Research, Society and Development, v. 14, n. 3, e10814348420, 2025
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v14i3.48420

The use of mesenchymal stem cells in the treatment of osteogenesis imperfecta: An integrative and qualitative review of literature

O uso de células-tronco mesenquimais no tratamento da osteogênese imperfeita: Uma revisão integrativa e qualitativa da literatura

El uso de células madre mesenquimales en el tratamiento de la osteogénesis imperfecta: Una revisión integradora y cualitativa de la literatura

Received: 02/27/2025 | Revised: 03/26/2025 | Accepted: 03/27/2025 | Published: 03/29/2025

Kamily Iracema Coimbra Lima
ORCID: https://orcid.org/0009-0004-1225-825X
Instituto Metropolitano de Ensino, Brazil
E-mail: kamilycoimbra@hotmail.com
Isac da Silva Monteiro
ORCID: https://orcid.org/0009-0000-9148-0692
Instituto Metropolitano de Ensino, Brazil
E-mail: isacmonteirooo@gmail.com
Klever Luiz Ribeiro
ORCID: https://orcid.org/0009-0000-6267-7736
Instituto Metropolitano de Ensino, Brazil
E-mail: klever.ribeiro@hotmail.com
Messias de Lima Azevedo
ORCID: https://orcid.org/0009-0008-0762-6010
Instituto Metropolitano de Ensino, Brazil
E-mail: messias.enfermeiro1@gmail.com
Mônica Regina Hosannah da Silva e Silva
ORCID: https://orcid.org/0000-0002-6707-2629
Instituto Metropolitano de Ensino, Brazil
E-mail: monicahosannah@gmail.com
Kadmiel Cândido Chagas
ORCID: https://orcid.org/0000-0001-8336-4210
Universidade Federal do Amazonas, Brazil
E-mail: candido.chagas@ufam.edu.br

Abstract
Osteogenesis Imperfecta (OI) is a hereditary bone disease that affects children, resulting in extreme bone weakness leading to musculoskeletal deformities and fractures. OI is caused by mutations in the genes that code to produce collagen in bones, a substance essential for the formation and strength of bones. Based on this, the objective of this review is to investigate the role of mesenchymal stem cells in the treatment of osteogenesis imperfecta as well as to investigate innovative therapies in the treatment of the disease. This study is a qualitative and integrative review of the literature carried out through an active search in the Medical Literature Analysis and Retrieve System Online (medline) database, in accordance with the precepts established by the Standards qualitative research guideline. For Reporting Qualitative Research (SRQR). Articles published in full without language restrictions were selected for analysis and inclusion based on the controlled DeCS/MESH descriptors: mesenchymal stem cells and osteogenesis imperfecta through the combination of words with the Boolean descriptors AND and OR in the information sources. It was observed in the study that treatment with mesenchymal stem cells brought hope to patients with osteogenesis imperfecta since pre-clinical studies in animal models and clinical studies demonstrated a reduction in the occurrence of fractures and an improvement in bone density with this type of therapy.
Keywords: Mesenchymal stem cells; Osteogenesis imperfecta; Treatment.

Resumo
Osteogênese Imperfeita (OI) é uma doença óssea hereditária que afeta crianças e causa extrema fraqueza óssea, levando a deformidades musculoesqueléticas e fraturas. A OI é causada por mutações nos genes que codificam a produção de colágeno nos ossos, uma substância essencial para a formação e resistência óssea. Com base nisso, o objetivo desta revisão é investigar o papel das células-tronco mesenquimais no tratamento da osteogênese imperfeita, bem como investigar terapias inovadoras no tratamento da doença. Este estudo trata-se de uma revisão qualitativa e integrativa da literatura realizada por meio de busca ativa na base de dados Medical Literature Analysis And Retrieve

System Online (medline), de acordo com os preceitos estabelecidos pelo guia Standards qualitative research. Para relatórios de pesquisa qualitativa (SRQR). Artigos publicados na íntegra, sem restrições de idioma, foram selecionados para análise e inclusão com base nos descritores controlados DeCS/MESH: células-tronco mesenquimais e osteogênese imperfeita, combinando palavras com os descritores booleanos AND e OR nas fontes de informação. O estudo descobriu que o tratamento com células-tronco mesenquimais trouxe esperança aos pacientes com osteogênese imperfeita, pois estudos pré-clínicos em modelos animais e estudos clínicos demonstraram uma redução na ocorrência de fraturas e uma melhora na densidade óssea com esse tipo de terapia.
Palavras-chave: Células-tronco mesenquimais; Osteogênese imperfeita; Tratamento.

