Research in Molecular Medicine

Clinical Applicability of Stem Cell Therapy in Dental Diseases: A Systematic Review of Available Clinical Trials

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ABSTRACT

Background: Developing cell-based therapeutic methods for differentiating various stem cells into dental tissues could be a revolutionary step toward using cell therapy for dental diseases. In the present study, we systematically reviewed the literature to determine the efficiency of stem cells in treating various dental diseases.

Materials and Methods: Using the search words "stem cell" and "dental disease" as well as all their equivalents and similar terms, we performed a literature search in September 2020 in the electronic databases: PubMed, Scopus, Science Direct, Web of Science, Embase, Ovid, and Google Scholar. The investigation was limited to clinical trials written in the English language.

Results: Overall, 22 articles with 400 study patients were found and used for qualitative data synthesis. Findings showed that various stem cells with different origins can be used for cell therapy of various dental diseases such as pulp necrosis, traumatic dental injuries, maxillofacial bony defects, impacted third molars, etc.

Conclusion: Stem cell therapy is an efficient method for treating dental diseases. It can regenerate whole dental pulp and may be useful for treating tooth injuries due to trauma.

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Introduction

Stem cells are undifferentiated cells that can regenerate and differentiate into a particular cell lineage, such as heart muscle, lung, adipocytes, osteoblasts, nerve, and dental cells [1, 2]. Nowadays, stem cell research has progressively expanded, encompassing the fundamental understanding of the mechanistic pathways and cellular processes in different conditions such as differentiation and pathobiology of diseases and in regenerative medicine as an effective therapeutic approach in various diseases [3]. In recent years, stem cell therapy has drawn attention as an efficient method, alone or in combination with conventional therapeutic methods for treating various illnesses.

The mouth is the main entry route of many agents, and oral health complications, such as tooth loss or dental infections, may affect other internal organs. Hence, oral and tooth health is important for human health [4]. Teeth are complex organs made up of hard and mineral tissues. Structurally, a tooth comprises an outer enamel layer, a middle dentin layer, and an inner dental pulp layer. The most conventional treatment of dental diseases includes dental implants, surgical restoration, and the old drill-and-fill method [5, 6]. A dental implant is not an option for some people with certain conditions. Also, despite advances in implant technology, dental implants have potential risks and problems, such as extended recovery time, prolonged implantation procedures, and a high probability of failure [7]. Conventional therapies for dental complications may have safety and durability concerns; therefore, developing stem cell-based therapies for improving dental and oral health is very important. New methods have been developed to use stem cell technology and tissue engineering in tooth restoration and reconstruction in recent years [8]. Scientists have been looking for an approach to use stem cells to generate new teeth in adults in recent decades. Using stem cells for tooth growth outweighs dental implants. The tooth contains different stem cells that have epithelial and mesenchymal sources. Proliferations of these cells lead to the generation of dentin-like tissue, which is an important step in creating or reconstructing dental tissue [9].

Dental stem cells (DSCs) are extremely accessible stem cells with remarkable self-renewal ability. They have shown therapeutic potential for treating various dental diseases in animal and human studies [10]. Studies have shown that DSCs have great therapeutic potential in regenerative medicine and can differentiate into multiple dental-like tissues.

The present study reviewed available clinical documents on the applicability and efficiency of stem cell therapy in tooth-associated diseases.

Materials and Methods

Study search and inclusion criteria

In the present study, a systematic literature search was performed in September 2020 in databases of Web of Science, Scopus, Medline via PubMed, Science Direct, Ovid, Embase, and Google Scholar to investigate the ability of stem cells in treating oral and dental-associated diseases. For this purpose, "stem cell" and "dental medicine," including all their equivalents, similar terms, and different written forms, were searched in PubMed as the search words. No strict limitations were applied as the inclusion criteria to minimize the risk of bias; however, the search was first limited to clinical trials. Hence, the book chapters, review articles, editorials, and conference papers were excluded. In addition, only English articles were selected for further evaluation. In Scopus, "stem cell" with all its similar terms was searched in the title, keyword, and abstract. Then, "dental medicine" was explored within the results. Finally, irrelevant articles were excluded from additional assessment. Accordingly, the inclusion criteria were as follows [11]:

- Articles reporting the effectiveness (positive or negative) of stem cell therapy in treating dental diseases

- Articles in English language

- Human studies

- Randomized and non-randomized clinical trials

Two authors independently performed the search and data collection, and the third author resolved any disagreement between them in each step by repeating the search. PRISMA (preferred reporting items for systematic reviews and meta-analyses) checklist 2009 was used for study design and article selection [12]. The study was designed to answer "whether there is sufficient data to support the efficiency of stem cell therapy in dental disease."

