AUCTORES
Globalize your Research

Clinical Orthopedics and Trauma Care

Emmanuel Bajo *

Open Access

Review Article

Exploring Mechano-Transduction in Physical Therapy: Biological Responses in Skeletal Tissue and the Impact of Aging on Regenerative Rehabilitation

Emmanuel Bajo

Blood Transfusion lab Colchester Hospital Turner Rd, Colchester CO4 5JL.

***Corresponding Author:** Emmanuel Bajo, Blood Transfusion lab Colchester Hospital Turner Rd, Colchester CO4 5JL.

Received Date: January 01, 2025; **Accepted Date:** January 14, 2025; **Published Date:** January 23, 2025

Citation: Emmanuel Bajo (2025), Exploring Mechano-Transduction in Physical Therapy: Biological Responses in Skeletal Tissue and the Impact of Aging on Regenerative Rehabilitation, *J. Clinical Orthopedics and Trauma Care*, 7(1); **DOI:10.31579/2694-0248/119**

Abstract

Mechanoreception is the biological process by which cells perceive mechanical stimuli through the action of different mechanical forces and convert them into cellular responses. Consequently, these changes in structure are mediated by interactions between effector proteins and transcription factors in the cytosol. This interaction controls a wide range of cellular activities, including adhesion, migration, shape, proliferation, differentiation of stem cells, intracellular signalling, and matrix turnover.

In this review, I referred to steps in cell signalling and discussed the use of mechanobiology in physical therapy as an approach to support cellular repair and regeneration of tissue. Particular attention was drawn to osteo-sarcopenia, the age-related loss of bone and muscle mass, and function, naturally occurring with aging and accelerating in the presence of chronic diseases-and to the role of mechano-transduction in bone adaptation under mechanical load.

I have examined the evidence supporting the use of mechanical forces to stimulate favourable cellular responses and promote adaptation in bone tissue through the study of the mechanical forces acting on both bone cells and muscles, and how these tissues respond to exercise as a countermeasure. Thereby concluding that:

Physical inactivity further diminishes the mechano-transduction associated with aging. Exercise can markedly improve health and musculoskeletal function in older age by improving autophagy and reducing oxidative stress, cellular senescence, and inflammation. However, the maintenance of general health and promotion of longevity necessitates unaccustomed mechanical loading through progressive resistance training.

Keywords: chronic illness; extracellular matrix; behaviour

Introduction

Mechano-transduction signifies the physiological progression by which cells sense mechanical stimuli and convert them into cellular responses, in response to various mechanical loads [1] Many cell types have been identified that can sense and respond to mechanical stimuli. Such cells include, but are not limited to, osteocytes, chondrocytes, fibroblasts, keratinocytes, and even stem cells. Proteins at the cell surface detect and send information from inside and outside of the cell. The signals via subsequent cellular response pathways induce cytosolic effector proteins and/or transcription factors, which eventually create structural changes. [17].

Integrins are transmembrane receptors with 2 subunits, α (alpha) and β (beta), which connect the cell to specific extracellular matrix (ECM) proteins through transmembrane associations with the cytoskeleton [8]. Thus, clustering to form multifaceted signalling complexes, or create cell-cell interactions, transmitting forces across the cell membrane and sensing of matrix stiffness. Thereby, influencing cell behaviour, including adhesion molecules, shape, proliferation, stem cell differentiation, intracellular signal cascades, and matrix turnover. A classic example is seen in osteo-sarcopenia where early onset of healthy ageing will inevitably lead to reduction in bone and muscle mass and function. Chronic illness patients will have accelerated decline. [19]. In this case, mechano-transduction is used in adapting bone to load. A little comparatively feeble weak bone that predispose patients to falls and fractures, decreased activity, musculoskeletal frailty can become thicker and stronger in response to specific load through the process of mechano-transduction and mechano-adaptation. In fracture repair, osteoblast exposed to tension upregulate osteo-pontin, and other bone morphogenic proteins. While mesenchymal stem cells differentiate in a direction of osteogenesis, changing the balance from fat storing to bone deposition [17,8]

Just like osteocytes, chondrocytes provide stress shielding because they are encapsulated in a complex matrix structure. Shear stress promotes transcription and translation of proteoglycans and collagen at a higher rate in bovine chondrocytes compared with compressive loading. This process disrupts NF-kB signalling, contributing to arthritic changes [8].

This review is targeted to highlight physical therapy based on mechanobiology mechanisms, in which the modulation of cellular healing and regeneration of tissues takes place, with reference to changes caused by aging of bone. I will outline the three steps of communication by cell signalling, taking the tendon as an example, but the basic steps apply also for other musculoskeletal tissues. The focus will be on force transfer and the integration of mechano-adaptation and remodelling across all length scales.

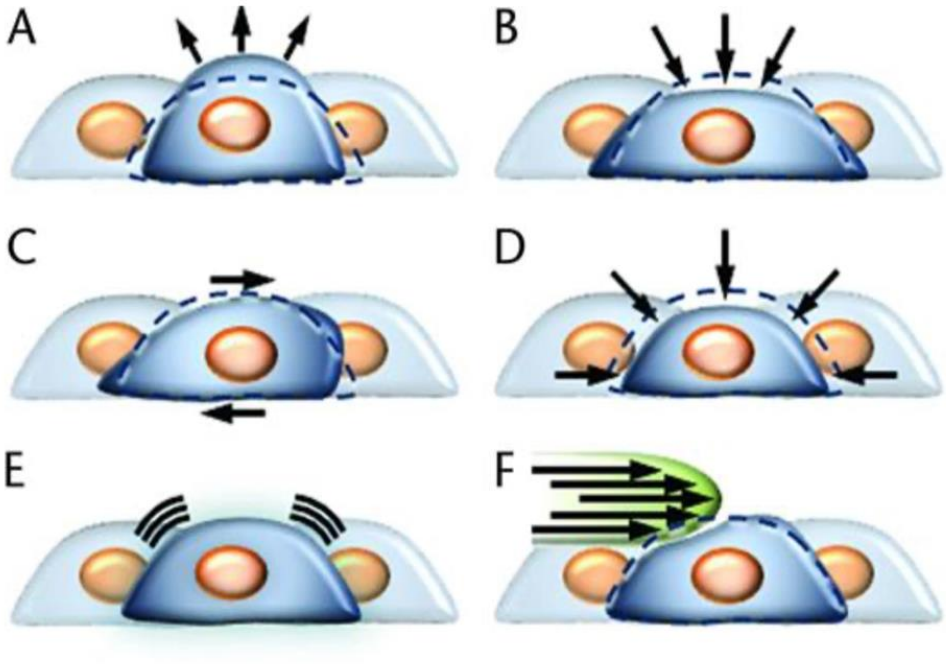

Figure 1 - Mechanotherapy in regenerative medicine is a relatively new field of study in which the mechanisms have not been entirely defined. Nevertheless, its underlying mechanism involves a process called mechano-transduction, the process of conversion of biophysical forces to cellular and molecular responses, as depicted in the above figure, which is critical for cells to sense mechanical signals and transfer this information to the surrounding microenvironment. [2,15]

Mechanotherapy

Musculoskeletal cells can experience a range of micromechanical stimuli, The nature of the various types of stimuli will be determined through interaction of the incoming mechanical forces, the extracellular matrix, and the cells' own mechanical properties [2].

Common examples of micromechanical stimuli include:
(A) **Tension** – indicated by the upward arrow, showing an increase in dimension in the direction of a pulling force;
(B) **Compression** – indicated by the downward arrow, showing a pushing force that decreases the cell's dimensions;
(C) **Shear forces** – distort the cell when parallel forces are applied in opposite directions, either pulling or pushing;
(D) **Hydrostatic pressure** – similar to a pushing force but exerted by surrounding fluid, changing the cell's volume;
(E) **Vibration** – involves oscillating, reciprocal back-and-forth shaking of the cell;
(F) **Fluid shear** – involves fluid flowing parallel to the cell membrane, with the force created pushing against the cell in one direction [2].

The Oxford English Dictionary defined mechanotherapy in 1890 as the employment of mechanical means for the cure of disease [1]. This definition was later updated in 2009 to refer to the use of mechano-transduction (the conversion of biophysical force into a cellular and molecular response) to prompt tissue repair and remodelling (Figure 1)[2]. This divergence draws attention to the molecular underpinnings of exercise recommendations as an efficient alternate-measure to osteo-sarcopenia.

