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Mechanotransduction and Alveolar Bone Remodelling: a Narrative Review of Dynamics and Mechanisms

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Mechanotransduction is the biological process by which physical forces are converted into biochemical signals, playing a central role in alveolar bone remodelling. This remodelling is influenced by external stimuli such as mechanical stress, bone loss, and medication-related osteonecrosis. While most in vivo studies have focused on mechanotransductive changes within the periodontal ligament (PDL), it is increasingly recognised that the alveolar bone itself plays a broader and more complex role in this dynamic process. This narrative review presents a qualitative synthesis of literature sourced from PubMed, Scopus and Web of Science, emphasising the cellular and molecular pathways involved in mechanotransduction within alveolar bone. A deeper understanding of these mechanisms is essential for advancing applications in orthodontic tooth movement, dental implant osseointegration, and musculoskeletal tissue engineering. Moreover, insights into the biomechanical regulation of bone may facilitate the development of improved biomaterials and regenerative strategies in clinical dentistry and orthopaedics.

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The process of translating the physical forces into biochemical signals which is subsequently incorporated in the biological response is known as mechanotransduction. These biochemical signals are mostly converted from mechanical energy such as electromagnetic forces, gravity, tension, strain and shear.[1] To elaborate, the physical forces influence cellular growth and remodelling in all living tissues and eukaryotic cells which are normally mechanosensitive. Further, the bone can respond accurately to extraneous influences modifying its morphology and metabolism to adapt to changes in the environment. In oral cavity, remodelling is important for alveolar bone repair and regeneration along with maintaining the periodontal homeostasis and bone health.[2] However, this particular adaptability of bone raises a number of scientific problems, including how mechanical or other types of signals are perceived, what receptors are used, and what biochemical pathways are involved in this adaptation.[3] This review aims to acknowledge these questions and discuss the process and signalling pathways involved in mechanotransduction with clinical relevance by deriving a qualitative summary of available literatures.

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Mechanotransduction system

Among the various types of bone cells, osteocytes are considered as the mechanosensory cell within the bone. External mechanical forces are converted into biochemical reactions via mechanotransduction, which allows osteocytes to orchestrate the remodelling process. The process of how these cells recognise mechanical stresses and encourage alterations in bone mass and structure, is currently unknown. There have been two

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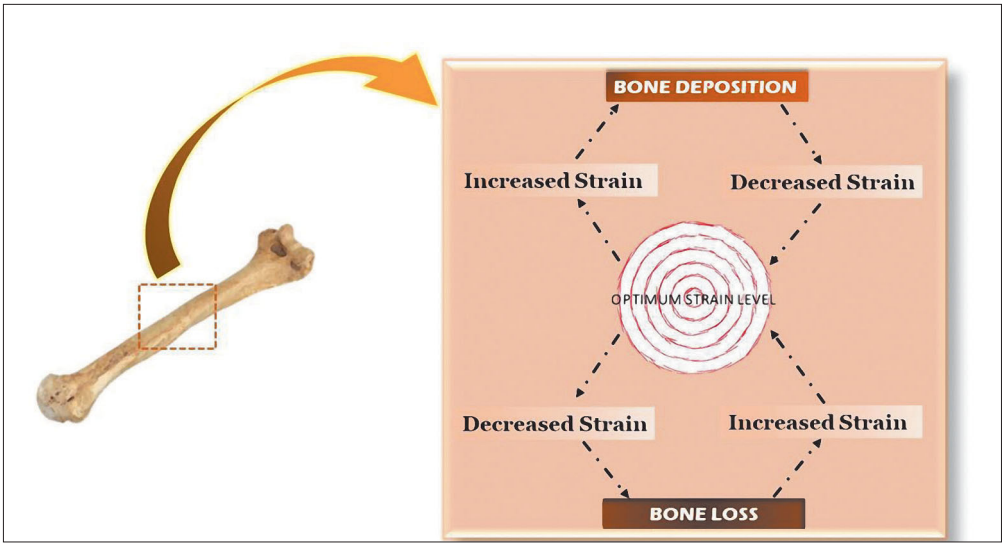

Fig 1 Frost's mechanostat theory model. The figure illustrates how bone responds to varying levels of mechanical strain, ranging from resorption at low strain and maintenance in the physiological range to formation and potential damage at higher strain levels.

approaches in mechanotransduction research. Some studies have sought to comprehend it from a macrosystem perspective, in which it is considered as a feedback and stability-required control system.[4,5] Others have approached it from a micromolecular perspective, aiming to characterise the unique molecular signalling pathways involved to better understand how it works.[6,7]

Mechanotransduction is a three-step process which begins as a mechanical loading that cause a physical signal at the cell level and it is detected by osteocyte.[6,8] The physical signal is then converted into a biochemical reaction and sent on to the effector cells, like osteoblasts and osteoclasts, via a series of subsequent steps. Electrical and flowing potentials, substrate elasticity, and flow-induced shear stress are few of the mechanisms postulated to explain how mechanical loading produces physical signals to be perceived by bone cells. An array of studies has been put forth to understand the events of mechanotransduction[9-11] and further many theories have been postulated on the mechanotransductive mechanism which are discussed as follow.