Resumen
La Osteogénesis Imperfecta (OI) es una enfermedad ósea hereditaria que afecta a los niños y provoca una debilidad ósea extrema que conduce a deformidades y fracturas musculoesqueléticas. La OI es causada por mutaciones en los genes que codifican la producción de colágeno en los huesos, una sustancia esencial para la formación y fortaleza de los huesos. En base a esto, el objetivo de esta revisión es investigar el papel de las células madre mesenquimales en el tratamiento de la osteogénesis imperfecta, así como investigar terapias innovadoras en el tratamiento de la enfermedad. Este estudio es una revisión cualitativa e integradora de la literatura realizada a través de una búsqueda activa en la base de datos Medical Literature Analysis and Retrieve System Online (medline), de acuerdo con los preceptos establecidos por la guía de investigación cualitativa Standards. Para informes de investigación cualitativa (SRQR). Se seleccionaron para análisis e inclusión artículos publicados íntegramente sin restricciones de idioma con base en los descriptores controlados DeCS/MESH: células madre mesenquimales y osteogénesis imperfecta mediante la combinación de palabras con los descriptores booleanos AND y OR en las fuentes de información. En el estudio se observó que el tratamiento con células madre mesenquimales trajo esperanza a los pacientes con osteogénesis imperfecta, ya que estudios preclínicos en modelos animales y estudios clínicos demostraron una reducción en la aparición de fracturas y una mejora de la densidad ósea con este tipo de terapia.
Palabras clave: Células madre mesenquimales; Osteogénesis imperfecta; Tratamiento.

1. Introduction

Osteogenesis imperfecta (OI) is a genetic and hereditary bone disease that affects the pediatric population, resulting in extreme bone fragility leading to osteomuscular deformities and fractures. It is highly variable in both its clinical and genetic aspects, with mutations identified in 19 distinct genes so far, responsible for a wide range of severities, from mild, severe to fatal manifestations (Infante et al., 2021).

Cross-sectional epidemiological studies demonstrate that approximately 10,000 to 20,000 children annually are affected by the disease, leading to bone malformation, fractures, and delay in childhood development (Götherström & Walther-Jallow, 2020).

Ninety percent of cases of the disease are related to dominant mutations in genes such as COL1A1 or COL1A2, which encode type I collagen present in the extracellular bone matrix. These mutations may interfere with the formation process of the triple helix that forms type I collagen, leading to clinical manifestations ranging from moderate to severe. However, the condition presents more than 1400 dominant mutations and over 150 recessive mutations identified so far, with new mutations still being discovered (Götherström & Walther-Jallow, 2020; Infante et al., 2021).

Patients with more severe forms of osteogenesis imperfecta face multiple fractures resulting from minor traumas, present low stature, multiple bone deformities, and chronic pain leading to disability and decreased quality of life (Infante et al., 2021).

In terms of its clinical characterization, the disease leads to abnormal bone development, osteopenia, recurrent fractures, and short stature, as well as dental malformation, hearing loss, and excessively mobile joints. During its natural history, untreated patients may present pulmonary complications, heart diseases, which often only manifest in adulthood or late childhood, as well as blood clotting disorders. Therefore, the search for new therapies brings hope and quality of life to patients affected by the disease (Götherström & Walther-Jallow, 2020).

Mesenchymal stem cells are stromal cells present in adult bone marrow, have non-hematopoietic and non-endothelial nature. They are multipotent and can be expanded in culture and differentiate into a variety of cell types, including osteoblasts, chondrocytes, myocytes, and adipocytes (Götherström et al., 2021).

The goal of new treatments is to increase strength and prevent bone fractures, maintaining mobility, functions, and promoting better quality of life for patients.

Based on the above, this review seeks to investigate the role of mesenchymal stem cell treatment in OI, as well as to evaluate the properties that make this therapy a promising option for the treatment of the disease and improvement of patients' quality of life.

2. Methodology

A bibliographic review research was carried out of a quantitative nature, with the number of articles and qualitative to the discussion about the articles (Pereira et al., 2018).

The present study is characterized as an integrative (Snyder, 2019; Anima, 2014; Crossetti, 2012), literature review structured according to the guidelines of the Standards For Reporting Qualitative Research (SRQR) qualitative research guideline extracted from the international network of transparency and research quality in health (EQUATOR NETWORK).

A diagram was used with the selection of controlled health descriptors in Portuguese from the DeCS/BIREME platform as well as their transcription into MESH terms in English, along with their synonyms (entry terms), from the Medical Literature Analysis And Retrieval System Online (MEDLINE) database. Active searches in the information sources occurred on March 11, 2024, at 3:45 PM in databases linked to the Medical Literature Analysis and Retrieval System Online (MEDLINE), using the search strategy described in the following Chart – 1, Search strategy based on data.

Chart 1 – Search strategy based on data.

Number	Search strategy	Articles numbers
1#	(((((Osteogenesis imperfecta[Title/Abstract])) OR (Brittle Bone Disease[Title/Abstract])) OR (Fragilitas Ossium[Title/Abstract])) OR (Osteogenesis Imperfecta Tardas[Title/Abstract])) AND (((((Mesenchymal Stem Cells[Title/Abstract]) OR (Bone Marrow Mesenchymal Stem Cells[Title/Abstract])) OR (Multipotent Bone Marrow Stromal Cells[Title/Abstract])) OR (Multipotent Mesenchymal Stromal Cells[Title/Abstract])) OR (Adipose Derived Mesenchymal Stem Cells[Title/Abstract]))	94
2#	(((((Osteogenesis imperfecta[Title/Abstract])) OR (Brittle Bone Disease[Title/Abstract])) OR (Fragilitas Ossium[Title/Abstract]))) AND ((((Fibrous Dysplasia of Bone) OR (Bone Fibrous Dysplasias)) OR (Osteitis Fibrosa Disseminata)) OR (Fibrocystic Dysplasia of Bone))	57

Source: Personal archive.