Preferably, the biology of osteo-sarcopenia is to be understood as a systemic alteration in the neuroendocrine system and immune or inflammatory responses that promote oxidative stress, inflammation, defective autophagy, and cellular senescence of bone and muscle tissue. The hallmark of muscle-bone deterioration with time is that the age-related changes in cytoskeletal mechanics indicated that separate load sensing and mechano-transduction in bone osteocytes and muscle fibres may lead to varied responses in injured and non-injured tissues. Because it captures how mechanobiology tickles mechano-adaptation and remodelling at all length scales, it is vital to understand mechanobiology in the context of organismal mechano-physiology. (Figure 2) [3]. Knowledge obtained through mechanobiology forms the basis for the development of mechanical physical therapy protocols so as to potentiate tissue healing and regeneration.

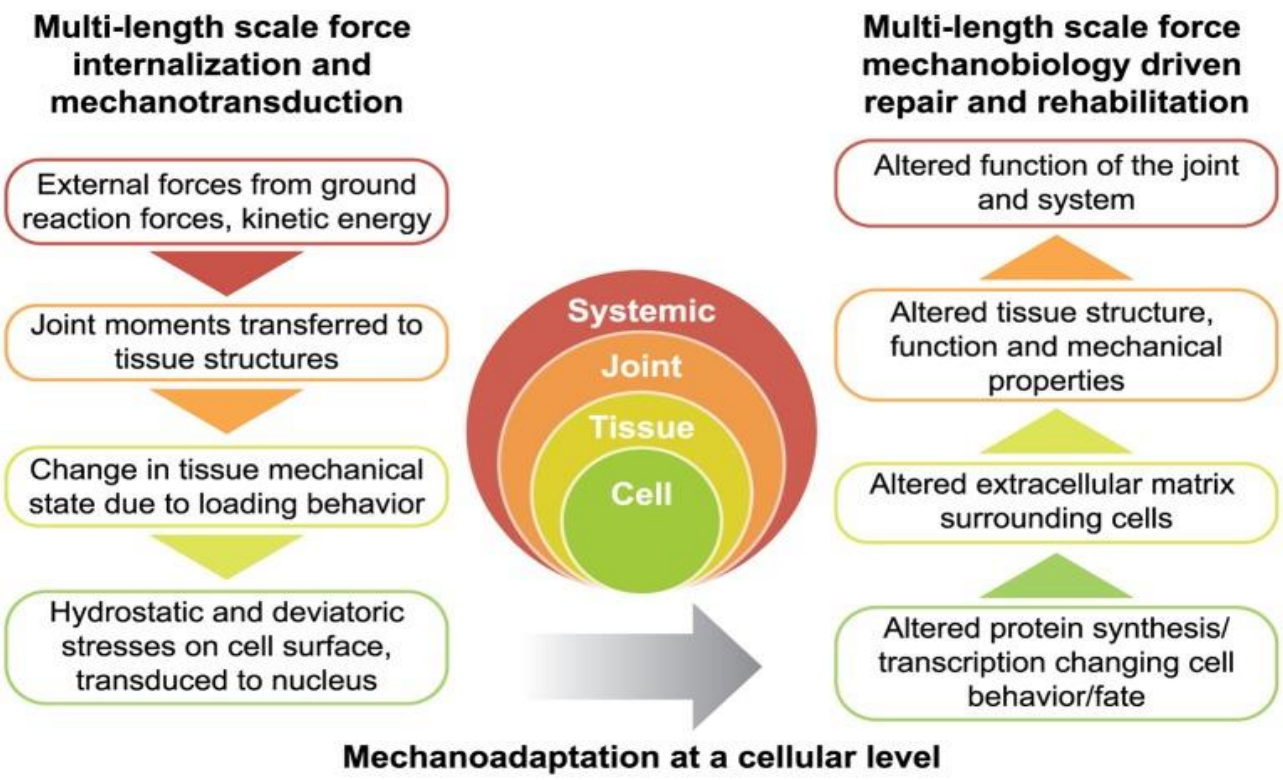

Figure 2 - This figure illustrates the very basis of physical therapy protocols in mechanotherapy, i.e., how the action of mechanical intervention or movement creates a cascade of mechanical stimuli from the organismal level through to its cellular inhabitants, while tissues adjust to the dynamic environment. Collectively, these processes constitute mechano-adaptation, creating a wholesome equilibrium of forces to prevent further injuries and maximize well-being [3,15].

To enable functional movement, musculoskeletal tissues generate, absorb, and transmit force. These mechanical forces are capable of directly influencing cellular activities, which induce tissue adaptation to the mechanical environment. This, in turn, influences tissue-level processes such as growth, modelling, remodelling, and repair, resulting in altered tissue mass, structure, and quality (Figure 2&3) [2].

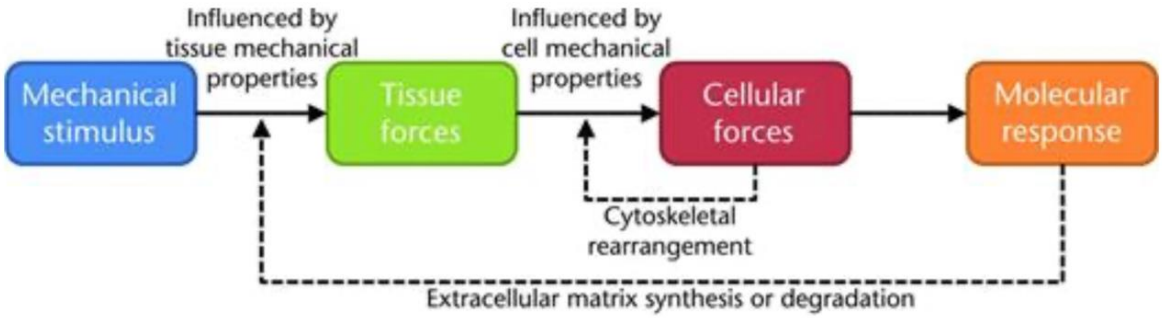

Figure 3: Extrinsic mechanical stimuli can be given, for example, by mobilising joints or tissues or by introducing external treatment methods. On the other hand, it may be intrinsic: given to the person by means of exercise therapy. In both instances, the musculoskeletal tissues will be loaded with the mechanical forces and the properties of the resulting tissue forces are dependent upon the ability of a tissue to resist those particular forces. The cellular forces properties and the way in which the forces from the tissue are transferred to the resident cell micromechanical environment are dependent on the cells' mechanical properties [2]

Through cytoskeletal rearrangement, cell changes the mechanical environment, thereby further changing the mechanical sensitivities of the cells to external forces. With these internal forces surpassing the threshold, the cells can instruct changes to the ECM through increasing its synthesis rate or because of degradation. In turn, these changes in the composition of the ECM mechanically alter the properties of the tissue, modulating the transmission of forces through the tissue and, consequently, cellular responses within it [2].

The body consists of four types of tissues (muscle, connective, epithelial, and nervous), each with distinct mechanical properties and tissue architectures. Muscles and connective tissues, as the primary structural components of the musculoskeletal system, play a crucial role in tissue-level mechano-transduction. The mechanical properties of these tissues are influenced by their cellular makeup and extracellular matrix components, including interstitial fluid (Knothe Tate, 2003; 3].

Most attention has been focused on the ECM-integrin-cytoskeletal signalling axis in terms of cellular force-sensing machinery (Figure 4), which are made

up of actin filaments, non-muscle myosin, and associated proteins [17]. This tensegrity architecture maintains structural integrity by balancing forces of compression and tension, creating a stable yet flexible framework.

