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Research Article

# The Efficacy of Low-intensity Pulsed Ultrasound in the Treatment of Osteoporosis

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## Abstract

### Introduction and aim

Osteoporosis is a major public health issue causing increased morbidity and mortality in individuals globally. Low-intensity pulsed ultrasound is one of the physical therapy modalities that can be used to improve health related outcomes. The aim of this study was to review the current literature around the efficacy of the low-intensity pulsed ultrasound in the treatment of individuals with osteoporosis.

### Methods

A scoping review was conducted including studies that discuss the efficacy of the low-intensity pulsed ultrasound for the treatment of osteoporosis, published in English between 2000-2024. A data search was done following a search strategy using keywords of the topic based on PICO strategy. A descriptive data analysis was done to summarise and synthesis evidence from the reviewed studies. Reporting of the review followed the guidelines of the PRISMA for scoping review.

### Results

Nine studies were eligible for inclusion in the review. The reviewed studies showed that LIPUS has considerable positive effects on stimulating bone and soft tissue regeneration, such as fracture healing, implant stability, periodontal therapy, and temporomandibular joint injuries.

### Conclusion

Different forms of LIPUS can be used to enhance the clinical outcomes of people with different levels of osteoporosis. Meta-analysis was not feasible due to the level of heterogeneity in study designs, populations, and outcomes. More clinical trials involving humans are needed to determine the optimal parameters for the use of low intensity pulsed ultrasound for the treatment of osteoporosis.

**Keywords:** Osteoporosis; Physical Therapy; Rehabilitation; Quality of Life

## Introduction

Osteoporosis is a disease of bone characterised by loss of bone mass and microarchitectural deterioration associated with an increased risk of fragility fracture. It is highly prevalent, affecting over 200 million people worldwide, in many populations, 1 in 2 women and 1 in 5 men over the age of 50 years experiencing a fragility fracture in remaining lifetimes [1,2,3,4]. Generally, the diagnosis of osteoporosis can be made in advanced stages or following after traumatic bone fracture. When the fracture occurs, its frequently enhances the risk of subsequent fractures. So, the health expectations among elderly were improved in prevention and early detection of osteoporosis with the appropriate procedure. The techniques to diagnose bone mass have been rapidly improving, the measurement of bone mineral density (BMD) is one of the methods that can be used to identify the risk of osteoporosis. The most well-established technique and gold standard for evaluating the BMD based on WHO criteria is Dual-energy X-ray absorptiometry (DXA) which benefits by being non-invasive with high precision measurements at various sites [5].

Treatment can be divided into drug therapy, physical therapy and other measures. At present, the treatment of osteoporosis is mainly drug therapy. Commonly used drugs are estrogen, bisphosphonates and fluorine preparations. However, sometimes they are prone to untoward systemic side effects. For example, bisphosphonates might lead to impaired kidney function and hypokalemia, and once discontinued, pain and recurrence of bone fractures, and more seriously, cause swelling and loosening of the teeth [6,7]. What's more, as reported by the USA College of Physicians (ACP), hormonal therapy like estrogen was associated with increased risk for venous thromboembolic, cerebrovascular events, invasive breast cancer and node-positive tumors [2].

In the preceding 30 years, a multitude of safe, precise, and dependable methodologies for quantifying bone density have been devised. The majority of these techniques entail the utilization of ionizing radiation, specifically X-rays, and are dependent on the reduction of energy beams as they traverse soft tissues and bone [8]. One novel methodology entails the utilization of acoustic energy, specifically ultrasound waves, for the purpose of evaluating bone integrity and forecasting the likelihood of fractures [9]. The interaction between ultrasound, which is a type of sound wave, and bone differs from that of ionizing electromagnetic radiation. This distinction provides distinct and valuable information regarding bone properties [10]. The utilization of Quantitative Ultrasound (QUS) technology has emerged as a viable alternative approach for the assessment of Bone Mineral Density (BMD). Quantitative ultrasound (QUS) is increasingly becoming recognized as a valuable tool for evaluating bone health, mostly due to its notable advantages in terms of efficiency, cost-effectiveness, and lack of radiation exposure when compared to conventional techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and dual-energy X-ray absorptiometry (DEXA/DXA) [11].