The Health Sciences Descriptors (DeCS)/MESH TERMS were combined as per the structure above for quantification and selection of articles.

From the Search Strategy Based on Data, we have got 151 studies. After that, exclusion criteria was applied to get to the final number of 21 relevant studies presented at Table 1 (Exclusion Criteria). Preclinical and clinical studies of original articles published in full were included. Studies that were not available in full, did not fit the proposed terms, and did not meet the aforementioned inclusion criteria were excluded.

Table 1 – Exclusion Criteria.

Step	Description	Number of Studies
Identification	Data based found studies	151
	Other sources identified studies	0
Screening	Removed duplicated studies	121
	Excluded studies after title and abstract analisys	90
Eligibility	Selected studies for the complete reading	64
	Excluded studies after complete reading	51
Inclusion	Studies included at the final review	21

Source: Personal archive.

The search and selection of studies were conducted by two reviewers who independently analyzed the studies. Initially, using the aforementioned DeCS/MESH terms. Since this is a qualitative literature review study, no time filters were applied to the search, and the analysis of titles and abstracts followed. At this stage, studies with animal models and opinion articles were excluded. Once this stage was completed, the full texts of the articles were retrieved for analysis of the remaining inclusion and exclusion criteria. Duplicate citations and studies not corresponding to the proposed review parameters were also excluded. Any disagreements were resolved through discussion with a third reviewer, with inclusion being decided upon consensus with the two main reviewers.

3. Results

During the screening process, using the combined DeCS/MESH terms and their respective Boolean operators, as a result, 21 studies were retrieved, as demonstrated in Table 2 - Succinct description of the selected studies for discussion. Subsequently, after excluding studies not available in full, those that did not fit the proposed terms, and studies that did not meet the aforementioned inclusion criteria, as well as removing duplicates, a total of 21 studies were selected for discussion. It is worth noting that although some studies addressed other types of interventions in OI, it was decided to discuss the data related to the use of mesenchymal stem cells and their association in the treatment of OI, as this is the central theme of the present work. Table 2 briefly describes the selected studies for discussion, considering the author, year of publication, study objective, and relevant aspects of each research. As this article is an integrative literature review of published works, no approval from the ethics committee was required.

Table 2 - Succinct description of the selected studies for discussion.

Author	Year	Objective	Relevant aspects
Dinulescu et al.	2024	To describe other therapies besides bisphosphonates that are used to treat patients with OI.	Highlighting 8 promising new therapies for the treatment of OI: 1. Mesenchymal Stem Cells. 2. Anti-RANK-L Antibodies. 3. Sclerostin Inhibitors. 4. Recombinant PTH. 5. Anti-TGF-β Antibodies. 6. Gene Therapy. 7. Phenylbutyric Acid. 8. Use of Salubrinal.

Lang, E., & Semon, J. A.	2023	To summarize clinical and preclinical aspects regarding the use of MSCs in the treatment of OI.	The studies demonstrate that MSCs, in addition to other aspects, are safe for clinical use, migrate to bone growth sites, improve clinical outcomes but with transient effects, among others.
Infante et al.	2022	To investigate the TGF-β signaling pathway in 2 pediatric patients in a phase I clinical trial, TERCELOI, with infusions of MSCs.	Modulation of the TGF-β pathway in the most severe patient with MSCs.
Götherström et al.	2021	To provide a brief overview of the history and justifications for treating children with OI using MSCs.	MSCs are safe and exhibit differentiation potential and low immunogenicity, making them a great alternative. Transplanting MSCs before and after birth to treat OI is still experimental, but more studies are seeking to evaluate the safety and efficacy of transplantation for treating severe types of OI.
Botor et al.	2021	To present new and prospective treatments for OI.	The study reports new and promising treatments for OI based on MSC transplantation, genetic engineering, and others. However, they are very recent and in experimental stages, which requires further studies.
Infante et al.	2021	To evaluate the safety and efficacy of cellular therapy with infused MSCs in non-immunosuppressed patients with OI.	After infusion, there was an increase in bone levels and improvement in the quality of treated individuals over a 2-year study period. MSCs have osteogenic capacity and paracrine stimulation in adjacent tissues.
Ramesh et al.	2021	To present a continuous clinical trial study, BOOST2B, in India, which reinforces the TERCELOI trial where MSCs are safe and viable.	The use of fetal MSCs in intraosseous doses is a viable alternative since when administered through this route, they facilitate engraftment in locations where they can proliferate and differentiate. However, there is a limitation regarding the amount of information to be considered regarding the risk of their use.
Arthur & Gronthos	2020	To address the challenges and limitations in the use of bone marrow-derived MSC-based therapies. Additionally, discussing recent advances for the treatment of OI and other diseases.	In the last decade, there has been an increase in contributions from various fields leading to significant advances in the treatment of bone dysfunctions. In the future, the combination of biomaterials and MSCs may enhance bone regeneration in affected areas in a controlled manner.
Götherström & Walther-Jallow	2020	To provide an overview of the treatment of OI with MSCs.	MSCs have osteogenic capacity as well as paracrine induction of adjacent tissues. In light of this, fetal MSCs have greater potential compared to cells from adult donors, making them more suitable for cellular therapy.
Sinder et al.	2020	To study the effects of fluorescence-labeled MSCs used to identify grafts in the short and long term.	The proof has been established that these cells proliferate and differentiate into osteoblasts. This positively affects the conformation of trabecular bone, increasing the physical properties and morphology of the site.
Li et al.	2016	To determine if Pigment Epithelium-Derived Factor (PEDF) regulates the expression of Vascular Endothelial Growth Factor (VEGF) by human MSCs.	The study suggests that PEDF regulates VEGF by human MSCs differently than in other cell types. This may be linked to mechanisms by which PEDF also regulates osteomineralization..
Westgren & Götherström	2015	Presenting viable treatment options for OI.	Although there are clinical benefits in children with OI, such as reduced fractures with growth and mobility, the use of MSCs still presents transient effects, requiring further study in the field.
Jones et al.	2014	To present the effects of injections of fetal chorionic stem cells (CSCs) on reducing fractures, increasing bone ductility and volume, and other aspects in the treatment of OI.	There was bone growth, as well as increased volume and ductility. There was also an increase in hypertrophic chondrocytes, as well as endochondral and intramembranous ossification. The findings of the study suggest the emergence of chondrogenesis and osteogenesis by osteoblasts formed through the use of these cells.

