ARTIGO DE REVISÃO

ADVEMENTS IN OSTEOGENESIS IMPERFECTA TREATMENT:
FROM GENETICS TO PERSONALIZED THERAPIES

Avanços no tratamento da osteogênese imperfecta: da genética às terapias personalizadas

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ABSTRACT

Osteogenesis imperfecta (OI) is a complex genetic disorder characterized by fragile bones and frequent fractures. It is primarily caused by mutations affecting collagen type I production. Recent advancements in genetic research have identified multiple genes involved in the disorder, broadening the scope of potential targeted therapies. This narrative review synthesizes the latest developments in the management and treatment of OI, focusing on personalized therapeutic interventions. OI is classified into several types based on genetic mutations, each with distinct clinical manifestations. Most cases are linked to mutations in the COL1A1 and COL1A2 genes, which directly affect collagen quality and the bone matrix structure. Emerging therapies explored in this review include bisphosphonates, genetic engineering techniques such as CRISPR/Cas9, and novel pharmacological agents targeting specific molecular pathways involved in bone metabolism and repair. Recent studies have shown promising results in using gene therapy to correct defective genes and employing targeted drug therapies to modulate bone formation and resorption processes. These advancements underscore the potential of personalized medicine in providing more effective management strategies for patients with OI. The genetic heterogeneity of OI necessitates a multifaceted approach to treatment that encompasses both the correction of genetic defects and the modulation of bone metabolism pathways. Innovations in genetic engineering and drug therapy are paving the way for more tailored and effective treatments, which promise to significantly improve the quality of life for individuals with OI. Ongoing research and clinical trials are crucial for furthering our understanding of the disease mechanisms and developing safer, more effective therapeutic options.

Palavras-chave: Osteogenesis imperfecta; genetic disorder; collagen-related gene mutations; personalized treatment; genetic engineering.

RESUMO

A osteogênese imperfeita (OI) é uma doença genética complexa caracterizada por ossos frágeis e fraturas frequentes. É causada principalmente por mutações que afetam a produção de colágeno tipo I. Avanços recentes na pesquisa genética identificaram múltiplos genes envolvidos na doença, ampliando o escopo de possíveis terapias direcionadas. Esta revisão narrativa sintetiza os mais recentes desenvolvimentos no manejo e tratamento da OI, com foco em intervenções terapêuticas personalizadas. A OI é classificada em vários tipos com base em mutações genéticas, cada uma com manifestações clínicas distintas. A maioria dos casos está ligada a mutações nos genes COL1A1 e COL1A2, que afetam diretamente a qualidade do colágeno e a estrutura da matriz óssea. As terapias emergentes exploradas nesta revisão incluem bifosfonatos, técnicas de engenharia genética, como CRISPR/Cas9, e novos agentes farmacológicos direcionados a vias moleculares específicas envolvidas no metabolismo e reparo ósseo. Estudos recentes mostraram resultados promissórios no uso da terapia genética para corrigir genes defeituosos e no emprego de terapias medicamentosas direcionadas para modular os processos de formação e reabsorção óssea. Estes avanços sublinham o potencial da medicina personalizada no fornecimento de estratégias de gestão mais eficazes para pacientes com OI. A heterogeneidade genética da OI necessita de uma abordagem multifacetada de tratamento que englobe tanto a correção de defeitos genéticos quanto a modulação das vias do metabolismo ósseo. As inovações na engenharia genética e na terapia medicamentosa estão a abrir caminho para tratamentos mais personalizados e eficazes, que prometem melhorar significativamente a qualidade de vida dos indivíduos com OI. A investigação e os ensaios clínicos em curso são cruciais para aprofundar a nossa compreensão dos mecanismos da doença e desenvolver opções terapêuticas mais seguras e eficazes.

Keywords: Osteogênese imperfecta; desordem genética; mutações genéticas relacionadas ao colágeno; tratamento personalizado; Engenharia genética.

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BACKGROUND

Osteogenesis imperfecta (OI), a genetic disorder influencing bone integrity, arises from mutations affecting collagen production and bone health. Collagen, particularly type I, is crucial in bone strength and resilience. The discovery of numerous genes associated with OI over the past two decades has significantly enhanced understanding of this disorder. Novel classification systems categorize OI into at least four mutation-based types, each presenting unique clinical and hereditary characteristics, which help differentiate individual variations and manage the disease more effectively.