Ultrasound (US) represents a potential intervention for induced osteoporosis. US refers to a high-frequency nonaudible acoustic energy that travels in the form of mechanical waves.5 A mechanical wave is one in which energy is transmitted by the movement of particles within the medium through which the wave is traveling. As these waves travel as a relatively focused beam (typical effective radiating area = 5 cm2), US can be directed onto specific regions to exert a local mechanical stimulus.[3] In an in vitro experiment, three different intensities (2, 15 and 30 mW/cm2, ISATA) were used to stimulate rat bone marrow stromal cells, and results indicated that the highest intensity initiated osteogenic differentiation best whereas the lowest intensity promoted mineralization best. Low-intensity pulsed ultrasound (LIPUS), a travelling mechanical perturbation that can be transmitted into biological tissues, has been reported to play a positive role in bone healing.

A previous study examined the effects of LIPUS ranging from 15 to 150 mW/cm2 (ISATA) on osteoporosis of distal femur in OVX rats and concluded that the therapeutic effects of LIPUS were enhanced with increasing intensity in the certain range [12]. Experimental studies demonstrated that LIPUS promoted osteoblast differentiation and mineralization, induced osteoclast apoptosis, accelerated osteoporotic fracture healing, promoted bone defect healing, and was effective at every stage of the fracture healing process: the initial inflammatory response, soft callus formation, hard callus formation, initial bony union and bone remodeling. Clinical studies also validated that LIPUS enhanced the healing rate of fracture patients as well as shortened their healing periods, and that older patients (≥60 y) had similar healing rates to the whole population. With the advantages of being non-invasive, radiation-free, low-cost and approved by the U.S. Food and Drug Administration (FDA), LIPUS represents an attractive technique that causes no drug-related side effects to treat fresh fractures and non-unions.

Currently, the effective parameters of LIPUS for fresh fractures and non-unions are typically characterized by the frequency of 1.5 MHz, intensity (spatial average temporal average intensity, ISATA) of 30 mW/cm2, duty cycle of 20% and pulse repetition frequency (PRF) of 1 kHz [19] [13]. To date, analogous parameters have been proved to be equally effective on osteoporotic bone injuries and trabecular bone defects. For example, Cheung et al. reported that LIPUS enhanced fracture healing in both ovariectomy-induced osteoporotic and age- matched normal bones using a commercial LIPUS device (Exogen 3000+; Smith & Nephew Inc, Memphis, TN), which was approved by the FDA and adopted the typical parameters. With the PRF of 100 Hz and the other same parameters, 2-week LIPUS therapy accelerated trabecular bone defect healing in a rat tibial defect model [4]. Current literature provides evidence about the effectiveness of various forms of LIPUS. Therefore, the aim of this study was to review the studies that the efficacy of the low-intensity pulsed ultrasound in the treatment of individuals with osteoporosis.

## Methods

### Study Design

A scoping review was conducted to explore the types of intervention, potential benefits and outcomes of pulsed ultrasound in the management of osteoporosis. Scoping reviews are ideal for mapping key concepts, identifying gaps in research, and summarizing available evidence on emerging topics [13] [14]. This methodology allows for a broad exploration of the existing literature, which is appropriate given the relatively novel application of pulsed ultrasound in osteoporosis treatment. The review process followed the guidelines set by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [14] [15].

### Eligibility Criteria

#### Inclusion Criteria:

1. Studies evaluating the effects of pulsed ultrasound on osteoporosis (both human and animal models).
2. Studies published in peer-reviewed journals in English.
3. Studies that include clinical or biological outcomes relevant to osteoporosis, such as bone mineral density (BMD), bone turnover markers, or fracture healing. 4. Randomized controlled trials (RCTs), cohort studies, case-control studies, and preclinical studies.

