VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

BASIC SCIENCE

The role of muscle tissue in the homeostasis and development of a joint

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ABSTRACT

The articular joint as an "organ" is interlinked with other tissues via metabolic and endocrine pathways and interacts via vascularization with muscle, adipose, nervous tissue and the circulatory system. In this review article, the mechanical action of muscles on the joint is analysed as well as the biological and endocrine effect of muscle tissue on joints metabolism and homeostasis. Pathological conditions such as degenerative osteoarthritis and inflammatory arthritides are also explained through pathways related to sarcopenia and obesity.

Mechanical load is an important factor in cartilage homeostasis. Muscle tissue has the ability to distribute mechanical stress in a joint. When mechanical stress is applied onto the cartilage, physical, electrochemical and biological phenomena occur through hydraulic pressure changes, fluid flow, osmotic pressure, diffusion and changes in the concentration of extracellular molecules, ions and pH. Furthermore, chondrocytes have mechanical stress receptors such as integrin receptors, connexins and Ca^{2+} ion channels, which induce the production and function of collagenases and aggrecans in the cartilage. It has also been found that low-intensity circular loading in joint prevents the production of inflammatory factors that induce articular cartilage catabolism. The role of proprioception through the muscular spindle regulate the function of the muscles around the joint providing articular stability through protective contraction.

Skeletal muscle, in addition to its basic function in motion, stance and stability of the body and joints, has a second role as an endocrine organ. Myokines belong to the family of cytokines. They are small peptides produced in muscle tissue either during normal conditions or in exercise and induce autocrine, paracrine and endocrine activity. The study of the role of myokines in the joint is recent and mainly focus on their action in the bone and subchondral bone. Some myokines have a negative effect on subchondral bone metabolism, such as IL-6, myostatin, activin and ciliary neurotrophic factor (CNTF). Other myokines have anabolic activity on bone metabolism such as IL-15, IGF-I, FGF-2, follistatin, and irisin. Finally, muscle contraction in fetal life, both biochemically and morphologically, determines joint growth, in terms of structure of articular surfaces, proliferation and differentiation of chondrocytes, expression of extracellular matrix components.

KEY WORDS: Muscle tissue; Myokines; Joint; Homeostasis; Osteoarthritis

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VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

Introduction

A skeletal muscle during contraction transmits mechanical loading onto the articular cartilage, inducing dimensional, hydraulic changes and finally structural changes in the extracellular matrix participating in the cartilage homeostasis. Muscular system is involved in normal homeostasis of the joints, their formation in fetal life, their metabolism, as well as in inducing pathological conditions such as degenerative osteoarthritis and inflammatory arthritis. This effect of the muscular system on articular cartilage, subchondral bone and synovial tissue occurs in two ways: through the biomechanical changes and mechanical loading and through its biological and endocrine action.

The role of muscle tissue in joint development

The interaction of muscle, bone and synovial tissue commence during fetal development during osteogenesis and myogenesis. Mesenchymal stem cells (MSCs) are multipotent stromal cells that differentiate, with appropriate stimuli, in analogous cell lines to produce osteogenesis, chondrogenesis or myogenesis. Muscle tissue through mechanical forces affects the growth of long bones by acting in the physeal growth plate. Regarding the morphology of the peripheral bones, it appears that during the final embryonic development of the skeleton, muscles exert loads by either traction or compression and affect the ossification centres. These loads play role to the development of the final architecture of the joints, shape, cavities, articular cartilage and apophyses (tubercles).

Two different stages, one creating an intermediate zone (interzone) and the other forming a cavitation perform the development of the joint. It appears that mechanical irritation through muscle contraction affects both stages of joint development. In 1966, studies on chicken embryos [1] found an association between the muscular system and the formation, shape and size of the cavities of the joints. In other studies [2,3] in mutant mice without muscles, the absence of hip, elbow and carpal joints was observed. Similar research was also performed in chick embryos where pancuronium bromide and decamethonium bromide were injected as muscle paralytics and absence of joint development, reduction of hyaluronic acid, reduction of expression of collagen XII and FGF2 in cartilage was observed [4].

