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Review

The efficacy of mesenchymal stem cells in regenerating structures associated with the temporomandibular joint: A systematic review

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ABSTRACT

Objectives: The objective of this systematic review is to evaluate the role of mesenchymal stem cells in the regenerative treatment of temporomandibular joint resorption.
Design: Search strategies were performed in the following databases: PubMed/MEDLINE, EMBASE, Cochrane Collaboration Library, and Web of Science. Two independent reviewers selected the included articles using a two-phase process based on the eligibility criteria. The reviewers independently collected the required information from the included articles. The methodological quality of the selected studies was assessed individually.
Result: In accordance with the inclusion and exclusion criteria, 703 studies were found and 8 articles were included. Thus, six studies using animal models and two human studies were included in this systematic review.
Conclusion: Based on the data of our systematic review, the use of mesenchymal stem cells is a promising method for the repair and regeneration of temporomandibular joint components.

1. Introduction

The continuous remodeling of tissues that make up the temporomandibular joint provides the capacity of long-term adaptation in a homeostatic medium (He, Ji, Du, Xu, & Luo, 2019). However, when the stimulus exceeds the adaptive capacity of the temporomandibular joint, resorption of the temporomandibular joint structure starts. This debilitating pathological process often results in fibrillation and subsequent degradation of the surrounding joint surface, which may also involve the subchondral bone (Chigurupati & Mehra, 2018; Nogami et al., 2017).

The resorption of the temporomandibular joint can be triggered by intrinsic mechanisms of the stomatognathic system, by accidents or even by orthognathic surgery of the jaws. Other risk factors are hormonal (estrogen and 17β-estradiol deficiency) and nutritional imbalances (vitamin D deficiency) (Gunson, Arnett, & Milam, 2012; Mercuri & Handelman, 2020).

Despite the development of different methods for the treatment of pathological processes associated with the resorption of temporomandibular joint components, patients with severe degenerative changes in the temporomandibular joint do not respond to conservative treatments and invasive surgical interventions are generally required (de Souza Tesch et al., 2018; Mercuri & Handelman, 2020). Regenerative medicine is a promising approach that can benefit patients with injuries that are difficult to manage clinically, such as condylar resorption, and has shown significant potential in the regeneration of bone and cartilage structures (Lalu et al., 2012; Squillaro, Peluso, & Galderisi, 2016).

In the last decades, different cell lines have been used for regenerative therapies in animal studies and in preclinical/clinical trials (de Souza Tesch et al., 2018; Squillaro et al., 2016). Among these cell lines, multipotent adult stem cells and/or cells differentiated from mesenchymal cell lines can be used safely. In view of their regenerative properties, multipotent mesenchymal stem cells may be useful for the treatment of condylar resorption.

Within this context, the objective of this systematic review is to evaluate the role of mesenchymal stem cells in the regenerative treatment of temporomandibular joint resorption. The PICO tool was used to identify the components of clinical evidence, which are as follows:

1 Population - Human and/or animal model diagnosed with temporomandibular degeneration.
2 Intervention - Treatment of joint degeneration using mesenchymal stem cells.

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3 Comparison - Healthy controls and/or patients who underwent other surgical techniques for treatment of temporomandibular degeneration.
4 Outcome - The repair of temporomandibular joint discs and/or bone structures using mesenchymal stem cells.

2. Materials and methods

2.1. Protocol and registration

The protocol of this study was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009) and is registered in the International Prospective Register of Systematic Reviews (PROSPERO) (protocol No. CRD42020212545).

2.2. Study selection and eligibility criteria

This systematic review was designed to answer the following question: Can mesenchymal stem cells be used to regenerate structures associated with the temporomandibular joint?

A search was conducted in the PubMed/MEDLINE, EMBASE, Cochrane Collaboration Library, and Web of Science databases in order to identify all primary research articles that assessed the use of mesenchymal stem cells for the treatment of temporomandibular joint resorption. All articles available in the selected databases until September 2020 were considered.

The search strategy was based on combinations of the following keywords: "temporomandibular joint" ([MeSH Terms] OR ("temporomandibular"[All Fields] OR "joint"[All Fields]) AND ("stem cells"[MeSH Terms] OR ("stem"[All Fields] OR "cells"[All Fields]) OR "stem cells" [All Fields]) AND "humans" [MeSH Terms]). The following keywords were used for studies employing animal models: (("temporomandibular joint"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint" [All Fields]) OR "temporomandibular joint" [All Fields]) AND ("stem cells" [MeSH Terms] OR ("stem" [All Fields] AND "cells" [All Fields]) OR "stem cells" [All Fields])) AND "animals" [MeSH Terms: noexp]).