Mutations in the COL1A1 and COL1A2 genes are identified as the most common causes, accounting for most diagnosed cases. These genetic abnormalities impact the quality and function of collagen and the entire bone matrix assembly, leading to varying degrees of bone fragility and systemic manifestations. Additional genes like CRTAP, LEPRE1, and PPIB, among others, contribute to the complexity of OI by influencing collagen post-translational modifications and bone cell signaling pathways.

The heterogeneity of OI presents challenges in clinical management and emphasizes the necessity for personalized treatment strategies. Recent advancements in genetic research and therapeutic technologies offer the potential for tailored treatments based on specific genetic profiles, thereby promising improved patient outcomes.

This narrative review explores the implications of these genetic insights and their translation into innovative treatment approaches, focusing on recent developments in genetic engineering, pharmacotherapy, and the combined therapeutic strategies enhancing both the understanding and management of osteogenesis imperfecta.

INTRODUCTION

Over the past two decades, there have been significant discoveries of approximately twenty novel genes associated with the regulation and function of collagen, mainly type I collagen, and other aspects of bone biology (1). Novel classification systems for Osteogenesis Imperfecta (OI) types have been introduced, leveraging clinical and genetic observations of affected individuals. These systems categorize OIs into at least four distinct mutation-based types, each with unique patterns and hereditary characteristics defining individual variation. The original classification of OI (type I) is characterized by a blue sclera and static disease progression, while type II OI is characterized by severe bone fragility and pronounced deformities. Type III, on the other hand, is characterized by progressive bone distortions and limited stature. Moreover, type IV fractures are characterized by severe bone fragility, albeit with a normal sclera (2). These new insights have revolutionized the understanding of diseases such as OI,
interpreting clinical cases through intrinsic genetics and enabling researchers to identify crucial links for understanding this syndrome via the biochemical profile of each type.

In light of these developments, genetic collagen disorders, especially OI, represent a heterogeneous group of hereditary conditions affecting the structure, genetic expression, and function of this vital bone matrix protein essential for bone integrity and resilience. Among its causes, mutations in the COL1A1 and COL1A2 genes are widely recognized as the most common causes of OI, accounting for more than 85% to 90% of diagnosed cases (3). These mutations are responsible for OI types I, II, III, and IV emergence.

However, beyond these mutations, a broad spectrum of other genetic alterations also contributes, albeit at lesser frequencies, to the manifestation of this condition. These genetic variations can impact collagen folding and assembly machinery components, directly interfering with essential tissue processes through posttranslational modifications of collagen. Examples include CRTAP, LEPRE1, PPIB, FKBP10, and SERPINH1 (4). Furthermore, genes related to bone formation, such as SP7, bone cell signaling genes such as SERPINF1 and WNT1, and a specific cation channel named TMEM38B, along with the IFITM5 gene, play roles in this pathogenesis (5).

Although correlations between the causative OI genotype and the presented phenotype are not fully established, understanding these generalizations can provide crucial insights for diagnosing and treating these complex and diverse conditions. Specific mutations can result in milder or more severe phenotypes, depending on their origins (5).

It is worth noting that this phenotype can be discerned at approximately one and a half months of age, a previously unexplored aspect. Bone fragility becomes more apparent at approximately nine weeks of age. This information indicates that the change in phenotype between weeks 6 and 9 is primarily linked to the weakening of bone properties. This influence arises from three factors: (1) cortical bone size and shape differences between normal bones and those with COL1A2+/p. The G610C mutation did not worsen over time, (2) the proportion of defective mineral matrix increased with age, and (3) the difference in bone strength persisted even after adjusting for bone size (6).

In this context, another causative mutation of OI is +/G610C Neo (G610C). This mutation occurs in the alpha-2 chain of type I collagen and involves the substitution of a glycine residue with a cysteine residue. This alteration, the α-2(I) G610C mutation, leads to a dominant form of OI and interferes with the structure of the collagen triple helix (7). Consequently, misfolded collagen trimers accumulate in the endoplasmic reticulum, resulting in stress within this organelle (5).

