



# Major approaches to bone regeneration process with gut microbiota, exosomes, and microRNAs: a systematic review

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## Abstract

**Introduction:** The incidence and mortality of bone diseases are still steadily increasing, creating a significant financial burden for societies across the world. To prevent the occurrence of bone diseases, slow their progression, or reverse the injuries they cause, new alternatives or complementary treatments need to be developed. The gut microbiota plays a role in bone metabolism and the pathogenesis of osteoporosis.

**Objective:** It was to analyze through a systematic review the main considerations and clinical findings of the bone formation process through the modulation of the gut microbiota, as well as the functions of microRNAs and exosomes. **Methods:** The systematic review rules (PRISMA) were followed. The search was carried out from August to September 2022 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, using scientific articles from 2001 to 2022. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 126 articles were found. A total of 34 articles were fully evaluated and 26 were included in this systematic review. Most studies showed homogeneity in their results, with  $I^2 = 98.8\% > 50\%$ . The symmetrical funnel plot does not suggest a risk of bias between small sample-size studies. The gut microbiota plays an important role in the modulation of bone healing and bone health through the traffic of inflammatory TNF+ T and Th17 cells to the bone marrow, influencing the inflammatory state of the patient, determining the "brain-gut-bone" axis. It has been shown that the diversity of the gut microbiota is decreased in patients with osteoporosis, leading to a state of dysbiosis. There is a relationship between the microbiome, osteoblasts, osteoclasts, and nuclear factor

ligand receptor-kappa-B (RANKL) activator. Studies have proposed several mechanisms of gut microbiome interaction with osteoclastogenesis and bone health, including microRNA, insulin-like growth factor 1, and immune system mediation. Therefore, bone regeneration requires that the basic biological principles of osteogenesis, osteoinduction, osteoconduction, and biocompatibility are followed.

**Keywords:** Bone diseases. Bone regeneration. Gut microbiota. Exosomes. MicroRNAs.

## Introduction

In the context of the bone formation process, bone diseases comprise a large group of common diseases, including fractures, osteoporosis, and osteoarthritis that affect a large number of individuals, particularly the elderly. Without intervention, the prevalence of osteopenia is projected to increase to 64.3 million Americans and that of osteoporosis to 11.9 million by the year 2030 [1].

With existing prevention and treatment methods, the incidence and mortality of bone diseases are still steadily increasing, creating a significant financial burden for societies across the world. To prevent the occurrence of bone diseases, slow their progression, or reverse the injuries they cause, new alternatives or complementary treatments need to be developed [1].

In this scenario, the gut microbiota plays a role in bone metabolism and the pathogenesis of osteoporosis. The gut microbiota is composed of about 100 trillion bacteria, viruses, fungi, and protozoa that live in perfect symbiosis with our organism [33]. About 90% of bacteria living in the human gastrointestinal tract belong to 5 main phyla: Bacteroidetes characterized by some

well-known genera such as Prevotella and Bacteroides [34], Firmicutes to which the genera Ruminococcus, Lactobacillus and Streptococcus belong [34]. Actinobacteria belong to the genus Bifidobacterium [35]. Proteobacteria (Gram-negative) and possibly pathogenic, and Verrucomicrobia, known mainly by the genus Akkermansia [36-38].

In this regard, the individual response to nutrients and non-nutritive molecules can be largely affected by three important biological layers. The gut microbiome can alter the bioavailability of nutrients and other substances, the genome can influence the kinetics and dynamics of molecules, while the epigenome can modulate or amplify genome properties. The use of omics and bioinformatics techniques allows the construction of individual multilayer networks and, thus, the identification of personalized strategies that have been considered recently in the health area [39].

Therefore, this study analyzed through a systematic review the main considerations and clinical findings of the bone formation process through the modulation of the gut microbiota, as well as the functions of microRNAs and exosomes.

## Methods

### Study Design

The present study followed a concise systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and metaanalysis-HTTP: [//www.prisma-statement.org/](http://www.prisma-statement.org/)).

