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Feasibility of Pulsed Electromagnetic Fields (PEMFs) in Talar Cartilage Injuries

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Abstract: ***Osteochondral Lesion of the Talus (OLT) is a common cause of ankle pain and its conservative treatment has limitations. However, there are few studies on pulsed electromagnetic fields (PEMFs) in the treatment of OLT. This study mainly explored the application feasibility of PEMFs in OLT.PEMFs can play a role through a variety of mechanisms such as promoting cell metabolism and regulating gene and protein expression. This study explored the potential of PEMFs in the treatment of OLT by combining the pathological mechanism of OLT and the mechanism of PEMFs through theoretical discussion. The findings suggest that PEMFs can accelerate initial healing such as promoting vascular remodeling, reduce inflammation, relieve pain, and prevent further cartilage damage. This study provides new insights into noninvasive treatment options for OLT.***

Keywords: Talus cartilage injury, Pulsed electromagnetic field, Cartilage, Theoretical investigation.

1. Introduction

Osteochondral Lesions of the Talus (OLT) often cause persistent ankle pain, especially in young and middle-aged people, showing the gender characteristics of more men and less women, often due to various traumas, Results in cartilage and subchondral bone damage of talus trochlea [1]. Cartilage injuries occur mostly in the anterolateral and posterolateral areas of the talus trochlear, which will destroy the stability of the ankle joint and lead to changes in the pressure of subchondral bone, which will evolve into subchondral bone necrosis, cyst formation and even bone defects, and eventually lead to bone joints [2,3]. Modern medical treatment for asymptomatic or mild early OLT, often by means of magnetic resonance imaging (MRI) to distinguish Hepple I to II lesions [4,5]. For this, treatment mainly includes behavioral guidance (e.g., attention to rest), oral non-steroidal anti-inflammatory drugs, extracorporeal shock wave, etc. [6-8]. However, these treatment methods have limitations to some extent, for example, behavioral intervention alone may not be effective for some cartilage injuries, oral nsaids may have side effects, and extracorporeal shock wave therapy may not achieve ideal results for all patients with talar cartilage [9,10].

Pulsed electromagnetic fields (PEMFs), as a non-invasive, safe and effective treatment method, have been widely used in various fields of orthopedics. Studies have shown that in terms of fracture healing, 85.6% of patients had significantly shorter fracture healing time after receiving PEMFs treatment [11]. A large number of studies have shown that PEMFs have achieved positive effects on fracture healing problems, such as osteonecrosis of the femoral head, osteomyelitis, osteoporosis, osteoarthritis, and postoperative rehabilitation of fractures [12,13]. With the deepening of the research on the effect of PEMFs on cartilage, and the effect of PEMFs on cartilage has been widely studied and recognized. Studies have found that PEMFs can stimulate the proliferation and differentiation of chondrocytes and promote the synthesis of extracellular matrix of chondrocytes [14,15]. However, there are relatively few studies on the use of PEMFs in the treatment of OLT. We discussed the pathological mechanism of OLT combined with the mechanism of PEMFs to explore whether PEMFs can also be used in the treatment of OTC alone or in the adjuvant treatment of OTC.

2. Mechanisms for the Study of Cartilage Damage in the Talus

2.1 Mechanical Injury

2.1.1 Effects on chondrocytes

Mechanical injury can affect the biosynthesis and metabolic activities of talar chondrocytes and cartilage degradation. Excessive mechanical load or injury may lead to increased intracellular stress, which in turn destroys the cytoskeleton and extracellular matrix, resulting in decreased biosynthetic activity of chondrocytes [16]. Furthermore, mechanical damage can also cause the destruction of cartilage matrix, including the degradation of proteoglycan and collagen, which in turn causes the stress response of chondrocytes and activates the expression of degradation enzymes such as matrix metalloproteinases (MMPs), leading to the degradation of macromolecules in cartilage matrix. It has been found that endothelial growth factor (VEGF), which may play a key role in the repair process after cartilage injury, may also exacerbate matrix degradation [17]. In addition, chondrocyte death can further aggravate matrix degradation and cartilage degradation [18-20]. Moreover, mechanical damage can directly lead to inflammation to produce reactive oxygen species (ROS), which can cause oxidative damage to cell membrane and DNA, leading to cell death, and may activate apoptotic pathways such as caspases in cells, leading to programmed cell death and apoptosis [20,21]. Some studies have shown that the gene expression of chondrocytes changes after mechanical injury, that is, mechanical injury causes changes in the gene expression of pro-inflammatory genes such as MMPs and ADAMTS and repair related genes such as COL2A1 and ACAN in articular cartilage. After injury, HIF-1, VEGF and other signaling pathways are activated, which in turn affect angiogenesis and inflammatory response [22,23].