Mechanostat theory

The mechanostat theory describes a continuous range of loading stimuli in microstrain units and the bone cell response in remodeling and/or modelling activity.[12] Subsequently, this hypothesis outlines how a straightforward feedback loop allows bone tissues to adjust to their mechanical surroundings. High mechanical load areas of bone become reinforced, whereas low-load areas are eliminated (Fig 1).

A mechanostat works by defining a mechanical reference condition (a setpoint, or broader "lazy zone") beyond which there is physical overworking of tissue and below which it is mechanically underworked. Bone adaptation has complex geographical and temporal dependencies, implying that the mechanical setpoint of the bone fluctuates both in space and time. Areas around the neutral axis of long bones, for example, undergo unloading without resorption. In addition, time taken for loading and rest have an impact on bone adaptation, resulting in load-history-dependent bone structures.[13,14] According to numerous experimental and observational investigations, bone is responsive to variable mechanical forces.[15] They are imposed on bone by the environmental factors like gravity, activity, etc. along with muscular movement during physical activity. These loads cause deformations along the length of the bone due to stress (forces per unit area) they apply. Axial, compression, tension, bending, twisting and/or shear are the several types of stress that determines the location of bone deformation. Increased activity levels increase the strain on bone, prompting a compensating alteration in bone size and/or shape to keep it adequately strong to avoid fracture. Similarly, decreasing stimulus reduces strain quotient, which reduces the quantity of bone required for maintaining strength; elimination of bone to reduce expenses of maintaining unnecessary tissue. Skeletal tissues adjust to changes in strains at cellular and tissue levels to balance an "equilibrium" or "customary" strain state inside bone.[16] Bone tissue adaptivity to the mechanical force through feedback loop. In high load area bone deposition is present while in less force area bone loss

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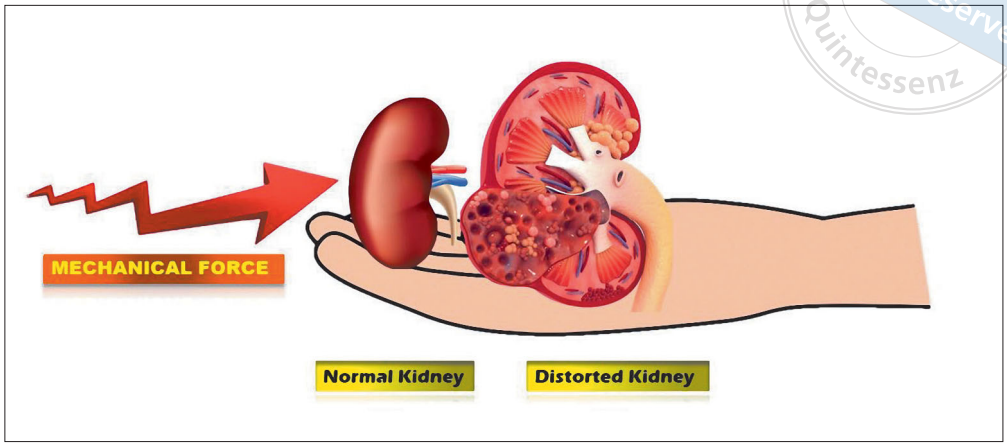

Fig 2 Tensegrity theory model, depicting how mechanical forces transmitted through the extracellular matrix (ECM) are integrated by the cytoskeleton via mechanoreceptors such as integrins. These forces influence molecular structure and cellular function, leading to organ-level deformation and adaptive responses.

is seen.