### Search Strategy and Search Sources

The literary search process was carried out from August to September 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2001 to 2022, using the descriptors (MeSH Terms): "*Bone diseases. Bone regeneration. Gut microbiota. Exosomes. MicroRNAs*", and using the Booleans "and" between the MeSH terms and "or" between the historical findings.

### Study Quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through

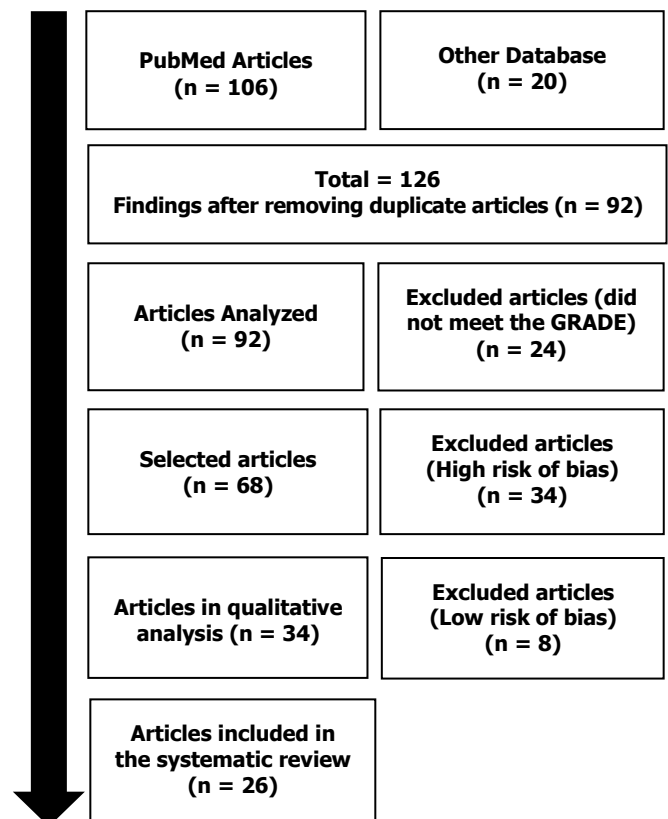
the analysis of the Funnel Plot (Sample Size versus Effect Size), using the Cohen test (d).

## Results and Discussion of the Systematic Review

### Summary of Findings

A total of 126 studies were analyzed and submitted to eligibility analysis, and then 26 of the 34 final studies were selected for this systematic review. The listed studies presented medium to high quality (**Figure 1**), considering in the first instance the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with I<sup>2</sup> =98.8% >50%.

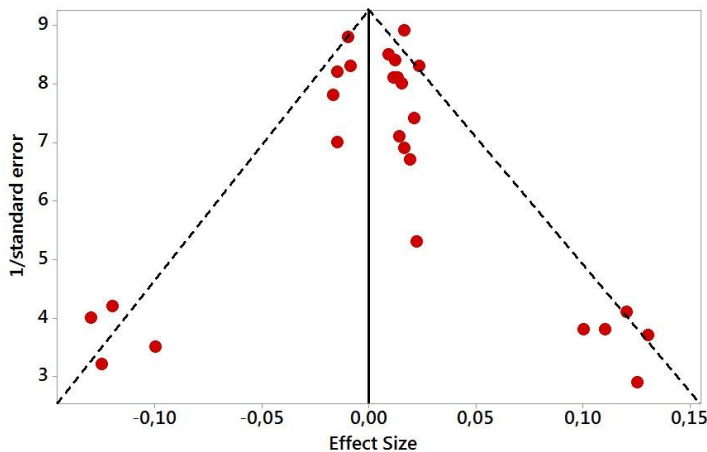
**Figure 1.** Flowchart showing the article selection process.



**Figure 2** presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the

graph and in studies with a large sample size that are presented in the upper region.

**Figure 2.** The symmetrical funnel plot does not suggest a risk of bias between the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=26 studies).