It is currently understood that a significant difference exists between genotypes
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and phenotypes of osteogenesis, particularly in rodent models with OI deformities (OIM). The alpha-2 chain of type I collagen is modified in rodents, affecting the formation of type I collagen. Heterozygous (OIM/+ ) rodents can experience fractures due to reduced trabecular disposition. Homozygosity (OIM/OIM) is responsible for OI type III, while wild-type (+/+ ) rodents do not exhibit significant alterations (8,9).

These findings have led to significant advances in understanding collagen-related diseases and their mechanisms, which impact bone health and integrity. This progress opens new avenues for early diagnosis, personalized treatments, and the development of more effective therapies to enhance the quality of life for patients affected by these conditions. In this context, this review aims to describe current innovative therapies for OI and their clinical implications.

RESULTS AND DISCUSSION

Initially, 97 relevant articles were identified. After screening, the titles and abstracts of 78 articles were assessed, and 28 were chosen for full-text examination. Following a thorough analysis, 26 articles were selected for inclusion in the review (see Figure 1).

Background and Current Situation in OI Treatment

Throughout history, researchers have presented a wide range of treatment options for Osteogenesis Imperfecta, seeking an optimal approach for this condition. Some of these treatments have demonstrated varying degrees of efficacy. This diversity of options creates

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Figure 1: Flowchart illustrating the article selection process.

Source: Primary Data (2023).

1. Identification
2. Title and eligibility
3. Included

(osteogenesis imperfecta AND treatment AND collagen)

Pubmed (n=95)  SciELo (n=2)

Total number of papers found (n=97)

Articles selected through inclusion and exclusion criteria (n=19)

Selected articles (n=78)

Duplicates (n=1)
Paper excluded after reading title and abstract (n=49)

Complete papers for eligibility (n=28)

Articles selected through inclusion and exclusion criteria (n=2)

Study included in this review (n=26)
uncertainty about the best therapeutic strategy for treating OI.

Concurrently, experts also recommend complementary treatment approaches, such as sunlight exposure, calcium and vitamin D supplementation, and physical activity.

### Bisphophonates: Fortifying Bone Resilience

**The impact of pamidronate**

Pamidronate, a stalwart bisphosphonate, has been a pillar in OI treatment for numerous years. A study led by Choi et al. bolsters the efficacy of this drug, forging connections between disease genotype and bisphosphonate utilization\(^{(10)}\). According to the study, patients bearing qualitative mutations experienced a notable decrease in fracture incidence and a surge in lumbar bone mineral density after pamidronate treatment. This study revealed that individuals with qualitative mutations (p.G560S in COL1A1 and p.G565A in COL1A2) exhibit better responses to therapy than their quantitative mutation counterparts. Qualitative mutations correlate with graver clinical symptoms, providing insight for enhanced treatment paradigms in OI.

### Striking a Balance: Zoledronate and Raloxifene Symphony

Studies investigated the fusion of bisphosphonate zoledronate and raloxifene to combat osteoporosis in women\(^{(11)}\). Zoledronate enhanced bone density, while raloxifene, a selective estrogen receptor modulator, promoted bone hydration via collagen interplay. One hypothesis underpinned the study: merging these drugs could offset each other’s shortcomings, culminating in heightened efficacy. Male wild-type (WT) mice and their heterozygous Osteogenesis Imperfecta (OIM+/-) counterparts were used to test this hypothesis. Our findings shed light upon the significance of early classification of the Osteogenesis Imperfecta type to improve treatment selection. WT mice bearing qualitative mutations registered no substantial shifts after drug administration. Conversely, OIM+/− mice, which exhibit quantitative mutations, responded positively to therapeutic intervention\(^{(12)}\).

### Personalized Precision: Tailoring Treatment for Optimal Resilience

This tapestry of revelations intimates that precise treatment selection is the linchpin, given the uniqueness characterizing each patient’s ailment, fostering more efficacious combat against osteoporosis\(^{(13,14)}\).

### Refined Approach: An Analog’s Promise

Despite the merits of raloxifene, its side effects, including its affinity for estrogen receptors, hot flashes, and thrombosis, hinder its application. Mounting a counteroffensive, Powell et al. engineered an analog of the drug, replacing the 6-hydroxyl radical with a 6-methoxyl group\(^{(11)}\). This blueprint was subjected to in vitro
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and in vivo examinations in marshaling female WT and OIM+/- mice (Murine Model of Osteogenesis Imperfecta). The results revealed that the raloxifene analog mirrored the effects of the original raloxifene, albeit with less influence on estrogen receptors, thereby circumventing undesirable side effects. This breakthrough suggests that amalgamating a raloxifene analog with zoledronate could herald a promising course in osteoporosis treatment (12).

