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Mesenchymal Stem Cell Therapy for Osteoradionecrosis of the Mandible: a Systematic Review of Preclinical and Human Studies

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Abstract

Background Osteoradionecrosis (ORN) of the mandible is a severe complication of radiotherapy for head and neck cancer and is arduously difficult to manage. Current treatment options carry risks with some patients remaining incurable. Mesenchymal stromal/stem cell (MSC) therapy has shown promising results supporting osteogenesis and regeneration of radiotherapy-damaged tissues. The aim of this study was to systematically review the literature on the safety and efficacy of MSCs in treating ORN.

Methods A systematic search was performed on MEDLINE, Embase, Cochranes Library online databases, and clinicaltrials.gov to identify preclinical and clinical studies examining the effect of MSCs on osseous healing of ORN. The preclinical studies were assessed according to the SYRCLEs guidelines and risk of bias tool.

Results Six studies ($n = 142$) from 5 countries were eligible for analysis. Of these four were preclinical studies and two clinical case studies. Preclinical studies found MSC treatment to be safe, demonstrating bone restorative effects and improved soft tissue regeneration. In the clinical cases, healing of bone and soft tissue was reported with no serious adverse events.

Conclusion The evidence from the included studies suggests that MSCs may have beneficial regenerative effects on the healing of ORN. None of the studies reported adverse events with the use of MSCs. More carefully controlled studies with well-identified cells are however needed to demonstrate the efficacy of MSCs in a clinical setting.

Keywords Osteoradionecrosis · Mesenchymal stem cells · Cell therapy · ORN · Systematic review

Introduction

Osteoradionecrosis of the mandible (ORN) is a complication of high-dose radiotherapy of the head and neck. The currently accepted definition of the condition is bone devitalization secondary to radiotherapy, where bone becomes exposed through the overlying skin or mucosa without healing for three months in the absence of recurrent tumor [1, 2]. ORN often occurs as a consequence of local trauma but may also arise spontaneously, and ranges from small asymptomatic bone exposures to severe necrosis with pathologic fractures necessitating surgical intervention and reconstruction [3]. Recently published data show that ORN affects approximately 5% of patients who undergo radiotherapy for head and neck cancer [4, 5].

The pathophysiological aetiology of radiation-induced damage of bone tissue is complex and not fully understood. In 1983, Marx et al. [6] presented the pathophysiology of ORN as a hypo-triad; hypoxia, hypocellularity, and hypovascularity. Consequently, aseptic bone necrosis will develop due to impaired regenerative capacity of the bone and soft tissue secondary to the radiation-injury and local trauma [7]. Another theory is that the initial event in developing ORN is the early radiational damage to osteoclasts, leading to decreased osteoclast-related bone turnover, preceding vascular changes and, ultimately, bone necrosis [8].

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Treatment of mild cases of ORN of the mandible consists of conservative prevention seeking to avoid further progression of the disease by good oral hygiene and avoiding predisposing factors such as tooth extraction, alcohol, tobacco, and poor nutritional status [1, 4, 9, 10]. Hyperbaric oxygen treatment (HBO) has proven to hinder further development of moderate ORN [6, 11, 12]. Severe cases are treated with surgical resection and free flap transplant in combination with HBO [13]. However, ORN is notoriously difficult to manage and a considerable percentage of patients remain incurable or experience recurrent ORN even after successful recovery. Several studies have recently suggested that treatment with mesenchymal stromal/stem cells (MSCs) might be a viable treatment option for ORN of the mandible [14–17].

MSCs are multipotent adult cells first discovered in the bone marrow (BM) to support haematopoiesis [18]. Since then, MSCs have been isolated from virtually all connective tissues where they have been shown to support tissue regeneration, as well as respond to injuries and inflammation [19]. MSCs are defined by their ability to adhere to plastic in cell cultures, positive expression of specific surface markers (CD90, CD73, CD105) combined with the absence of others (e.g. CD45 and CD14), and the tri-lineage differentiation capacity into osteoblasts, adipocytes, and chondroblasts [20–22]. An important mechanism of action is believed to be the secretion of bioactive molecules promoting angiogenesis, anti-apoptosis, immune modulation, antifibrosis, and support of local stem cells [21, 23–26]. These properties make MSCs promising candidates for clinical cell therapy [19] and a treatment option worth considering in radiation-induced diseases, including ORN [14–17, 24, 27–32].

The above mentioned effects of MSCs could promote regeneration and soft tissue healing also in ORN, when taking into consideration the pathophysiology of the hypo-triad, as proposed by Marx et al. [6]. MSCs also have the capacity to directly differentiate into bone-forming osteoblasts [33, 34]. This osteogenic differentiation ability may contribute to the bone tissue regeneration [21] together with the proposed theory of decreased osteoclast-related bone turnover, both of which are needed for restoring the lost bone structure and turnover.

There is an unmet need for new treatments for mandibular ORN with no systematic reviews providing evidence of the potential of MSCs. The objective of this review was thus to assess the safety and efficacy of MSCs on mandibular ORN in preclinical and human studies and thereby evaluate the potential use of MSCs for ORN in future human trials.

Methods

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [35]. The approach, method, and search string were agreed within the author group. We considered animal studies, which examined the effects of MSCs for ORN of the mandible versus a control group, and all eligible human studies regardless of their publication date. Studies examining the effects of MSCs in combination with other treatment regimens, studies without original data as well as preclinical studies without a control group were excluded. The primary outcome was safety. The secondary outcome was signs of osseous healing.