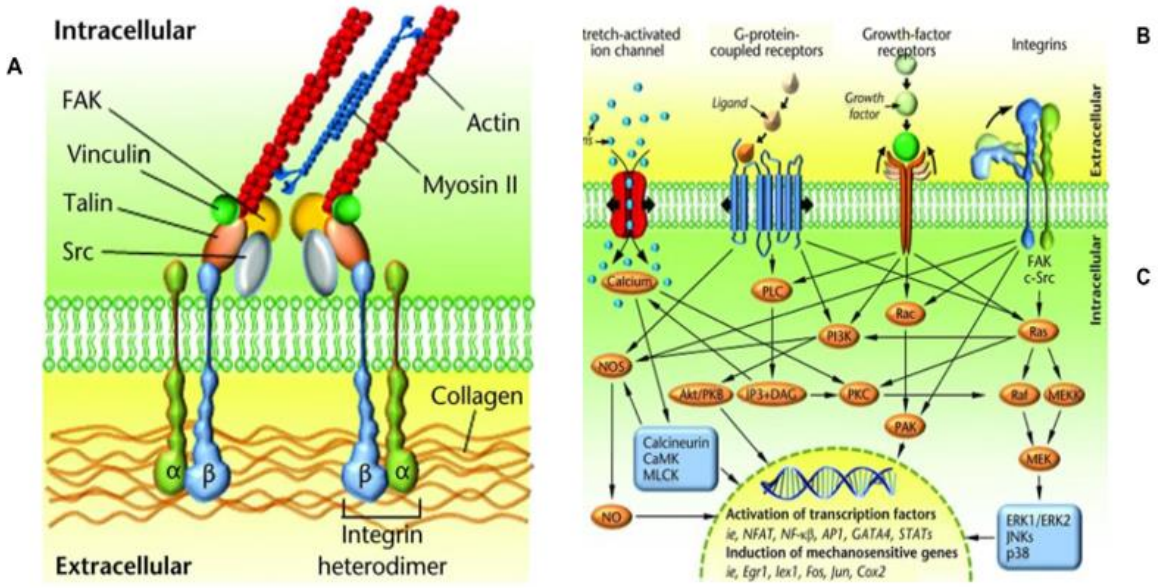

Figure 4 (A, B): These mechano-sensors include stretch-activated ion channels, which open in response to mechanical deformation of the cell membrane, allowing ions to flow in or out; G-protein-coupled receptors with seven transmembrane domains that span the cell membrane; and growth factor receptors that bind to extracellular growth factors. Mechanical loading may enhance their activity, leading to increased cell growth or repair. Integrins are transmembrane proteins that connect the extracellular matrix to the cell's internal structure. When mechanical forces are applied, integrins can change their affinity for their binding partners, impacting cell adhesion and signalling pathways. The mechanical stimulation of these proteins can alter their interaction with other molecules or change their ion conductivity, leading to various cellular responses such as growth, differentiation, and adaptation. This mechano-transduction process is crucial for maintaining the health and function of musculoskeletal tissues [2].

(C) – Mechanical stimulation of mechano-sensors in musculoskeletal cells initiates biochemical coupling, where the mechanical signal is transformed into a biochemical signal through conformational changes in these proteins. These changes trigger various intracellular signalling cascades, many of which share common signalling molecules. This overlap allows for a coordinated response to the mechanical stimulus. The signalling pathways converge to activate specific transcription factors, which include:

NFAT (Nuclear Factor of Activated T Cells), which regulates immune responses and muscle function; NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells), involved in inflammatory responses and cell survival; AP-1 (Activator Protein 1), which plays a role in cell proliferation and differentiation; GATA4, which binds to specific DNA sequences to regulate gene expression, particularly in cardiac and muscle cells; STATs (Signal Transducers and Activators of Transcription), involved in cell growth and apoptosis.

Once activated, these transcription factors move into the nucleus, where they bind to specific regions of DNA and modulate the expression of target genes (mechanosensitive genes). Mechanosensitive genes include:

Egr1 (Early Growth Response 1), involved in cell growth and response to stress; Lex1; Fos and Jun, which are components of the AP-1 complex and are important for cellular responses to growth factors and stress; Cyclo-oxygenase-2 (Cox2), an enzyme involved in inflammation and pain signalling.

The overall effect of these changes in gene expression determines the cellular response to the mechanical stimulus. These pathways are mediated by the

following kinases: Akt/PKB - protein kinase B; CaMK - calcium/calmodulin-dependent kinase; ERK - extracellular signal-regulated kinase; FAK - focal adhesion kinase; IP3 - inositol triphosphate; JNKs - c-Jun N-terminal kinases; MEK - mitogen-activated protein kinase; MEKK – mitogen-activated protein kinase; MLCK - myosin light-chain kinase; PAK - p21-activated kinase; PI3K - phosphoinositide 3-kinase; PKC - protein kinase C; PLC - phospholipase C; Raf - rapidly accelerated fibrosarcoma kinase; Rasrat sarcoma small GTPase, and the following signalling molecules: Ca^{2+}, DAG - diacylglycerol; NO - nitric oxide; NOS - nitric oxide synthase. It is the complex interaction of all major variables described that finally allows cells from the musculoskeletal tissue to adapt and respond appropriately to the mechanical demands placed upon them as integrity and function are preserved [2].

Many kinases are activated, as described in Figure 4, by the transduction of membrane strain working through integrins. These signals activate the Akt pathway, which in turn activates both a downstream effector, β-catenin nuclear translocation, that alters transcriptional control and RhoA that causes an increase in stiffness and represses adipogenic genes, leading to reduced fat formation from MSC precursors [2,15].

Another great example is how force can regulate intracellular calcium entry as shown in Figure 4. In many cases, anabolic responses in bone are reduced because of the pharmacological inhibition of mechanosensitive calcium channels. Recent studies have focused on the mechanical activation of osteocytes through the implicated effect of an auxiliary voltage-sensitive calcium channel subunit, that is partial anchored in the cell membrane and capable of attaching to the ECM [2,20].

Furthermore, these channels also contribute importantly to cartilage, where their inhibition diminishes load induced osteoarthritis in mice. Altogether, many other pathways intermediary molecular players and pathway communications remain to be characterized; however, the real challenge of this study is deciphering in which respect, and when particularly do these channels, and individual pathways are activated because some are complementary and others are redundant [2].

Mechanoreception or the mechanobiology of living tissues underlines the importance of mechano-transduction in musculoskeletal rehabilitation. To delineate what exactly mechano-transduction is, three steps were given: mechano-coupling as the mechanical induction or catalyst, cell-to-cell communication as the interactions throughout a tissue to dispense the loading communication, and the effector response, the cellular response which involves a change in tissue function, i.e., the tissue "factory" that manufactures and assembles the correct materials aligned upon. These three steps are detailed (Figures 5,6,7) below, using the tendon as an illustration [1].

Mechano-coupling

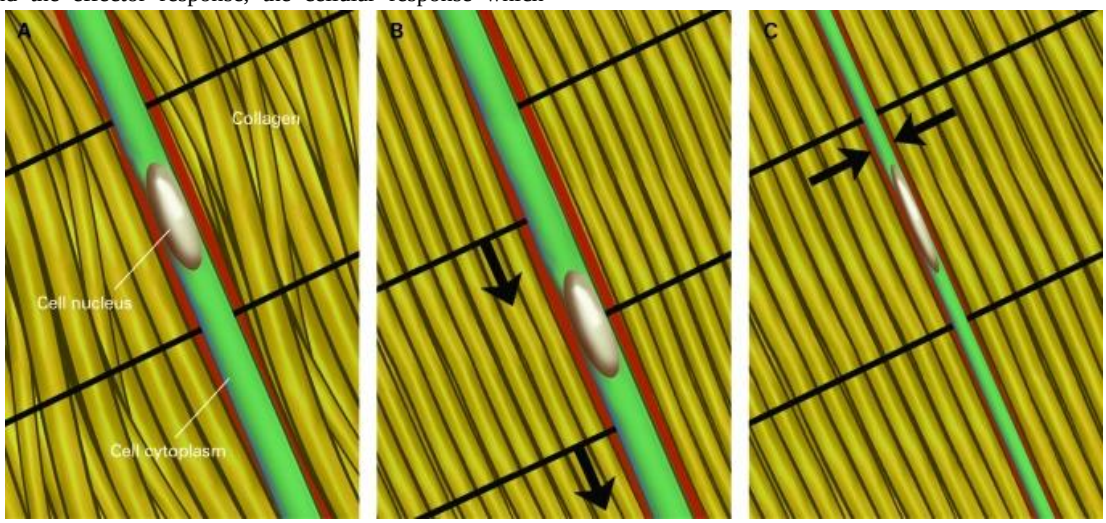

Figure 5: This diagram illustratively represents the mechano-coupling occurring to the tendon cells as a result of physical load shear **(A, B)** and compression **(C)** during loading of tendon. As such, this is a physical perturbation of several orders of magnitude in terms of magnitude right down to, or indirectly, into the cells composing the tissue and is subsequently transduced into a range of chemical signals over and within the cells [1]).