Quality assessment

The Newcastle-Ottawa assessment scale, recommended to verify the quality of randomized controlled trials, was used to evaluate the included articles. In the Newcastle-Ottawa scoring method, 3 different parts with overall 8 questions (maximum 9 stars) score each article based on "selection," "com-

parability," and "outcome." For quality assessment, a star is given for each item, and an article with appropriate design and reports can obtain a maximum of 9 stars on this scale. The Newcastle-Ottawa quality assessment scale's questions and description were provided as supplementary data (Table 1).

Data analyses and the variables

All informative data, including the author's name, publication date, demographic information of patients, the type of stem cells, and the type of disease, were extracted and summarized in Table 2. Moreover, each study's primary outcome and major findings were collected and used for qualitative data description.

Results

General information and demographic data

Overall, 46821 articles were collected in the first step: 15595 articles from PubMed, 31086 from Scopus, and 128 from other databases. Also, 12 additional articles were found by manual reference list search of the included articles. After the exclusion of irrelevant articles in several steps, 22 articles remained. The process of article selection is demonstrated in Figure 1. Overall, 400 patients were enrolled in the 22 included articles: 119 were male, 103 were female, and 178 were unknown. The age group of patients varied between 8 to 75 years, and the follow-up length ranged from 3 to 24 months.

Table 1. Quality assessment of included articles

No.	Authors. Year	Newcastle-Ottawa Score	Jadad Score
1	U et al. 2019 [21]	6	4
2	Redondo et al. 2018 [22]	5	4
3	Ferrarotti et al. 2018 [23]	5	3
4	Hernández-Monjaraz et al. 2018 [20]	5	4
5	Xuan et al. 2018 [24]	7	4
6	Barbier et al. 2018 [25]	6	4
7	Gjerde et al. 2018 [26]	5	3
8	Bajestan et al. 2017 [27]	5	3
9	Weng et al. 2017 [30]	6	3
10	Castillo-Cardiel et al. 2017 [13]	5	3
11	Chen et al. 2016 [18]	5	3
12	Ou et al. 2016 [31]	4	2
13	Bertolai et al. 2016 [17]	6	4
14	Kaigler et al. 2015 [14]	7	4
15	Wildburger et al. 2014 [19]	6	3
16	Rajan et al. 2014 [32]	6	3
17	Rickert et al. 2014 [33]	5	3
18	Behnia et al. 2012 [15]	6	3
19	Gonshor et al. 2011 [34]	7	4
20	Rickert et al. 2011 [35]	5	3
21	Yamagata et al. 2011 [36]	5	3
22	Gimbel et al. 2007 [16]	5	3

Table 2. Demographic information and the outcomes of stem cell therapy in the included studies