The titles and abstracts of the studies identified in the systematic search were independently assessed by two researchers. Disagreements in the selection of articles were resolved by discussion and consensus among the reviewers. After the initial selection, the full text of potentially relevant articles was read. In this final screening, studies were included if they met the following criteria: *in vivo* animal and human studies that used mesenchymal stem cells for bone regeneration and that reported measurable clinical, radiographic and/or histological results for the treatment of temporomandibular joint resorption. No language restrictions were applied. *In vitro* studies, literature reviews and studies that did not use mesenchymal stem cells and/or did not evaluate the treatment of temporomandibular joint resorption were excluded.

2.3. Data extraction

After selection of the studies that met the established inclusion criteria, the following data were extracted using a form developed for this review: authors, year of publication, objective, sample characteristics, methods and design of the study, characteristics of the intervention [cells used, preparation of conditioned medium, method of administration, type of diagnostic or induced temporomandibular joint resorption (in the case of animal studies), duration of the intervention performed, study groups, outcomes evaluated (bone/cartilage regeneration and possible secondary outcomes), and conclusions of the study.

2.4. Quality assessment

The risk of bias was assessed using the Systematic Review Centre for Laboratory animal Experimentation tool (Hooijmans et al., 2014) for animal studies and the Cochrane's risk of bias tool (Higgins et al., 2019) for human studies. The risk of bias in the included studies was classified as high, low, or unclear. In the case of non-experimental studies, quality assessment was performed using the CARE checklist for case reports (Gagnier et al., 2013).

3. Results

3.1. Study selection and characterization

The initial electronic search of the literature retrieved 703 potentially relevant publications from the selected databases (Fig. 1). Of these publications, 681 articles were excluded after reviewing the titles and abstracts and removal of duplicates. In addition, 14 articles were excluded after full-text reading of the pre-selected studies because they did not meet the established inclusion criteria. Thus, six studies using animal models (Ahtiainen et al., 2013; Ciocca et al., 2013; Gomez, Wittig, Diaz-Solano, & Cardier, 2020; Wu et al., 2014; Zaki, Zaghloul, Helal, Mansour, & Grawish, 2017; Zhang et al., 2017) and two human studies were included in this systematic review (De Riu et al., 2019; de Souza Tesch et al., 2018).

In the animal studies, the temporomandibular joint injury was created by removing or inducing a defect in the articular disc of the temporomandibular joint (Ahtiainen et al., 2013; Ciocca et al., 2013; Wu et al., 2014). Zaki et al. (2017) evaluated degenerative changes in the temporomandibular joint associated with arthritis induced in rabbits by the injection of 0.1 ml bovine collagen type II at the base of the animal's tail and on the back at three points. Zhang et al. (2017) induced unilateral anterior crossbite, whereas Gomez et al. (2020) induced condylar damage.

de Souza Tesch et al. (2018) proposed a regenerative approach using autologous nasal septum cells expanded *in vitro* and applied to a patient with condylar resorption. De Riu et al. (2019) evaluated the reliability of intra-articular injection of bone marrow nucleated cells in patients with degenerative temporomandibular disorders.

Tables 1 and 2 show the cell lines and methodologies used and the main outcomes obtained in the selected studies. In the selected studies that removed the articular disc, the biomaterial was used in conjunction with mesenchymal stem cells in order to replace the articular disc. Ahtiainen et al. (2013) designed a polylactide disc to replace the articular disk, while Ciocca et al. (2013) developed prototyped porous hydroxyapatite scaffolds using computer aided design and manufacture technology to replace the two condyles removed from the animals included in the study.

Assessment of the quality of the studies is shown in the Supplementary Material 1. None of the selected studies using animal models reported random sequence generation or allocation concealment. The study by De Riu et al. (2019) used bias-free selection and, finally, the article by de Souza Tesch et al. (2018) was classified as low risk of bias by the CARE checklist.

3.2. Main outcomes in animal studies

Ahtiainen et al. (2013) investigated the signs of chronic arthrosis in histological sections. The authors observed an irregular cartilage-bone interface in the control group, especially in the 12-month group. The authors observed an irregular interface between the cartilaginous and bone tissues in the control group, especially in the one-year follow-up group. The superficial cartilage of the joint treated with polylactide discs and differentiated autologous adipose stem cells was more regular than in the control group. No adverse events were observed in cases treated with a polylactide disc with differentiated adipose stem cells. As a biomaterial, the polylactide allowed the regeneration of the adjacent tissue in the temporomandibular joint.