Search Strategy

In July 2019, we systematically searched for English and Scandinavian language articles in MEDLINE, Embase, Cochrane Library online databases, and ongoing clinical trials were searched for in clinicaltrials.gov. MEDLINE and EMBASE were searched using the following keywords (including MeSH terms): Osteoradionecrosis, mesenchymal stem cells, MSC, stem cells, bone marrow mesenchymal stem cells, bone marrow aspirate concentrate, adipose stem cells, adipose derived stem cells, stem cell transplantation, mesenchymal progenitor cells, and Wharton's jelly cells. The full search terms including all specific search terms, and the details of the search are described in Appendix. Besides the search of databases reference lists were evaluated for further relevant articles.

Data Extraction

Two authors (AG and LF) independently identified studies against the inclusion criteria to determine the eligibility. The following information was recorded from included studies using the Covidence systematic review software (Covidence 2020): year of publication, author, study design, the species and number of animals used in the study, the graft donor species, patient demographics, the origin of the MSCs, the treatment model/intervention, number of cells, statistical tests used, the method used for inducing osteoradionecrosis, information on blinding, allocation, control groups, outcomes, adverse events, and follow-up time.

Data Analysis

The preclinical studies were evaluated according to the SYRCLEs guidelines and risk of bias tool. The publication bias was evaluated using funnel plot and small-study effect using Egger regression.

Results

Six studies published in 2010–2017 met the inclusion criteria (Fig. 1). Four animal studies ($n = 139$, intervention groups $n =$

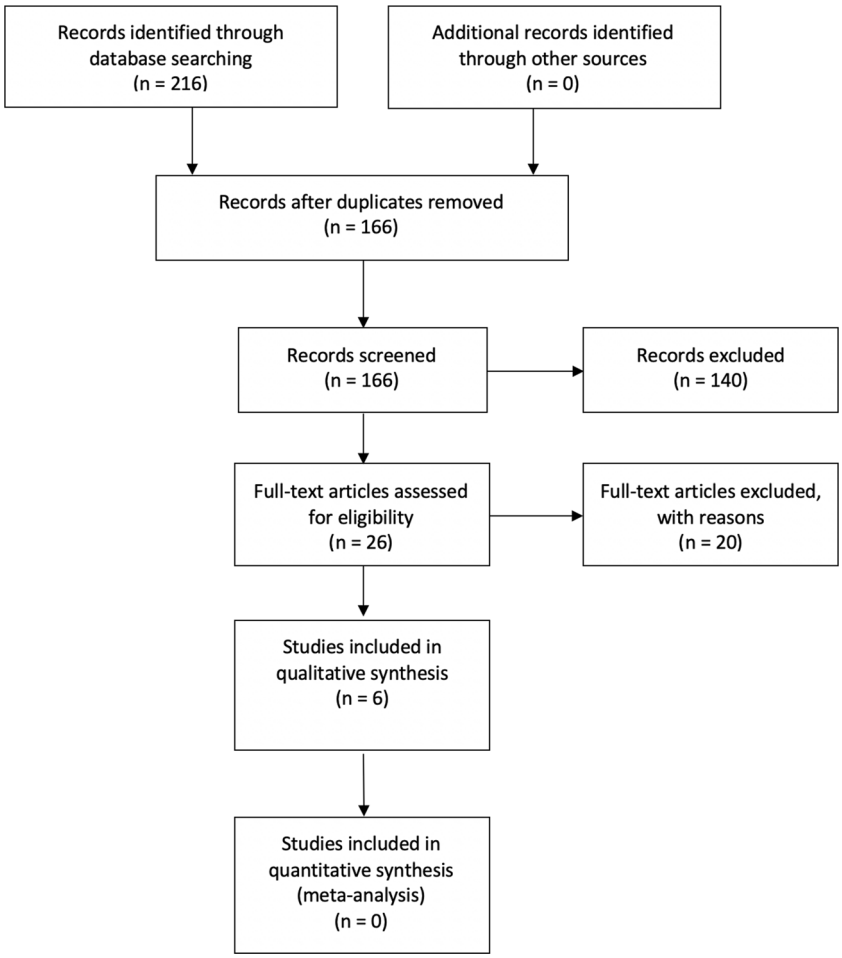

Fig. 1 PRISMA chart showing the screening process for the selection of eligible studies

49) (Table 1) and two human case studies ($n = 3$) (Table 2) were identified. Clinicaltrials.gov showed one randomised controlled trial including human ORN cases, which might have met the inclusion criteria, but the authors of that trial did not respond to our requests, nor have any results been published so far. Cochrane Library did not present any studies meeting our inclusion criteria.

Owing to the limited number and the heterogeneity of the studies, it was not possible to perform meta-analysis or evaluate small-study effects using a funnel plot or Egger regression.

Safety of MSC

All studies described the MSC-based cell therapy as safe with no reported serious adverse events. The loss of experimental animals ($n = 9$) was due to unrelated events such as death during anaesthesia and complications of producing the bony defect. The case reports revealed no adverse events or complications.

Description of the Animal Models

Four articles investigated the safety and efficacy of MSCs for mandibular ORN in a total of 139 animals (intervention groups $n = 49$) of different species (Table 1). The research groups used variations of the same model to mimic ORN, by radiating the hemimandible with 20–30 Gy, followed by tooth extraction to induce a bone defect (Table 1). The source of the MSCs also varied between the studies (Table 1).