No.	Authors/Date	Country	Stem Cell Type	Disease/Condition	Patient Number (M/F)	Age (y)	Primary outcome	Follow-up (mo)	Efficiency of Therapy (%)	Quality Score*
1	U et al. 2019 [21]	India	BMSCs	Maxillofacial bony defects	15 (8/7)	24	Bone healing	3	100	5
2	Redondo et al. 2018 [22]	Spain	BMSCs	Maxillofacial bony defects	9 (2/7)	36	Bone healing	7	-	4
3	Ferrarotti et al. 2018 [23]	Italy	DPMSCs	Intrabony defect	29 (13/14)	50.7	Periodontal regeneration	12	>66.7	5
4	Hernández-Monjaraz et al. 2018 [20]	Mexico	DPMSCs	Periodontal disease	1 (1/-)	61	Bone regeneration	6	-	6
5	Xuan et al. 2018 [24]	China	hDPSC	Apical periodontitis, pulp necrosis	30 (26/4)	7.13	Pulp regeneration	24	-	6
6	Barbier et al. 2018 [25]	Spain	DPMSCs	Impacted 3rd molars	30 (8/22)	23	Socket bone resorption	6	-	5
7	Gjerde et al. 2018 [26]	Norway	BMSCs	Mandibular ridge resorption	11 (4/7)	65	Bone regeneration	12	90	5
8	Bajestan et al. 2017 [27]	USA	BMSCs	Alveolar cleft, trauma defects	17 (12/5)	27	Craniofacial bone regeneration	4	60	5
9	Weng et al. 2017 [30]	Taiwan, USA	PBSCs	Bone injury	11	-	Osseointegration	4	76	5
10	Castillo-Cardiel et al. 2017 [13]	Mexico	BMSCs	Mandibular angle fracture	20 (20/-)	31.2	Bone healing, ossification, bone quality	12	90	6
11	Chen et al. 2016 [18]	China	PDLSCs	Periodontal intrabony defects	30	26	The magnitude of alveolar bone regeneration	12	100	7
12	Ou, 2016 [31]	Taiwan	PBSCs	Bone injury	11	41.7	Osseointegration	3	100	5
13	Bertolai et al. 2016 [17]	Italy	MSCs	Expansive mandibular lesions	10 (6/4)	-	Bone regeneration, reduced healing time	12	90	5
14	Kaigler et al. 2015 [14]	USA	BMSCs	Maxillary sinus augmentation	26	-	Bone reconstruction, bone volume	12	65	7
15	Wildburger et al. 2014 [19]	Austria	MSCs	Atrophic maxilla	7	58	Bone formation, sinus augmentation	6	36.2	6
16	Rajan, 2014 [32]	USA	BMSCs	Craniofacial trauma	1 (-/1)	45	Jaw reconstruction	4	94	6
17	Rickert et al. 2014 [33]	Netherlands	BMSCs	Maxillary sinus floor elevation	12		Osseointegration	12	91	6
18	Behnia et al. 2012 [15]	Iran	MSCs	Maxillary cleft defects	3 (1/2)	10	Cleft bone volume	3	51.3	5
19	Gonshor, 2011 [32]	Canada	BMSCs	Maxillary sinus augmentation	5 (1/4)	25-75	Bone formation	4	88.9	6
20	Rickert et al. 2011 [35]	Netherlands	MSCs	Atrophic maxilla	12	60.8	Bone formation, sinus augmentation	3	-	7
21	Yamagata , 2011 [36]	Japan	HSCs	Impacted the 3rd molar	34 (18/16)	29	Odontogenic infection, gingival swelling	16	-	5
22	Gimbel et al. 2007 [16]	USA	BMSCs	Alveolar cleft defects	69	8.4	Bone formation, pain score	6	86	5

Abbreviations: hDPSC: Human deciduous pulp stem cell; DPMSCs: Dental pulp mesenchymal stem cells; BMSCs: Bone marrow-derived mesenchymal stem cells; PDLSCs: Periodontal ligament stem cells; PBSCs: Peripheral blood stem cells; HSCs: Hematopoietic stem cell.

*Quality score is based on the Newcastle-Ottawa quality assessment scale for clinical trials.