Wu et al. (2014) found no of signs of tissue repair in the group not

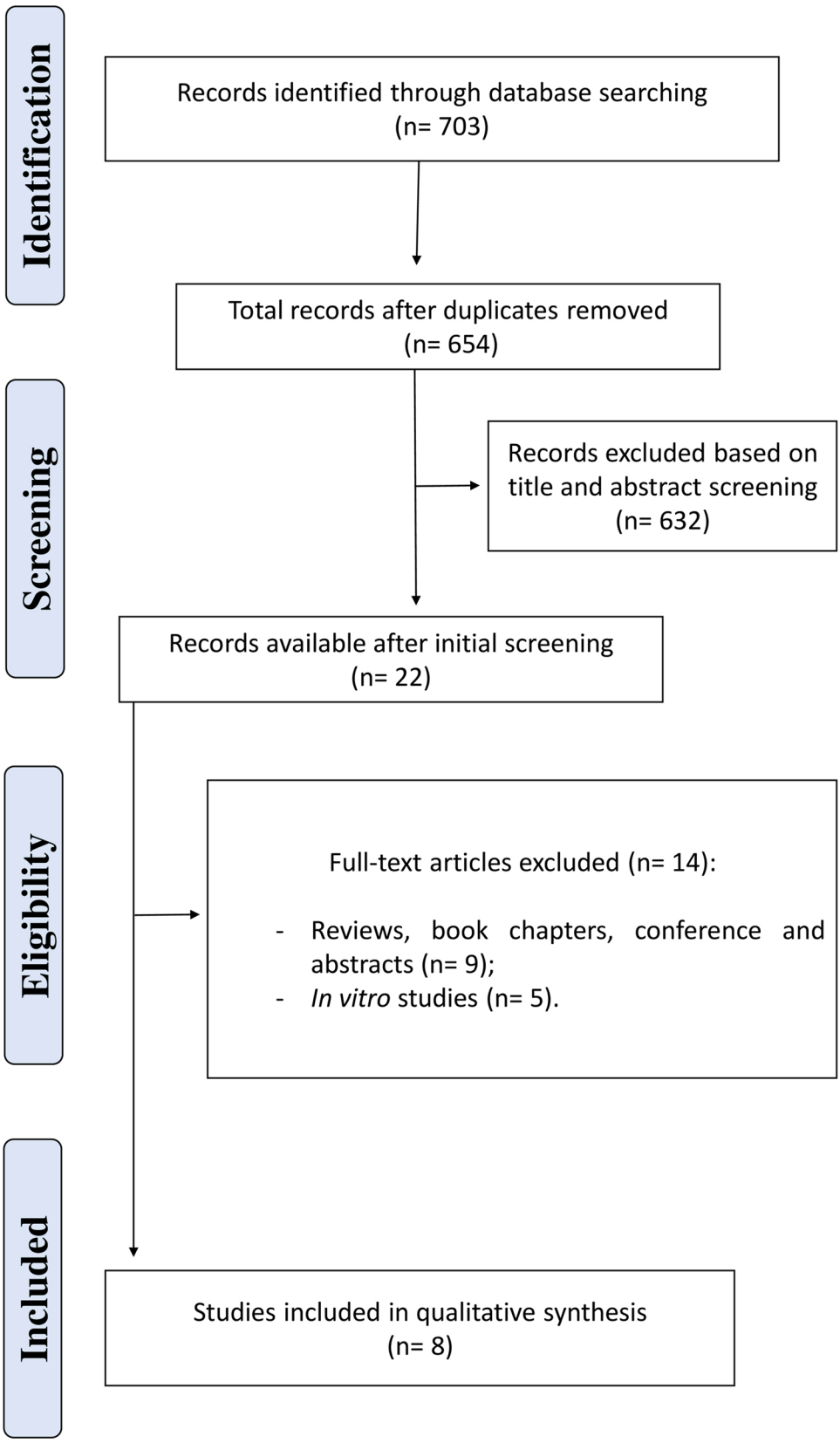

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of article selection for inclusion in the systematic review.

Table 1
Main characteristics and results of studies included in the qualitative analysis evaluating the efficacy of mesenchymal stem cells on the regeneration of structures associated with temporomandibular joint in animal model (n = 6).