2.1.2 Effects on articular surfaces

Osteochondral injury of the talus can significantly affect joint function, may lead to long-term complications such as osteoarthritis, and may aggravate the condition over time. Mechanical injury of the talus affects the relevant structures of the joint. Studies have shown that the cartilage model is damaged immediately after mechanical injury, and the surface layer of the cartilage is more affected than the deep area [24]. Singh [25] et al. found that the level of glycosaminoglycan in cartilage affected for a long time was low and the water content was high, which further proved that the joint surface structure changed after talar cartilage injury. Osteochondral injury of the talus destroys the normal biomechanics of the ankle joint, resulting in abnormal stress distribution of the ankle joint during movement and aggravating cartilage damage [26]. For example, when an athlete suffers a mechanical injury to the ankle joint, if the injury area is large, the instability of the joint will be obviously felt when performing actions such as emergency stop and steering, because the injury disrupts the normal structure and mechanical balance of the joint [27]. Studies have shown that the stability of the ankle joint will change significantly when the injury area exceeds 6mm2 in sports situations [28]. In addition, mechanical damage destroys the structure of collagen and proteoglycan in cartilage, reduces the compression and shear stiffness of cartilage, and makes cartilage more prone to deformation when subjected to physiological load, which affects the normal buffering and supporting function of the talar articular surface and increases the risk of secondary osteoarthritis [29,30].

2.1.3 Vascular issues

The talus does not have independent nutrient vessels, which means that its nutrient supply is relatively limited and depends on the diffusion of surrounding tissues, so the healing after injury is slow [31]. Lutz [32] et al. found that 51% of ankle injuries had vascular problems in their cartilage fractures. Studies have shown that after articular cartilage injury, its blood vessels will be invaded, leading to cartilage calcification and loss of joint function [33]. Bruns [34] et al. noted that most cartilage injuries are trauma related, while the etiology of pure osteochondritis is still under discussion and may be related to osteonecrosis due to vascular disorders, highlighting the potential influence of vascular factors in cartilage injuries. At present, in view of the vascular problems of osteochondral injury of the talus, some studies are exploring methods to improve local blood circulation to promote injury repair, such as vascular interventional therapy, but no clear and widely applicable results have been achieved [11].

2.1.4 Other factors

Genetic factors play an important role in osteochondral damage of the talus. Studies have shown that while trauma is a common cause, genetic factors and genetic predispositions are also key factors influencing the development and progression of these injuries. Szwedowski [35] et al. identified genetic factors as key determinants of cartilage damage, profoundly affecting biochemical pathways critical for cartilage structure and stability. Boukhemis [36] et al. observed identical lesions in twins, suggesting a genetic predisposition to OLT. Although trauma often results in osteochondral lesions of the talus, genetic predisposition can exacerbate the susceptibility to such injuries, potentially leading to severe complications such as avascular necrosis. In addition to genetic factors, osteochondral lesions of the talus are affected by certain hormones, especially sex hormones and glucocorticoids. Estrogen, progesterone, and androgens have been shown to have significant effects on cartilage quality and bone density [37]. Notably, the deficiency of these hormones (most pronounced during menopause) is associated with an increased incidence of osteoarthritis (OA) [37]. Further studies have shown that elevated glucocorticoid signaling in osteoblasts is associated with age-related cartilage damage [38], suggesting that interventions interfering with this pathway can alleviate OA progression, illustrating a detrimental role for glucocorticoids in maintaining cartilage health. However, there are still many challenges on how to regulate these hormones to improve talar cartilage damage. For example, the role of sex hormones in the differentiation of articular cartilage cannot be improved by the combination of glucocorticoid, but may accelerate the hypertrophy of chondrocytes [39]. How to effectively regulate these hormones to improve specific types of tissue damage is also one of the directions that future research needs to focus on.