As stepwise illustrated, the Achilles tendon, created by the three-elements complex of the gastrocnemius soleus, accommodates tensile loading. Consequently, A and B tendon cells are subjected to tensile and shearing forces, whereas in C, the tendon is under compressive forces, which may elicit deformation of the cells that can lead to a wide variation of responses depending on the type, degree, and duration of the acting load [1]

Cell-cell communication

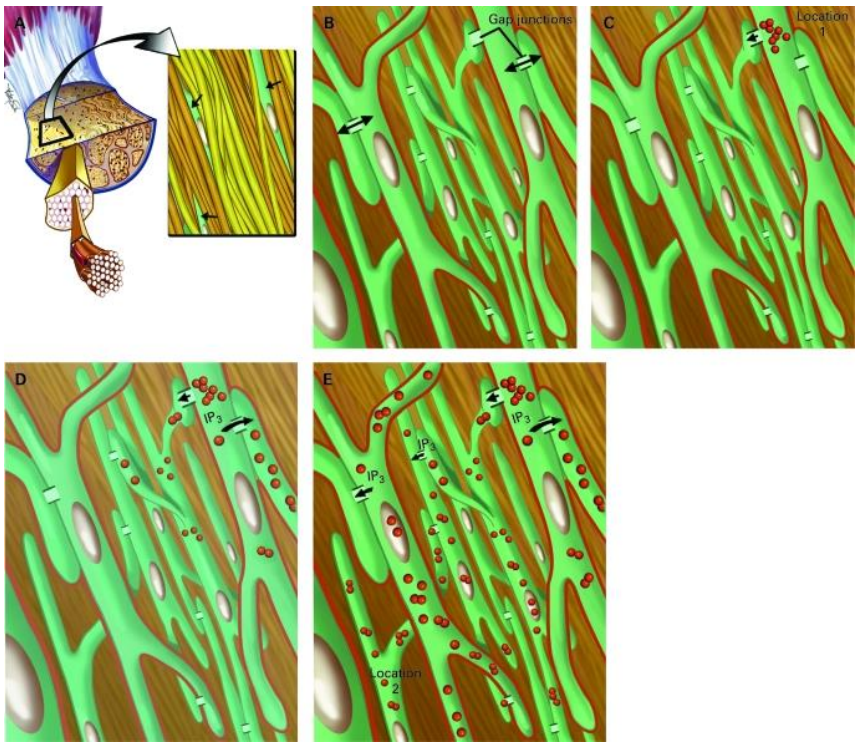

Figure 6: Tendon tissue, in fact, represents one of the best examples of cell-cell communications: **(A)** In a larger tissue area, the specialisation of tendon cells is evident by arrowheads and hundreds of cells in an extra cellular matrix containing collagen. The signalling proteins are the inositol triphosphate and calcium.

In (B), Tendon tissue provides a very good example of cell-to-cell communication. The anastomosing cell network is evident in, where the collagen of the tendon has been removed to reveal how the cells are communicating with each other and thus allowing cell-to-cell communication. The gap junctions are regions of specialisation where the cells join and share small, charged particles. They are identified by their distinctive protein connexin (B) and labelled in through (E).

Even though the distant cells do not receive a direct mechanical stimulus, the important thing to see here is that a stimulus at one site causes cells remote from that site to register a new signal. This signal reflects the time course of cell-to-cell communication originating at (C), passing through the midpoint (D) to termination at (E) [1].

Effector cell response

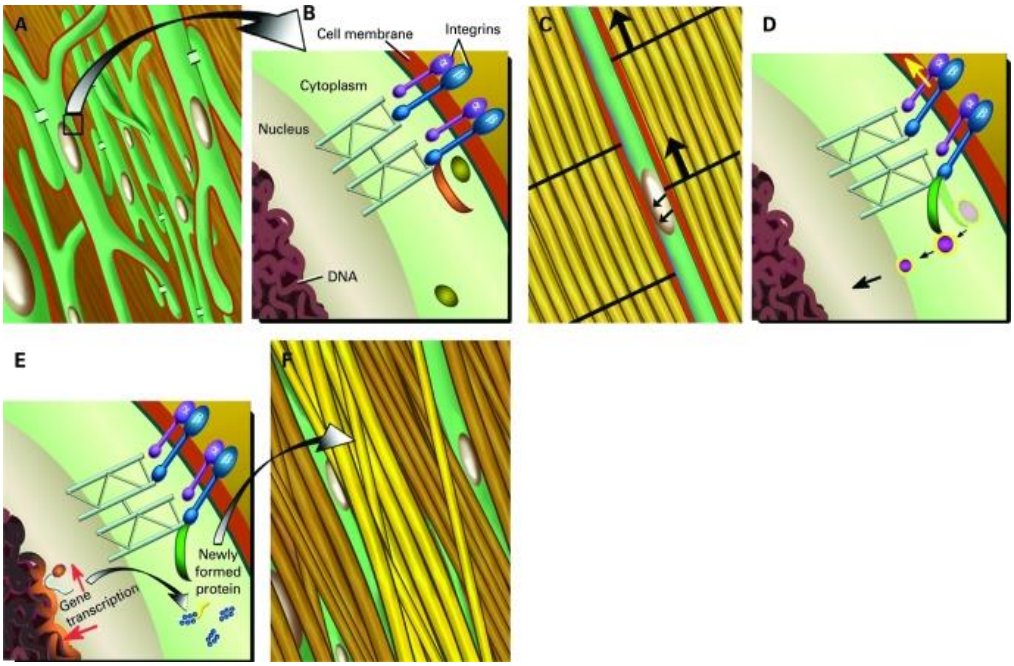

Figure 7: Part three of mechano-transduction is the effector cell response. Although Image A is a larger-scale view of the tendon cell network to provide orientation, Image B focusses on the border between a single cell and the extracellular matrix-a very small area. The structure visible by zooming in on this area includes the cell membrane, the cell nucleus, and DNA; the integrin proteins connecting the intracellular and extracellular spaces; and the cytoskeleton-distributing mechanical strain and preserving cell integrity [1].

Shearing with motion is shown in **Image C**; by now, the integrins have fired at least two divergent pathways. Two such divergent pathways are indicated in **Image D**: i) the cytoskeleton that mechanically couples and signals to the nucleus and ii) a pathway originating from integrins, which activate a host of biochemical signing agents, typically second messengers, that influence gene expression in the nucleus.

In **Image E**, Specific DNA is transcribed into mRNA, which in turn undergoes transcription into the endoplasmic reticulum in the cell's cytoplasm, following which translation into protein takes place when the appropriate signals are received by the cell's nucleus. Subsequently, the protein is secreted and becomes part of the extracellular matrix. The entire molecular process, though highly regulated via transduction, transcription, and translation to transport of protein, is prone to mechanical disruption.

Finally, in **Image F**, the extracellular mechanical stimulus promotes intracellular processes that lead to matrix remodelling [1].

Osteocytes: mechanosensitive cells in bone, are exposed to compression and bending, increasing intramedullary pressure and causing fluid shear signal in skeletal mechano-transduction. Bone is a poroelastic material that modulates force transfer from joint to surrounding musculoskeletal components. Interventions in preclinical development to induce bone adaptation include oscillatory muscle stimulation, dynamic flow stimulation, and dynamic joint loading. This is evident in osteoporosis, where curved or bent, long bones are axially loaded to generate compressive forces and tensile stresses. MSC in the bone marrow also perceive force, particularly direct membrane strain, which restricts MSC adipogenesis. Dynamic compression may also enhance cartilaginous graft formation and mechanical competence [2].

However, tendon is exposed to tension due to the function of the tissues in which they reside. In their role of transmitting muscle forces (tensile loading of collagen), tendon is exposed to large tensile forces, which can cause cell occupying space to narrow, thus resulting in the generation of compressive forces. An example of cells located in tendon that can be exposed principally to compressive, rather than tensile forces are cells within the supraspinatus tendon as it passes through the subacromial space, or the achilles tendon near its calcaneal insertion. While the nature and timing of applied forces are crucial for cellular responses, the biochemical and physical properties of the ECM are equally significant. Recent studies are promoting the use of stem cells instead of progenitor cells, arguing that increasing ECM stiffness promote stem cell differentiation into mechanically robust tissues like cartilage and bone, while stopping the cells from differentiating into adipose and neuronal tissues. For example, stem cells forced to bind on small fibronectin island-like posts take on a rounded shape, unlike cells attached to larger islands results in in enhanced osteogenic commitment due to their elongated morphology with increased Ras homolog gene family A (RhoA) and Rho-associated protein kinase (ROCK) activity. Advances in tissue engineering aims to create synthetic environments that effectively direct stem cell differentiation for tissue regeneration, potentially enhanced by appropriate physical stimuli [2].