### Major Cells and Molecules For The Bone Regeneration

In this scenario, adult stem cells, such as mesenchymal stem cells (MSC), point to an alternative for cell therapy and human tissue engineering, since it was found that they have a high degree of plasticity, with the ability to self-regenerate, renewal and differentiation into specialized progenitors [9].

Also, MSCs induce the expression of junction proteins and increase microvascular integrity and the production of nitric oxide (NO) by macrophages [10]. The vascular stromal fraction (VSF) from MSCs is a heterogeneous mixture of cells, including fibroblasts, pericytes, endothelial cells, blood cells, and mesenchymal stem cells derived from adipose tissue (AMSC) [11]. Exosomes stand out together with AMSC. Exosomes are extracellular vesicles with a size of 40-100 nm in diameter and a density of 1.13-1.19

g/mL, containing proteins, mRNAs, miRNAs, and DNAs. Exosomes change the

biochemical characteristics of recipient cells through the delivery of biomolecules and play a role in cellular communication. These vesicles are produced from body fluids and different types of cells. Evidence suggests that the AMSC-derived exosome (AMSC EXO) exhibits AMSC-like functions with low immunogenicity and no tumorigenesis [12,15].

Furthermore, exosomes contain RNAs or non-coding fragments, including overlapping RNA transcripts, protein-coding region, structural RNAs, transfer RNA fragments, YRNAs, short hairpin RNAs, small interfering RNAs (siRNAs), microRNA (miRNA),

messenger RNA (mRNA) and DNA [16]. Regarding miRNA, exosomes present miR-1, miR-15, miR-16, miR-17, miR-18, miR-181 and miR-375 [17]. In addition, various cytokines such as Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), Granulocyte

Macrophage Colony Stimulating Factor (GM-CSF), Interleukin (IL)-2, IL-6, IL-8, IL-10, IL-15, IL-1 $\beta$ , are expressed in exosomes [18].

Based on this, normal bone formation and tissue repair involve coordinated interaction between bone-forming cells and biological signals. The main force in this process is osteoblasts and their precursors [19]. Osteoblasts can produce new bone along with biomaterials and can initiate the release of biological signals that guide bone formation and remodeling.

These biological signals attract bone-forming cells to the receptor site. Growth factors and other proteins are some of the biological signals that may be involved in bone neoformation and tissue remodeling. In addition, through chemotaxis, there is a migration of bone-forming cells to the application area, as the stimulation of cell migration occurs in response to chemical stimuli [20].

In this sense, monocytes, macrophages, and endothelial cells contribute to bone remodeling, either through contact with osteogenic cells or through the release of soluble factors such as cytokines and GF [20]. In the skeletal system, TNF- $\alpha$  stimulates bone and cartilage resorption and inhibits collagen and proteoglycan synthesis. IL-1 induces the expression of a wide variety of cytokines. LIF and IL-6 are two such molecules that are known to stimulate the differentiation of mesenchymal progenitor cells in the osteoblastic lineage, they are also potent anti-apoptotic agents for osteoblasts. In bone, the main sources of IL-6 are osteoblasts and not osteoclasts. Prostaglandin E2 (PGE2) is also directly related to the expression of the cytokine IL-6 [21,22].

### Gut microbiota and Bone Regeneration

The gut microbiota plays an important role in the modulation of bone healing and bone health through the traffic of inflammatory TNF+ T and Th17 cells to the bone marrow, influencing the inflammatory state of the patient, determining the "brain-gutbone" axis [23-25]. In this sense, the inflammatory cells recruited to the wound site by a series of growth factors and chemokines begin to establish the extracellular matrix for the new bone, forming a fibrous callus [26]. After the disappearance of the acute inflammation, mesenchymal stem cells, which have differentiated into osteogenic cells, begin the process of periosteal ossification, successively forming thin layers of bone between

healthy bone or cartilage and the fibrous callus, gradually replacing or strengthening the callus. The bone healing process can only occur when there is a balance of osteoclast and osteoblast activity [27], thus bone healing and remodeling processes are tightly coupled through various signaling pathways, providing an appropriate balance between bone resorption and bone formation new [28].