Similarly, fetal chicken knees treated with decamethonium bromide were studied histologically, analysed by the expression of specific molecules and genes and finally compared with 3D digital imaging of the knee joint. Paralysed embryos found to have reduced height and width of the femoral condyles, narrower femoral notch, more flat and shallow articular surfaces and morphological simpler joints. Cellular proliferation and differentiation were affected histologically with changes in the articular structure. [5,6]

In another experimental research, the effect of muscle contraction on the development and maturation of the hip joint was studied. [7] Botulinum toxin A was inserted intramuscularly to newborn rats by paralysing gluteus and quadriceps muscles and hip joint was studied retrospectively by micro-tomography scanning (μCT scan). The results were evident in rats with insufficient contraction in hip flexors and hip extensors, which act as stabilizers, showing dysplastic hip, hypoplastic triradiate cartilage of acetabulum and hypoplastic femoral head.

It appears that mechanically irritated cells induce the expression of certain genes and molecules involving in joint development. These genes are called mechanosensitive or mechanoresponsive and have been studied in cell cultures, however, in vivo studies are still limited [5]. (**Table 1**)

Although the regulation of joint development by the muscular system appears to be experimentally proven, there are still some unclear fields. One such unclear field is the theory that mechanical stimuli regulate the size of the progenitor cell pool necessary for joint formation. The Wnt / β-catenin signalling pathway is the key mechanism of early joint development, chondrocyte differentiation and inhibition of chondrogenesis. Experimentally it appears that muscle contraction induces activation of β catenin. However, it does not explain clearly the mechanism, as in mice models with absence of muscle tissue, some joints remained intact (knees, fingers), while others like the elbow were absent in the embryos. These findings suggest that other mechanisms may also be involved in fetal development of the joints. [2-5].

VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

TABLE 1 *Mechanosensitive genes (modified by Rody et al. [5])*

Genes	Function	Evidence
BMPs	Chondrocyte maturation and proliferation	In vivo
CD44	Formation of joint cavity	In culture
INTEGRIN β1	Formation of interzone	In scaffolding
PTHLP	Chondrocyte proliferation	In culture
FGF2	Joint cavity formation, chondrocyte maturation	In vivo
FGFR2	Proliferation of osteoprogenitor cells	In culture
COL2A1	Matrix component, chondrocyte proliferation index	In vivo
TNC	Cartilage matrix component	In vivo

The mechanical effect of muscle tissue in joint

Mechanical stress and joint homeostasis

The articular cartilage is biphasic; it has a solid phase that depends on the structure of the matrix and a liquid phase that depends on the movement of the water inside it. During loading and movement of the joint, water is transported to and from the synovial fluid through the diffusion of macromolecules, thus affecting their metabolism and concentration. A three-phase theory has also been proposed, in which a third parameter is introduced, that of ionic diffusion and flow and their electrokinetic effects [8]. Thus, the interaction of these three phases (solid, liquid and ionic) through mechanical load, shear and compressive forces, stress and strain deformation of cartilage, osmotic and hydrostatic fluid pressure, cartilage viscoelasticity, flow and diffusion of molecules and ions synthesize the theory of the three-phase model of articular cartilage. [9]

Chondrocytes also have mechanoreceptors that detect mechanical stress. Such mechanosensitive receptors are integrin receptors, connexins and Ca^{2+} ion channels which, on the stress stimulation, induce the production of collagenases and aggrecans. Mechanical joint stimulation increases the concentration of aggrecan and reduces the expression of MMP-3 (matrix-metalloproteinase-3) in chondrocytes. The activity of MMPs and ADAMTS is also controlled by chondrocytes with tissue inhibitors of metalloproteinases (TIMPs). Aggrecan is an extracellular proteolytic enzyme belonging to the family of metalloproteinases ADAMTS (A Disintegrin And Metalloprotease with Thrombospondin Motifs) and its role is to break down the aggrecans of proteoglycans (PGs).

The role of Integrins

Significant mechanoreceptors for the transmission of mechanical signals to chondrocytes are the integrins [10, 11]. They carry mechanical signals between matrix and chondrocytes. Various types of integrins are connected with collagen II, fibronectin, osteopontin, vitronectin and other matrix proteins. The activation of many signaling pathways, such as the MAPK pathway, p38, SAPK, and ion channel function, is mediated by initial stimulation of the integrins [12]. Their action is related to the cellular connectivity of the chondrocytes, their survival, their differentiation and development as well as the production of the matrix. The linkage between chondrocytes and matrix proteins via integrins appears to be regulated by IGF-1 and TGF and the opposite.