The Effect of MSCs on Osseous Healing of the Mandible in Animal Model ORN

Four animal studies ($n = 139$) investigated the effect of MSCs on osseous healing in mandibular ORN (Table 1) [14–17]. Primary outcome of the studies differed. All studies could demonstrate an increase of osseous healing in animals treated with MSCs for ORN. Based on micro-CT results, two studies ($n = 89$) showed a significant increase of the bone volume (BV) for animals treated with MSCs compared to untreated animals [14, 17]. Two studies found a significant increase of the bone mineral density (BMD) compared to untreated animals [15, 17]. Finally, one study found a significant increase in bone volume/tissue volume (BV/TV) compared to untreated animals [16].

Histologically, all studies found increased bone formation in the MSC groups compared to controls. Janus et al. found a

Table 1 Animal ORN models

Author (Year)	Animals	Origin of MSCs	Intervention	Groups	Method for ORN	Focus of interest	Statistic tests	Study design
Park HS. et al. (2017) [15]	Adult male Sprague Dawley rats (250 g–300 g) $n = 36$	Tonsil derived-MSCs (TMSCs) from a 5-year old boy who underwent tonsillectomy. Xenograft	Control group received only tooth extraction, no radiation. The other rats are divided into 5 groups. First group is the ORN group, receiving both radiation and tooth extraction, but no treatment. Two other groups underwent same procedure but received the received matrigel directly into the wound of the tooth extractions, one group received it immediately, and one after 4 weeks. Same for the last two groups, although they received the TMSCs instead of only matrigel. Animals were killed 8 weeks after receiving matrigel or TMSCs.	1. Control group. Tooth extraction. (TE) n = 3 2. Radiation therapy (RT) + TE / ORN $n = 4$ 3. RT + TE + Matrigel application immediately. $n = 9$ 4. RT + TE + TMSCs immediately. $n = 6$ 5. RT + TE + Matrigel 4 weeks post. n = 6 6. RT + TE + TMSCs 4 weeks post. $n = 8$	Left mandibular body irradiated with single dose 20Gy. One week later, three left molars are extracted to induce ORN.	A study of the effect of tonsil derived MSCs for the treatment of ORN. It is also a study of the effect of immediate application of the TMSCs, versus application 4 weeks post teeth extraction.	Micro-CT, as well as histological analysis were conducted. The micro-CTs were analysed using the Mann-Whitney U test, to test for significance of data. The histological analyses were not analysed statistically.	Controlled trial. The analysis of the micro-CT scans was done blinded.
Jin IG et al. (2015) [17]	Seven weeks old Sprague-Dawley rats. Avg. weight 205 g. (Originally 114 animals, but 49 lost during development of ORN). $N = 65$.	Bone marrow mesenchymal stem cells cultured from bone marrow aspirate from rat tibias. Allogenous.	Rats were split into two overall groups apart from control and pilot experiments group. Group 1 received the implant of hydrogel loaded with rat MSCs (rMSCs) or bone-morphogenetic protein-2 (BMP-2) or a combination immediately after producing the bone defect. Group 2 received the loaded hydrogel 4 weeks postoperatively while also undergoing curettage. The follow-up period for the rats were 4 weeks after the insertion of the hydrogel i.e. 4 weeks postoperatively for the rats in group 1 and 8 weeks for group 2.	1. Control group, surgery, but no radiation. N = 6 2. Pilot experiments group, to determine doses and confirm ORN development. $N = 9$ 3. Group 1, radiation, and defect formation. Received the hydrogel immediately. Subdivisions a-e below. 4. Group 2, same as gr. 1, but received hydrogel 4 weeks post-surgery. Subdivisions a-e below. a: Defect formation only ($n = 5$ each grp.) b: Hydrogel only (n = 5 each grp.) c: Hydrogel loaded with rMSCs (n = 5 each grp.)	Single dose of 30 Gy administered to the right mandible. One week later three right mandibular molars were extracted, and a bony defect created surgically to induce the ORN.	The study investigates the effect of MSCs, BMP-2 and a combination, on the osseous healing in ORN, at two different administration times.	The normality of distribution for the data confirmed with the Kolmogorov-Smirnov test. Two-way analysis of variance (ANOVA) with Bonferroni correction was used to analyse effects of application time and material. One-way ANOVA was used to analyse the differences within the groups. Groups with abnormal distribution had the Kruskal-Wallis test run to compare CT data. Results considered significant at p value of <0,05.	Controlled trial

Table 1 (continued)

Author (Year)	Animals	Origin of MSCs	Intervention	Groups	Method for ORN	Focus of interest	Statistic tests	Study design
				d: Hydrogel loaded with BMP-2 (n = 5 each grp.) e: Hydrogel loaded with both rMSCs and BMP-2. (n = 5 each grp.)				
Janus JR et al. (2017) [14]	7 weeks old athymic nude rats. *N* = 23.	Human adipose-derived mesenchymal stem cells (ADSCs) donated by people who had restorative surgery for ORN. Xenograft.	Control group received no radiation. The other 4 groups received radiation and tooth extraction 7 days later. 35 days post irradiation injections of either saline, ADSCs, Platelet Rich Plasma/ Collagen (PRP/COL), or combinations thereof, were done. 28 days post injections the rats were sacrificed for analysis.	1. Control group, no irradiation n = 4 2. Saline injections n = 5 3. Saline + ADSCs n = 5 4. PRP/COL n = 4 (loss of 1 animal) 5. ADSCs + PRP/COL n = 5	Left mandible irradiated with single dose 20 Gy. 7 days later, second left molar was extracted to induce ORN.	A study to investigate the regenerative and restorative properties of ADSCs in a validated model for ORN.	Initial Chi-square analysis, followed by 2-tailed t-tests for unpaired samples for p value <0,05. Pathologists were blinded for histological analysis.	Controlled trial. Histological analysis was done blinded.
Xu J et al. (2012) [16]	Inbred miniature pigs, 7–8 months old, 25–30 kg. *N* = 15.	Bone marrow mesenchymal stromal cells (BMMSCs) were harvested and cultured from the ilium of the irradiated pigs 5 months post radiation. Autologous.	No radiation in control group. The remaining pigs received irradiation of the mandibular body, and two months later had tooth extraction. The treatment group received autologous BMMSCs + HA/TCP 6 months post radiation. The control group received only HA/TCP at the same time. Six months post-transplant i.e. 1 year after radiation.	1. Control group. Irradiation, no tooth extraction. *N* = 3 2. Sample group, with tooth extractions, for observations at set points. N = 3 3. Treatment group, transplant of BMMSCs with hydroxyapatite/ tricalcium phosphate (HA/TCP). *N* = 5 4. Control group with only HA/TCP implants. *N* = 4	Mandibular body irradiated with a single dose of 25 Gy. First molar extracted 2 months post irradiation.	A study of the effect of autologous implantation of BMMSCs in a swine ORN model.	Data was analysed statistically with a one-way analysis of variance (ANOVA), with values compared with control groups. *p* value of <0.05 was significant. Adjusted by the Bonferroni method for multiple comparisons.	Randomly controlled trial.