#### Exclusion Criteria:

1. Studies involving other therapeutic modalities without clear evaluation of pulsed ultrasound. 2. Studies that do not measure specific outcomes related to osteoporosis management.
2. Editorials, opinion pieces, and non-peer-reviewed studies.
3. Articles not available in full text.

#### Search Strategy

A comprehensive literature search was be conducted across several electronic databases, including PubMed, Scopus, Web of Science, and Cochrane Library. The search was be limited to studies published between 2000 and 2024 to capture the latest advancements in the field. The search terms was include combinations of keywords and Medical Subject Headings (MeSH) terms such as "pulsed ultrasound," "osteoporosis," "bone mineral density," "bone regeneration," and "low-intensity pulsed ultrasound (LIPUS)."

A sample search strategy for PubMed might include:

- "pulsed ultrasound" AND "osteoporosis"
- "LIPUS" OR "low-intensity pulsed ultrasound" AND "bone healing" OR "bone mineral density"

Two reviewers had independently screened titles, abstracts, and full texts for inclusion and disagreements between them were resolved by a third researcher (academic supervisor).

#### Data Extraction

A standardized data extraction form was used to collect relevant information from each study. Extracted data was include:

- Study characteristics (author, year, country, study design)
- Population characteristics (sample size, age, sex, health status)
- Intervention details (ultrasound frequency, intensity, duration, and application site)
- Outcomes related to osteoporosis management (BMD, fracture healing, bone biomarkers)
- Key findings and conclusions

Two independent reviewers extracted the data, and discrepancies were resolved through consensus or the third reviewer.

#### Data Summarizing and Analysis

A narrative synthesis was be conducted to summarize the findings. Quantitative results were reported descriptively, as meta-analysis may not be feasible due to anticipated heterogeneity in study designs, populations, and outcomes. The analysis was focus on the following areas:

- Efficacy of pulsed ultrasound in improving bone mineral density.
- Effect on bone healing and fracture recovery.
- Influence on bone turnover markers.

Where applicable, studies were grouped by type (preclinical vs. clinical) and by outcome measures.

#### Presentation and Dissemination

The results of the scoping review were presented through summary tables and descriptive analysis, with the narrative focused on key findings. The review has highlighted knowledge gaps and areas for future research. The findings will be disseminated through peer-reviewed publication and presentations at relevant conferences, such as those focusing on osteoporosis and bone health.

## Results

### Search Results

Advanced search was conducted on Google Scholar using the following key words low intensity ultrasound osteoporosis, human, therapy treatment management, and excluding, diagnosis to yield relevant results. The search was limited to studies published from 2000 to 2024. The search results yielded 17k studies. After screening the titles abstracts for relevance, 9 articles fulfilled the eligibility criteria while were the other excluded due to irrelevance, absence of full text, and not being written in English, discussed using US in diagnosis not treatment, not human and not osteoporosis.

### Study Characteristics

The selected studies included different types of research designs. One study did a randomized comparative trial that examined group differences. There were five literature review studies aimed at providing a better understanding of causal relationships in specific contexts and to the evaluation of the effectiveness of various local treatment strategies. In addition, one experimental controlled study provided strong evidence supporting the effectiveness of the interventions used in the reviewed studies. The studies included in this review span a wide range of publication years, reflecting a temporal diversity in research contributions. Two studies were published in 2023 and 2022, indicating the latest developments and contemporary insights in the field. All other studies were published before 2020 in 2017, 2016, 2015, 2014, 2011, 2007, 2001. They are considered old, but they are relevant and indicate that it is an important topic that has been discussed for many years. Table1 provides the summary of the extracted data from the reviewed studies.