The role of Ion channels, TRPs and osmotic pressure

Chondrocytes respond to changes in osmolarity when moving the fluids through their membrane and changing their volume. The membrane contains protein water channels (Aquaporins - AQP) that al-

VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

low the water to move based on osmotic gradient. The regulation of Ca^{+2} and Na^{+} ions is done through ion channels such as: VGSC (voltage-gated sodium channels), VGCC (voltage-gated calcium channels), ENaC (epithelial Na channels) and Na^{+}/Ca^{+2} pumps. These ion channels are mechanical signals for chondrocytes by regulating cell volume, intracellular calcium concentration and membrane polarity, thereby determining gene expression [11]. TRPs (transient receptor potential) are Ca^{+2} channels in the chondrocyte membrane. They are a link between mechanical, osmotic, hydrostatic stimuli and cellular metabolism and differentiation in homeostasis of both normal and osteoarthritic cartilage.

The role of extracellular hydrostatic pressure

During walking, hydrostatic pressure varies cyclically between 0.2 MPa and 5 MPa. This change appears to affect chondrocytes in the matrix composition. The possible involving mechanism is the deformation of the morphology and volume of cartilage exerted via the cytoskeleton and their Golgi system. In addition, hydrostatic pressure indirectly affects membrane permeability, transmembrane ion channels and osmolality, and therefore also determines the intracellular concentration of molecules and pH [10, 11].

Signalling pathways involved in homeostasis through stress stimulation

Mitogen-Activated Protein Kinase (MAPK) pathway is a mechano-inducive pathway that acts on chondrocytes through loading as described above [12]. The Hedgehog (Hh) / Smoothened (Smo) pathway contains molecules expressed in chondrocytes in response to mechanical stimuli and activate the expression of RUNX2, the aggrecanase ADAMTS 5 and Parathyroid Hormone related Protein (PTHrP). Expression of PTHrP in mature articular cartilage induces the differentiation and maturation of chondrocytes [12]. Nuclear Factor-Kappa B (NF-κB) pathway mainly regulates inflammatory and immune responses as regards differentiation and survival of chondrocytes by mediating factors such as TNF, COX-2, NO, IL, various cytokines, metalloproteinases and catabolic enzymes [12]. Wnt / β-catenin pathway participates not only in homeostasis and in development of cartilage but also in its lesions and mechanisms of osteoarthritis pathophysiology. Wnt are glycoproteins that bind to Frizzled (FZD0 receptors in the cell membrane and activate the β-catenin nuclear factors that translate specific target genes [12,13]

The role of Fibrin Growth Factors (FGFs)

FGFs (fibroblast growth factors) are a family of growth factors that have mixed activity. Two factors have been studied mainly in cartilage homeostasis, the FGF-2 (or bFGF) and FGF-18 [14]. FGF-2 is a mechanosensitive factor and is released from chondrocytes in cartilage injuries and lesions as well as in normal mechanical stimulation. It appears to act as a transducer of protective mechanical signals to the cartilage matrix by inhibiting the expression of collagenases and aggrecans (MMPs, ADAMTS). Its action is controversial though. Studies [14] report its anabolic activity and role in repairing cartilage through its effect on chondrocyte differentiation and proliferation. Conflicting studies have shown that FGF-2 exerts mainly catabolic activity on cartilage, promotes chondrocyte degeneration and fibrous cartilage synthesis, increases MMP3 and ADAMTS 4,5 and cytokines such as IL1 and TNF. In addition, it has been reported the antagonistic activity of FGF-2 by the positive effect on BMP7 and IGF-I in articular cartilage. Therefore, the effect of FGF-2 may be dependent on the force or the mode of mechanical loading (circular, static) or on the type of its receptor, so FGF-2 has sometimes protective and sometimes catabolic role in the joint.