Table 2 Human case studies

Author	Patients	Origin of MSCs	Intervention	ORN diagnosis	Focus of interest	Statistic tests
Mendonca JJ et al. (2010) [37]	3 Patients, but only one diagnosed with ORN, one 63-year-old male subject. N = 1	Autologous MSCs/ tissue repair cells, obtained from patient's posterior ileum.	Following the development of advanced osteoradionecrosis, this patient received an autologous transplantation of BMMSCs harvested from the posterior ileum. These were then concentrated, cultured and prepared for transplantation with platelet-rich and poor plasma and HA/TCP. The prepared cells were then injected into the ORN defect, and surrounding tissue, following a debridement of necrotic tissue.	Patient diagnosed with advanced ORN with pathological fracture, following radiation treatment of tonsillar cancer, and a following tooth extraction. HBO chamber, antibiotics and other treatment tried.	Case study of the effects of MSCs in the treatment of ORN and other advanced craniofacial diseases.	No statistical data, as it is a case study.
Manimaran K. et al. (2014) [36]	One 48-year-old male and a 47-year-old male subject. N = 2	One case (1) with autologous bone marrow aspirate conc. (BMAC). Second case (2) is allogenic dental pulp stem cells (DPSCs).	Case 1 patient received autologous BMMSCs, harvested from his iliac crest, this was then concentrated and injected into the socket around his bone defect. Case 2 patient received allogenic DPSCs from extracted teeth. Stem cell graft consisting of PRP and alloplastic graft as scaffold was inserted into the defect.	ORN diagnosed in the two patients, as they both have had oropharyngeal cancers.	A case study of the effect of MSCs as a treatment for ORN.	No statistical data.

significant decrease in osteoclasts in MSC, MSC + platelet-rich-plasma (PRP)/collagen (COL) group, and PRP/COL groups when compared to saline injections only. They also found a significant increase in the number of osteoblasts in MSC + PRP/COL and PRP/COL group, but not in MSC group [14].

The Administration Time of the MSCs for ORN

Two studies with rats ($n = 101$) investigated how the timing of MSC administration altered the outcome of ORN [15, 17]. Both applied the MSCs either immediately after producing the bony defect or four weeks later. Jin et al. [17] found that the application of allogenic rat BM-MSCs only had a significant improvement in BV and BMD when applied four weeks after tooth extraction. In contrast, Park et al. [15] found that only immediate application of human tonsillar-derived MSCs after extracting teeth showed a significant improvement in BMD.

The Effect of MSCs on Mandibular ORN in Human Case Studies

Manimaran et al. [36] introduced a case study with two patients with confirmed ORN diagnosis treated either with BM aspirate concentrate (BMAC) or dental pulp stem cells (DPSCs). The first patient was a 48-year-old male with recurring symptoms of advanced ORN over a period of 1.5 years (with chronic osteomyelitis and a suspected pathological fracture) following radiotherapy for carcinoma of the soft palate in combination with tooth extraction. After curettage, this patient received autologous BMACs via local injection as well as mixed in a hydroxyapatite/tricalcium phosphate (HA/TCP) matrix. Two months later the patient showed signs of improvement with early bone formation as demonstrated on radiographs, by pain reduction, and cessation of discharge from the intraoral lesion. Six months after the treatment, there was a resolution of the suspected pathological fracture. Complete bone remodeling was noticed in radiographs after one year, and two years after treatment the patient was still asymptomatic with no apparent adverse effects. The second patient, a 47-year-old male, with a history of radiotherapy for oral cancer, presented with signs of advanced ORN. The patient was treated with allogenic DPSCs, extracted from teeth removed for orthodontic management. Following surgical curettage, unspecified dose of DPSCs in PRP combined with TCP as a scaffold was inserted into the defect, and DPSCs in PRP were also injected into nearby soft tissue. Two months later bone formation was appreciable, and six months later, clearly noticeable on radiographs. Further follow-up was not reported.

Mendonca et al. [37] presented a case study including one 63-year-old male with severe advanced ORN including intra- and extraoral fistulas. Before surgical curettage of necrotic

tissue, the patient was treated with an injection of 5×10^8 culture-expanded BM-derived total nuclear cells (TNCs) of which approx. 36% expressed CD90 [22]. However, approx. 67% of TNCs also expressed CD45, which is a common leucocyte antigen that should be negative in MSCs. The cells were mixed with PRP and platelet-poor plasma and HA/TCP, forming a bioactive matrix. As another temporary scaffold, a membrane made by compressing platelet-poor plasma and injected with cells, was used. Cells were also inoculated into nearby soft tissues. Three months post-operatively the patient showed signs of osteogenesis on CT-scans. During a dental prosthesis procedure, a bone biopsy was performed. It showed a pure cortical morphology and osteoblast/osteoclast activity. Twenty-months post-operatively, the patient reported no complications nor sequelae.