Tensegrity theory

The tensegrity model suggests a mechanism for explaining how macroscopic mechanical forces can alter the molecular structure and function of living cells (Fig 2). For example, we contribute mechanical energy to an existing mechanical equilibrium in our body when we move our muscles and bones, which causes stress to be channelled inside the load-bearing features, leading to organ malformation.[17] Further, each whole organ is made up of different types of cells which are adhered to the matrisome. Moreover, extracellular matrix (ECM) is linked to the cells by definitive cell-based receptors known as integrins. Hence, integrins are considered as a common mediator of mechanosensation. By stretching across the cell membrane and communicating to the cytoskeleton on one end and ECM on the other, they act as cell mechanoreceptors.[18]

The forces transmitted through the ECM trigger alteration of load-bearing mechano-transducer molecules such as stress-sensitive ion channels, protein kinases and G proteins, and the integrins are transformed into biochemical changes within the cell.[19] As a result, the most important determinants of tensegrity theory are architecture and the cytoskeleton's degree of prestress, referred to as isometric tension. Load distribution prevents harm to individual cells, whilst a little mechanical stimulation can have a significant impact on a vast number of cells.[20]

Mechanosomes theory

The formation of mechanosomes, a multiprotein complex consisting of proteins linked with adherens junc-

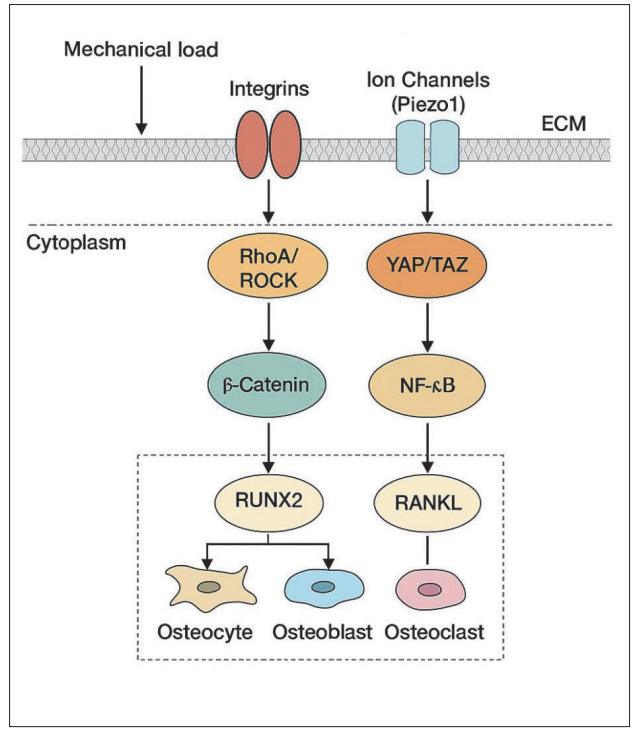

Fig 3 Schematic representation of key molecular signalling pathways involved in mechanotransduction during alveolar bone remodelling. Mechanical load is sensed by integrins and Piezo1 ion channels in the ECM, triggering intracellular cascades.

tions or focal adhesions, is a key feature.[21] The sensor cell membrane deforms because of the load-induced bone distortion, changing the shape of the membrane protein. The solid-state transmission scaffold that releases mechanosomes is related to some of these membrane proteins, which can transmit mechanical information into the nucleus. The transformation of mechanical energy to chemical energy results in modifications to DNA

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geometry, phosphorylation, protein structure, and the synthesis of nascent signalling complexes (Fig 3).[22]

Role of osteocytes in mechanotransduction

Osteocytes are found in lacunae, fluid-filled holes in the bone matrix. They connect to osteoblasts at the surface of the bone through their cell processes, which extend through canals known as canaliculi. They appear to be the most common cell of bone tissue and are uniformly distributed in the ECM. They are functionally mechanosensitive and help translate mechanical stress into a biological reaction. Effector cells of bone include osteoblasts and osteoclasts. A 3D network of electrically connected osteocytes and lining cells serves as a communication mechanism for bone homeostasis and structural strain adaption. According to a recent study in a mouse model, osteocyte ablation resulted in enhanced porous changes in the cortical region and reduced reactivity to unloading, indicating that osteocytes play a role in bone mechanotransduction.[23] It is also expected that osteocytes entrapped deep within the mineralised matrix may detect significantly more mechanical changes than those located near the periphery. As a result, osteocytes trigger bone remodelling in response to external mechanical loads, leading to global architectural adaptation of the bone structure rather than mere trabecular (strut) thickening.