3. The Mechanism of Action of Pulsed Electromagnetic Fields (PEMFs) in Orthopedics.

3.1 Promotes Cartilage Healing

3.1.1 cellular metabolism

PEMFs may affect bone healing by regulating cell metabolism and function. Within cells, studies have shown that it promotes the proliferation and differentiation of osteoblasts by up-regulating key genes such as IGF-1 (insulin-like growth factor-1, which plays an important role in promoting cell proliferation, differentiation and survival) and Runx2 (which is a key transcription factor for osteoblast differentiation), thereby triggering a surge in intracellular calcium transient events [40]. Moreover, PEMFs have been shown to catalyze mitochondrial efficiency and promote ATP production, thereby enhancing cellular activities essential for bone repair and regeneration [41]. Outside the cell, it has been found that PEMFs stimulation of synthesis of extracellular matrix components enhances structural integrity within the framework of bone and cartilage [42]. In human adipose-derived stem cells (hASCs), PEMFs triggered enhanced cell proliferation accompanied by a marked transition to osteogenic differentiation [15]. And Lei [43] et al. found that PEMFs hindered osteoclast maturation, reduced excessive bone resorption and promoted coordinated bone turnover rate by inhibiting Akt/mTOR pathway. In addition, Daou [44] et al. found that PEMFs stimulation and activation of the immune regulatory cascade in hMSC can promote angiogenesis and osteogenesis, while accelerating the metabolic rate of chondrocytes, thereby accelerating the recovery and regeneration ability of damaged cartilage structures.

3.1.2 Genes and Protein Expression

PEMFs may affect bone healing through gene and protein

expression. Enhancement of cell proliferation, migration, differentiation, and angiogenesis by up-regulating the transcription of osteogenic markers, including Runx2, ALPL, COL1A1, and BSP, along with stimulation of genes encoding growth factors, such as TGF - β and VEGF, fosters a supportive microenvironment [45,46]. Specifically, PEMFs are able to promote the activation of intracellular signaling pathways such as the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase-protein kinase B (PI3K-Akt) pathways, which are essential for the regulation of gene expression [47,48]. PEMFs play a key role in the regulation of genes associated with apoptosis and cell survival, particularly affecting members of the Bcl - 2 family and cysteoaspartic enzymes [15,49,50], which help maintain the proper cell survival and apoptosis balance and are essential for bone tissue homeostasis and repair. PEMF treatment significantly altered the intracellular calcium ion concentration ([Ca2+]i), which acts as a key second messenger in various cellular processes and is an indispensable messenger in bone metabolism [51]. Importantly, PEMF promotes mechanical cues sensed by osteocytes, mainly osteoblasts, to convert these signals into biochemical responses through mechanical transduction, a process that profoundly affects gene expression and protein synthesis related to bone healing [52].

3.2 Anti-inflammatory Effect

3.2.1 anti-inflammatory action

As a non-invasive treatment, PEMFs have demonstrated their potential for controlling acute and chronic inflammatory responses while effectively relieving pain, swelling and stiffness, and accelerating the healing process in a wide range of inflammatory conditions, from musculoskeletal to autoimmune spectrum [53,54]. PEMFs therapy alleviated the inflammatory response in a mouse model of rheumatoid arthritis (RA) by inhibiting the synthesis and release of inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β). These inflammatory mediators are key cytokines in the inflammatory process, and their overproduction can lead to an overactive inflammatory response and cause tissue damage. Some studies have found that after PEMFs treatment, the content of IL-6 in mice decreased by 5% and the content of TNF-α decreased by 3% [53]. In addition, PEMFs up-regulate the expression of adenosine receptors (especially A2A and A3 subtypes) and down-regulate the levels of most pro-inflammatory cytokines, demonstrating its powerful anti-inflammatory effect [54]. Moreover, PEMFs create a microenvironment conducive to bone repair by regulating NF-κB activity and indirectly reduce inflammation [55,56]. PEMFs also effectively contain the secondary injury caused by excessive immune response by limiting the migration and infiltration of T cells into the inflammatory area, which is particularly important for preventing the spread of inflammation [57].