Joint Homeostasis and Motion

The role of low intensity cyclic loading

Although the mechanisms are not yet fully clear, in vivo and in vitro studies seem to indicate the beneficial effects of motion and stress on the joint and the cartilage. Specifically, in vitro low intensity cyclic loading of the joint was found to prevent the production of inflammatory factors including the pro-inflammatory IL-1 cytokine, the TNF-a (tumour necrosis factor), NO (nitric oxide), prostaglandin PG-

VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

TABLE 2 *The role of muscle tissue on the onset and progression of osteoarthritis (modified by Bennel K, 2013 [21])*

OA Onset	OA Progression
Quadriceps muscle weakness may increase the risk of knee osteoarthritis (mainly women)	Controversial results, increased muscle strength may be associated with slow progression in women and patellofemoral joint
Hamstrings weakness does not seem to be associated with the onset of OA	Quadriceps, hamstrings, hip abductors weakness is associated with functional joint decline
Knee proprioception does not seem to be associated with the onset of radiological and symptomatic OA	Poor proprioception is associated with functional joint decline

E2 and cyclooxygenase COX-2. Activation of chondrocyte mechanoreceptors through a p38 kinase pathway (MAPK) inhibits IL-1 formation and prevents transcription of NF-κB. In contrast, in other animal model studies, joint immobilization results loss of proteoglycans concentration in articular cartilage by increasing MMP-3 and ADAMTS-5 as described above. [15]

The role of of static loading on articular cartilage

MAPK (mitogen activated protein kinase) signalling pathways are mechanical pathways that act on chondrocytes through compression and load. In static loading, they are activated by phosphorylation through EPK1 / EPK2, p38 kinase pathways and the stress activated protein kinase (SAPK) pathway. The effect of these processes is through WNT signaling, increasing expression of metalloproteinases MMP3, MMP13, ADAMTS-4, ADAMTS-5 and reducing aggrecan content and collagen II in the matrix of cartilage. Therefore, the raise of degradation proteins and the reduction of proteoglycan synthesis potentially leads to destruction of articular cartilage in some studies. [15]

The absorption of mechanical stress by the muscle tissue

Muscle tissue has the ability to redistribute voluntarily or involuntarily the mechanical stress and the energy that is exerted both in space and in time by discharging the joint. During the impingement phase, muscle initially plays the role of a spring, providing a non-linear deceleration and then the role of a suspension, through viscosity properties, for absorbing energy of the loading. Although many studies have focused on muscle elasticity, their viscosity has been underestimated and some studies have shown that viscous resistance to active muscle is comparable to the force of isometric contraction.

Muscle strength and arthropathy

Numerous studies have shown that there is a correlation between muscle weakness and joint cartilage damage. The problem in most studies was the accurate measurement and comparison of muscle strength among individuals as it is determined by various factors such as the length of the limb being studied (different torque), the BMI of the individuals, whether they are athletes, etc. There is a small number of studies seem to be able to have comparable results by meeting the measurement criteria and the somatometric characteristics of the individuals. Ikeda et al, [17] demonstrated that patients with knee osteoarthritis had 20-40% less quadriceps strength than healthy control groups. Also, it was found a loss of 12% cross-section of quadriceps in women with radiographic knee osteoarthritis and higher rates in advanced OA stages. On the other hand, it is not clear whether reduced muscle strength existed before the OA or possibly caused after OA due to pain, inflammation and oedema of the area. In another clinical study [18] in 280 volunteers with a 31-month average follow-up, showed that absolute quadriceps power was 18% lower in those who developed radiological signs of OA than those who did not develop such signs. Similar results, were found in a large study group of 3081 people; those with increased quadriceps strength, had a 55% reduced risk of developing osteoarthritis [19]. In experimental level, rabbits were injected with botulinum toxin A in their one-leg quadriceps to induce muscle weakness [20]. The results showed that car-

VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

tilage degeneration developed in the weak leg and concluded that muscle weakness may be a risk factor for osteoarthritis. A recent review of the literature [21] comparing the results of long-term studies on the role of muscle tissue in the development and progression of osteoarthritis. (**Table 2**)

Proprioception and arthropathy

During movement, stretched ligaments - through their mechanoreceptors - activate γ-motor neurons in the spinal cord and increase the tone of the fibres of the muscular spindle, making it more sensitive to the stimuli. Therefore, muscular reflexes result to muscle contraction protection against disproportionate and harmful articular loads, coordination in movement and joint stabilization in the static position.