Primary cilia functions in mechanotransduction

Primary cilium consists of microtubules and protrudes from the surface of the cell membrane to resemble an antenna; it is an intriguing element that functions as a mechanical loading sensor. Studies on primary cilia as mechanosensors have been conducted in the kidney and liver. Primary cilia present in renal epithelia bent mechanically in response to changes in flow of fluid during which a substantial rise in intracellular Ca^{2+} was seen, which was reversed when the cilia were removed.[24] Further, in liver cholangiocytes, TRPV4 and polycystin 1/2 complex were shown to be localised in main cilium and displayed the ability to detect fluid shear stress and osmotic changes.[25] Adenylyl cyclase 6 (AC6) is located in the primary cilium of osteocytes, in the same way as it is in cholangiocytes, and fluid movement leads to an increase in intracellular calcium and reduced cAMP, both of which are mediated by AC6.[26]

Some computer models have been created to assess how cilium influences the response of external triggers.[27,28] Current research has used this information to highlight the role of cilium in mechanical responses and its ability to create structural alteration and control cellular process.[26,29] Changing the structure of primary cilia was found to influence the degree of mechanical response.[27,30] Cilia that are lengthier will have increased tensile pressure in the membrane; however, bending stiffness can affect a cilium's capacity to operate as a projectile in altering mechanical signals to molecular signals.

Primary cilia not only detect mechanical stimuli but also respond to them. Increases in the quantity of microtubules around the cilia base were noticed with heightened fluid flow, as an adaptive mechanism to tolerate stress.[31] Structural manipulation of cilia is being increasingly employed as a technique to control cellular mechanosensing. The length of osteocyte cilia increased with treatment of fenoldopam or lithium.[32] Furthermore, osteocytes with longer cilia are more mechanosensitive, responding to fluid flow with enhanced osteogenesis. Fenoldopam also resulted in an increase in the length of primary cilia in endothelial cells.[33] Mechanically stimulated endothelial cells release considerably more nitric oxide when cilia length is increased, implying improved mechanosensitivity. These findings show that the shape of primary cilia is a prospective and practical pharmaceutical target for controlling cell mechanosensitivity and tissue function.

Molecular mechanotransducers

The conversion of mechanical signals into biochemical responses within bone tissue is mediated by a complex network of molecular transducers. Key components include ion channels such as potassium (K^+) and calcium (Ca^{2+}), intracellular signalling molecules like inositol 1,4,5-triphosphate (IP_3), transmembrane proteins such as integrins, and mechanically induced mediators including prostaglandins and nitric oxide.[34]

Calcium ion signaling

Calcium ion signalling is important in osseous mechanobiology, according to several studies. In vitro experiments have found that fluid flow produces a rise in intracellular calcium in osteoblastic cells within minutes, and gadolinium blocks the channel and inhibits the action.[35,36] Similarly, calcium channel blockers verapamil and nifedipine have exhibited a dramatically reduction in mechanically stimulated bone growth in animal models. Additionally, inositol 1,4,5-triphosphate (IP3) has expressed the ability to trigger cellular Ca^{2+} discharge needed to modify fluid movement–related response.[37]

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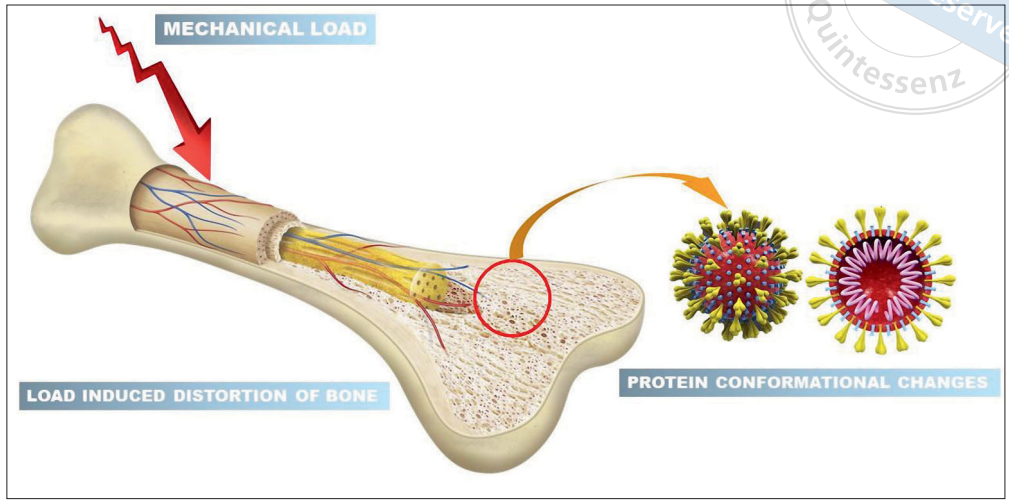

Fig 4 Mechanosome theory model. The figure illustrates how mechanical load-induced deformation of the bone cell membrane leads to conformational changes in membrane proteins, initiating intracellular signalling cascades through mechanosome complexes that transmit mechanical information to the nucleus.