Harnessing the TGF-β Mechanism

A contemporary widely explored avenue involves inhibiting growth factor β (TGF-β) in patients with osteogenesis imperfecta. Osteoclasts release this factor to stimulate bone resorption, disrupting its signaling in the context of OI. By obstructing this activity, bone deposition is enhanced, while exacerbated TGF-β expression is linked to bone remodeling and reduced bone mass (15). This approach holds promise for potential therapies for OI treatment.

Untangling TGF-β’s Code

A study conducted by Greene et al. investigated the inhibition of TGF-β growth factor signaling using a pan-specific murine neutralizing antibody, 1D11, in mice bearing recessive, dominant G610C, and WT (control) osteogenesis imperfecta mutations. The results revealed that WT mice responded positively to treatment, while OI mice of other types did not respond favorably. Nevertheless, the TGF-β inhibition pathway displayed promise, holding the potential to lead patients closer to normal bone remodeling (16).

Fine-Tuning TGF-β for Optimal Impact

Tauer et al. examined TGF-β signaling pathways in WT, CRTAP -/-, +/G610C, and COL1A1 Jrt/+ mice (17). Remarkable TGF-β over signaling was observed in the latter group. The use of 1D11 caused bleeding and fatalities in some WT and COL1A1 Jrt/+ mice, indicating potential dosing errors, such as excessive antibody-caused epithelial hyperplasia.

WT mice showed more favorable responses to treatment, while CRTAP and +/G610C mice also exhibited improvements. Conversely, COL1A1 Jrt/+ mice showed limited progress, consistent with the findings of Lonning et al. (18).

Rebalancing Bone Quality: Tapping LRP5 and TGF-β

Kaupp et al. embarked on a combined therapy study using enhanced LRP5 gene signaling and TGF-β inhibition in OI patients (19). The theory was that heightened LRP5 gene signaling, which is responsible for bone mineralization, fortifies bones. At the same time, TGF-β inhibition enhances bone quality, as the former is pro-anabolic and the latter is anti-resorptive.

However, anabolic therapies involving LRP5 and the anticatabolic neutralization of TGF-β showed varying effects across different OI mouse models: WT mice demonstrated positive effects, whereas G610C OI carriers did not respond, consistent with the findings of Boyden et al. (20).
Unleashing Myostatin Potential

In their study, Omosule et al. inhibited myostatin, a TGF-β superfamily cytokine, in OI mice using both pharmacological and postnatal genetic approaches with an antimyostatin monoclonal antibody (Regn647) \(^{(21)}\). The results indicated increased muscle mass in both types of OI (Wt and +/G610C) mice with both treatments. However, significant bone volume and strength improvements were observed only in +/G610C mice when myostatin inhibition was genetically induced. Furthermore, only male WT mice showed enhanced bone mass and strength.

The influence of myostatin

Jeong et al. inhibited postnatal myostatin in +/G610C and oim/oim OI mice, employing soluble activin type IIB receptor-mFc fusion protein (sActRIIB-mFc) \(^{(22)}\). Treatment enhanced the bone phenotype in +/G610C mice, increasing the number of osteoblasts and reducing the number of osteoclasts. However, the effects in oim/oim mice were less pronounced, potentially because of the affinity of activin A for the ActRIIB receptor, possibly affecting outcomes.

In Omosule et al.’s study, the musculoskeletal effects of myostatin and activin A inhibition were examined in OI WT and +/G610C mice using specific monoclonal antibodies \(^{(23)}\). Beyond earlier findings (Omosule et al. in 2022), additional conclusions surfaced \(^{(21)}\). Inhibition of activin A alone was detrimental to bone strength in male +/G610C and female WT mice. Nonetheless, significant benefits, including enhanced bone biomechanics, have emerged combined with myostatin inhibition. This synergy suggests avenues worth exploring individually and in tandem as therapies for OI. This study paves the way for future research on more effective therapeutic strategies for OI.