The role of proprioception in the pathophysiology of osteoarthritis has been established by clinical and experimental studies. Eleven studies [22] of 387 osteoarthritic knees showed a significant reduction in proprioception and position sensation, by studying proprioception with different protocols. Two other studies [23] linked the severity of radiological osteoarthritis with reduced proprioception. In a clinical study of Hassan et al. [24], 77 subjects with symptomatic and radiographic knee osteoarthritis compared to normal, were found to have a reduced proprioception response, lower strength and rate of quadriceps activation in voluntary contraction. These results did not clearly answer to the question of whether the lack of proprioception is the cause of osteoarthritis or osteoarthritis causes this deficit. Significant conclusions, however, appear to be extracted from other studies [25-27] where proprioception was analysed in unilateral knee osteoarthritis. In the normal knee, a deficit in proprioception seems to be measured with the decrease in sense of movement and position. These results may lead to the conclusion that abnormal proprioception may be a risk factor for the progression and pathogenesis of osteoarthritis, but further investigation is certainly needed.

The biological effect of muscle tissue on joint homeostasis

For many years, despite the fact that interaction of muscle tissue with distant targets was assumed, the pathways were unknown. Recently, it has been found that muscle cells and satellite muscle cells, interacted with neighbouring cells by secreting molecules and their concentration depended on muscle contraction. These molecules are called myokines. They are cytokines; thus, peptides produced in the muscle tissue and exert autocrine, paracrine and endocrine activity [28-31]. Some myokines have a common origin and secretion from the adipose tissue and are called adipomyokines. The first myokine that was discovered 20 years ago was IL-6 followed by myostatin. (**Table 3**)

TABLE 3 *The most important myokines belonging to different families with different actions and targets.*

• Myostatin (MSTN)
• Decorin, (DCN)
• Activins και Inhibins
• Follistatin
• Irisin
• Interleukins IL-6, IL-7, IL-8, IL-15
• CNTF (ciliary neutrophic factor),
• BDNF (brain-derived neurotrophic factor)
• VEGF (vascular endothelial growth factor)
• FGF-21 (fibroblast growth factor)
• IGF-I (insulin-like growth factor)
• Myonectin (CTRPs)
• Osteonectin
• Follistatin-like protein-1 (Fstl1)
• Chitinase-3-like protein-1 (CHI3L1)
• Angiopoietin-like 4 (ANGPTL4)
• Secreted protein acidic and rich in cysteine (SPARC)

During or after exercise, the concentration of some cytokines and proteins in muscles appeared to be increased, by introducing the name exercise-regulated human myokines. These are IL-1,6,8,10,15, CCL, Angiopoietin-like 4 (ANGPTL4), SPARC, BDNF, Irisin, Decorin, IGF1 and many others.

The muscles are connected to bones and joints via

VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

ligaments, tendons, cartilage and connective tissue. Periosteum constitutes a natural filter between the two structures and contributes to the functional exchange of molecules and fluids. Experimentally, using fluorescent-labeled myokines, the periosteum has been found to be permeable for molecules of approximately 40 kDa. Myokines that fulfil this criterion such as IGF-1, interleukins and FGF are likely to diffuse through the periosteum from muscles to bone [32]. Other myokines can reach the bone and joint through vascular circulation. Factors that affect the transfer of these molecules to their target are quantity of secretion, polarity, muscle activity, age or co-existed disease.

The role of Myostatin

Myostatin (MSTN), the most common myokine, is a member of the superfamily of TGF-β proteins and is mainly expressed in muscle tissue. Myostatin is a negative regulator of muscle growth and lack of myostatin promotes muscle hypertrophy. In conditions of long-term immobility, chronic inflammation and decreased gravity, myostatin has been found to lead to loss of muscle mass. In exercise, myostatin concentration appears to be decreased. Myostatin is distributed at the cell surface receptors and common kinases with other members of the TGF-β family. In bone tissue, it appears that myostatin affects negatively the differentiation of osteoblasts. It has been found experimentally in myostatin-deficient mice that myostatin increases the differentiation of mesenchymal stem cells in osteoblasts and in vitro calcification [33]. In addition, myostatin enhances expression and activity of RANKL by regulating Smad2 of the activated T cell nuclear factor (NFATc1) leading to a raise of osteoclastic differentiation [33, 34]. Thus, in addition to the negative regulation of muscle mass, myostatin also regulates negatively bone formation and positively bone resorption, resulting to reduced bone mass.