Risk of Bias

The animal studies were assessed using SYRCLEs guidelines and risk of bias tool with eight questions to determine potential biases for animal studies [38]. The assessment revealed risk of bias for all studies: particularly selection bias, as none of the studies described how the randomization of intervention/control groups was performed (Fig. 2).

None of the studies reported blinding of investigators, and none reported random housing. All of the studies had a low risk of bias concerning attrition and detection bias, but Xu et al. and Jin et al. did not report blinding of the outcome assessment [16, 17]. Case reports have a great risk of publication-bias, as cases with negative results would most likely not be published, and there are no requirements to report if such cases exist.

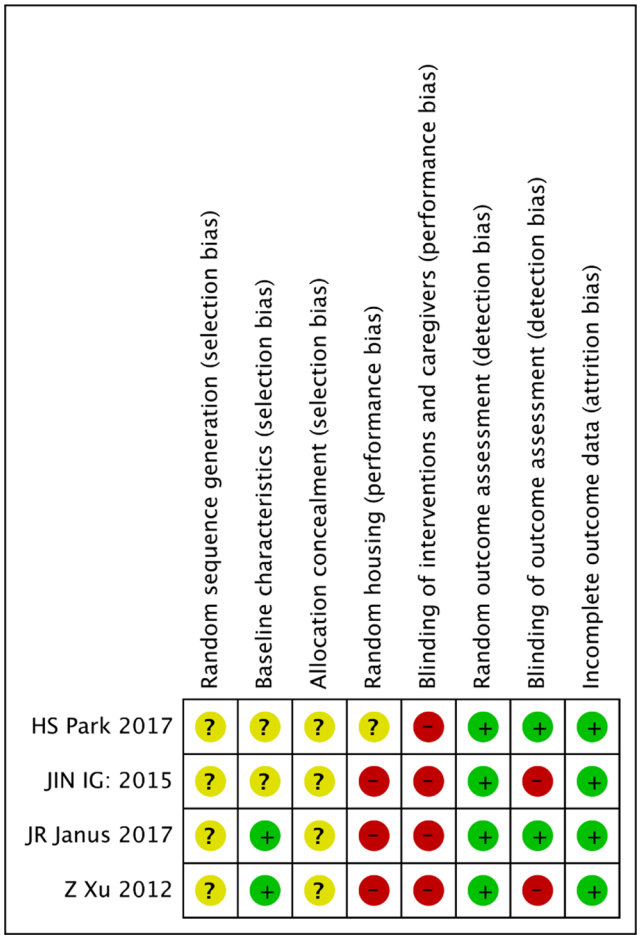

Fig. 2 SYRCLEs Risk of bias assessment tool. (?) = Unclear risk of bias, (+) = Low risk of bias, (−) = High risk of bias

Discussion

We aimed to systematically evaluate MSCs as a treatment for mandibular ORN. Our search identified four animal studies and two case reports comprising three patients investigating the efficacy and safety of MSCs on mandibular ORN. MSC administration was safe and studies included in this review demonstrated a positive effect either as an increase in BV or BMD.

There were differences regarding the impact of the MSC administration time as two animal studies had conflicting results; one study [15] identified an effect only if the MSCs were administered immediately after a bony defect was created, whereas another study [17] showed significant results, when administering the MSCs four weeks postoperatively. The difference might be due to the tissue source, being xenograft and allogenic respectively, but other differences in study design might also influence the results. The animal studies [14–17] observed soft tissue regeneration, increased epithelialization and soft tissue healing with the use of MSCs, although none of the studies quantitatively verified this effect. Janus et al. found a significant increase of fibrosis in all their treatment groups, compared to control and saline groups [14]. As all groups, the ones receiving MSCs and the one that did not, showed this effect, it is unlikely that MSCs, and not some other confounder, would have caused this outcome. One preclinical study found a significant increase in the density of microvessels [16], another found the same effect, which however was not quantified nor blinded [15]. In the clinical study by Mendonca et al., MRI was used to identify neoangiogenesis and a positive angiogenic effect was observed [37]. There are also other previous studies, which have concluded that MSCs can enhance vasculogenesis after irradiation-induced tissue damage e.g. in bone [28], skeletal muscle [32], and colon [27]. Thus, MSCs may be beneficial in improving hypo-vascularity.

To be identified as MSCs, the cells must meet certain criteria established by the International Society for Cell & Gene Therapy, ISCT [22]. The criteria include morphology,

growth kinetics, surface marker expression, plastic adherence, and multipotential differentiation capacity; however, all these characteristics are defined by the "golden standard" i.e. BM-derived MSCs. Therefore, new statements have been made concerning the adipose tissue derived stromal cells and the ability of MSCs to influence the immune system [39, 40]. Even though the gross phenotypic appearance, such as marker expression and differentiation potential would be similar, MSCs from different tissues and species are not identical [41]. For example, it has been reported that bone marrow and adipose tissue derived MSCs differ in gene expression, angiogenic potential, and secretion of various factors [42].