Aging related factors may disrupt the very machinery that bone or muscle cells use to sense and respond to mechanical stimuli. 100 Words

As individuals age, cellular dysfunction (impaired mechano-transduction) results in a significant decrease in musculoskeletal formation, thus favouring catabolic processes leading to osteopenia and sarcopenia (osteo-sarcopenia) (figure 8) [19].

As people age, their bones and muscles lose the ability to effectively sense and adapt to mechanical loading, requiring significantly greater forces to stimulate bone formation compared to younger individuals. A young individual could build bone or muscle mass using ~200 lbs, whereas an old individual would have to use >300 lbs to build new bone [19]. This is particularly challenging for those affected by sarcopenia as adding more loads could cause fracture or more damage.

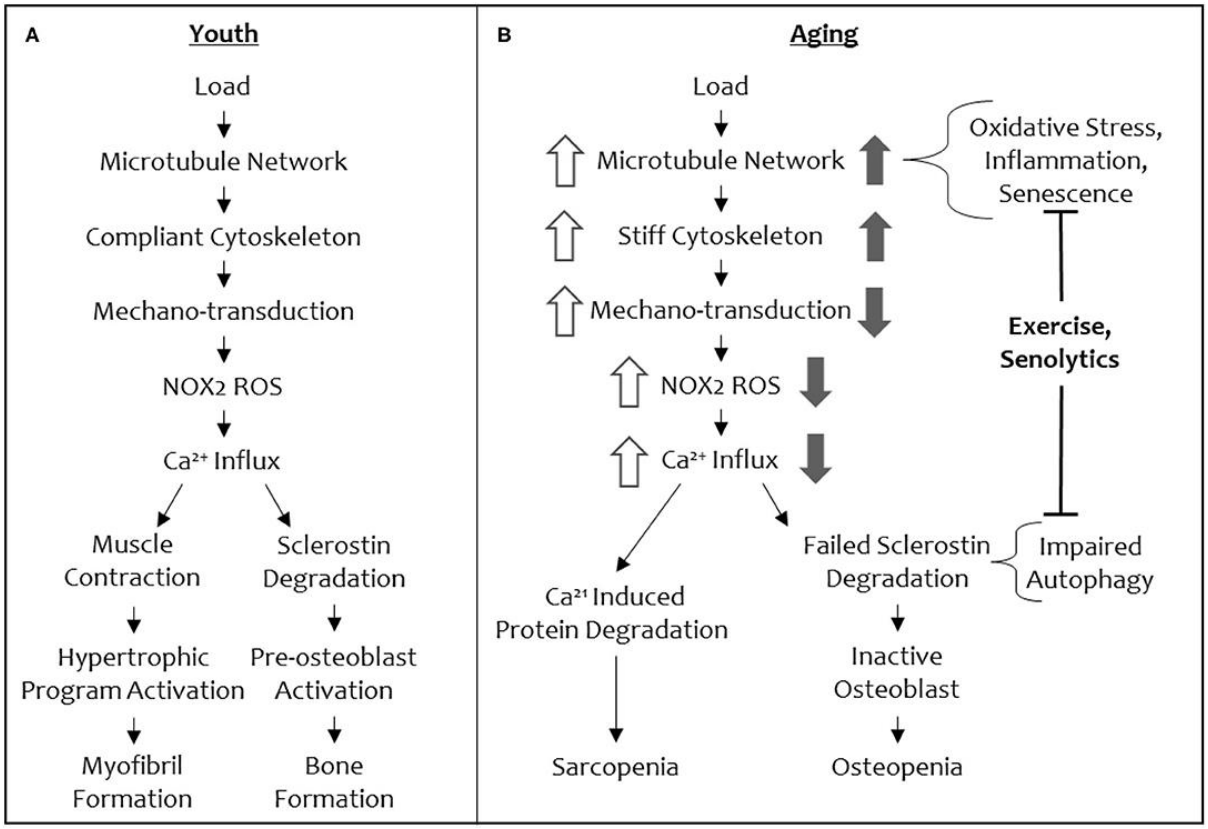

Figure 8 - A schematic of the shared mechano-transduction pathway in youth and in aging [19]. This mechanosensory pathway in bone and muscle involves a microtubule network that regulates cell stiffness, ROS production from NADPH oxidase 2 (NOX2), and intracellular calcium responses, all of which are essential for responding to mechanical loading. Activation of this pathway promotes bone formation and increases bone mineral density, while in muscle, it facilitates myofibril formation and enhances muscle mass.

When cytoskeletal stiffness exceeds optimal levels, it triggers opposing calcium signalling and ROS responses in muscle and bone, leading to muscle injury and atrophy due to excessive ROS production and calcium influx, while bone experiences reduced ROS and calcium responses. This distinction highlights the inhibition of calcium and NOX2 as promising focus for addressing sarcopenia and emphasizes the need to tackle osteo-sarcopenia holistically. In contrast to muscle, beyond this Goldilocks zone, the cytoskeletal stiffness leads to a loss in the mechano-activated formation of NOX2-ROS and influx of calcium through TRPV4 in bone [19].

Representation of the shared mechanical load pathway in youth **(A)** and in aging elderly **(B)** [19] showing the changes in signal because of aging-related problems are indicated in open arrows (muscle) and solid arrows (bone) [19].

The other major contributor to age-related changes involves the accumulation of senescent cells, which activate the innate immune system to promote inflammation and oxidative stress in response to worn-out cells. Proliferating senescent cells produce a variety of factors including ROS and inflammatory cytokines as part of the senescence-associated secretory phenotype. These overflow into the surrounding tissues and deplete the osteoprogenitors, disrupting function in the neighbouring cells. The senescence is characterised by increased stability and tubulin acetylation of the microtubule network. Targeting senolytics can, with good efficiency, deal with this reorganisation of the microtubule network successfully (Figure 9) [19]. These have shown promise to improve musculoskeletal health in rodent models and may have the potential to enhance mechano-transduction in these tissues as well. Moreover, due to altered protein expression, reduced mitochondrial function, and extreme exposure to oxidant molecules, bone mineral density is lost in aging individuals. Co-occurring together with loss of sex hormones, this acts synergistically to decrease gait speed and increase frailty.

Chronic low-grade inflammation in aging, known as 'inflammaging,' arises from the overproduction of pro-inflammatory cytokines like TNF, IL-1, and IL-6, and is linked to diseases such as cancer and musculoskeletal disorders. This inflammation promotes excessive bone resorption through mechanisms involving RANKL, leading to decreased bone density. It is associated with osteopenia, sarcopenia, frailty, and higher mortality, although inhibiting IL-6 can help prevent muscle atrophy. Additionally, skeletal progenitor cell function can be impaired,

but this dysfunction can be reversed through genetic knockout of NF-Kb1 in mice or pharmacological intervention. Adding metformin shows promise in improving autophagy and redox buffering, as well as enhancing bone formation in osteoporotic models [19; Bharath et al., 2020). However, while metformin demonstrates benefits in rodent studies, it may hinder muscle hypertrophy in aging humans, suggesting that its effects may not fully translate to human aging [22].

Autophagy (a crucial lysosome-dependent process that helps maintain cellular balance by recycling damaged proteins and organelles) efficiency declines with aging due to post-translational modifications, or MAPs restricting lysosome localization within the cell [21]. This in turn, limit lysosomal activity, acidity, and the expression of autophagy-related proteins. Hence, issues such as protein aggregation and diminished bone and muscle health [24].

Additionally, mechanical loading stimulates autophagy in both muscle and bone, and defects in this process, exacerbated by excess reactive oxygen species (ROS), can hinder hypertrophic signalling and contribute to age-related muscle deficits and bone loss. Therefore, targeting aging-related effects on microtubules could enhance catabolism in both bone and muscle by improving autophagy and activating mechano-transduction synergistically [21]; Pal et al., 2014).