Author (year)	Animal model	Stem cell type	Methodology	Evaluated measurements	Follow-up period	Summary of the main outcomes
Ahtiainen et al. (2013)	Rabbit (n = 10)	Autologous adipose stem cells	Animals submitted to the removal of the joint disc bilaterally. Group I - containing the polylactic discs with stem cells. Group II - Control group.	-Radiological evaluation (cone beam tomography); - Histology (hematoxin and eosin or Masson's trichrome); - Gene expression of the extracellular matrix components of fibrocartilage at implantation.	6 months (5 animals) and 12 months (5 animals).	The use of autologous adipose stem cells improved the morphological pattern of bone and joint disc.
Ciocca et al. (2013)	Sheep (n = 1)	Stem cells derived from the bone marrow of the iliac crest	Animals submitted to the removal of the joint disc bilaterally. Pure porous hydroxyapatite scaffolds were prototyped to replace the two temporomandibular condyles of the same animal.	- Histological and histomorphometric evaluation.	4 months	The study confirmed an increment of bone regeneration into the porous hydroxyapatite scaffold upon application of mesenchymal stem cells.
Wu et al. (2014)	Rats (n = 30)	Synovium derived mesenchymal stem cells	Five groups of temporomandibular joint disc explants were set: Group I: temporomandibular joint disc within chondrogenic induced cell/fibrin/chitosan scaffold; Group II: temporomandibular joint disc within chondrogenic induced cell/chitosan scaffold; Group III: temporomandibular joint disc within cell-free fibrin/chitosan scaffolds; Group IV: temporomandibular joint disc within cell-free chitosan scaffold; Group V: temporomandibular joint disc with cell-free fibrin scaffold.	- Histological and histomorphometric evaluation.	4 weeks	The regenerative ability of temporomandibular joint-synovium derived mesenchymal stem cells could be applied for repairing temporomandibular joint disc perforation.
Zaki et al. (2017)	Rabbit (n = 50)	Bone marrow-derived stem cells.	Three groups of temporomandibular joint disc explants were set: Group I: did not receive treatment (n = 10). Group II: was divided into 2 subgroups according to the type of treatment. One subgroup received an intra-joint injection of saline solution (n = 10) and the other received an injection of saline solution plus stem cells (n = 10). Group III: received an oil emulsion injection before treatment with saline solution or saline solution plus stem cells (n = 20).	Clinical, histological and histomorphometric evaluation.	3 weeks	Bone marrow-derived stem cells effectively repair degenerative changes of rabbits' temporomandibular joint.
Zhang et al. (2017)	Female rats	Bone marrow-derived stem cells.	Group I - Exogenous bone marrow stromal cells were injected weekly into temporomandibular joints, starting from 3 weeks of unilateral anterior crossbite stimulation and continuing for 4, 8 and 12 weeks. Group II - The group stopped receiving injections for 4 weeks after 8 weeks of injections.	Assessments were focused on morphological alterations.	15 weeks	The use of stem cells was able to reverse the degenerative processes caused by the unilateral anterior crossbite.
Gomez et al. (2020)	Rats	Bone marrow-derived stem cells.	Group I - Human mesenchymal stem cells embedded into preclotted platelet-rich plasma were placed on the surface of condyle cartilage damage (n = 2). Group II - Control group (without any treatment) (n = 2).	A macroscopic and histological analysis was performed.	6 weeks	Transplantation of mesenchymal stem cells induces regeneration of temporomandibular joint-condyle cartilage damage.

treated with mesenchymal stem cells derived from the synovial membrane. Overexpression of collagen and a greater tissue repair capacity demonstrated by morphological analysis were observed in the group seeded with synovium-derived mesenchymal stem cells.

In the study by Zaki et al. (2017), the cases treated with phosphate-buffered saline did not show significant architectural changes in the temporomandibular joint. On the other hand, the temporomandibular joint treated with a combination of phosphate-buffered saline and bone marrow-derived stem cells exhibited smooth joint surfaces, adequate thickness and consistent staining of the condylar cartilage. In this study, the use of stem cells derived from bone marrow provided better results for all parameters analyzed.

Gomez et al. (2020) also analyzed bone marrow-derived stem cells and macroscopic analysis revealed the presence of cartilage-like tissue at the site of condyle cartilage damage. Histological analysis showed complete repair of the articular surface with the presence of

Table 2
Main characteristics and results of studies included in the qualitative analysis evaluating the efficacy of mesenchymal stem cells on the regeneration of structures associated with temporomandibular joint in human study (n = 2).