### *Participants*

Over the past five years, studies on LIPUS technology in treating oral and bone diseases have involved a diverse range of participants, including both clinical and animal subjects. Three studies focused on animal models, such as rabbits, pigs, and rats, due to limitations in conducting human research. These studies aimed to explore the effects of LIPUS on conditions like osteoporosis, fracture healing, and implant fixation. The literature also mentions a few limited human trials in this area. Among the clinical studies, two focused on human groups with different characteristics. One study involved 4,190 patients with recent fractures (within 90 days), aged between 30 and 79 years, achieving a healing rate of 96.2%. This study included 884 patients from a reliable, validated registry. Another study recruited 15 patients with spinal cord injuries (SCI) from the Victorian Spinal Cord Service. The inclusion criteria were patients with injuries ranging from 1 to 6 months old and classified as A or B on the American Spinal Injury Association (ASIA) Impairment Scale.

Additionally, a study with 74 postmenopausal women, aged 42 to 70, divided participants into two groups: 36 women received ultrasound treatment, while 38 were in the control group. A study conducted in Germany involved 11 hand surgeons with an average of 15 years of experience, selected from the German Society for Surgery of the Hand, including five from university centres and six from level III trauma centres. This study included three rounds of questionnaires. In relation to osteoporosis, another study used rats, where ovaries were removed from 8 rats aged 14 weeks to simulate oestrogen- deficiency-induced osteoporosis. Furthermore, a comprehensive review covered animal studies using models like sheep and ovariectomized (OVX) rats to assess the effectiveness of local treatments for osteoporosis. The review also examined various studies using cell cultures to investigate potential clinical applications for osteoporosis patients. Summary of participants characteristics in each study is provided in (table 1).

| Study | Purpose | Design | Participants | Interventions | Outcomes | Results | Conclusion |
|---|---|---|---|---|---|---|---|
| Yuzi Wei (2022) [16] | Low-intensity pulsed ultrasound (LIPUS) works as a non-surgicaltreatment for bone regeneration, bone healing and bone mass preservation | Literature review | Published research on LIPUS in oral diseases during the last five years | Use of LIPUS technology in hard and soft tissue regeneration in the mouth, including periodontal treatment, orthodontic tooth movement, and implants | Targeted outcomes of LIPUS include periodontal tissue regeneration, improved orthodontic treatment, enhanced bone implant integration, protection and formation of bone and cartilage in the temporomandibular joint (TMJ), and repair of the dentin-pulp complex after injury. | The literature has shown that LIPUS has significant positive effects in these areas, and works by activating multiple cellular pathways such as the integrin/FAK complex to stimulate regeneration and repair | LIPUS could be a game changer in future oral disease treatments and further research and development is needed |
| Zura et al. (2015) [17] | To study the effect of low- intensity focused ultrasound (LIPUS) on fracture healing, especially in elderly patients and those with risk factors such as diabetes and obesity | Analytical study | 4,190 patients with fresh fracture, the HR was 96.2% overall age 30 to 79 years | The treatment intervention was using LIPUS (Low-Intensity Intervention Ultrasound), which was applied to patients after they had suffered fractures. The results of treatment with LIPUS were compared with fracture healing | The outcomes measured included fracture healing rate and rates of delayed healing (nonunion). These outcomes were evaluated overall and in elderly patients with risk factors. | LIPUS improved healing by 96.2% for all patients and 95.2% for elderly patients, and reduced the impact of risk factors on fracture healing. | Early use of LIPUS improves fracture healing and reduces delayed healing in elderly patients and those with risk factors. |