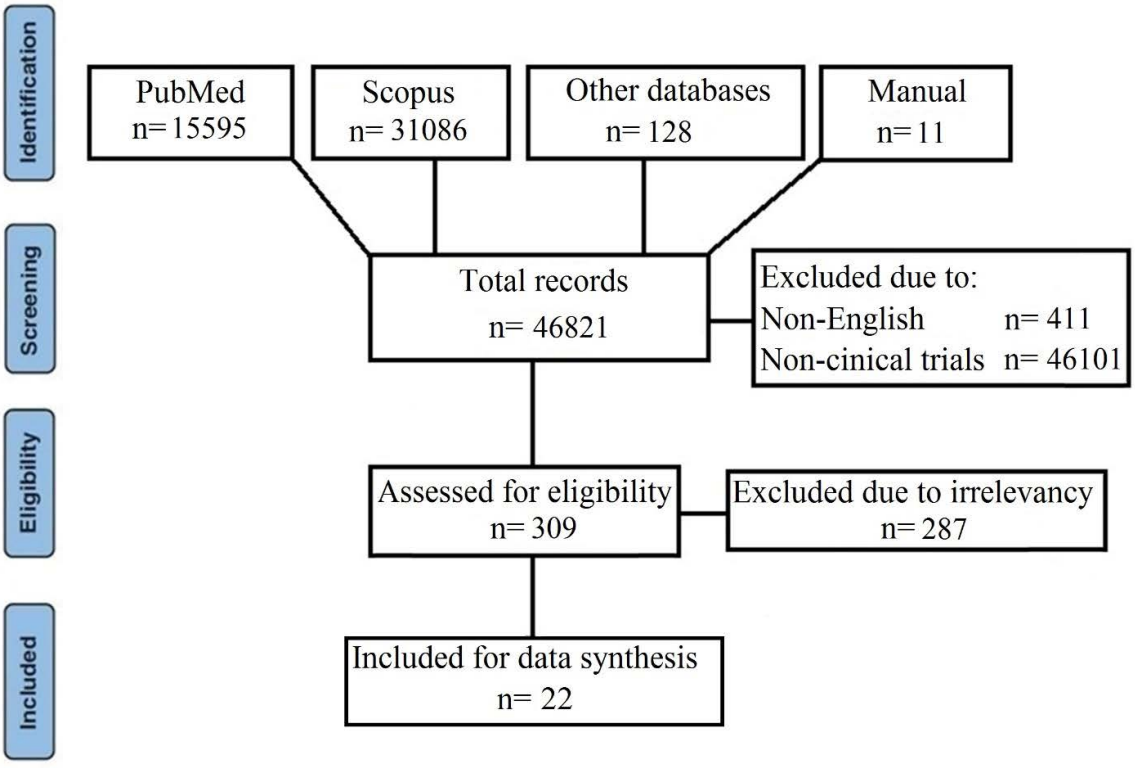

Figure 1. Schematic diagram of article selection

Study results

In the included studies, various types of stem cells, including human deciduous pulp mesenchymal stem cells (hDPMSC), bone marrow-derived MSCs, periodontal ligament stem cells (PDLSCs), and peripheral blood-derived (hematopoietic) stem cell (BSCs) had been used for cell therapy of various dental complications. These dental complications include apical periodontitis, pulp necrosis after traumatic dental injuries, impacted mandibular third molars, alveolar cleft, severe mandibular ridge resorption, periodontal disease, maxillofacial bony defects, edentulous atrophic ridges, mandibular angle fractures, craniofacial trauma, and osseointegration.

The results of most studies showed that stem cells, due to their higher safety and efficiency, are an excellent choice for treating dental diseases. Findings revealed that those treated with autologous mesenchymal stem cells (AMSCs) had a 36.48% higher rate of ossification. In addition, bone healing rate and bone quality were significantly better in the stem cell-treated group [13]. The height of alveolar bone and the engineered bone density showed a 5-fold increase in the stem cell therapy group [14]. Another study demonstrated a mean of 51.3% higher cleft bone volume than the control group, 3 months post-operation [15]. The mean pain score, including pain frequency and intensity, was more favorable in the stem cell-treated group. Moreover, only 1 out of 21 patients in the stem cell therapy group experienced pain, while 17 of 25 patients (68%) had pain 6 weeks after therapy [16]. Stem cell therapy also demonstrated rapid healing in patients with mandibular lesions with a 90% ossification rate after 12 months [17]. However, 3 studies reported no significant difference between the stem cell therapy and other therapeutic approaches as control [18, 19] although the outcome analysis demonstrated that bone density was higher in patients receiving stem cells [14]. The patients under therapy with stem cells showed no sign of rejection or side effects [20]. Findings of each study with demographic data as well as the rate of efficiency are summarized in Table 2.

Discussion

Over the past decade, numerous studies have reported the extraction of stem cell populations from various dental sources and suggested the potential application of stem cell therapy in dental diseases. Based on clinical evidence, stem cell-based methods can provide new therapeutic modalities based on biological phenomena for treating dental diseases. The promising results of stem cell-based therapies in vitro and in vivo animal models have brought speculation about using these cells

in future treatment programs in human dentistry. Stem cells, particularly DSCs, can differentiate into multiple cell lines, such as progenitor cells of adipocytes, osteoblasts, and neurogenic cells. Therefore, these cells can be used for tissue engineering and to evaluate their potential in clinical applications. In the present study, all available clinical data on the efficiency of stem cell therapy were reviewed [21-24].