Author (year)	Sample	Stem cell type	Methodology	Evaluated measurements	Follow-up period	Summary of the main outcomes
de Souza Tesch et al. (2018)	A 27-year-old male	Autologous mesenchymal cells from nasal septum	The study proposed an approach regenerative medicine approach using autologous cells. The cells were injected into each joint by arthrocentesis.	Results were monitored by functional assays and image analysis using computed tomography. Variables evaluated: joint pain, maximum mouth opening, joint noises.	6 months	The cell injection reverted the condylar resorption, leading to functional and structural regeneration.
De Riu et al. (2019)	30 patients (44.5 ± 12.6 years)	Bone marrow nucleated cell	Patients affected by degenerative joint mandibular disorders were enrolled in this study. Group I - Temporomandibular joint arthrocentesis and hyaluronic acid injection. Group II - Patients in the bone marrow nucleated cell group were inoculated with bone marrow nucleated cell inside the joint.	Results were monitored by: (1) maximum interincisal opening; (2) assessing pain at rest and during motion; (3) joint noises; (4) chewing efficiency. Magnetic resonance imaging scan was performed.	12 months	The bone marrow nucleated cell group presented pain relief, chewing efficiency and maximum interincisal opening significantly better than the hyaluronic acid group.

cartilaginous tissue and subchondral bone filling the condyle cartilage damage area. Chondrocytes were observed in an extracellular matrix of collagen and glycosaminoglycans filling the repaired tissue. There was no evidence of subchondral bone sclerosis. The untreated condyle cartilage damage exhibited osteochondral lesions with no signs of cartilage repair. The authors concluded that transplantation of bone marrow-derived stem cells induces regeneration in cases of condyle cartilage damage.

3.3. Clinical outcomes in human studies

In a pioneering study, de Souza Tesch et al. (2018) used *in vitro* autologous cells expanded from the nasal septum in a patient who had degenerative changes in both temporomandibular joints. The cells were injected into each joint by arthrocentesis. The results were monitored by functional tests and image analysis using computed tomography. The use of autologous cells completely reversed condylar resorption, leading to functional and structural regeneration six months after application. Computed tomography images showed new cortical bone formation filling what was in the process of resorption. The overlapping of the condyle models showed the regeneration of the bone defect, reconstructing the original shape of the condyle.

De Riu et al. (2019) conducted a randomized and controlled clinical trial to evaluate the reliability of intra-articular injection of bone marrow nucleated cells in patients with degenerative temporomandibular disorders, comparing its effectiveness with that of hyaluronic acid. In both groups, significant clinical improvements were detected up to 1 year after the procedure. The bone marrow nucleated cells group exhibited significantly better pain relief after 6 months ($p = 0.028$) and 12 months ($p = 0.000$). In terms of masticatory efficiency, significant positive differences were observed after 12 months in the bone marrow nucleated cells group ($p = 0.0001$). However, no magnetic resonance imaging evidence of cartilage regeneration was reported.

4. Discussion

Resorption of temporomandibular joint components can cause severe morbidity and may require invasive treatments with a high risk of recurrence (Chouinard, Kaban, & Peacock, 2018; Mercuri & Handelman, 2020). Condylar resorption occurs in situations that cause wear of the mandibular condylar bone and loss of condylar volume. Articular cartilage is a highly specialized tissue that acts as a shock absorber, allowing low-friction movement of synovial joints. The repair potential of articular cartilage is limited because of its avascular, aneural and alymphatic structure (Goldberg, Mitchell, Soans, Kim, & Zaidi, 2017). It is noteworthy that the ideal treatment aims not only to repair the bone or cartilaginous tissue defect, but also to restore the structure and functionality of the temporomandibular joint.

Therefore, there is a growing interest in regenerative medicine, which comprises two main types: cell therapy in which cells are injected directly into the blood or tissues, and tissue engineering in which combinations of skeletal stem cells are used to repair or regenerate tissues (Goldberg et al., 2017; Vyas et al., 2020). Regenerative medicine and tissue engineering approaches have been widely explored to develop new approaches to repair and regenerate damaged temporomandibular joint tissue (Ahtiainen et al., 2013; Ciocca et al., 2013; De Riu et al., 2019; de Souza Tesch et al., 2018; Gomez et al., 2020; Wu et al., 2014; Zaki et al., 2017; Zhang et al., 2017).