Increased secretion of myostatin by synovial cells has been reported during rheumatoid arthritis. In an experimental study of Dankbar et al. [34] in Rheumatoid Arthritis mice, deficiency of myostatin and its inactivation with an antibody lead to an improvement in clinical arthritis and a reduction in joint destruction. Another in vitro study on synovial fluid samples from rheumatoid arthritis patients showed that the expression of myostatin and IL1-β, a major proinflammatory cytokine for the pathogenesis of rheumatoid arthritis (RA), was increased [35]. Myostatin has been shown to increase dose-dependent expression of IL1-β through signal pathways of ERK, JNK and AP-1 [35]. It therefore appears that myostatin is involved in the formation and differentiation of osteoclasts, in bone resorption and arthritic lesions of rheumatoid arthritis and it is an interesting field for future research into the treatment of clinical effects of RA on joints by targeting its inhibition.

The role of Activin and Follistatin

Activin is expressed in various tissues, among them in the muscle and bone tissue. It is a ligand of the myostatin ACVR2B receptor. Activin has been found to affect negatively osteoblastic differentiation through the BMP pathway and increase the number of osteoclasts [36]. Follistatin enhances bone metabolism and induces osteoblastic activity by signalling myostatin and activin. It substantially antagonizes myostatin or activin-induced phosphorylation of Smad2 / 3 and the ACVR receptor.

The role of Interleukins

During exercise, interleukin 6 (IL-6) levels are increased in the circulation and been expressed in type II muscle cells in response to muscle contraction. IL-6 is generally characterized as a proinflammatory cytokine and at high chronic levels is associated with the pathophysiology of rheumatoid arthritis [37]. On the other hand, the transient increase of IL-6, associated with exercise, (except that it exerts endocrine action on fat tissue by promoting fat oxidation), has anti-inflammatory activity and offers beneficial activity on bone metabolism. The anti-inflammatory activity of IL-6 may possibly be due to inhibition of TNF-α factor by IL-6 and IL-10 [37,38]. On one hand, IL-6 enhances osteoclastogenesis by stimulating RANKL secretion from osteoblasts resulting to bone resorption and it is correlated to postmenopausal osteoporosis [38]. On the other hand, IL-6 appears to raise

VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

the differentiation of osteoblasts in the early stages and possibly exerts osteoanabolic action.

In an experimental study [39], secreted cytokines-myokines were counted in autoimmune arthritis (SKG/Jcl) mice following continuous stimulation as exercise at the onset of the disease. Exercise increased the levels of IL-6,10,15 and reduced the secretion of TNF-α in systematic circulation. Exercise-stimulated mice had histologically reduced arthritic joint lesions, thicker articular cartilage and more chondrocyte accumulations compared to the control group. They also had a delay in the onset of the disease and a slower progression. These results show the potential anti-inflammatory activity of IL-6 and IL-10 in exercise by inhibiting the inflammatory activity of TNF-α.

IL-15 has been detected and secreted in many tissues but mainly in muscle tissue. In population of volunteers, IL-15 was elevated in muscle tissue after intensive exercise for twelve weeks [40]. IL-15 is a myokine that affects the metabolism of glucose, fat and bone tissue. The raise of IL-15 levels in both muscles and circulation seems to lead to increased bone mass and muscle hypertrophy. It is likely involved in the induction of osteoblasts depositing an organic foundation. Similar to the findings for IL-6, IL-15 has an anti-inflammatory effect through exercise in the onset and progression of rheumatoid arthritis. [39]

IL-7 secreted by muscle cells affects bone metabolism in both osteoblasts and osteoclasts. Overexpression of human IL-7 in female mice was found to increase bone mass. [41] Additionally, in bone marrow cultures, IL-7 was found to be an inhibitor of osteoclastogenesis.

The role of CNTF

CNTF or ciliary neurotrophic factor is part of the IL-6 cytokine family. It has recently been identified as a myokine along with the sCNTFR receptor and it is probably a bone formation inhibitor [42]. Specifically, in female mice, in vitro overexpression of CNTF has led to inhibition of osteoblast differentiation. Female mice deficient in CNTF showed increased bone density. Because the results were not correlated with male mice, it is likely that the mechanism would also involve sex hormones. Therefore, CNTF may be associated with osteoporosis in people who have increased sedentary life and reduced muscle activity. On the other hand, secretion from inactive muscle fibres may protect the muscles and joints from ectopic ossification.