As the studies included in our systematic review utilized MSCs from various species and tissues, direct comparisons are very challenging. Either autologous or allogeneic cells as well as xenografts were used in the preclinical animal studies and the cells were originally derived from various tissues, including bone marrow, tonsils or adipose tissue (Table 1) [14–17]. In the two human case studies, the cells were autologous but isolated from either bone marrow or dental pulp [36, 37]. Furthermore, the isolation methods and possible culture expansions varied between different studies, both of which are known to affect the biological characteristics of MSCs.

In none of the preclinical or clinical case studies, were the cells fully identified according to the above-defined MSC criteria. Janus et al. described testing the tri-lineage differentiation potential [14] and Xu et al. performed Stro-1 and CD146 surface marker expression profiling but no data is shown. In one of the clinical cases, Mendonca et al. reported a partial MSC surface marker expression profile with 36% of cells positive for CD90 and 14% for CD105, but 67% of cells were positive also for the hematopoietic marker CD45, indicating that only a minority of cells in their study fulfilled the surface marker criteria for MSCs. Also, in the one clinical case by Manimaran et al., the cells injected were a very heterogenous cell population from uncultured bone marrow containing only a minor fraction of MSCs. [43]

In addition, despite of current attempts to unify the MSC nomenclature [44], there is still discrepancy and confusion in the current literature. Tissue-derived stromal cells can partially possess the same properties as MSCs and thus are sometimes incorrectly stated as "stem cells". This raises further difficulty in comparing study outcomes and represents another source of confusion in cell therapy development.

In addition to the risk of bias identified using the SYRCLEs risk of bias tool, there is a considerable risk of bias in the preclinical studies. A lot of methodology regarding selection and housing of the animals, and blinding/randomization of the trials is either unreported or executed in a way resulting in increased risk of bias in the experiments.

The human case studies provide important initial clinical data, although the very limited number of patients, the lack of control groups, lack of well-characterized cells, as well as potential bias and blinding precludes the possibility of detailed, quantitative analysis. The longest follow-up period was two years, which may not expose potential long-term side effects. However, these studies can be used as a model for potential upcoming human clinical trials.

In conclusion, current preclinical literature suggests that MSCs are safe with promising positive effects on osseous and soft tissue regeneration in ORN of the mandible. Our systematic review furthermore highlights the need for performing more controlled studies with well-characterized cells to verify their efficacy.

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Author Contributions AG, CDL, CG and CvB conceived the study design. AG, CL and LF were responsible for search preparation, literature search, article screening and selection. The initial draft of the manuscript was written by AG and CDL, and all authors critically revised the work. The final manuscript was read and approved by all authors.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest.

Appendix

Advanced search strategy

The final search was conducted on the 25th of March 2020. The complete search strings can be found below. The MEDLINE search revealed 89 results, including MeSH terms. The EMBASE search revealed 128 studies including all paper types. These results were imported into Covidence.org 2020 review software for screening. The screening process flowchart can be seen in Fig. 1.

Cochrane Library was searched with fewer central keywords in order to identify reviews of interest. The keywords for condition were:

"osteoradionecrosis" OR "ORN" OR "Osteoradionecrosis of the jaw" OR "ORNJ" OR "ONJ".

This search revealed five Cochrane reviews. None of these reviews investigated the use of mesenchymal stem/stromal cells as a possible treatment for osteoradionecrosis, and thus the included studies of the reviews were not included in our analysis. ClinicalTrials.gov was searched for all trials including the condition "osteoradionecrosis". 14 results were found. Only one trial seemed to fit our inclusion criteria, and none of the exclusion criteria. However, in that study no results have been published, and the author did not respond to our inquiry.

Table 3 MEDLINE Search

Osteoradionecrosis	"osteoradionecrosis"[MeSH Terms] OR "osteoradionecrosis"[All Fields]
ONJ	"Open Neuroendocrinol J"[Journal] OR "Open Nanomed J"[Journal] OR "onj"[All Fields]
Mesenchymal stem cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields]
Mesenchymal stem cell	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cell"[All Fields]) OR "mesenchymal stem cell"[All Fields]
Mesenchymal stromal cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("mesenchymal"[All Fields] AND "stromal"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stromal cells"[All Fields]
Mesenchymal stromal cell	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("mesenchymal"[All Fields] AND "stromal"[All Fields] AND "cell"[All Fields]) OR "mesenchymal stromal cell"[All Fields]
Stem cell	"stem cells"[MeSH Terms] OR ("stem"[All Fields] AND "cells"[All Fields]) OR "stem cells"[All Fields] OR ("stem"[All Fields] AND "cell"[All Fields]) OR "stem cell"[All Fields]
Stem cells	"stem cells"[MeSH Terms] OR ("stem"[All Fields] AND "cells"[All Fields]) OR "stem cells"[All Fields]
Mesenchymal stem cell transplantation	"mesenchymal stem cell transplantation"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cell"[All Fields] AND "transplantation"[All Fields]) OR "mesenchymal stem cell transplantation"[All Fields]
Stem cell transplantation	"stem cell transplantation"[MeSH Terms] OR ("stem"[All Fields] AND "cell"[All Fields] AND "transplantation"[All Fields]) OR "stem cell transplantation"[All Fields]
Bone marrow	"bone marrow"[MeSH Terms] OR ("bone"[All Fields] AND "marrow"[All Fields]) OR "bone marrow"[All Fields]
Bone marrow mesenchymal stem cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("bone"[All Fields] AND "marrow"[All Fields] AND "mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "bone marrow mesenchymal stem cells"[All Fields]
Stem Cell, Mesenchymal	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("stem"[All Fields] AND "cell"[All Fields] AND "mesenchymal"[All Fields])
Stem Cells, Mesenchymal	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("stem"[All Fields] AND "cells"[All Fields] AND "mesenchymal"[All Fields]) OR "stem cells, mesenchymal"[All Fields]
Bone Marrow Stromal Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("bone"[All Fields] AND "marrow"[All Fields] AND "stromal"[All Fields] AND "cells"[All Fields]) OR "bone marrow stromal cells"[All Fields]
Bone Marrow Stromal Cell	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("bone"[All Fields] AND "marrow"[All Fields] AND "stromal"[All Fields] AND "cell"[All Fields]) OR "bone marrow stromal cell"[All Fields]
Bone Marrow Stromal Cells, Multipotent	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("bone"[All Fields] AND "marrow"[All Fields] AND "stromal"[All Fields] AND "cells"[All Fields] AND "multipotent"[All Fields])
Multipotent Bone Marrow Stromal Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("multipotent"[All Fields] AND "bone"[All Fields] AND "marrow"[All Fields] AND "stromal"[All Fields] AND "cells"[All Fields]) OR "multipotent bone marrow stromal cells"[All Fields]
Adipose-Derived Mesenchymal Stem Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("adipose"[All Fields] AND "derived"[All Fields] AND "mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "adipose derived mesenchymal stem cells"[All Fields]
Adipose Derived Mesenchymal Stem Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("adipose"[All Fields] AND "derived"[All Fields] AND "mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "adipose derived mesenchymal stem cells"[All Fields]
Mesenchymal Stem Cells, Adipose-Derived	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields] AND "adipose"[All Fields] AND "derived"[All Fields])