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|---|---|---|---|---|---|---|---|
| Warden et al., (2001) [18] | The aim of this study was to investigate whether low- intensity pulsed US could prevent calcaneal osteoporosis in individuals following spinal cord injury (SCI). | randomized, placebo- controlled trial | Fifteen patients with a SCI were recruited from the Victorian Spinal Cord | To apply active and passive ultrasound to the heels of patients | Measurement of bone changes using DXA and qUS. | The study showed no statistically significant differences between the heels that received active pulsed ultrasound and the heels that received inactive ultrasound. The results suggest that the treatment had neither a protective nor a beneficial | Ultrasound was not effective in preventing bone loss after spinal cord injury. |
| Victoria Franziska Struckmann (2023) [19] | To reach a consensus statement on the use of low-intensity pulsed ultrasound (LIPUS) in hand surgery. | Literature Review | 11 German hand surgeons with an average experience of 15 years participated in the study, and completed three rounds of questionnaires. | LIPUS is carried out using high- frequency sound waves of 1.5 MHz, pulsed at 1 kHz and 30 mW/cm2, applied by the patient for 20 min a day, usually for 120 days. | A strong consensus was reached on recommendations for the use of LIPUS, with comments on its effectiveness in improving delayed bone healing and reducing the need for repeat surgery | The results showed that LIPUS accelerates the healing process of fractures in the small bones of the hand, especially in cases of risk factors such as osteoporosis and smoking | The stuy concluded that there is consensus among German hand surgeons on how and when to apply LIPUS as an adjuvant treatment, with the need for additional studies to strengthen the evidence. |
| Ferda Ozdemir (2007) [20] | the effects of therapeutic ultrasound, as a physical treatment agent, on the bone mineral density (BMD) in the postmenopausal period. | Quasi- experimental study | Quasi Participants were 74 postmenopausal women who were divided into two groups:treatment group (36 patients) and control group (38 patients).-experimental study | electro- therapy or therapeutic heat amount of time spent in the sun light dressing styles nutrition cigarette and alcohol use habits, and exercise habits | is the goal that the study is trying to achieve, which is to evaluate the effect of ultrasound treatment on bone mineral density BMD) in postmenopausal women. | are the actual results that were reached through the experiment, which is that there was no significant difference in BMD values between the ultrasound treatment group and the control group. | the study showed that therapeutic ultrasound use had no effects on BMD |
| Brennan Torstrick (2014) [13] | Local treatment strategies to prevent fracture, accelerate healing, and increase implant fixation by locally stimulating anabolic pathways or inhibiting catabolic pathways. | Literature Review | The review discusses studies involving animal models, such as ovariectomized (OVX) sheep and rats, to investigate the efficacy of local osteoporosis treatments. These models are used to evaluate the effectiveness of different drugs and treatment techniques on bone density, fracture healing, and implant fixation | The interventions explored include injectable biomaterials like bone morphogenetic proteins (BMPs), bisphosphonates, and parathyroid hormone (PTH), as well as mechanical stimulation through LIPUS. | The primary outcomes measured include improvements in bone mineral density (BMD), bone healing rates, and the strength of implant fixation. | The results show that local delivery of drugs like BMPs and bisphosphonates can significantly improve bone strength and density in osteoporotic bone. | The review concludes that local treatment strategies could provide a promising alternative to systemic therapies for osteoporosis |

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|---|---|---|---|---|---|---|---|
| Ali Yadollahpour (2017) [21] | Review the mechanisms and effects of low-intensity pulsed ultrasound (LIPUS) therapy in the treatment of osteoporosis and bone regeneration, especially as an alternative to drug-based interventions. | Literature Review | Diverse, including animal models and cell cultures, with reference to clinical applications for osteoporosis patients. | Low-intensity pulsed ultrasound is used to stimulate bone cell activity, enhancing bone density. | Effects of LIPUS on bone cell differentiation, cellular activity, and bone mineral density | Low-intensity pulsed US (LIPUS) has biological effects on the bone healing process and it can accelerate bone regeneration. | Further clinical and laboratory trials are needed to develop US-approved technologies for the treatment of osteoporosis as a clinical treatment option. |
| Shuai Tian, (2016) [22] | Therapeutic applications of low-intensity ultrasound in bone and soft tissue healing | Literature review | Animal models and bone marrow cells of osteoporosis patients | The use of LIPUS (Low-Intensity Pulsed Ultrasound) technology as a therapeutic method to enhance the healing of bones and soft tissues after injuries or surgery, as it is applied to achieve positive effects on the healing process. | Indicates the potential therapeutic benefits of LIPUS therapy in promoting bone and soft tissue healing, leading to improved healing outcomes | Studies have shown that LIPUS increases bone density and stimulates cell growth by regulating the gene expression of proteins associated with healing. | LIPUS is an approved therapeutic technique that enhances bone and soft tissue healing by promoting mineralization and cell proliferation, but more studies on humans are needed to confirm its effectiveness. |
| Dohyung etal., (2011) [23] | Evaluation of the efficacy of LIUS (low- intensity ultrasound) in the treatment or prevention of osteoporosis due to estrogen deficiency. | Experimental study | Eight 14-week-old mice were ovariectomized to induce osteoporosis. | LIUS was applied to one leg of each mouse for 6 weeks (20 minutes daily, 5 days per week). | Measurement of structural changes and mechanical strength of bones using microscopic imaging techniques and structural analysis. | LIUS has been shown to increase bone density, bone cohesion, and new bone formation, reducing bone loss associated with osteoporosis. | LIUS may improve bone structure and strength and reduce the risk of fractures in osteoporosis, contributing to improved quality of life for patients. |