Wingless-type (Wnt)/β-catenin signalling

Wnt signalling via the canonical Wnt/β-catenin pathway is critical and intricately involved in skeletal mechanotransduction. LDL receptor-related protein-5 (LRP5) mediates the signalling process. According to recent research, this signalling pathway was found to be enhanced during stretching in the calvaria of animal models.[38,39] Furthermore, Wnt ligands and their downstream signalling components also promote the differentiation of osteoblasts and formation of minerals. Based on different studies, Wnt signalling in maturing osteoblasts must be downregulated for a mineralised bone matrix to form.[40-42] Wnt signalling was also noted to inhibit osteogenic differentiation from pluripotential stem cells. Despite an early increase in catenin levels in human osteoblastic cells stretched for 15 minutes, Wnt signalling is eventually downregulated. Reduced Wnt signalling in end-stage osteoblasts can cause terminal differentiation and matrix mineralisation, therefore this biphasic Wnt signalling level is likely to be essential.[43]

Nitric oxide and prostaglandins

Osteocyte reactions to mechanical stimulation are initiated with movement of Ca^{2+} ions through the interior and exterior of the cellular environment. This response further extends to the nearby cellular network, resulting in interaction and synchronisation. Therefore, this leads to the release of ATP, nitric oxide and prostaglandin E2 (PGE2), which are all essential downstream signalling pathways.[44] By suppressing the production of osteoclasts and stimulating the differentiation of osteoblasts, nitric oxide (NO) increases bone production. This anabolic regulator regulates osteocyte viability and PGE2 production.[45] PGE2 is a crucial signalling molecule as it improves osteogenic activity and promotes recruitment and differentiation of precursor cells, resulting in an increase in osteoblast output. Insulin-like growth factor is another chemical that works in a similar way to PGE2 in terms of osteogenic signalling.[46]

YAP/TAZ signalling in mechanotransduction

Recent studies highlight Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) as critical mechanosensitive regulators. These proteins shuttle between the cytoplasm and nucleus in response to mechanical cues such as matrix stiffness and fluid shear stress. Upon activation, YAP/TAZ translocate to the nucleus and regulate osteogenic genes, including RUNX2 and CTGF, thereby influencing osteoblast differentiation and alveolar bone formation.[47] The Hippo pathway tightly controls this signalling, and its dysregulation can impair bone remodelling and osseointegration.[48] The integration of mechanical signals into cellular responses involves multiple pathways, including integrins, ion channels like Piezo1 and transcriptional regulators such as YAP/TAZ and β-catenin. These signalling axes culminate in the regulation of key osteogenic and osteoclastogenic genes (Fig 4), orchestrating bone remodelling at the cellular level.

PIEZO1 ion channels and mechanosensitivity

PIEZO1 is a mechanically activated ion channel central to osteocyte mechanosensing. PIEZO1, a mechanically activated ion channel, plays a significant role in osteocytes by detecting mechanical strain and initiating Ca^{2+}

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influx. This triggers downstream activation of integrin-linked kinases and transcription factors like NFATc1, promoting osteogenesis and modulating osteoclast activity. PIEZO1 mutations are associated with bone density anomalies, underscoring its relevance in mechanobiology.[49]

RhoA/ROCK pathway and cytoskeletal tension

The RhoA/ROCK pathway is instrumental in regulating cytoskeletal dynamics in response to mechanical load. It facilitates stress fibre formation and focal adhesion assembly, thereby modulating cell stiffness and matrix interaction. This pathway interacts with YAP/TAZ and integrin signalling, integrating mechanical stimuli with nuclear gene expression in osteoblasts and periodontal ligament (PDL) cells during alveolar remodelling.[50,51]

Mechanotransduction mechanism in alveolar bone

The shape and function of the alveolar bone are distinct from those of the bones present in the axis and appendicular skeleton. Due to its sensitivity to external stimuli such mechanical stress, bone loss stimuli and medication-related osteonecrosis of the jaw, alveolar bone rendering is regarded as an important component in many dental surgical therapies. In general, mechanical stimuli from occlusion and/or orthodontics are converted into biological signals, which result in catabolic and anabolic bone modelling, as well as a local increase in the pace of dentoalveolar remodelling. Most in vivo studies have focused on changes in the PDL,[52,53] but only some of the mechanisms underlying dentoalveolar remodelling can be explained by the PDL, and greater focus has subsequently been placed on the broader reaction of the alveolar bone.[52] This necessitates probing of the role of mechanotransduction in alveolar bone.

