, Bischoff-Ferrari HA, Fielding RA, and Dawson-Hughes B. Multi-step immunofluorescent analysis of vitamin D receptor loci and myosin heavy chain isoforms in human skeletal muscle. J Mol Histol. 2010; 41(2-3):137-142.
4. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a metaanalysis of randomized controlled trials. Arch Intern Med 2009; 169(6):551-61.
5. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA 2004; 291:1999-2006.
6. Pfeifer M, Begerow B, Minne HW, et al. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int 2009; 20:315-322.