Physical therapy, Muscle and Joint Biomechanics

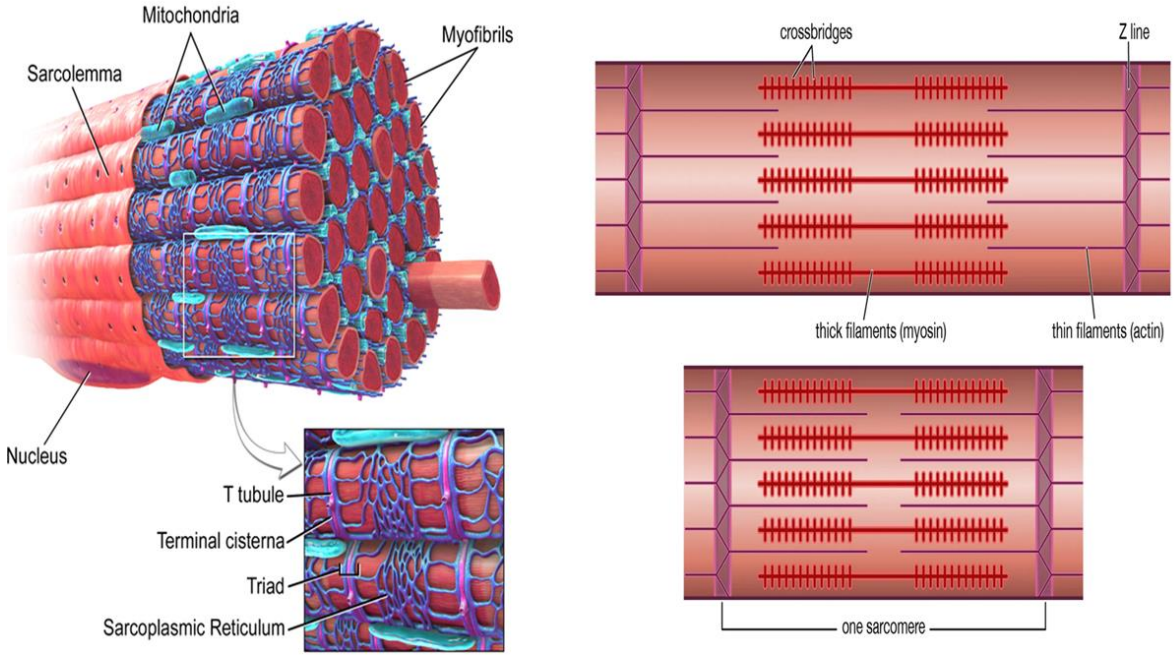

Figure 9: Muscle is the major contributor to joint support, stability, propulsion moving forward, and absorption of shock [3]. It is composed of bundles of muscle fibres (myofibers), which are surrounded by connective tissue (endomysium, perimysium, and epimysium). Each muscle fibre contains myofibrils made up of sarcomeres, the contractile units of muscle. Z-discs separate each sarcomere and are important for mechanical stability. A deficiency in Z-discs is associated with many human diseases [8].

The unit of muscular tendon produces torque in the joint and thus movement through the force produced by contraction and relaxation. The cell cytoskeleton contains actin filaments and tubulin which are tenacious and able to resist stress and compression respectively. Similarly, focal adhesions influence the holistic shape and rigidity of cells by preventing deformation by stimulation using mechanical means (Jalilian et al., 2015). There is abundant collagen fibre that maintains the tissue and does not allow the muscling tissue to be deformed by getting injured with high tensile loads. Serve as organic physical demonstration of a spring/dampers system (Zimmermann and Tate, 2011; Knothe Tate et al., 2016; 3].

Regenerative medicine has created the possibility of complete restoration of damaged or degenerated musculoskeletal tissues because myofibers are capable of distinguishing between chronic longitudinal tension-which favors their elongation by deposition of sarcomeres in series-and chronic resistive overload of muscle, which favors cross-sectional hypertrophy. Precision is required in type, frequency, and duration of loading for this effect on muscle [21]

Physical therapy

Different treatment modalities used in physiotherapy management in rheumatoid arthritis and osteoarthritis comprise movement of the joints, through techniques of exercise therapy, that is, strength training exercises, aerobic activities, and manual therapy comprising inactive physiological and accessory joint movements (Figure 10) [3]. Coupled with engineering principles, these exercises are important in the regeneration of function, improvement in physical health [11-12], management of pain, and improvement of patient satisfaction, where range of motion exercises and joint movements can be likened to joint loading and torques in biomechanics [4,10, 13].

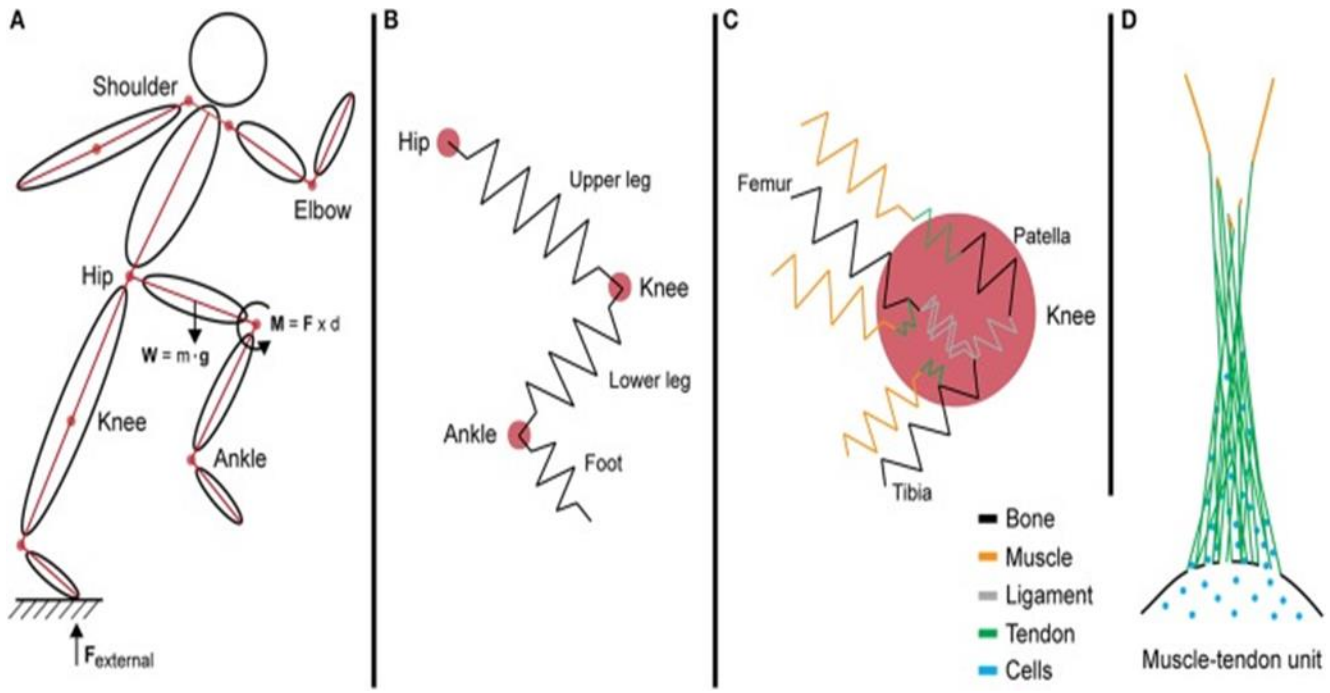

Figure 10 - Torques in the joint cannot be considered in isolation to the whole system, as the movement or changes of the body position are determined by Newton's 2nd Law, defined as force equals mass times acceleration (F = ma). Hence, the resulting moments of ground response force vectors are the torques in the joint, influenced by the rotational and translational dynamics of angular velocity and angles of joint involved [4,20,3]. Therefore, force vectors and positional changes at other joint compliment a joint with changes in its torque [6,1,3].

(A) Model of connected segment of the thigh and lower leg representing the force vectors that produce joint torque during motion.

(B) Limbs are represented in the form of leaf springs, which resist mechanical loading resulting from forces between segments [3].

(C) The presence of many tissues in the knee joint that are endowed with different mechanical properties and stiffness expands the complexity of the model.