The role of decorin

Decorin is a leucine-rich proteoglycan. It is released from the muscles after acute and chronic muscular exercise. Its secretion is associated with raised gene expression of the follistatin and MyoD. Decorin competes with myostatin activity directly binded with it. Studies show that decorin binds to type I collagen and induces collagen mineralization by osteoblasts [43]. Additionally, decorin appears to bind to TGF-β factor and enhance its activity when bound to osteoblast receptors.

The role of irisin

Irisin is a newly found myokine produced by the muscles during exercise and mechanical stress. Generally, it appears to exert a protective effect on insulin resistance, metabolic syndrome, cardiovascular disease and reduces fat tissue increasing brown adipose tissue. In the subchondral bone of the joint, irisin enhances osteoblastic activity and differentiation through the known mechanisms of Wnt / β-catenin, p38 MAPK and ERK [44]. In addition, Qiao et al, [44] has shown in vitro that irisin increases transcription factor-2, Ostrix / sp7, ALP, col1-a1, osteocalcin, osteopontin and calcium deposition in cell cultures. Irisin, besides inducing bone production, also reduces bone resorption by inhibiting the RANKL / NFATc1 pathway. An in vivo mice study found that insertion of irisin increased cortical bone [45]. Finally, in humans, it was found a correlation of level of irisin with the incidence of osteoporotic fractures in osteopenic postmenopausal women [46].

The role of IGF-I

IGF-I (insulin-like growth factor) is secreted by the muscles during mechanical loading. It is expressed to a large level by the muscles, but also by the bone, liver and systemic circulation. It has a direct effect

VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

on bone and muscle growth and is implicated in the pathogenesis of sarcopenia. IGF-I acts on bone remodelling by enhancing osteoblastic activity and osteoclastic absorption and is associated with achieving bone density [47]. Associated proteins with IGF (IGFBP2, IGFBP-5), inhibitors and regulatory proteins of IGF-I, are produced in the muscle tissue and potentially exert a negative effect on bone osteoblastic activity. However, because IGF-I is not specifically expressed in the muscle tissue, the role of muscle IGF-I is not clearly defined.

The role of FGF

FGF-2 or bFGF (fibroblast growth factor-betta) is produced from various tissues, chondrocytes, bone and muscle cells. In muscles, it is expressed in heavy exercise and muscular injuries. It is a growth factor involved in osteoblastic anabolic activity, cartilage and bone regeneration, chondrogenesis and fracture callus [48]. In the cartilage, it is stored in the matrix and after an injury it is released inducing cell proliferation and increases the expression of catabolic enzymes such as metalloproteinases (MMPs) and aggrecanases. Probably its paracrine effect as myokine enhances the action of FGF-2 derived from other tissues.

In an in-vitro study [49], FGF-2 was administered to cultured human mesenchymal cells. It was found that this population developed enhanced chondrogenesis. Increased levels of Sox9 protein, a transcriptional factor that activates chondrocyte genes for chondrogenesis, were found.

The role of CHI3L1

CHI3L1 or Chitinase-3-like protein 1 (YKL-40) is secreted by many tissues such as chondrocytes, fibroblasts, macrophages, hepatic, endothelial, epithelial cells, adipose tissue and others [50]. Recently, the expression and secretion of CHI3L1 by muscle cells was discovered. Muscle cell differentiation decreases its levels. Mechanical load, exercise and inflammatory cytokines increase its levels. In vitro studies in cultures of guinea pig and rabbit cells have shown that normal concentrations raise chondrocyte and synovial cell proliferation and synthesis of proteoglycans. It acts as inhibitor of cellular apoptosis, induces myoblastogenesis and participates in glucose metabolism and insulin resistance. On one hand, some studies show its anti-inflammatory activity, on the other hand, it correlates with chronic inflammatory arthritis by activating the PAR-2 receptor. Other studies report the increased concentration of CHI3L1 in osteoarthritic cartilage and characterize it as a potential marker of osteoarthritis progression. An in-vitro research [51], however, reveals the protective anti-inflammatory effect of CHI3L1 as it inhibits TNFα and IL1β and reduces the metalloproteinases MMP1, MMP3. CHI3L1 needs further research as a promising molecule.

