**RESEARCH PAPER**

# Role of Mechanosensitive receptors (Piezo 1 & Piezo 2)in osteoporosis by therapeutic Effects of Wet Cupping.

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**Abstract:**

Osteoporosis is a skeletal disorder characterized by reduced bone mass and deterioration of bone microarchitecture, which increases bone fragility and susceptibility to fractures. Treatment strategies focus on reducing bone loss, enhancing bone formation, and lowering the risk of fractures. Existing treatments don't work for every patient. Certain drugs, such as denosumab and bisphosphonates carry a lot of side effects. The goal of current therapies is either bone production or resorption. In order to provide more potent treatments that strengthen bones, research investigates novel molecular and biological mechanisms. Mechanosensitive ion channels called piezo receptors, especially Piezo1 and Piezo2 have drawn a lot of attention due to their role in bone physiology . PIEZO, mechanosensitive receptor on the bone, has a prime role in maintaining the balance between the bone formation and bone resorption, determining the density of the bone. The receptor dysregulation is linked to osteoporosis and forms a great therapeutic potential. It is believed that the suction and skin tension in wet cupping creates the bone remodelling by activating these mechanoreceptors , thereby promoting the bone formation

**Key words:** Wet Cupping, Piezo receptor, Mechanosensitive receptors ,osteoporosis

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**Introduction:**

The physical activity tends to affect bone strength and size. Physical stress especially on weight bearing joints improves bone density by mechanism of Piezo mechanosensitive receptors and hence stumilating bone building cells (osteoblasts).On the other hand decreased forces and stress on the bones tend to cause the bone loss and raises the risk of fractures. The osteocytes found in bones coordinate the production of new bone in response to the stress. Exercises like running, jumping and specific physical exercises improve the bone density of Hip bones, Jaw bones,Knee joint,Spine as stated by Walffs . The balance between the bone synthesis and resorption or the process of bone remodelling maintains the skeletal health, calcium channels that sense the mechanical stress on the bone and accordingly modulate the bone formation .The contemporary researches on the calcium channels in osteocytes discovered that Piezo1,a mechano sensitive ion channel which was highly abundant [1.]Mechanotransduction is an essential biological process found amongst all living organisms. It allows cells to detect mechanical forces and turn them into biochemical signals, enabling vital functions in the body. The 2010 discovery of Piezo channels added to our knowledge of how this process works at the molecular and cellular level.[2] The Piezo family, which includes Piezo1 and Piezo2, specializes in assessing a shear stress and hence transforming them into electrical signals. Piezo1 is a specialized ion channel that detects mechanical forces and plays a vital role in bone renewal. This ongoing process involves osteoclasts removing old bone and osteoblasts building new bone. Piezo1 acts as a biological sensor that responds to physical stresses and strains[3] Notably, scientists have found that Piezo1 plays a key role in osteoporosis, as its mechanical sensing ability directly affects bone strength and density[4]

This reveiw provides a summary of the structure and characteristics of Piezo channels, with a particular emphasis on their role in bone remodeling processes and how wet cupping is a mode of mechanical stimulation of peizo receptors, thereby a potential therapy to enhance the remodelling process.

**Piezo-distribution in the tissues :**

Piezo1 was detected in the bladder, colon, kidney, lung, and skin consistent with earlier Northern blot findings in rats [5]

**Piezo1 in bone cells:**

Emerging clinical reports have highlighted the fact that skeletal abnormalities are linked to Piezo1 gene mutations, thereby demonstrating the broad physiological influence of these channels. Deleting wide range of mechanical forces such as tension and Piezo1 gene in Osteoblast cells (in the experiments) resulted in lower trabecular and cortical bone mass.[6]

**Piezo1 in Bone marrow derived mesenchymal stem cells (BMSCs)**

BMSCs can develop into osteogenic, adipogenic and chondrogenic lineages depending on loading circumstances.[7]Piezo1 is a key mechanotransducer in biological processes such as bone formation. It is expressed in differentiating osteoblasts. It is expressed in growing skeletal tissues and their expression rises during postnatal development in response to mechanical stress.[8]Piezo1 is critical for BMSC development under mechanical stimulation. Sugimoto et al. (2017) found that hydrostatic pressure (HP) increases the expression of Piezo1 in human BMSCs which promotes osteoblast differentiation while inhibits adipocyte differentiation. Yoda1 therapy reduces bone loss from microgravity and ageing, while simultaneously promoting BMSC proliferation and osteogenic differentiation.[9] Researchers developed a wearable triboelectric nanogenerator that activates the Piezo1 channel and promotes osteogenic differentiation through human motion. This is proposed as a potential target for bone regeneration, particularly in elderly individual [10].Static magnetic fields (SMF) can improve BMSC migration capability via Piezo1 (Sun et al., 2023). Piezo1 regulates the development of BMSCs into chondrocytes. [10]

**Piezo1 in osteoblasts:**

Osteoblasts mainly originate from mesenchymal stem cells (MSCs), which are present both inside and outside the periosteum, as well as within the bone marrow matrix. [11]. In mice where Piezo1 was deleted , several skeletal abnormalities were observed, including recurrent fractures, shorter femurs, pelvic malformation, and a marked reduction in trabecular bone mass below the growth plates.[12] Collagen type I (Col1), a major protein in extracellular matrix bone, is expressed from early osteoblast precursors to fully differentiated osteoblasts. Deletion of Piezo1 in Col1-expressing cells (Piezo1 Col1-CreERT) leads to enhanced bone resorption, reduced collagen levels, decreased bone density and structural changes in trabecular bone.