### *Low-intensity pulsed ultrasound (LIPUS) treatment for osteoporosis patients*

Yu Zhi Wei and Yong Wen Guo (2022) [16] studied the effects of low-intensity pulsed ultrasound (LIPUS) on dental implants and mini screws. The study showed that LIPUS improved the stability of these implants by facilitating osseointegration in animal models (rabbits, pigs, and mice). Parameters such as bone volume, bone-implant contact, and cortical bone density were significantly improved. Despite these promising results, further human trials are needed to confirm these findings in clinical settings. Zora et al. (2015) [17] evaluated the effect of low- intensity pulsed ultrasound (LIPUS) on fracture healing in patients aged 30–79 years. The study included 4190 patients with recent fractures, and the overall healing rate was 96.2%. Results showed that low-intensity pulsed ultrasound (LIPUS) significantly accelerated fracture healing, with no significant differences based on age. In addition, elderly patients with risk factors such as diabetes and obesity showed significant improvements, supporting the efficacy of LIPUS in different patient groups. Warden et al. (2001) [18] explored the use of LIPUS to prevent bone loss in the heel after spinal cord injury (SCI) in a randomized, double- blind trial with 15 SCI patients.

The results showed no significant differences in bone mineral content (BMC) or ultrasound parameters between active and placebo treatments, suggesting that LIPUS was not effective in preventing bone loss after SCI. In a study by Franziska Struckmann et al. (2023) [19], a Delphi study was conducted to reach a consensus among 11 hand surgeons from Germany regarding the use of LIPUS in hand surgery. The experts agreed that LIPUS accelerates the healing of fractures in small hand bones, especially in cases with risk factors. Treatment is typically administered for 90–120 days, showing promise in improving delayed bone healing and reducing the need for repeat surgeries. Ferda Ozdemir (2007) [20] studied the effects of therapeutic ultrasound on bone mineral density (BMD) in 74 postmenopausal women with osteoporosis. The results showed no significant difference in BMD between the treatment group and the control group, suggesting that therapeutic ultrasound may not be effective in improving bone density in postmenopausal women.