Götherström et al.	2014	To report on the clinical evolution of patients with OI. They received MSCs before birth and postpartum infusions from the same donor.	The study indicates a likely clinical efficacy of the treatment where patients showed progress in reducing fractures and increased bone growth, although studies of this magnitude are still experimental.
Liu et al.	2014	To describe advances in animal studies and preliminary clinical studies from previous years related to treatment with MSCs.	No immune response against MSCs was observed. Up to that moment, more than 265 clinical trials had been conducted and registered by the regulatory agency. However, only 3 were for OI.
Wong	2011	To provide an overview of the benefits and drawbacks of using MSCs and their clinical implications.	The author lists 5 implications for the use of MSCs, including general treatment use, patients at risk of developing cancer, cancer patients, tumor modulation, and malignancy of MSCs in genetic manipulation.
Satija et al.	2009	To provide an overview of research involving the use of MSCs in regenerative medicine up to the present moment.	Clinical trials suggest the safe use of both autologous and allogeneic cells, but highlight concerns regarding their immunomodulatory and tumorogenic functions.
Undale et al.	2009	To update on the clinical applicability of MSCs for bone disease repair and metabolism.	The use of adult bone marrow-derived MSCs in clinical practice was being employed at that time as an innovative treatment for various dysfunctions, including fractures and many other metabolic bone diseases.
Chevrel et al.	2006	Introducing new treatment methods for OI beyond medications like bisphosphonates.	The approach with MSCs was still underutilized but considered a promising treatment option.
Kindler et al.	2006	To justify the use of MSCs and hematopoietic cells as therapeutic cells.	MSCs can be used as precursors to bone cells, as well as they act in immunoregulation, targeting only desired sites through antigen-dependent processes.
Le Blanc et al.	2005	To evaluate the transplantation of MSCs in a 32-week-old fetus.	There was improvement in the patient with severe OI. Trabecular bone organization was observed, and there was no immune response against the donor cells. Treatment was complemented with bisphosphonates, and at 2 years of age, her psychomotor development was considered normal.

Source: Personal archive.

4. Discussion

Osteogenesis Imperfecta (OI) is a genetic disorder characterized by bone fragility due to defects in type I collagen synthesis. Conventional treatment includes the use of bisphosphonates, but recent advances indicate that mesenchymal stem cells (MSCs) may offer a promising therapeutic approach. This review analyzes preclinical and clinical studies on the use of MSCs in the treatment of OI, comparing different strategies and their results. MSCs have osteogenic differentiation capacity and may contribute to bone formation and reduction of bone fragility in patients with OI. Their therapeutic potential is based on the replacement of defective osteoblasts and the secretion of trophic factors that promote tissue regeneration.

According to Sinder et al. (2020) local transplantation needs to inject MSCs directly into a local site, fracture or local bone fragility. An approach in an animal model, demonstrating structural and mechanical improvements in bone. It was demonstrated that direct transplantation of BMSCs into the femur of OIM mice resulted in robust engraftment of donor cells, with 18% of the endosteal surface covered by donor osteoblasts after one month. In addition, they observed significant improvements in cortical thickness, bone strength, and stiffness three months after transplantation. The study also highlighted the persistence of engrafted progenitor cells for up to six months, with the ability to differentiate into osteoblasts both in vitro and in vivo after secondary transplantation. These results suggest that local transplantation of BMSCs may be an effective strategy to improve bone structure and strength in patients with OI, although the local approach may have limitations in treating a systemic disease.