The RANKL/OPG signalling pathway is pivotal in regulating osteoclastogenesis during alveolar bone remodelling. RANKL, expressed by osteoblasts and PDL cells, binds to its receptor RANK on osteoclast precursors, promoting their differentiation into active osteoclasts. OPG, a decoy receptor produced by osteoblasts, inhibits RANKL-RANK interaction, preventing osteoclast activation. The RANKL/OPG ratio dictates the extent of bone resorption or formation. Mechanical loading reduces the RANKL/OPG ratio, favouring bone formation, while unloading increases this ratio, enhancing resorption. Orthodontic forces induce localised changes in this ratio, resulting in site-specific bone remodelling.[54]

The mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway is a critical mechanotransductive signalling cascade in alveolar bone remodelling. Mechanical loading activates MAPK/ERK signalling in osteoblasts and PDL cells, promoting their proliferation, differentiation and survival. This pathway modulates RANKL expression, influencing osteoclastogenesis. Furthermore, MAPK/ERK signalling regulates the expression of matrix metalloproteinases (MMPs), facilitating ECMx remodelling, and osteogenic genes such as RUNX2, which enhance bone formation.[55] Mechanotransduction in the alveolar bone involves a complex interplay of osteoclasts, PDL cells, signalling pathways, cytokines and growth factors. These mechanisms ensure adaptive remodelling in response to mechanical stimuli, maintaining structural integrity and functional capacity.

Biological responses during orthodontic tooth movement

Orthodontic tooth movement is a result of mild reversible periodontal injury combined with physiological alveolar bone response to mechanical stresses. Under normal/healthy circumstances, highly coordinated and efficient bone turnover, which necessitates the coupling of bone production and resorption, performs such movement. Recent studies have proposed that orthodontic stress may stimulate bone remodelling by causing microdamage or encouraging the development of a regional acceleratory phenomenon as a reaction to trauma when bone remodelling occurs more quickly than normal tissue activity.[56] During orthodontic tooth movement, when mechanical load is applied to alveolar bone, the orthodontic force is translated into intracellular signals in the mechanosensitive cells. Consequently, this signal is transmitted to the surrounding non-mechanosensitive cells to generate a coordinated response. The following events must occur for it to work; at the first stage, the external orthodontic pressures must be transformed into a signal that the cell can recognise (transduction mechanism), followed by expression of mechanosensitive cells in the PDL and alveolar bone, which detects the mechanical loading–induced signals. To sense these signals, a mechanism is required that is carried out by mechanoreceptors and these receptors transduce the loading information into intracellular signals.[57] Finally, intracellular signals within mechanosensitive cells trigger the production and release of cellular mediators for mechanical loading information to be communicated to other cells.

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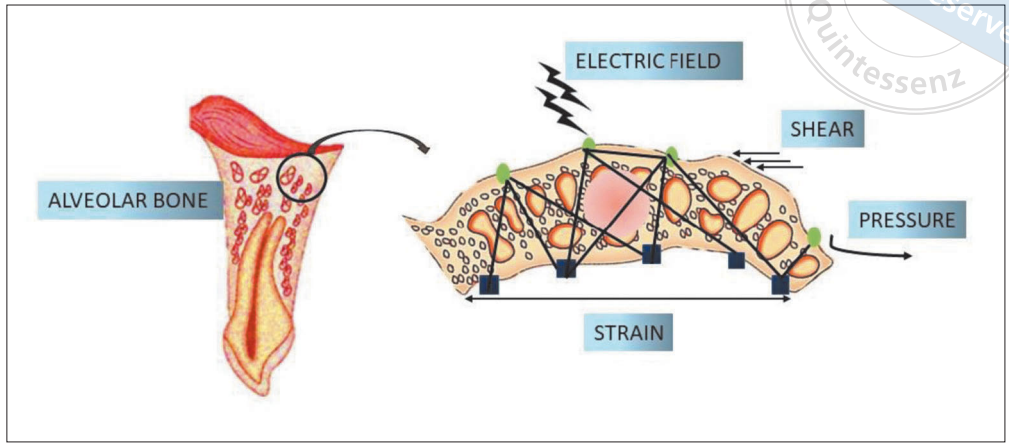

Fig 5 Mechanical force and the cellular environment. This figure illustrates how mechanical stimuli, such as strain, fluid shear stress and electric potentials, are sensed by osteocytes and other mechanosensitive cells in the alveolar bone. These signals are transduced through cell–matrix interactions and intracellular pathways, influencing cellular behaviour and bone remodelling outcomes.