3.2.2 Antioxidant, cytoprotective and vascular conditions

PEMFs mainly play a role in anti-oxidation, cell protection and vascular conditions. PEMFs therapy can activate mitochondrial function, enhance energy production efficiency of cells, inhibit excessive generation of reactive oxygen species (ROS) in hypoxic environment, and thus reduce inflammation [58,59]. At the same time, PEMFs stimulate the synthesis of heat shock proteins (HSP), especially by activating the p38 kinase pathway, increasing the expression of HSP70, strengthening the defense line of cells against oxidative damage and avoiding abnormal protein aggregation [60,61]. In addition, PEMFs have a regulatory effect on nitric oxide (NO) level, which can promote vasodilation and blood flow, and have an auxiliary effect on the resolution of inflammation and wound healing process [62]. This improves microcirculation, increases tissue oxygen saturation, and enhances resistance to oxidative stress [56].

4. Application of PEMFs in OLTs

4.1 Acceleration of the Initial Healing Process: Role of Rapid Revascularization and Cellular Activity

The inherent blood supply of talus cartilage is insufficient, and there is a high complication rate of vascular injury [32-34]. Meanwhile, the contradictory dual roles of VEGF in angiogenesis and matrix degradation also aggravate this problem [17]. This highlights the critical importance of addressing vascular factors in therapeutic interventions to optimize repair and mitigate long-term degeneration. PEMFs can enhance angiogenesis and tissue perfusion by up-regulating vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2) and activating the PI3K-Akt-eNOS pathway [62-64], which can accelerate the healing process. The treatment of PEMFs for OLT opens up new possibilities. Some studies have shown that a study on acute limb ischemia model and brain microvessels in diabetic rats showed that PEMFs significantly increased the number and diameter of blood vessels and promoted angiogenesis [65]. In addition, PEMFs can up-regulate the expression of osteogenesis-related genes, promote the proliferation and differentiation of osteoblasts, and stimulate the activity and proliferation of chondrocytes, thereby accelerating the regeneration of cartilage tissue. These effects are particularly prominent under specific PEMFs frequency and intensity, which provides strong support for osteochondral regeneration of the talus [66-68]. For example, in a rabbit experiment treated with PEMFs at a specific frequency, researchers observed a significant increase in chondrocyte proliferation and enhanced cartilage matrix synthesis [69]. Together, these findings reveal the strong potential of PEMFs in promoting healing of talar cartilage injuries, especially in improving vascular conditions and enhancing cell activity.

4.2 Reduces Inflammation and Promotes Tissue Repair

Another important advantage of PEMFs in the treatment of osteochondral lesions of the talus is their anti-inflammatory and promoting tissue repair effects. PEMFs can reduce local inflammatory responses by regulating the secretion of inflammatory mediators, such as reducing the levels of interleukin-6 (IL-6) and tumor necrosis factor α(TNF-α) [54,59]. In addition, PEMFs can also enhance the antioxidant capacity and resistance of cells by activating the synthesis of heat shock proteins (HSPs) [60,61]. In an experiment in rats, researchers found that PEMFs significantly reduced swelling and inflammation at the injured site and accelerated the

process of cartilage repair [70]. These findings again validate the utility of PEMFs in reducing inflammation and promoting tissue repair, making them a viable tool for the treatment of osteochondral injury in the talus.

4.3 Pain Management and Functional Recovery

PEMFs also showed advantages in pain management and functional recovery. By stimulating nerve endings, PEMFs can reduce the sensitivity of pain receptors, thereby achieving analgesic effects [71]. In addition, PEMFs can also improve blood circulation, increase oxygen and nutrient supply to the injured site, and promote its faster functional recovery [72]. In clinical practice, many patients experience pain relief and improved motor function after PEMFs treatment [73,74]. These effects not only improve the quality of life of patients, but also shorten the recovery time, making PEMFs an important part of the treatment of osteochondral lesions of the talus.

5. Conclusion

In summary, this study provided a detailed review of the underlying mechanisms of osteochondral lesions of the talus and an in-depth analysis of the operational mechanisms of PEMFs in the field of orthopedics, with a focus on the potential of PEMFs for the treatment of osteochondral lesions of the talus. However, there are still many unanswered questions regarding the application of PEMFs in the treatment of talar cartilage injuries, such as determining a personalized treatment plan and evaluating the synergistic effect with existing treatments. In the future, with the in-depth exploration of the mechanism of action of PEMFs and the development of technical innovation, PEMFs will be more applied in the field of talar cartilage injury.

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