Meanwhile, Jones et al. (2014) focused on the systemic transplantation using placenta-derived early fetal chorionic stem cells (e-CSCs) to treat OI in a murine model. It was demonstrated that intraperitoneal injection of e-CSCs into neonatal mice with OI resulted in a significant reduction in fractures, increased bone ductility, and increased bone volume. Furthermore, the transplanted cells differentiated into osteoblasts and stimulated endogenous chondrogenesis and osteogenesis. These results suggest that e-CSCs have significant therapeutic potential, especially given their availability and lack of ethical restrictions, since they are obtained from the placenta during pregnancy.

Le Blanc et al. (2005) explored intrauterine transplantation in a human patient, showing the feasibility of fetal cell engraftment in an immunocompetent environment. These complementary studies suggest that while local transplantation may be effective in improving bone structure in specific areas, systemic transplantation, especially in the intrauterine setting, may offer broader benefits for patients with OI. On the other hand these authors have reported the first case of intrauterine transplantation of fetal MSCs in a human fetus with severe OI. The study demonstrated that allogeneic fetal cells, even in an immunocompetent and HLA-mismatched recipient, were able to engraft and differentiate into bone tissue. Analysis of bone biopsies revealed the presence of donor cells (0.3% to 7.4%) expressing osteogenic markers, such as osteocalcin and osteopontin, nine months after transplantation. Furthermore, there was no evidence of immune reaction against the donor cells, suggesting that fetal MSCs have immunomodulatory properties that facilitate their engraftment. The study also highlighted that complementary treatment with bisphosphonates may have contributed to the observed clinical improvement, although the exact role of donor cells in the OI phenotype remains to be further explored.

Infante et al. (2021) described a phase I clinical trial that investigated the repeated administration of MSCs in two pediatric patients with OI. The study demonstrated that sequential infusions of MSCs improved bone parameters and quality of life of patients, in addition to eliciting a pro-osteogenic paracrine response. The authors suggest that the beneficial effects of MSCs may be mediated by paracrine mechanisms, such as the secretion of factors that modulate the bone microenvironment, rather than a direct differentiation of the transplanted cells into osteoblasts. The study also highlighted the importance of continuous infusions to maintain clinical benefits, especially in patients with more severe forms of disease.

Infante et al. (2022) investigated the TGF-β pathway in pediatric patients with OI undergoing MSC therapy, demonstrating that patients with severe forms of the disease had elevated levels of circulating TGF-β and greater bioactivity of this pathway. After MSC therapy, there was a modulation in the expression and bioactivity of TGF-β, suggesting that cell therapy may positively influence bone homeostasis in these patients. These findings indicate that modulation of the TGF-β pathway may be a viable therapeutic strategy for the treatment of OI.

Furthermore, Arthur and Grönthos (2020) also discussed the use of genetically modified MSCs to express osteogenic factors such as BMP-6, which have shown efficacy in bone regeneration in vertebral fractures. The use of MSC-derived exosomes has also been mentioned as a cell-free approach to promote osteogenesis and angiogenesis, with promising results in non-union fracture models.

Ramesh et al. (2021), focused on the trophic effects of repeated administration of MSCs in children with OI. The authors discuss the TERCELOI study, which demonstrated that multiple administration of MSCs can induce pro-osteogenic effects through paracrine mechanisms, such as activation of TGF-beta and BMP signaling pathways. The article also mentions the BOOST2B study, which used fetal liver-derived MSCs and intraosseous administration, showing an increase in growth rate and improvement in quality of life of patients. However, the authors highlight the need for more evidence to confirm the long-term effects and safety of this approach.

Götherström et al. (2014) reported the clinical experience of pre- and postnatal transplantation of fetal MSCs in two patients with OI. The authors describe that prenatal transplantation of fetal MSCs was safe and resulted in clinical improvements, such as reduced fractures and increased linear growth. Furthermore, postnatal retransplantation with cells from

the same donor was feasible and associated with additional benefits. However, the engraftment levels of donor cells were low, suggesting that the therapeutic effects may be mediated by paracrine mechanisms rather than direct differentiation of the transplanted cells.

The study conducted by Westgren and Götherström (2015), explored the feasibility of MSC transplantation before birth as a therapeutic option for OI. The authors highlight that MSC transplantation can improve bone structure, fracture healing, and linear growth in patients with OI. However, the effects are transient, suggesting the need for retransplantation. The article also discusses the ethical and technical challenges associated with prenatal diagnosis and cell transplantation in fetuses, emphasizing the importance of additional studies to determine the clinical efficacy of this approach.

Lang, E., & Semon, J. A. (2023) provided a detailed review of preclinical and clinical studies that have investigated the use of MSCs in the treatment of OI, while Götherström et al. (2021), focused on ongoing clinical trials, such as BOOSTB4, which evaluates the safety and efficacy of fetal MSC transplantation in patients with OI.