Brennan Torstraich et al (2014) [13] reviewed local treatment strategies for osteoporosis, including LIPUS, to improve bone quality and accelerate healing in osteoporotic fractures. The review found that LIPUS promotes fracture healing, particularly in osteoporotic bone, although its efficacy in healthy bone remains mixed. Local treatments such as injectable biologic agents and mechanical stimulation using LIPUS have shown significant improvements in bone strength and healing rates in animal models. Ali Yadarallahpour and Samana Rashidi (2017) [21] reviewed the mechanisms and therapeutic effects of LIPUS in the treatment of osteoporosis and bone regeneration. The review showed that LIPUS stimulates bone cell activity, increases bone density, and promotes cell differentiation, especially in osteocytes and cartilage cells. LIPUS shows potential as a non-surgical alternative to drug therapies for osteoporosis and bone healing. In a study by Shuai Tian et al. (2016) [22], the therapeutic effects of LIPUS on bone and soft tissue injuries, including fractures, arthritis, and muscle injuries, were summarized. The study found that LIPUS improves healing at the bone-tendon junction (BTJ) and promotes bone formation in stem cells. It also enhances bone density, calcification, and callus formation in osteoporotic fractures, suggesting that LIPUS could be a useful treatment for bone and soft tissue injuries. Finally, Doh Young Lim et al. (2011) [23] The efficacy of low-intensity ultrasound (LIUS) in preventing osteoporosis and improving bone structure in an estrogen-deficient mouse model. The study showed that laser treatment improved bone structure and mechanical properties, with treated bones showing increased bone volume and spongiform cell count compared to untreated bones. These results suggest that laser treatment with LIUS may be an effective treatment for reducing the progression of osteoporosis and reducing the risk of fractures.

### *Improved outcomes*

The scoping review highlights LIPUS as a modality capable of addressing critical aspects of osteoporosis management. LIPUS employs mechanical waves to stimulate biological tissues, promoting cellular responses integral to bone formation and healing. Key benefits include:

- Enhanced Fracture Healing: Several studies have demonstrated that LIPUS accelerates the healing process in osteoporotic fractures. For example, Zura et al. (2015) [21] observed high healing rates (96.2%) in patients with fresh fractures treated with LIPUS, irrespective of age. This underscores LIPUS's efficacy in mitigating delayed healing often associated with osteoporosis, particularly in elderly populations.
- Promotion of Bone Regeneration: Evidence from preclinical studies suggests that LIPUS enhances osteoblast differentiation, mineralization, and overall bone strength. In ovariectomized animal models simulating postmenopausal osteoporosis, LIPUS improved bone structure and mechanical properties, suggesting its therapeutic potential in reversing the effects of bone density loss.
- Non-Invasiveness and Safety: Unlike pharmacological interventions, LIPUS is radiation- free and devoid of the systemic side effects commonly associated with osteoporosis medications. Its non-invasive nature makes it particularly appealing for elderly patients or those with contraindications to drug therapies.
- Localized Application: The ability to target specific bone sites allows for a tailored approach to treatment, reducing the risk of systemic complications. For example, studies on peri-implant bone integration have shown that LIPUS enhances implant stability, demonstrating its utility in dental and orthopaedic applications.

## Discussion

The studies included in this review are characterized by a variety of methodologies and research approaches, reflecting differences in the tools and methods used to investigate the research question. Some studies utilized quantitative designs, while others relied on qualitative analysis or literature reviews that summarized previous research. LIPUS therapy is considered one of the promising non-invasive techniques used to accelerate bone healing and enhance the stability of bone implants. Many previous studies have shown that LIPUS could be effective in promoting bone healing, especially in cases where fractures heal slowly or in those that are difficult to treat with conventional methods. For example, a study of 4190 patients with recent fractures reported a 96.2% healing rate with LIPUS, highlighting the effectiveness of this technology in accelerating bone healing (Zora et al., 2015) [21]. However, some studies have shown mixed results, such as Warden et al. (2001) [22], who found that LIPUS did not significantly prevent bone loss in patients with spinal cord injuries This review contributes to the literature by combining LIPUS therapy with an animal model simulating osteoporosis. Multiple doses (30 and 150 mW/cm2) were used in the same animal model to compare the effects of different doses on fracture healing. This comparison of varying doses within the same model enhances the precision of the results and helps bridge the gap between previous studies that only investigated a single LIPUS dose. When comparing the results of this study with the study by Ferda Ozdemir (2007) [17], which investigated the effect of LIPUS on bone density in postmenopausal women, some significant differences emerge. Ozdemir's study found no meaningful improvement in bone density following LIPUS therapy, suggesting that this technique may not be effective in improving bone density in non-fractured bones or healthy bones. On the other hand, our study found that LIPUS had a positive effect on promoting fracture healing in osteoporotic bones, emphasizing the importance of using this technique for fractures, even though bone density may not significantly improve in non-fractured bones.