Transduction mechanism subjected to orthodontic force

Three different pathways for mechanotransduction in alveolar bone have been proposed to date (Fig 5). First, it was thought that loading of the PDL and bone causes the matrix to deform, and the degree of deformation or strain experienced by PDL cells, osteoblasts and osteocytes was related to their mechanosensitivity. Second, it has been argued that cells do not experience considerable deformation but are susceptible to fluid shear stress caused by matrix deformation.[57] Bone has been described as a "water-soaked sponge", in which interstitial fluid flows towards the other side in response to compressive stress on one side. The force is applied at a rate that is inversely proportional to the fluid's flow rate. Osteocytes and bone lining cells experience shear stress as fluid passes through the canalicular-lacunar network.[58] Third, it has been postulated that the consequences of mechanical loading on bone are caused by stress-generated potentials. Various ions can be found in bone fluid. Mechanical pressures cause ions to move, resulting in a stress-generated potential, and bone cells have been demonstrated to respond to electric fields.[59] However, current research suggests that when compared to the electric potential difference created by muscular contractions, the real changes in potential difference produced by streaming potentials are minor. The local potential difference at the bone surface is fully overwhelmed by the electric potential difference from the muscles. Because the mechanical loading–induced cell signalling in bone is frequently coupled with muscle activity, streaming potentials appear to play a modest role in the mechanical loading–induced cell signalling in bone.[60] When performing orthodontic tooth movement, mechanical loading causes alveolar bone deformation, resulting in strain across the cell surface and fluid movement through the canalicular-lacunar network, and interstitial fluid rushes across charged bone crystals, generating dynamic electric fields and shear forces across the cells. It is still unclear whether the transduction mechanism is predominantly produced by fluid movement or by the actual deformation of the cell due to the orthodontic force. Mechanical loading, such as compression or tension, has been demonstrated to promote overexpression of a range of genes in the PDL. Furthermore, pulsating-fluid shear stress of 0.6 MPa has been demonstrated to elicit elevation of interleukin-8 (IL-8) gene expression, NO and prostaglandin synthesis; however, it is unclear whether orthodontic tooth movement causes this degree of fluid shear stress in the PDL.[61] Moreover, in vitro research shows that strain is not the mechanotransducer in bone cells on its own. Osteoblastic cells were cultured on polystyrene film and exposed to unidirectional linear strains by stretching the film between 500 and 5,000 times.[62] After loading, there was no increase in the production of NO and PGE 2, two substances known to be significant in mediating loading effects on bone. On contrary, increased fluid flow caused both PGE 2 and NO generation in osteoblastic cells. Other research used a technique that produced consistent levels of strain and fluid shear stress while allowing both to be altered individually.[63] The anabolic response of MC3T3-E1 osteoblastic cells was measured using osteopontin (OPN) messenger ribonucleic acid (mRNA) expression, a hallmark of osteoblastic development. Neither strain magnitude nor strain rate were linked with OPN expression when fluid forces were modest; however, regardless of the strain magnitude or rate, higher magnitudes of fluid shear stress dramatically raised OPN message levels. The findings show that fluid shear stress, rather than strain, may be more crucial

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when bone adjusts to mechanical force. Additionally, the fluid flow disturbs integrins by applying shear stress to the bone ECM and cell membrane, which also initiates signalling cascades in osteocytes. The activation of integrins on the cell surface, which releases intracellular chemicals that alter osteocyte gene expression, enables the molecular differentiation of osteoblasts and osteoclasts for bone formation and resorption. Further, focal adhesion kinases (FAKs) are involved in a signalling cascade that is initiated by integrin-mediated stress loading of cells and that modifies gene expression, cytoskeletal architecture, proliferation and differentiation, ultimately leading to tissue remodelling during orthodontic tooth movement.[64] Similarly, during orthodontic stress, fibroblasts in the PDL become mechanically deformed, stimulating mechanosensitive receptors and ion channels on the cell surface, resulting in tissue remodelling.[65]