Both studies agree that MSCs have a favorable safety profile and are well tolerated in clinical trials. Lang, E., & Semon, J. A. (2023) highlight that MSCs can be isolated from various sources, such as bone marrow, adipose tissue, and umbilical cord blood, and that these cells have been shown to be safe in several clinical applications. Götherström et al. (2021) emphasize that fetal MSCs have greater osteogenic and proliferative capacity compared to adult MSCs, which makes them promising candidates for the treatment of OI.

Götherström et al., (2021) analyzed pre-clinical cases of prenatal fetal MSC transplantation, showing that the treatment was safe and associated with clinical benefits, such as reduced fractures and improved growth. The BOOSTB4 study is a multicenter clinical trial that aims to evaluate the safety and efficacy of fetal MSC transplantation in patients with severe OI, both prenatally and postnatally.

Arthur and Grönthos (2020) reviewed the role of bone marrow MSCs (BMSCs) in bone regeneration, highlighting their osteogenic differentiation capacity, immunomodulatory properties, and paracrine effects. They emphasized that the combination of BMSCs with biomaterials, such as hydrogels and scaffolds, has shown encouraging results in the repair of fractures and bone defects, both in animal models and in clinical trials. For example, scaffolds composed of hydroxyapatite and tricalcium phosphate (β-TCP) have been used to deliver BMSCs to the injury site, promoting new bone formation and graft integration.

Kindler et al. (2006) address the use of HSCs and MSCs in cell therapies, used to promote bone regeneration in patients with osteogenesis imperfecta. The authors also discuss the generation of dendritic cells (DCs) from HSCs, which can be used to induce specific immune responses against tumors. In addition, the article mentions the possibility of genetically modifying MSCs to secrete therapeutic proteins, expanding their clinical potential. However, the authors warn of the need for further research to ensure the safety and efficacy of these approaches, especially regarding the use of viral vectors and the possible formation of teratomas.

Satija et al. (2009) focused specifically on MSCs, highlighting their plasticity and ability to differentiate into osteoblasts, chondrocytes, adipocytes, and even cardiac, hepatic, and neuronal cells. The authors discuss the use of MSCs in preclinical and clinical studies, including the treatment of osteogenesis imperfecta, myocardial infarction, and Graft-Versus-Host Disease (GVHD). They also address the genetic modification of MSCs to improve their differentiation and tissue targeting, as well as their use in tissue engineering. However, the authors highlight important challenges, such as the lack of specific markers to isolate pure MSCs, the low survival and engraftment of cells after transplantation, and the risk of malignant transformation after prolonged expansion in vitro. Furthermore, the article emphasizes the need for further studies to fully understand the mechanisms of action of MSCs and their interaction with the immune system.

According to Dinulescu et al., (2024) and Botor et al., (2021), the use of bisphosphonates is currently considered the gold standard in the treatment of OI. Highlight the initial efficacy of these drugs in increasing Bone Mineral Density (BMD) but emphasize the lack of consensus on optimal dosages and administration regimens, in addition to adverse effects. On the other hand, stem cell transplantation is discussed in depth by them who presented promising evidence from both murine studies and clinical trials with children. The article highlights that, despite the benefits in BMD and reduction in fracture rate, the duration of the therapeutic effect is still uncertain. Botor et al. (2021) also emphasizes the potential of stem cells, mentioning that their prenatal use can prevent early skeletal complications, although there are technical and ethical challenges associated with this approach.

Chevrel and Cimaz (2006), the authors review conventional treatments for OI, such as rehabilitation therapy and orthopedic surgery, and discuss the emerging use of bisphosphonates, particularly intravenous pamidronate, in children. They highlight that pamidronate reduces the incidence of fractures and increases Bone Mineral Density (BMD) in pediatric patients, but its effect in adults is not yet well established. In addition, the authors mention that although bisphosphonates are effective in reducing bone resorption, they do not have a significant impact on bone formation in adults, which may explain their lower efficacy in this population. The need for more controlled studies is emphasized, especially to determine the optimal dosage and duration of treatment.

According to Li et al. (2016) addresses a molecular perspective, focusing on the role of PEDF in the regulation of VEGF and its influence on the differentiation and mineralization of hMSCs. The authors demonstrate that PEDF increases the expression of VEGF in hMSCs, both in maintenance medium and during osteogenic differentiation. This increase is mediated by the ERK signaling pathway, suggesting that PEDF may modulate bone mineralization through the regulation of VEGF. Furthermore, the authors highlight that the balance between PEDF and VEGF is crucial for osteoblast differentiation and bone matrix mineralization. This finding is particularly relevant for OI type VI, where the lack of PEDF leads to severe defects in bone mineralization.

Götherström nd Walther-Jallow (2020) provided an overview of the use of MSCs in the treatment of OI, with a special focus on fetal MSCs. The authors discuss the advantages of fetal MSCs, such as greater proliferative and osteogenic capacity compared to adult MSCs. In addition, the article reviews preclinical and clinical studies supporting the use of MSCs in the treatment of OI, including prenatal and postnatal transplantation. The article also mentions the BOOSTB4 clinical trial, which is investigating the safety and efficacy of fetal MSCs in the treatment of severe forms of OI. The authors highlight that early treatment, especially in the prenatal period, may be more effective due to the rapid growth and immature immune system of the fetus, which may facilitate engraftment and distribution of the transplanted cells.