The role of sarcopenia in the joint

The most important myokine involved in the pathophysiology of sarcopenia is the IGF1 associated with muscle growth and most probably the GH / IGF axis. Myostatin is also increased as an anti-anabolic factor of muscle tissue, IL-1,6, TNF and NfκB.

Sarcopenia associated with osteoarthritis is not only related to the neighbouring muscles of the affected joint but to the whole muscular system. [52] Sarcopenic obesity is more common than non-sarcopenic obesity in osteoarthritis. There is an interrelated association, a vicious circle, between the muscular tissue and the joint, osteoarthritis causes sarcopenia and sarcopenia is also a causal factor in the onset and progression of osteoarthritis.

On one hand, the role of adipokines and other paracrine molecules such as leptin, adiponectin and resistin, contribute to the state of chronic low-grade inflammation resulting to sarcopenia [53]. Furthermore, indirect biomechanical factors such as decreased joint range of motion, pain, decreased physical activity and obesity contribute to the pathogenesis of OA-related sarcopenia. On the other hand, pathologically reduced muscle mass appears to be associated with increased damage to the cartilage. Sarcopenia, due to muscle weakness, causes increased joint loads, reduced stability, and possibly decreased neuromuscular response to movement, gait and stasis. Clinical studies in populations [54-59] correlate the weakness of the quadriceps as a risk factor for the progression of osteoarthritis, pain and knee dysfunction.

VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

Inflammatory muscle markers were studied after biopsy from vastus lateralis of quadriceps in osteoarthritic patients during total arthroplasty surgery. [60] Muscle inflammatory factors were isolated such as IL-6, MCP1 (monocyte chemotactic protein 1), NF-κB and STAT3 and correlated to reduced muscle activity, slower gait and increased joint dysfunction, according to WOMAC grading and patient walking analysis. Although MCP1 is normally secreted by muscle cells and macrophages during muscle inflammation and injury, it appears to be elevated also in osteoarthritis. In addition, the systemic raise of IL-6 has been clearly associated with loss of articular cartilage and radiographic osteoarthritis [61]. Therefore, questions are raised about the role of inflammatory processes in the correlation of muscle weakness and osteoarthritis progression.

Conclusions

Muscle tissue plays an important role in joint homeostasis, metabolism, repair, protection, fetal joint development and probably in the pathogenesis of articular cartilage. This role is achieved by mechanical and biological interactions.

Muscle derived mechanical loading of the joint, propagates biomechanical changes to cartilage, involving physical, electrochemical and metabolic phenomena through fluid flow, hydrostatic pressure, cartilage deformation, osmotic pressure, diffusion and changes in concentrations of molecules, ions and pH. Chondrocytes have mechanical stress receptors such as integrin receptors, connexins and Ca^{2+} ion channels which induce the function of collagenases and aggrecans in the cartilage matrix. At the same time, muscle tissue protects and offers stability to the joint either intentionally or inadvertently by proprioception.

The biological interactions are still not very well known. Myokines secretion by muscle tissue during exercise or even in the absence of it, affects bone metabolism and the joint as a whole organ. Some myokines have a negative effect on subchondral bone metabolism, such as IL-6, myostatin, activin and CNTF. Other myokines have anabolic activity on bone metabolism such as IGF-I, FGF-2, IL-15, follistatin, and Irisin. It seems to be at an early stage about understanding how muscle tissue affects the metabolism of both articular cartilage and bone. Questions arise on how myokines affect osteoblastic and osteoclastic activity and how they interact with adipocytes and overall body metabolism. It is still a question on how muscle function in terms of, concentric or eccentric loading, prolonged or repeated loading, affect joint structural integrity. Although growth factors and cytokines secreted by muscle tissue have already been detected, it seems that new myokines are emerging from research. On the other hand, existing myokines need further investigation about the effect of their molecular and cellular signal pathways on bone and joint. This research is likely to be helpful for understanding the pathophysiology of arthropathies, and planning new therapeutic strategies.

Conflict of interest:

The authors declared no conflicts of interest.

VOLUME 70 | ISSUE 1 | JANUARY - MARCH 2019

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