In vitro studies have indicated a possible therapeutic role of several mesenchymal stem cell lines in the repair of the temporomandibular joint. Chen, Man, Zhang, Hu, and Zhu (2013) evaluated the *in vitro* effect of autologous mesenchymal stem cells on cartilage and on the repair of subchondral spongy bone in temporomandibular joint osteoarthritis. The authors showed that intra-articular injection of mesenchymal stem cells can delay the progression of temporomandibular joint osteoarthritis and *in vitro* chondrogenic induction may enhance the therapeutic effects. Other studies corroborate these findings (Alhadlaq et al., 2004; Cui et al., 2017).

Our systematic review describes the potential use of mesenchymal stem cells for the treatment of resorption of temporomandibular joint components in an animal model and in humans studies. Although still scarce, studies in the scientific literature indicate that stem cell therapy is viable and is promising for the prognosis of patients diagnosed with temporomandibular joint disorders.

With the advances of tissue engineering, autologous intra-articular mesenchymal stem cell grafting has been proposed as an effective biological therapy because of its plasticity and the ability of these cells to differentiate into different tissues (bone, cartilage, muscle), as well as good host receptivity in which the autologous graft does not trigger an immune response (De Riu et al., 2019; Han et al., 2019). There are two main sources of stem cells: mesenchymal stem cells and embryonic stem cells (Ahtiainen et al., 2013; Zaki et al., 2017). Among the sources of stem cells reported for temporomandibular joint repair and tissue engineering, mesenchymal stem cells were the most widely used. These cells were isolated from different tissues, with bone marrow being the main source used in the studies of our systematic review (Ciocca et al., 2013; De Riu et al., 2019; Gomez et al., 2020; Zaki et al., 2017; Zhang et al., 2017).

Intra-articular injection is the most effective route for therapy with mesenchymal stem cells, and it has previously been observed that

intravenous or intraperitoneal administration of mesenchymal stem cells does not migrate to the joints to exert their therapeutic effects (Kehoe, Cartwright, Askari, El Haj, & Middleton, 2014; Zaki et al., 2017). In this context, Emadedin et al. (2012) studied the effect of intra-articular injection of autologous mesenchymal stem cells in six patients with knee osteoarthritis. The comparison of MRI images at the beginning and six months after the injection of stem cells showed an increase in the extent of repair tissue over the subchondral bone. The animal and human studies selected in this systematic review indicate a strong capacity of mesenchymal stem cells to induce tissue regeneration and restore the functionality of the temporomandibular joint.

In addition to its potential use in the regeneration of temporomandibular joint tissue, De Riu et al. (2019) highlights that the procedure can be performed on an outpatient basis under local anesthesia and no complications were detected in the donors or recipients during the course of the study. In their clinical trial, although no regeneration of the cartilaginous tissue was observed, De Riu et al. (2019) demonstrated relief of painful symptoms, increased masticatory capacity and improvement in maximum interincisal opening. This result was expected since the specific cell population used (bone marrow nucleated cells) has a limited capacity for chondrogenic differentiation; however, these cells are able to inhibit proinflammatory activities, as well as the proliferation, cytokine production and cytotoxic activity of natural killer cells at rest, thus promoting analgesia and inhibiting the progression of the pathological process (Shadmanfar et al., 2018). The concomitant use of cell populations capable of inhibiting the inflammatory process and triggering the tissue repair process may enhance the therapeutic effects of mesenchymal stem cells in temporomandibular joint regeneration.

The present systematic review points to promising results in the use of mesenchymal stem cells in the regenerative treatment of the resorption of the temporomandibular joint in human model. However, further studies are needed to determine possible contraindications, evaluate the therapeutic effects at the clinical, imaging, and microscopic level and to identify the most appropriate cell lines to be used in the treatment, as well as to evaluate at what stages of the joint resorption process could feasibly use of therapy with mesenchymal stem cells.

5. Conclusion

Based on the data of our systematic review, the use of mesenchymal stem cells is a promising method for the repair and regeneration of temporomandibular joint components. The use of combined therapies employing cell populations with different purposes (regenerative capacity and inhibition of the inflammatory process) may enhance the therapeutic effects of mesenchymal stem cells. Further studies using animals models are necessary to better understand the biological mechanisms associated with this type of *in vivo* treatment and to identify the most appropriate cell populations for the type of tissue to be regenerated and the most effective surgical and management techniques. Although scarce, human studies have provided highly promising results; hence, new clinical studies are needed to confirm the use of mesenchymal stem cells as an effective and safe means to treat pathological processes that cause damage to temporomandibular joint structures.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.archoralbio.2021.105104.

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