According to the results of the included articles, stem cell implantation at the site of dental injury can lead to the regeneration of pulp tissue containing blood vessels and sensory nerves with no morbidity and adverse events after therapy [25]. In addition, treatment with stem cells can lead to increased root length and reduced apical foramen width compared to the control or other treatment groups [24]. Stem cell therapy also led to 1.5±1.5 mm mean bone gain in patients with alveolar cleft and trauma defects under cell therapy. The treatment efficiency was 60% compared to the control group [27]. Findings showed that the success rate can also reach 100%, and early bone regeneration and faster wound healing can be expected by applying bone marrow aspirate in patients with maxillofacial bone defects [21]. Moreover, bone-defected area and bone mineral density demonstrated a significant increase after stem cell implantation at the implant site [20, 28] In recent research on the application of dental pulp stem cells for bone and neural tissue regeneration in the oral and maxillofacial region, much evidence strongly suggests that dental pulp stem cells (DPSCs), which are derived from the neural crest, are among the most suitable cell sources for bone or neural regeneration therapy in the oral and maxillofacial region [29]. Studies have shown that grafting DPSCs can lead to the formation of bone-like tissue and improved clinical parameters of periodontal regeneration [20, 23]. Jaw reconstruction was also found as a successful application of stem cell therapy in craniofacial trauma cases with almost 100% success rate [30-32]. Implantation of stem cell therapy also demonstrated significantly higher rate of bone tissue healing in patients with dental implant compared to dental implants without stem cell therapy, with no experience of postoperative pain or discomfort after cell therapy [30, 31]. However, the results of one study demonstrated lower implant survival in cases of therapy with MSCs [33]. Many studies recommended using stem cells in implant placement due to the high percentage of vital bone content, short healing time, and higher success rate in the stem cell therapy group [34]. It was also found that stem cell therapy during dental implants significantly enhanced bone healing compared to dental implants without stem cells [30, 35, 36].

The evoked-bleeding technique has also been indicated to deliver stem cells into the root canal in teeth with apical lesions, and stem cell therapy was found as an alternative approach for treating maxillary bone defects, mandibular angle fractures, and other losses of bone substance [22, 37]. Regeneration of whole dental pulp was also possible using stem cell therapy, which may be of high importance and value for treating tooth wounds and large alveolar defects after traumatic dental injuries [24]. Healing of alveolar cleft defects using bone marrow stem cells resulted in reduced site morbidity and improved pain scores [16].

According to the results of studies, stem cell therapy is a recommended therapeutic method for dental implants, jaw reconstruction, expansive mandibular lesions, mandibular angle fractures, and maxillary sinus floor reconstruction. In addition, stem cell therapy can successfully treat craniofacial bone defects, impacted third molar, alveolar cleft defects, and bone tissue injury and defects after treatment of oral malignancies. Oral lesions, each with clinical and historical features and indicators surrounding this clinical diagnosis profile, make lesions possible for clinicians. These symptoms make accurate diagnosis difficult and may explain the frequent delay in early treatment. Higher healing rates minimized surgical procedures, and high efficiency are the most significant advantages of stem cell therapy in dental diseases [38, 39]. Regenerative dentistry has progressively been recognized as a state-of-the-art field of medicine among dental clinicians during dental treatments as a procedure of getting stem cells (from deciduous teeth, third molars, gingiva, etc.) and storing them for possible future autologous therapies. For achieving the last purpose, craniofacial regeneration, there has remained a long way to be covered in identifying the effective factors in immunomodulatory functions of adult mesenchymal stem cells and pluripotent stem cells. Such information is required for a more effective outcome of stem cell-based bone and periodontal tissue restoration, especially for transplanting at the aggravated sites [40]. Finally, it should be stated that stem cell therapy has a valuable therapeutic potential in oral diseases and regenerative medicine. Stem cell treatment provides less invasive and more conventional treatment to future patients. In brief, further research is necessary to understand the pathways and biology of healing processes in regenerative dental medicine, thus making the treatment more affordable and less complex [41].

Conclusion

Stem cell therapy can induce new bone formation and regeneration of dental tissue with no serious side effects or morbidities. The current study reviewed the variety and extension of stem cell applications in tissue-regenerative dentistry. Our findings favor using stem cells to treat dental diseases, including dental implants, traumatic tooth injury, and bone defects.

Ethical Considerations

Compliance with ethical guidelines

All methods were carried out in accordance with relevant guidelines and regulations.

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Authors contribution's

Conceptualization, study design, data interception, date analysis and supervision: Atena Shiva; Data acquisition, drafting of the manuscript, and critical revision for important intellectual content: Nika Rezaeikalantari; Administrative, technical, and material support: Parastoo Namdar; Statistical analysis: Rezvan Yazdian Robati; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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