Significance of mechanotransduction in dental implants

Dental implants are increasingly frequently utilised for cranial reconstructions, replacing lost teeth in people who are missing all or some of their teeth. Failure risks, which might have disastrous effects, are still high and challenging to predict. Biomaterials inserted into bone tissue are kept stable by multiscale biomechanical (bone–implant interlocking) and biological (mechanotransduction) activities.[60] The features of the bone–implant interface are influenced by the mechanical properties of the bone tissue around the interface and the quantity of implant surface in close contact with mineralised bone tissue.[66] Similarly, the amount of new bone development at the bone–implant interface affects the secondary stability of a dental implant. Wolff's Law states that to optimise occlusal load absorption and transfer mechanical stimuli to the surrounding bone, the subsequent stage of load-orientated bone remodelling requires the replacement of the main woven bone with realigned lamellar bone.[67] As a result, at the end of the remodelling phase, between 60% and 70% of the implant surface is surrounded by bone tissue. The term "bone–implant contact" was coined to describe these phenomena, and is commonly employed in studies to determine the degree of osseointegration.[68] During osseointegration, the mechanical stimuli along with the osteocytes play a role that is essential for mechanotransduction. The good clinical outcomes of both the immediate and progressive loading protocol show that physiological and mechanical stimuli can allow for successful osseointegration and demonstrate the importance of therapeutic mechanotransduction in modern implantology.[69]

Implications of mechanotransduction in bone tissue engineering

Bone, muscular, cellular and molecular processes, as well as biomaterial remodelling, are all affected by physiological stimulation. Dynamic fluid flow stimulation can function as a mechanobiological mediator in scaffolds to regulate cellular and tissue regeneration and proliferation. This allows the effects of mechanobiology to be channelled.[70] These signals must be produced and carried out in real time, and they may be used in a non-intrusive manner. The field of mechanobiology is expanding quickly as the significance of biophysical and biomechanical aspects is recognised and incorporated into tissue regeneration studies. Mechanobiology is an interdisciplinary field that investigates how stem cells detect changes in their mechanical environment (mechanosensation) and react to them (mechanotransduction). Stem cells use macromolecular complexes known as mechanosensors to monitor their physical and mechanical environments, and when the mechanical environment is not favourable, they initiate an adaptive response.[70] Recent research has demonstrated the mechanical sensitivity of adult and embryonic stem cells, which are isolated from a range of tissues, including bone marrow, fat, and tendon. To translate mechanical inputs into cellular actions, such as the production of growth factors and ECM proteins, particular signalling pathways must be activated by the stressors to which stem cells and their mechanosensory macromolecular complexes are subjected. Some of the downstream signalling systems that are triggered include YAP/TAZ, Rho/ROCK, FAK, mitogen-activated protein kinase (MAPK), G protein-related and calcium signalling.[71]

The mechanotransduction phenomenon could be used to achieve the integrity and function of an artificial scaffold for musculoskeletal applications, which could lead to tissue healing. The scaffold deformation may interfere with mechanical signals delivered to bone cells, so this should be considered. This warrants further study to explore the role of mechanotransduction in bone tissue engineering using biomaterials.[72,73]

Summary and future perspectives

Understanding the molecular mechanisms underlying mechanotransduction signalling pathways necessitates developing integrated techniques for orthodontic tooth movement, osseointegration of dental implants and

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musculoskeletal tissue engineering. A better comprehension of the mechanical principles underlying tissue regulation can aid in the creation of superior medical devices, synthetic tissues and biomaterials for tissue repair and regeneration. Research into the molecular link between shape and function in living cells and tissues may result in the development of new biomaterials and microdevices for tissue repair and rebuilding. To enhance patient care in the 21st century, we should add mechanics to our understanding of the molecular foundation of the disease in addition to uncovering its genetic causes.

Conclusion

In conclusion, the transduction of orthodontic forces into biochemical and cellular responses within alveolar bone represents a complex, finely regulated process involving multiple interconnected pathways. While early theories emphasised direct matrix deformation, emerging evidence suggests that fluid shear stress within the canalicular lacunar network serves as the primary mechanical cue governing osteocyte and osteoblast activation. This shear-induced signalling, mediated through integrins, FAKs and downstream gene expression, promotes coordinated osteogenic and osteoclastic activity essential for bone remodelling during tooth movement. Moreover, the contribution of ionic fluxes and minor stress generated potentials provides additional modulatory input to the signalling microenvironment. Collectively, these mechanisms ensure that orthodontic loading is translated into precise biological responses, maintaining structural integrity while enabling controlled tooth displacement. A deeper understanding of these cellular and molecular processes may facilitate the development of biologically optimised orthodontic strategies that enhance tissue regeneration and treatment outcomes.

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Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Drs Ramya RAMADOSS, Reena DAS, Abigail Viola E, Rajashree PADMANABHAN and Pratibha RAMANI conceptualised the study; Drs Ramya RAMADOSS and Reena DAS contributed to the methodology, validation, data curation and visualisation; Drs Ramya RAMADOSS, Reena DAS and Pratibha RAMANI contributed to the manuscript writing, editing and revision. All authors read and approved the final manuscript.

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