(D) The muscle-tendon junction has an important role in locomotion and force transmission. The muscle-tendon unit demonstrates the complex biological tissues anatomical structures, driven by their normal gradients in force, which are understood in terms of structure and function to help avoid concentrating stress and the resulting structural weakness) [3]

Joint momentum and ground reactive forces are integrated into tissue structures at systemic level. These forces are enhanced by transverse component muscular co-contractions, such that compressive and fluid flow shear forces act on bone: via muscle attachments and periosteal Sharpey's fibres, collectively. Hydrostatic pressures in the extracellular matrix and fluid shear deformative forces affect the cellular level cytoskeletal tension tensegrity of the cell [3]

Mechanical intervention

Mechanical intervention, including joint loading, low-level intensity vibrations, and hydraulic stimulations, can stimulate the body to heal. Low-magnitude signals can increase bone mass and trabecular density in patients. Dynamic hydraulic stimulation can increase bone volume and apposition rate by 83% and 190%, respectively. Extracorporeal shockwave therapy can heal and remodel tissues through microdamage, modulation of inflammatory pathways, growth factor upregulation, and protein synthesis. Joint loading can create chemical gradients and streaming potentials, facilitating tissue remodelling and increasing tibial and femoral cortical thickness. It stimulates the body's sensor, the osteocyte network (selectively recruiting either osteoblasts in high-load situations or osteoclasts in low-load situations), and the mechanostat [3].

Exercise therapy

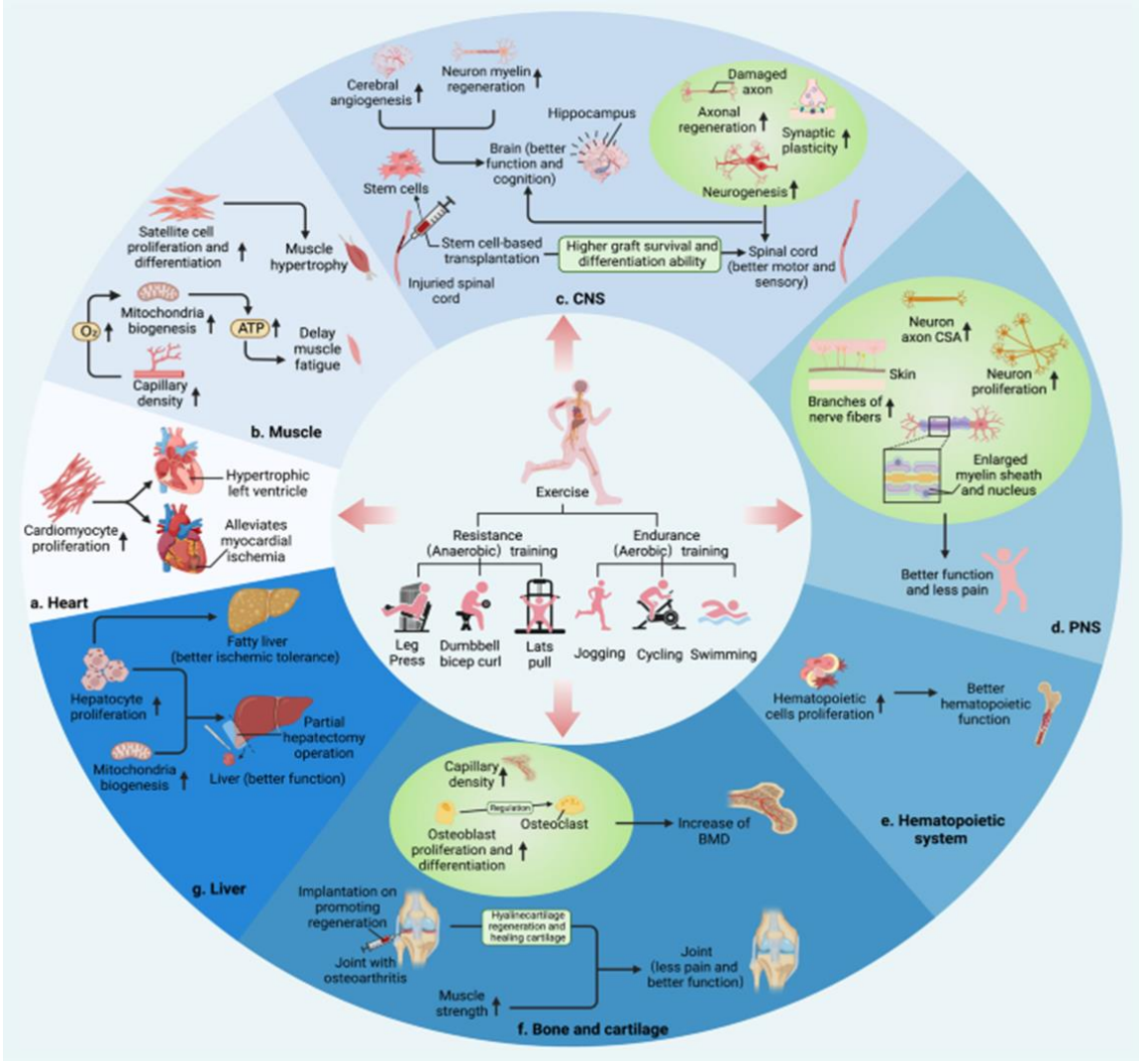

Figure 11 - Ironically, exercise also makes use of oxidative stress and inflammation as a low-level stressor to increase the transcriptional regulation of redox buffering and anti-inflammatory cytokines. However, such a response became disadvantageous for exercise adaptation in young recreational athletes: it would usually remain useful among the elderly exposed to nothing but exercise, in contrast to those elderly treated with metformin, inhibitor of oxidative stress and inflammation [19,22].

Image represents the benefits of exercise in tissue regeneration according to Chen et al., 2022: (A) Reduction of myocardial infarction. Evidently, in the setting of heart failure, AMPK activation could reverse the pathological changes in the microtubule network, an observation indicating that similar interventions might improve musculoskeletal mechano-transduction and are therefore worth investigating further [19].

(B) Causes proliferation of the satellite cells muscular hypertrophy in physiological as well as pathological states. Delays muscle fatigue by angiogenesis. Improvement in mitochondria by PCG-1α pathway.

(C) It promotes the overall degree of motor, sensory, and cognitive functions by stimulating hippocampal neurogenesis, myelin regeneration, axon regeneration, and cerebral angiogenesis. In addition, sensory and motor functions are also improved after spinal cord injury, and it promotes survival and differentiation of the grafted stem cells.

(D) To aim at facilitating the release of prostaglandin and anti-inflammatories, pain relief improves sensation and motor function of patients suffering from peripheral neuropathy. Exercise promotes the branching of nerve fibres in the proximal skin and enhances axon CSA, myelin sheath thickness, Schwann cell's nucleus area, and neurogenesis. (E) Exercise may activate the bone marrow, senescence osteocytes, and enhance the osteogenic differentiation potential of MSCs and inhibit the adipogenic potential of MSCs, proliferation of hematopoietic stem and progenitor cells. (F) Exercise controls skeletal stem cell differentiation into osteoblasts and chondrocytes, promotes bone angiogenesis, hence increases bone mineral density. Besides, the manual exercise therapy can induce the regeneration of post-traumatic cartilage lesions. Biomaterials and medical devices serving as an effective adjuvant to stem cell-based therapy for the purpose of achieving cartilage regeneration. (G) Exercise promotes the differentiation ability of fatty liver, therefore improving ischemia resistance. Furthermore, in patients that underwent partial hepatectomy, physical exercise promoted hepatocytic proliferation, which improved liver functional restoration. Created with BioRender [18].

One study, however, proved that exercise provides added value by stimulating autophagy and mitochondrial protein synthesis via the PCG-1α pathway in aged rodent muscle models and improves mitochondrial capacity in older healthy humans [19]. Interestingly, lifelong exercise in

aging is associated with higher protein levels related to autophagy, such as microtubule-associated proteins LC3II/LC3I (Figure 11) and sequesterome-1 and activation of lysosomal function via multiple pathways, including the AMPK/ULK1 and AKT/FOXO3 axes [24]

Not all forms of exercise offer the same physiological advantages; resistance exercise is crucial for maintaining and improving bone and muscle mass in both young and elderly individuals, However, in older adults, conditions like osteo-sarcopenia can make it challenging to perform the necessary levels of resistance training, which are essential for stimulating anabolic processes. Therefore, combining regular activity like walking with progressive resistance training will enhance muscle and bone quality while adapting to the body's changing needs over time in aging individuals [21,19].