Table 3 (continued)

Mesenchymal Stem Cells, Adipose Derived	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields] AND "adipose"[All Fields] AND "derived"[All Fields])
Adipose-Derived Mesenchymal Stromal Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("adipose"[All Fields] AND "derived"[All Fields] AND "mesenchymal"[All Fields] AND "stromal"[All Fields] AND "cells"[All Fields]) OR "adipose derived mesenchymal stromal cells"[All Fields]
Adipose Derived Mesenchymal Stromal Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("adipose"[All Fields] AND "derived"[All Fields] AND "mesenchymal"[All Fields] AND "stromal"[All Fields] AND "cells"[All Fields]) OR "adipose derived mesenchymal stromal cells"[All Fields]
Adipose Tissue-Derived Mesenchymal Stem Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("adipose"[All Fields] AND "tissue"[All Fields] AND "derived"[All Fields] AND "mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "adipose tissue derived mesenchymal stem cells"[All Fields]
Adipose Tissue Derived Mesenchymal Stem Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("adipose"[All Fields] AND "tissue"[All Fields] AND "derived"[All Fields] AND "mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "adipose tissue derived mesenchymal stem cells"[All Fields]
Adipose Tissue-Derived Mesenchymal Stromal Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("adipose"[All Fields] AND "tissue"[All Fields] AND "derived"[All Fields] AND "mesenchymal"[All Fields] AND "stromal"[All Fields] AND "cells"[All Fields]) OR "adipose tissue derived mesenchymal stromal cells"[All Fields]
Adipose Tissue Derived Mesenchymal Stromal Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("adipose"[All Fields] AND "tissue"[All Fields] AND "derived"[All Fields] AND "mesenchymal"[All Fields] AND "stromal"[All Fields] AND "cells"[All Fields]) OR "adipose tissue derived mesenchymal stromal cells"[All Fields]
Stromal Cell, Mesenchymal	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("stromal"[All Fields] AND "cell"[All Fields] AND "mesenchymal"[All Fields]) OR "stromal cell, mesenchymal"[All Fields]
Stromal Cells, Mesenchymal	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("stromal"[All Fields] AND "cells"[All Fields] AND "mesenchymal"[All Fields])
Multipotent Mesenchymal Stromal Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("multipotent"[All Fields] AND "mesenchymal"[All Fields] AND "stromal"[All Fields] AND "cells"[All Fields]) OR "multipotent mesenchymal stromal cells"[All Fields]
Mesenchymal Stromal Cells, Multipotent	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("mesenchymal"[All Fields] AND "stromal"[All Fields] AND "cells"[All Fields] AND "multipotent"[All Fields])
Mesenchymal Progenitor Cell	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("mesenchymal"[All Fields] AND "progenitor"[All Fields] AND "cell"[All Fields]) OR "mesenchymal progenitor cell"[All Fields]
Mesenchymal Progenitor Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("mesenchymal"[All Fields] AND "progenitor"[All Fields] AND "cells"[All Fields]) OR "mesenchymal progenitor cells"[All Fields]
Progenitor Cell, Mesenchymal	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("progenitor"[All Fields] AND "cell"[All Fields] AND "mesenchymal"[All Fields])
Progenitor Cells, Mesenchymal	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("progenitor"[All Fields] AND "cells"[All Fields] AND "mesenchymal"[All Fields])

Table 3 (continued)

Wharton Jelly Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("wharton"[All Fields] AND "jelly"[All Fields] AND "cells"[All Fields]) OR "wharton jelly cells"[All Fields]
Wharton's Jelly Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("wharton's"[All Fields] AND "jelly"[All Fields] AND "cells"[All Fields]) OR "wharton's jelly cells"[All Fields]
Wharton's Jelly Cell	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("wharton's"[All Fields] AND "jelly"[All Fields] AND "cell"[All Fields]) OR "wharton's jelly cell"[All Fields]
Whartons Jelly Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("whartons"[All Fields] AND "jelly"[All Fields] AND "cells"[All Fields]) OR "whartons jelly cells"[All Fields]
Bone Marrow Stromal Stem Cells	"mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields] OR ("bone"[All Fields] AND "marrow"[All Fields] AND "stromal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "bone marrow stromal stem cells"[All Fields]