Denosumab: A Dual-Edged Sword

Denosumab, a neutralizing anti-RANKL antibody known for mediating osteoclastogenesis and osteoclast survival, has been used since 2010 for treating postmenopausal osteoporosis in women \(^{(24,25)}\).

In 2019, Hoyer-Kuhn et al. conducted exploratory research on the use of Denosumab for treating OI in children \(^{(26)}\). However, it is crucial to note that this use lacks official approval and is not advised for children due to the lack of studies addressing treatment duration and appropriate dosing. Furthermore, prior reports indicated severe side effects \(^{(27–29)}\). Research on 7 COL1A1-type and 3 COL1A2-type OI children yielded inconclusive yet promising results. This raised questions about the treatment mechanism and administration, particularly to avert potential clinical issues related to high doses.

On the other hand, Kobayashi et al. reported a case series on long-term denosumab use in 8 patients with osteoporotic OI, including 6 COL1A1-type patients and 2 unidentified patients \(^{(30)}\). The outcomes were encouraging, with nearly 90% of patients avoiding multiple fractures.
during the study. This finding underscores the promise of Denosumab for OI treatment, although further research is needed to grasp its effectiveness and safety better.

**Endoplasmic reticulum stress (ER stress) and potential therapies**

**Illuminating ER stress: unfolding the path**

Endoplasmic reticulum (ER) autophagy induction has emerged as a promising avenue for treating OI. Within this context, a syndrome of unfolded protein response (UPR) ensues due to flawed collagen, fostering inadequate chaperone activity and abnormal pro-collagen accumulation in the ER lumen. This contributes to the pathogenesis of OI \[29\].

**Rapamycin’s Quest: Seeking ER Autophagy Enhancement**

Bateman et al. studied rapamycin, an immunosuppressant that promotes ER autophagy, in mice bearing the α2(I)-G610C OI type \[5\]. The intent was to resolve the UPR. However, the intricate and inconclusive outcomes suggest that mTOR depends on this pathway. This complexity connects rapamycin-induced apoptosis and altered mTOR signaling. This recommendation is echoed to target more precise pathways in upcoming experiments.

**Unveiling Challenges: Carbamazepine’s Trial**

In parallel, Blank et al. investigated carbamazepine, an autophagy stimulant for malformed collagen, to ameliorate skeletal pathology in COL1A2+/p. G610C OI \[6\]. Surprisingly, the endeavor hampered healthy bones, detrimentally affecting guinea pig bone’s lateral and transverse growth.

**ER Autophagy: The Promising Frontier**

Although the induction of ER autophagy is promising for OI treatment, the landscape is complicated and complex. Grasping these intricate pathways and pinpointing specific targets remain paramount to ensure the efficacy and safety of future treatments \[27,29\].

**4-Phenylbutyric Acid (4-PBA): Navigating Potential**

The induction of ER autophagy via strategies such as 4-PBA and rosemary extract represents a promising frontier in OI treatment. Diverse authors have unraveled compelling results \[31–33\].

**Unraveling the Labyrinth: ER Autophagy Mechanics**

The autophagy system is complex and orchestrated by an orchestra of proteins tethered to autophagy genes. Grasping these mechanics is a challenging endeavor. However, these approaches have shown efficacy in mitigating ER stress and enhancing the OI phenotype in study models \[34,35\].
Onward Quest: Paving the Path for Clinical Application

Further studies could guide our understanding of these pathways and their clinical applicability. Unceasing research will unveil how ER autophagy induction can be harnessed as a therapeutic weapon to heal or alleviate the impact of OI, championing the cause for patients experiencing this condition.

Genetic Engineering: Pioneering Osteogenesis Imperfecta Treatment

Genetic Engineering’s Prime Role

Genetic engineering has emerged as the most promising avenue for addressing OI. Many studies have explored various methods, such as gene silencing and mesenchymal cell application, to correct the underlying cause of OI.

Exploring the Genetic Frontier

A seminal study by Tauer et al. examined the viability of isolating adipose tissue-derived stem cells from OI patients. Although complex, this biological material holds the key to future research endeavors.