Both Infante et al. (2021) and Götherström and Walther-Jallow (2020) agree that MSCs have a favorable safety profile and may offer significant clinical benefits for patients with OI. However, while the study by Infante focuses on the repeated administration of MSCs and the underlying paracrine mechanisms, emphasizes the advantages of fetal MSCs and the importance of early treatment, including prenatal therapy. Both studies suggest that MSCs may be a promising therapeutic option for OI but highlight the need for further research to optimize the treatment protocol and fully understand the mechanisms of action.

Meanwhile, Liu et al. (2015), provided an overview of the use of MSCs in various bone diseases, including OI. The authors highlight that MSCs have anti-inflammatory and immunomodulatory properties, as well as the ability to differentiate into osteoblasts, which make them promising candidates for the treatment of bone diseases. In the case of OI, preclinical and clinical studies have shown that MSCs transplantation can improve bone density and reduce the incidence of fractures. However, the authors also point out that the long-term efficacy and exact mechanisms of action of MSCs are not yet fully understood.

Despite promising results, several challenges remain. The long-term efficacy of MSCs therapy is still uncertain, and optimal administration protocols need to be established. Additionally, ethical and technical challenges associated with prenatal transplantation require further investigation.

In conclusion, MSCs represent a promising therapeutic option for OI, with potential benefits in bone structure, fracture reduction and growth improvement. However, further research is needed to optimize treatment protocols, understand the underlying mechanisms and address the challenges associated with their use.

5. Final Considerations

The use of Mesenchymal Stem Cells (MSCs) in the treatment of Osteogenesis Imperfecta (OI) has shown promising results. Preclinical and clinical studies suggest that MSCs have the potential to improve bone density, reduce the number of fractures, and promote greater bone growth in OI patients. This potential is based on the ability of MSCs to differentiate into osteoblasts, for example, as well as their immunomodulatory, anti-inflammatory, and regenerative properties.

There is an advantage in using these cells, which is their ability to be obtained from various sources such as bone marrow, adipose tissue, umbilical cord, and even teeth. This diversity of sources offers a range of variations to tailor treatments according to the needs and characteristics of each individual.

Despite potential benefits, there are challenges and limitations associated with the use of MSCs in OI. Long-term safety, treatment consistency across different OI subtypes, optimization of cell culture and differentiation conditions, and the development of effective delivery methods are among these challenges.

More randomized controlled clinical studies are needed to assess the long-term safety and efficacy of MSC transplantation in OI therapy. Additional research is also needed to better understand the mechanisms underlying the effects of MSCs, identify treatment response markers, and optimize cell therapy strategies.

The therapy of OI with MSCs should be part of a multidisciplinary approach, integrating pharmacological therapies, rehabilitation, and orthopedic care to provide comprehensive and individualized treatment for patients.

The therapeutic potential of these cells lies not only in their ability to differentiate into osteogenic cells but also in their ability to modulate the inflammatory response by reducing the immune response and promoting tissue regeneration.

Therefore, the use of Mesenchymal Stem Cells represents a promising alternative in the treatment of Osteogenesis Imperfecta, with the potential to improve quality of life and reduce complications associated with the disease.

References

Anima. (2014). Manual de revisão bibliográfica sistemática integrativa: uma pesquisa baseada em evidências. Grupo Anima. https://biblioteca.cofen.gov.br/wp-content/uploads/2019/06/manual_revisao_bibliografica-sistematica-integrativa.pdf.

Arthur, A., & Gronthos, S. (2020). Clinical application of bone marrow mesenchymal stem/stromal cells to repair skeletal tissue. Em International Journal of Molecular Sciences, 21(24), 1–27.

Botor, M., Fus-Kujawa, A., Uroczynska, M., Stepien, K. L., Galicka, A., Gawron, K., & Sieron, A. L. (2021). Osteogenesis imperfecta: Current and prospective therapies. Em Biomolecules, 11(10).

Chevrel, G., Cimaz, R. (2006). Osteogenesis Imperfecta: New Treatment Options. Current Rheumatology Reports 8(6) 473-479.

Crossetti, MGM (2012). Revisão integrada da investigação em enfermaria com o rigor científico exigido. Rev. Gaúcha Enferm. 33(2): 8-9.

Dinulescu, A., Păsărică, A. S., Carp, M., Duşcă, A., Dijmărescu, I., Pavelescu, M. L., Păcurar, D., & Ulici, A. (2024). New Perspectives of Therapies in Osteogenesis Imperfecta—A Literature Review. Em Journal of Clinical Medicine (Vol. 13, Número 4). Multidisciplinary Digital Publishing Institute (MDPI).

Götherström, C., David, A. L., Walther-Jallow, L., Åström, E., & Westgren, M. (2021). Mesenchymal Stem Cell Therapy for Osteogenesis Imperfecta. Clinical Obstetrics & Gynecology, 64(4), 898–903.

Götherström, C., & Walther-Jallow, L. (2020). Stem Cell Therapy as a Treatment for Osteogenesis Imperfecta. Em Current Osteoporosis Reports 18(4), 337–343. Springer.