Biomechanical interventions, when combined with exercises, have a profound effect on the joint rehabilitation process, whose principle is to increase muscular strength, therefore minimizing joint loading and reducing disease advancement. Moreover, the muscles involved in spanning the joint would be able to absorb most of the forces, hence reducing pain and impairment associated with osteoarthritis and physical disability [4, 3]Lateral heel wedge shoe pads and valgus bracing used in osteoarthritic treatment in combination with exercises have the ability to show unloading of the injured joint and alignment of the knee centre of rotation with the ground reaction force line of action. Thus, reducing the knee adduction moment by 13% in gait cycle respectively [20, 1, 3].

Pharmacologic options may have short-term action, adverse effects and sometimes addictive. They are even more toxic in older patients who are more prone to musculoskeletal disease. NSAID administration prior to joint loading interacts adversely with mechanotherapy hence, disrupting prostaglandin release, reducing collagen synthesis and ECM formation, resulting in suboptimal responses [16]

Colchicine offers a promising approach to reduce inflammation and restore microtubule-driven cytoskeletal stiffness by inhibiting neutrophil migration and preventing microtubule polymerization, which may help mitigate cardiovascular events linked to increased microtubule density in cardiomyocytes [20]. Similarly, parthenolide, a blocker of the enzyme that produces de-tyrosinated tubulin, has been shown to enhance cytoskeletal stiffness and mechano-transduction in myocytes and osteocytes, suggesting that both drugs could help return a stiff cytoskeletal network to an optimal state for improved musculoskeletal function [20]. In conclusion, it should be mentioned that higher response might be achieved in case of using pharmacological agents together with an appropriate mechanotherapy, and thus the overall anabolic stimulus would be greater compared to either mechanotherapy or pharmacological intervention [19].

Conclusion

Although this review was planned to focus on the process of mechano-sensors or mechano-transduction pathways in bone, tendons, cartilage, and muscles, especially at the level of shared microtubules, and of their influence following systemic changes with aging; It became obvious that each one of these pathways would be a legitimate object for interventions against frailty. This frailty results from an inability to activate anabolic programs and developments in catabolic pathways leading to osteo-sarcopenia. All of these are accentuated by age-dependent widespread declines in mechano-transduction as a result of less physical activity. Indeed, exercise can significantly improve health and musculoskeletal function in the elderly by reducing cellular senescence such as p16 and p21 in muscles-oxidative stress, and inflammation while improving autophagy. Undeniably, progressive resistance training through unaccustomed loading definitely makes a contribution to overall health and longevity.

References

1. Khan, K.M. and Scott, A. (2009) 'Mechanotherapy: How physical therapists' prescription of exercise promotes tissue repair', *British Journal of Sports Medicine*, 43(4), pp. 247–252. doi:10.1136/bjsm.2008.054239.
2. Thompson, W.R. *et al.* (2016) 'Understanding mechanobiology: Physical therapists as a force in Mechanotherapy and musculoskeletal regenerative rehabilitation', *Physical Therapy*, 96(4), pp. 560–569. doi:10.2522/ptj.20150224.
3. Ng, J.L. *et al.* (2017) 'Establishing the basis for mechanobiology-based physical therapy protocols to potentiate cellular healing and tissue regeneration', *Frontiers in Physiology*, 8. doi:10.3389/fphys.2017.00303.
4. Wardrope, J. *et al.* (2008) 'Soft tissue injuries: Principles of biomechanics, physiotherapy and imaging', *Emergency Medicine Journal*, 25(3), pp. 158–162. doi:10.1136/emj.2007.052555.
5. Farrokhi, S. *et al.* (2013) 'A biomechanical perspective on physical therapy management of knee osteoarthritis', *Journal of Orthopaedic & Sports Physical Therapy*, 43(9), pp. 600–619. doi:10.2519/jospt.2013.4121.
6. Block, J.A. and Shakoor, N. (2010) 'Lower limb osteoarthritis: Biomechanical alterations and implications for therapy', *Current Opinion in Rheumatology*, 22(5), pp. 544–550. doi:10.1097/bor.0b013e32833bd81f.
7. Yaari, L. *et al.* (2015) 'A novel non-invasive adjuvant biomechanical treatment for patients with altered rehabilitation after total knee arthroplasty: Results of a pilot investigation', *Clinics in Orthopedic Surgery*, 7(2), p. 191. doi:10.4055/cios.2015.7.2.191.
8. Dunn, S.L. and Olmedo, M.L. (2016) 'Mechanotransduction: Relevance to physical therapist practice—understanding our ability to affect genetic expression through mechanical forces', *Physical Therapy*, 96(5), pp. 712–721. doi:10.2522/ptj.20150073.
9. Knothe Tate, M.L., Gunning, P.W. and Sansalone, V. (2016) 'Emergence of form from function—mechanical engineering approaches to probe the role of Stem Cell Mechanoadaptation in sealing cell fate', *BioArchitecture*, 6(5), pp. 85–103. doi:10.1080/19490992.2016.1229729.
10. Lamb, S.E. *et al.* (2015) 'Exercises to improve function of the rheumatoid hand (Sarah): A randomised controlled trial', *The Lancet*, 385(9966), pp. 421–429. doi:10.1016/s0140-6736(14)60998-3.
11. Abbott, J.H. *et al.* (2013) 'Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: A randomized controlled trial. 1: Clinical effectiveness', *Osteoarthritis and Cartilage*, 21(4), pp. 525–534. doi:10.1016/j.joca.2012.12.014.
12. Jansen, M.J. *et al.* (2011) 'Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: A systematic review', *Journal of Physiotherapy*, 57(1), pp. 11–20. doi:10.1016/s1836-9553(11)70002-9.
13. French, H.P. *et al.* (2013) 'Exercise and Manual Physiotherapy Arthritis Research Trial (EMPART) for osteoarthritis of the hip: A multicenter randomized controlled trial', *Archives of Physical Medicine and Rehabilitation*, 94(2), pp. 302–314. doi:10.1016/j.apmr.2012.09.030.
14. PAGE, C.J., HINMAN, R.S. and BENNELL, K.L. (2011) 'Physiotherapy management of knee

osteoarthritis', *International Journal of Rheumatic Diseases*, 14(2), pp. 145–151. doi:10.1111/j.1756-185x.2011.01612.x.
15. Huang, C. *et al.* (2013) 'Mechanotherapy: Revisiting physical therapy and recruiting mechanobiology for a new era in medicine', *Trends in Molecular Medicine*, 19(9), pp. 555–564. doi:10.1016/j.molmed.2013.05.005.
16. Dr. Liji Thomas, M. (2024) *Mechanotherapy: Exploiting mechanobiology for tissue rehabilitation and regeneration*, *News*. Available at: https://www.news-medical.net/health/Mechanotherapy-Mechanical-Means-for-Treating-Disease.aspx (Accessed: 07 November 2024).
17. Loghmani, T.M. and Whitted, M. (2016) *(PDF) soft tissue manipulation: A powerful form of Mechanotherapy*.
18. Chen, J. *et al.* (2022) 'Molecular mechanisms of exercise contributing to tissue regeneration', *Signal Transduction and Targeted Therapy*, 7(1). doi:10.1038/s41392-022-01233-2.
19. Leser, J.M. *et al.* (2021) 'Aging, osteo-sarcopenia, and Musculoskeletal Mechano-transduction', *Frontiers in Rehabilitation Sciences*, 2.
20. Roubille, F. *et al.* (2013) 'Colchicine: An old wine in a new bottle?', *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, 12(1), pp. 14–23..
21. Lee, H. *et al.* (2019) 'Exercise training increases skeletal muscle strength independent of hypertrophy in older adults aged 75 years and older', *Geriatrics & Gerontology International*, 19(3), pp. 265–270.
22. Gao, Y. *et al.* (2010) 'Effect of the anti-diabetic drug metformin on Bone Mass in ovariectomized rats', *European Journal of Pharmacology*, 635(1–3), pp. 231–236.
23. Bharath, L.P. *et al.* (2020) 'Metformin enhances autophagy and normalizes mitochondrial function to alleviate aging-associated inflammation', *Cell Metabolism*, 32(1).
24. Pal, R. *et al.* (2014) 'Src-dependent impairment of autophagy by oxidative stress in a mouse model of Duchenne Muscular Dystrophy', *Nature Communications*, 5(1).
25. Robert, D.E. *et al.* (2024) *Encyclopædia Britannica*.

DOI:10.31579/2694-0248/119