Table 4 Embase Search

1. ORN.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2. ORNJ.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. ONJ.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4. Mesenchymal stem cells.mp. or exp. mesenchymal stem cell/
5. Mesenchymal stem cell.mp. or exp. mesenchymal stem cell/ or exp. stem cell/ or exp. mesenchyme cell/
6. Mesenchymal stromal cells.mp. or exp. mesenchymal stroma cell/
7. Mesenchymal stromal cell.mp. or exp. mesenchymal stroma cell/
8. MSC.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
9. MSCs.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. Stem cell.mp. or exp. stem cell/
11. Stem cells.mp. or exp. stem cell/
12. Mesenchymal stem cell transplantation.mp. or exp. bone marrow transplantation/ or exp. mesenchymal stem cell transplantation/
13. Stem cell transplantation.mp. or exp. bone marrow transplantation/ or exp. stem cell transplantation/
14. Bone marrow aspirate concentrate.mp.
15. BMAC.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
16. Bone marrow mesenchymal stem cell.mp. or exp. bone marrow derived mesenchymal stem cell/
17. Bone marrow mesenchymal stem cells.mp. or exp. bone marrow derived mesenchymal stem cell/
18. exp. mesenchymal stroma cell/ or exp. bone marrow cell/ or Bone marrow mesenchymal stromal cell.mp. or exp. mesenchymal stem cell/
19. exp. mesenchymal stroma cell/ or Bone marrow mesenchymal stromal cells.mp. or exp. mesenchymal stem cell/
20. BMMSC.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
21. BMMSCs.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

Table 4 (continued)

22. Stem Cell, Mesenchymal.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
23. Stem Cell, Mesenchymal.mp. or exp. mesenchymal stem cell/
24. exp. stem cell transplantation/ or exp. mesenchymal stem cell/ or Stem Cells, Mesenchymal.mp.
25. Bone Marrow Stromal Cells.mp. or exp. bone marrow stroma cell/
26. Bone Marrow Stromal Cell.mp. or exp. bone marrow stroma cell/
27. exp. mesenchymal stroma cell/ or Bone Marrow Stromal Cells, Multipotent.mp.
28. Multipotent Bone Marrow Stromal Cells.mp. or exp. bone marrow stroma cell/
29. exp. mesenchymal stem cell/ or Adipose-Derived Mesenchymal Stem Cells.mp. or exp. adipose derived stem cell/
30. exp. stem cell/ or exp. adipose derived stem cell/ or exp. mesenchymal stem cell/ or Adipose Derived Mesenchymal Stem Cells.mp.
31. exp. bone marrow derived mesenchymal stem cell/ or exp. adipose derived stem cell/ or exp. stem cell transplantation/ or Mesenchymal Stem Cells, Adipose-Derived.mp. or exp. mesenchymal stem cell/
32. exp. mesenchymal stem cell/ or Mesenchymal Stem Cells, Adipose Derived.mp. or exp. stem cell transplantation/ or exp. adipose derived stem cell/
33. exp. mesenchymal stroma cell/ or Adipose-Derived Mesenchymal Stromal Cells.mp. or exp. adipose derived stem cell/
34. exp. mesenchymal stroma cell/ or Adipose Derived Mesenchymal Stromal Cells.mp. or exp. adipose derived stem cell/
35. exp. mesenchymal stem cell/ or Adipose Tissue-Derived Mesenchymal Stem Cells.mp.
36. exp. mesenchymal stem cell/ or Adipose Tissue Derived Mesenchymal Stem Cells.mp.
37. exp. mesenchymal stroma cell/ or Adipose Tissue-Derived Mesenchymal Stromal Cells.mp.
38. exp. mesenchymal stroma cell/ or Adipose Tissue Derived Mesenchymal Stromal Cells.mp.
39. ADMSC.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
40. ADMSCs.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
41. exp. mesenchymal stroma cell/ or exp. mesenchymal stem cell/ or Stromal Cell, Mesenchymal.mp.
42. exp. mesenchymal stroma cell/ or exp. mesenchymal stem cell/ or Stromal Cells, Mesenchymal.mp.
43. exp. mesenchymal stroma cell/ or exp. multipotent stem cell/ or Multipotent Mesenchymal Stromal Cells.mp.
44. exp. mesenchymal stroma cell/ or exp. mesenchymal stem cell/ or Mesenchymal Stromal Cells, Multipotent.mp.
45. Mesenchymal Progenitor Cell.mp. or mesenchymal stem cell/
46. Mesenchymal Progenitor Cells.mp. or exp. mesenchymal stem cell/
47. exp. mesenchymal stem cell/ or exp. stem cell/ or Progenitor Cell, Mesenchymal.mp.
48. exp. mesenchymal stem cell/ or Progenitor Cells, Mesenchymal.mp. or exp. stem cell transplantation/
49. Wharton Jelly Cells.mp. or exp. mesenchymal stroma cell/
50. exp. mesenchymal stem cell/ or exp. mesenchymal stroma cell/ or exp. Wharton jelly/ or Wharton's Jelly Cells.mp.
51. exp. mesenchymal stem cell/ or exp. mesenchymal stroma cell/ or exp. Wharton jelly/ or Wharton's Jelly Cell.mp.
52. exp. mesenchymal stem cell/ or exp. mesenchymal stroma cell/ or exp. Wharton jelly/ or Whartons Jelly Cells.mp.
53. exp. bone marrow stroma cell/ or Bone Marrow Stromal Stem Cells.mp.
54. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. Osteoradionecrosis.mp.
56. 1 or 2 or 3 or 55
57. 54 and 56

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