Götherström, C., Westgren, M., Shaw, S. W. S., Åström, E., Biswas, A., Byers, P. H., Mattar, C. N. Z., Graham, G. E., Taslimi, J., Ewald, U., Fisk, N. M., Yeoh, A. E. J., Lin, J.-L., Cheng, P.-J., Choolani, M., Le Blanc, K., & Chan, J. K. Y. (2014). Pre- and Postnatal Transplantation of Fetal Mesenchymal Stem Cells in Osteogenesis Imperfecta: A Two-Center Experience. Stem Cells Translational Medicine, 3(2), 255–264.

Infante, A., Cabodevilla, L., Gener, B., & Rodríguez, C. I. (2022). Circulating TGF-β Pathway in Osteogenesis Imperfecta Pediatric Patients Subjected to MSCs-Based Cell Therapy. Frontiers in Cell and Developmental Biology, 10.

Infante, A., Gener, B., Vázquez, M., Olivares, N., Arrieta, A., Grau, G., Llano, I., Madero, L., Bueno, A. M., Sagastizabal, B., Gerovska, D., Araúzo-Bravo, M. J., Astigarraga, I., & Rodríguez, C. I. (2021). Reiterative infusions of MSCs improve pediatric osteogenesis imperfecta eliciting a pro-osteogenic paracrine response: TERCELOI clinical trial. Clinical and Translational Medicine, 11(1).

Jones, G. N., Moschidou, D., Abdulrazzak, H., Kalirai, B. S., Vanleene, M., Osatis, S., Shefelbine, S. J., Horwood, N. J., Marenzana, M., De Coppi, P., Bassett, J. H. D., Williams, G. R., Fisk, N. M., & Guillot, P. V. (2014). Potential of human fetal chorionic stem cells for the treatment of osteogenesis imperfecta. Stem Cells and Development, 23(3), 262–276.

Kindler, V., Suva, D., Soulas, C., & Chapuis, B. (2006). Hematopoietic stem cells and mesenchymal stem cells as tools for present and future cellular therapies. Swiss Medical Weekly, 333–337.

Lang, E., & Semon, J. A. (2023). Mesenchymal stem cells in the treatment of osteogenesis imperfecta. Em Cell Regeneration, 12(1). Springer.

Le Blanc, K., Götherström, C., Ringdén, O., Hassan, M., McMahon, R., Horwitz, E., Anneren, G., Axelsson, O., Nunn, J., Ewald, U., Nordén-Lindeberg, S., Jansson, M., Dalton, A., Åström, E., & Westgren, M. (2005). Fetal mesenchymal stem-cell engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. Transplantation, 79(11), 1607–1614.

Li, F., Armstrong, G. B., Tombran-Tink, J., & Niyibizi, C. (2016). Pigment Epithelium Derived Factor upregulates expression of Vascular Endothelial Growth Factor by human Mesenchymal Stem cells: Possible role in PEDF regulated matrix mineralization HHS Public Access. Biochem Biophys Res Commun, 478(3), 1106–1110.

Liu, Y., Wu, J., Zhu, Y., & Han, J. (2014). Therapeutic application of mesenchymal stem cells in bone and joint diseases. Em Clinical and Experimental Medicine, 14(1), 13–24).

Pereira, A.S et al. (2018). Metodologia da pesquisa científica. [e-book gratuito]. Editora. UAB/NTE/UFSM.

Undale, A., Westendorf, J., Yaszemski, M., Khosla, S. (2009). Mesenchymal stem cells for bone repair and metabolic bone diseases. Mayo Clinic Proceedings. 84(10) 893-902.

Ramesh, S., Daniel, D., Götherström, C., & Madhuri, V. (2021). Trophic effects of multiple administration of mesenchymal stem cells in children with osteogenesis imperfecta. Clinical and Translational Medicine, 11(4).

Satija, N. K., Singh, V. K., Verma, Y. K., Gupta, P., Sharma, S., Afrin, F., Sharma, M., Sharma, P., Tripathi, R. P., & Gurudutta, G. U. (2009). Mesenchymal stem cell-based therapy: A new paradigm in regenerative medicine. Journal of Cellular and Molecular Medicine, 13(11–12), 4385–4402.

Sinder, B. P., Novak, S., Wee, N. K. Y., Basile, M., Maye, P., Matthews, B. G., & Kalajzic, I. (2020). Engraftment of skeletal progenitor cells by bone-directed transplantation improves osteogenesis imperfecta murine bone phenotype. Stem Cells, 38(4), 530–541.

Snyder, H. (2019). Revisão de literatura como metodologia de pesquisa: visão geral e diretrizes. Jornal de pesquisa empresarial, 104, 333-339.

Westgren, M., & Götherström, C. (2015). Stem cell transplantation before birth - a realistic option for treatment of osteogenesis imperfecta? Prenatal Diagnosis, 35(9), 827–832.

Wong, R. S. Y. (2011). Mesenchymal stem cells: Angels or demons? Em Journal of Biomedicine and Biotechnology (Vol. 2011).