CRISPR/Cas9’s Precision: A Game-Changer

Jung et al. harnessed induced pluripotent stem cells (iPSCs) derived from patients for in vitro gene mutation correction via CRISPR/Cas9. iPSC differentiation into osteoblasts successfully rectified mutations in the COL1A1 and COL1A2 genes associated with defective α collagen chain production in OI, restoring normal collagen I expression and osteogenic capacity. Given the genotypic-phenotypic heterogeneity of OI, they highlighted the complexity of treatment choice.

NELL1’s Promise: Fusing Potential

Liu et al. explored recombinant mouse NELL1 protein (rmNELL1) coupled with adipose-derived stem cells (ADSCs) or genetically modified ADSCs and showed improved gene expression in OI. Systemic administration yielded promising results, facilitating bone formation in the tested mice.

Silencing Gene Defects: Paving the Way

Marueli et al. silenced the COL1A2 allele in COL1A2 +/- mice, attenuating their bone phenotype. Efficiently suppressing COL1A2 expression using a specific siRNA promoted normal collagen formation and improved gene expression.

Mesenchymal Marvels: Pioneering Progress

Sinder et al. transplanted healthy donor bone marrow stem cells (BMSCs) into OI mice, yielding healthy bone matrix after months. This promising treatment controls the OI phenotype, highlighting its potential.
Clinical Leaps: Advancing OI Treatment

Clinical studies, such as those of Infante et al. have shown that the safe administration of mesenchymal stem cells (MSCs) to OI patients improves bone parameters over 2 years \(^{(42)}\). A subsequent study revealed that TGF-β superactivation in severe OI patients was successfully inhibited by MSC therapy \(^{(43)}\). However, the efficacy of these treatments varies based on mutation type, suggesting that genotyping could guide personalized TGF-β treatments.

Conclusion and Future Prospects

Genetic engineering has revolutionized OI treatment. The arsenal of approaches, from iPSCs to gene silencing, has shown exciting results. Rigorous studies have illuminated the potential of engineered solutions, but the road ahead demands in-depth research and translation into clinical practice. As complexity permeates, collaboration among scientists, medical professionals, and patients remains paramount for successful outcomes.

CONCLUSIONS

This research encompassed a wide array of treatments for OI, a condition affecting bone health due to genetic mutations. Through the analysis of various studies and approaches, it becomes evident that OI is a complex condition requiring a multifaceted treatment strategy. This review highlighted several methods, including using bisphosphonates, inhibiting TGF-β growth factor, myostatin inhibition, denosumab therapy, induction of ER autophagy, and even genetic engineering.

While standard treatment with bisphosphonates such as pamidronate has been widely employed and offered by healthcare systems, alternative approaches such as TGF-β inhibition have shown promising results in restoring normal bone formation. Myostatin inhibition also appears promising, particularly when combined with other strategies. Furthermore, Denosumab therapy and the induction of ER autophagy have also been explored, albeit with complexities and challenges.

Genetic engineering has emerged as an advanced and promising approach to correct the underlying mutations causing OI. Studies utilizing corrected iPSCs via CRISPR/Cas9, stimulation of proteins such as NELL1, and specific gene silencing are underway. The genetic engineering approach appears particularly promising because it has the potential to rectify the root cause of OI rather than merely address symptoms.

However, despite promising advancements, many of these treatments are still in experimental stages, and numerous details need to be refined before they can become viable treatment options for OI patients.
The complexity of the condition and genetic variability pose challenges in pursuing more effective treatments.

Therefore, this research underscores the continuous importance of scientific investigation and the development of personalized treatments for OI patients. Through diversified approaches, ranging from pharmacological treatments to innovative genetic therapies, the goal is to eventually provide OI patients with an improved quality of life and the possibility of an effective cure.

METHODS

This narrative review was conducted based on articles from the PubMed and SciELO databases. The utilized descriptors were osteogenesis imperfecta AND treatment AND collagen. The search encompassed full-text articles in Portuguese, English, and Spanish, with the publication period spanning from 2018 to June 2023.

The article selection process was carried out double-blind using the Rayyan platform for systematic reviews and literature analysis (available at https://www.rayyan.ai/). Subsequently, the Mendeley platform was employed for the comprehensive reading of the selected articles (available at https://www.mendeley.com/).

REFERÊNCIAS

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Observação: os/(as) autores/(as) declaram não existir conflitos de interesses de qualquer natureza.