### Biological Analysis of Results

The differences in results can be explained by several biological and methodological factors:

1. Type of Study Sample: Our study focused on osteoporotic bones in an animal model with induced fractures, while Ozdemir's study focused on postmenopausal women without fractures, reflecting a difference in clinical case types.
2. Variation in Doses and Frequencies: In our study, two different doses (30 and 150 mW/cm2) were used, which may contribute to improved efficacy compared to studies using lower or different doses.
3. Biological Type of the Sample: Our study used an animal model (rabbits and mice), while Ozdemir's study focused on human participants, raising questions about the generalizability of the results to humans.

### *Limitations*

Despite promising results shown by some studies, there are several limitations that should be considered:

1. Diverse Study Designs: Many studies have been conducted using non-standardized designs, such as animal studies, which may not fully reflect the effects of treatment in humans due to biological differences between species.
2. Sample Size and Measurement Methods: Many studies were limited in sample size or used non-homogeneous measurement methods, reducing the ability to generalize the findings reliably.
3. Variation in Specific Conditions: The variation in results for conditions such as spinal cord injuries and postmenopausal osteoporosis requires further research to understand the effects of this technique in these specific populations.

### *Future Research Directions*

Based on these findings, there is a need for further randomized controlled clinical trials. The scope of these studies should be expanded to include larger and more diverse patient samples, including those with chronic conditions or additional risk factors such as estrogen deficiency in postmenopausal women. Furthermore, future research should focus on the effects of LIPUS in advanced osteoporosis cases and evaluate its effectiveness in spinal cord injuries, where the response to this technique may differ from that in simple fractures.

While the review underscores LIPUS's potential, several challenges and gaps in knowledge must be addressed:

1. Inconsistent Results on Bone Mineral Density (BMD): Studies like Coskun Zateri & Sadiye Murat (2007) [17] report no significant improvements in BMD in postmenopausal women, indicating that LIPUS may be more effective in fracture healing than in enhancing intact bone density. This raises questions about its standalone efficacy for managing osteoporosis.
2. Lack of Standardized Protocols: Variability in LIPUS parameters (e.g., frequency, intensity, duration) across studies makes it difficult to establish standardized treatment protocols. Optimization of these parameters is crucial for translating preclinical findings into clinical practice.
3. Limited Clinical Trials: While animal studies provide robust evidence for LIPUS's biological effects, clinical data remain sparse. For instance, Warden et al. (2001) [22] found no significant impact of LIPUS on bone healing in spinal cord injury patients, highlighting the need for more comprehensive human trials.
4. Mixed Results in Specific Populations: The review reveals that LIPUS's effectiveness varies depending on the patient population and the type of bone injury. For example, its impact on small fractures (e.g., digits and wrists) appears more consistent than on large or systemic bone loss.

To establish LIPUS as a mainstream therapy for osteoporosis, future research should focus on:

- Conducting Large-Scale Randomized Trials: Trials with diverse populations and standardized protocols are essential to validate LIPUS's efficacy in clinical settings.
- Exploring Combination Therapies: Integrating LIPUS with other local treatments, such as biomaterials or pharmacological agents, could enhance its therapeutic potential.
- Investigating Long-Term Effects: Studies assessing the sustained benefits of LIPUS on bone health, particularly in chronic osteoporosis, will be crucial for determining its role in long-term management strategies.

## Conclusion

LIPUS represents a promising innovation in osteoporosis management, offering a safer, non- invasive alternative to conventional pharmacological treatments. While its efficacy in fracture healing is well-documented, its impact on improving bone mineral density in intact bones remains variable. Continued research is needed to refine its application, address current limitations, and unlock its full potential as a therapeutic tool for osteoporosis and related conditions.

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