As a key regulator of bone mineralization and calcium metabolism, osteocalcin (OCN) is highly abundant in the osteoblasts. Mice lacking Piezo1 in OCN-expressing cells (Piezo1 OCN-Cre) exhibited impaired cranial suture fusion, shortened weight-bearing bones, and severe reductions in bone.

Several studies demonstrate that Piezo1 plays a role in osteoblast differentiation when exposed to different mechanical forces, including hydrostatic pressure, static magnetic forces [12]and fluid shear stress."According to mechanical stimulation upregulates Piezo1 and improves osteoblast function, while disuse conditions downregulate Piezo1, leading to weakened bone structure. This confirms Piezo1's mechanical force-dependent regulation in osteoblasts.

**Piezo1 in osteocytes:**

Osteocytes, the most abundant cells in bone, develop from osteoblasts. Research shows they contain much more Piezo1 than Piezo2 [13]. The compound Yoda1 boosts calcium signaling in these cells and reduces sclerostin (Sost) production, which enhances the bone formation [14]On the other hand, blocking Piezo1 in osteocytes increases RANKL (a protein that triggers bone breakdown) and decreases OPG (a protective protein), leading to more bone loss [13]Additionally, deleting Piezo1 gene in osteocytes weakens ultrasound-induced bone formation in lab studies, reducing key markers like ALP in osteoblasts [15].Recent studies demonstrate that conditional deletion of Piezo1 in osteocytes leads to reductions in bone mass[16] Complementary work by [16]reveals that Piezo1 ablation in osteocytes and osteoblasts specifically impairs alveolar bone volume and vertical height in craniofacial structures. These collective findings determine the Piezo1's contribution dependent regulation of bone homeostasis.

**Piezo1 in osteoclasts:**

Osteoclasts( which are cells that break down bone), develop from bone marrow stem cells. Research in mice found that removing the Piezo1 in osteoclasts did not change the bone density. However, when Piezo1 was deleted in bone-building cells or the osteoblasts, it increased the osteoclast activity . This indicates that Piezo1 in osteoblasts helps regulate bone breakdown by controlling osteoclasts[15]

**Piezo1 signaling in bone remodeling :**

Piezo1 generates mechanical-sensitive ion currents, allowing calcium ($Ca^{2+}$) to enter cells (Sun et al., 2019).

This calcium influx triggers important signaling pathways, such as NFAT [18]and CaMKII [18]which is essential for bone development and biological processes in the skeletal system.

**Piezo1 and clinical therapy**:

Osteoporosis (OP) is defined by reduced bone strength, significantly increasing the risk of fractures, particularly in the hip, spine, and wrist.. Its development is influenced by multiple factors, including hormonal changes, aging, genetic factors, lifestyle habits, and certain medical conditions [13]Studies have shown that osteoporosis (OP) patients exhibit significantly reduced levels of Piezo1 mRNA and protein compared to healthy individuals. Additionally, [18]found an inverse relationship between age and the expression of Piezo1 and Piezo2 genes in human bone marrow mesenchymal stem cells (MSCs). Furthermore, [9]demonstrated that mechanical loading, which intensifies with body weight in late adolescence, can stimulate Piezo1 activation. Bone fractures can occur even under minimal pressure, and the healing process typically takes 4 to 8 weeks, depending on factors such as age, health status, and fracture severity [7]. Research indicates that Piezo1 downregulation hinders fracture repair in the callus[10], whereas its activation via Yoda1 accelerates healing by promoting the cartilage formation and osteogenesis in periosteal stem cells (PSCs), as well as speeding up cartilage-to-bone conversion .[11]Additionally, Piezo1 activation upregulates vascular endothelial growth factor A (VEGF-A), implying a potential role in angiogenesis—the formation of new blood vessels to supply oxygen and nutrients to the injury site [10] Piezo1 receptors could be a key target for treating broken bones and osteoarthritis (OA) because they help the body senses and responds to physical forces. Activating Piezo1 speeds up healing by turning stem cells into bone and cartilage and also improving blood flow to the injury. Since OA is caused by wear and tear on joints, Piezo1 might protect cartilage by adjusting how cells handle pressure.

**Piezo Receptors, Wet Cupping, and Their Potential in Treating Bone Fractures and Osteoporosis (OA):**

Wet cupping is a traditional therapy that combines suction and the blood letting to enhance circulation and reduce inflammation. While no direct studies link wet cupping to Piezo receptors, some theoretical possibilities exist suggesting it might also influence Piezo1 receptors by the following ways, Mechanical Activation: The suction from cupping creates localized pressure on tissues, which could mechanically stimulate Piezo1, similar to how exercise or manual therapy activates these receptors. This may promote tissue repair in osteoporosis.

Improved Blood Flow and Oxygen Delivery – By removing stagnant blood, wet cupping enhances circulation, ensuring more oxygen and nutrients to reach the damaged areas. Since Piezo1 helps regulate blood vessel formation (angiogenesis), cupping might enhance its effects and hence the bone formation. Anti-Inflammatory Effects – Chronic inflammation worsens OA and slows fracture healing. Wet cupping reduces inflammatory markers and since Piezo1 helps control immune responses, combining the two could provide a stronger anti-inflammatory benefit.

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