Related to this, it has been shown that the diversity of the gut microbiota is decreased in patients with osteoporosis, leading to a state of dysbiosis [29]. Based on the abundance of metabolites and cellular and molecular signaling, particularly short-chain fatty acids such as butyrate [30], produced by the gut microbiota, it stands to reason that these states of imbalance may be connected and should be investigated. Furthermore, preclinical animal models have shown that alterations in the gut microbiota can decrease the quality and therefore the strength of bone tissue [31], and in germ-free mice (i.e., mice lacking gut microbiota), the number of osteoclasts was reduced, leading to increased bone mass [32].

Furthermore, there is a relationship between the microbiome, osteoblasts, osteoclasts, and nuclear factor ligand receptor-kappa-B (RANKL) activator. Studies have proposed several mechanisms of gut microbiome interaction with osteoclastogenesis and bone health, including micro-RNA, insulin-like growth factor 1, and immune system mediation [29].

The literature on probiotics and their mechanisms of action is examined in the context of bone healing. Known and hypothetical interactions between common osteoporosis drugs and the human gut microbiome are examined. Since dysbiosis in the gut microbiota may function as a biomarker of bone metabolic activity, it may also be a pharmacological and nutraceutical therapeutic target (i.e. pre and probiotics) to promote bone homeostasis [25].

Therefore, bone regeneration requires that the basic biological principles of osteogenesis, osteoinduction, osteoconduction, and biocompatibility are followed. The success of regenerative procedures may depend on the internal structural, mechanical, and metabolic condition of the host bone in which the implants are to be inserted, the surgical technique, and the biomaterial used. The patient's aging process appears to be relevant. It may be associated with metabolic diseases that lead to systemic functional deterioration, which involves a gradual and constant decline in hormonal, immunological, and osteometabolic activity, affecting the positive results of bone reconstruction and implant therapy. The final characteristics of the regenerated bone must be able to withstand the load forces transmitted by the implants,

regardless of body location, and must be individualized according to the different conditions of each patient [33].

A systematic review study analyzed that the beneficial activity of resveratrol is evidenced by analyzing the changes in the gene expression of the host and the gastrointestinal microbial community with its administration. The possibility of identifying individual microbial families may allow tailoring treatment plans with targeted polyphenolic diets when associated with microbial dysbioses, such as bone tissue regeneration [34].

## Conclusion

It was concluded that exosomes change the biochemical characteristics of recipient cells through the delivery of biomolecules and play a role in cellular communication. These vesicles are produced from body fluids and different types of cells. Exosomes contain RNAs or non-coding fragments, including overlapping RNA transcripts, protein-coding region, structural RNAs, transfer RNA fragments, YRNAs, short hairpin RNAs, small interfering RNAs (siRNAs), microRNA (miRNA), messenger RNA (mRNA) and DNA normal bone formation and tissue repair involve coordinated interaction between bone-forming cells and biological signals. The gut microbiota plays an important role in the modulation of bone healing and bone health through the traffic of inflammatory TNF+ T and Th17 cells to the bone marrow, influencing the inflammatory state of the patient, determining the "brain-gut-bone" axis. It has been shown that the diversity of the gut microbiota is decreased in patients with osteoporosis, leading to a state of dysbiosis. There is a relationship between the microbiome, osteoblasts, osteoclasts, and nuclear factor ligand receptor-kappa-B (RANKL) activator. Studies have proposed several mechanisms of gut microbiome interaction with osteoclastogenesis and bone health, including microRNA, insulin-like growth factor 1, and immune system mediation. Therefore, bone regeneration requires that the basic biological principles of osteogenesis, osteoinduction, osteoconduction, and biocompatibility are followed.

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## Informed consent

Not applicable.

## Data sharing statement

No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.

## Similarity check

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