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REVIEW ARTICLE

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State-of-the-Art of the Clinical use of Stem Cells from Deciduous Teeth: A Review

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Abstract: Introduction: In recent years, mesenchymal stem cells derived from dental tissue have gained popularity for applications in tissue engineering and regenerative medicine. **Objective:** To present the main considerations about stem cells of primary teeth, as well as the importance of their clinical application. **Methods:** Experimental and clinical studies were included (case reports, retrospective, prospective and randomized studies), following the rules of systematic review-PRISMA. The search strategy was performed on Medline / Pubmed, Web Of Science, ScienceDirect Journals (Elsevier), Cochrane Library, Harvard Library, Scopus, and OneFile (Gale). **Major findings and Conclusion:** Dental pulp stem cells from primary teeth have very promising properties and potential for bone TE; however, based on these findings and the well-known restrictions in stem cell research, it may be beneficial to at least standardize the methods currently used in animal models based on the bone defect to heal, in order to achieve a higher level of reliability results, enabling safe clinical use.

Keywords: Stem cell; Mesenchymal Stem cells; Deciduous Teeth; Harvesting; Clinical Applications.

1. Introduction

In recent years, mesenchymal stem cells (MSCs) derived from dental tissue have gained popularity for applications in tissue engineering and regenerative medicine [1]. The highly proliferative and self-renewing population of dental stem cells has the neural crest as its source. This expands its applicability for tissue regeneration of ectoquime and mesenchymal origin [1].

The ease of tissue collection, high initial cell yield, low population doubling time, plasticity, multipotential capacities, and immunomodulatory properties make MSC a suitable candidate for various therapeutic strategies. In addition, cells derived from dental tissue can be transformed into induced pluripotent stem cells to customize cell-based regenerative approaches [2].

Despite this, comparative profiles of these dental tissues and their regenerative applications are lacking. It is also necessary to perform morphofunctional analyzes and tissue engineering applications of MSCs that are derived from tooth germ, exfoliated primary teeth, periodontal ligament, gingiva, dental pulp, alveolar bone, dental follicle, and apical papilla. The immunoregulatory properties of dental stem cells provide the potential for autologous and allogeneic tissue engineering approaches [2].

Also, *in vitro* and animal studies show the promise of using dental stem cells in regenerative medicine. Eventually, the orchestration of clinical trials will require systematic monitoring of spontaneous in vitro transformations and complications associated with the graft versus host response, as well as a complete understanding of the underlying anabolic mechanisms [2].

In this sense, among the various sources of stem cells, the tooth pulp provides mesenchymal stem cells, multipotent and immunocompatible, that is, they can serve not only the donor but also the whole family [3]. Stem cells are cells that differentiate, giving rise to new cells of good quality, which can originate osteoblasts and, thus, achieve bone integration in less time for a dental implant, and maxillary bone elevation, and being able to reconstruct the dentin, in relation to tissue lesions [3,4].

In this context, stem cells of dental origin have tissue regeneration capacity and still induce bone regeneration of the maxilla. Therefore, they are indicated for treatments of degenerative diseases like traumatic bone loss [5]. The collection of the milk tooth is done during the period of changing the child's teeth between 5 to 12 years. With this, we conclude that the tooth is not an invasive process because the collection is only done when the tooth begins to exfoliate [6]. Since the nineteenth century, stem cells have been the subject of numerous studies, through which it has been discovered that pulp of deciduous teeth is a precious way of obtaining them, the collection of which has several advantages, such as not being invasive and respecting the period of teething exchange [7-9].

Therefore, the present study aimed to present the main considerations about stem cells of primary teeth, as well as the importance of their clinical application.

2. Methods

Experimental and clinical studies were included (case reports, retrospective, prospective and randomized studies) with qualitative and/or quantitative analysis. Initially, keywords were determined by searching the DeCS tool (Descriptors in Health Sciences, BIREME base) and then verified and validated by the MeSH System (Medical Subject Headings, the US National Library of Medicine) to achieve a consistent search.

2.1 MeSH Terms

The main descriptors (MeSH Terms) used were Stem cell; Mesenchymal Stem cells; Deciduous Teeth; Harvesting; Clinical Applications, following the rules of systematic review-PRISMA (Transparent reporting of systematic reviews and meta-analyzes-https: //www.prisma-statement.org/).

2.2 Sources of Information

The search strategy was performed on Medline/Pubmed, Web Of Science, ScienceDirect Journals (Elsevier), Cochrane Library, Harvard Library, Scopus and OneFile (Gale).

2.3 Eligibility

A total of 103 articles were found involving stem cells of deciduous teeth. Initially, the existing title was excluded and duplicated according to the interest described in this study. After this process, the abstracts were evaluated and a new exclusion was performed. A total of 35 articles were evaluated in full and 24 were included and discussed in this study (Figure 1).

3. Development and Literature Review

Mesenchymal stem cells (MSCs) are used clinically in tissue engineering and regenerative medicine. The potential for proliferation and osteogenic differentiation of MSCs varies according to factors such as tissue origin and heterogeneity of the cell population [9]. Dental tissue has received attention as an easily accessible source of high-quality stem cells. One study compared the in vitro characteristics of stem cells from human exfoliated deciduous teeth (SHED), human dental pulp stem cells (hDPSCs), and human bone marrow mesenchymal stem cells (hBMSCs). SHED exhibited greater proliferative activity and levels of gene expression of bFGF and BMP-2 compared to BMMSCs and DPSCs. The ease of collecting cells and the ability to avoid invasive surgical procedures suggest that SHED can be a useful source of cells for application in bone regeneration treatments [10].

The SHED were first obtained by Miura *et al.,* (2003) [11] and can differentiate into adipocytes, chondroblasts, osteoblasts, odontoblasts, and muscle cells in vitro. They can also differentiate into neural cell lines. In vivo, SHED does not differentiate directly into osteogenic cells, but they induce bone formation and assist in the process of angiogenesis. Furthermore, SHED has a higher rate of cell proliferation, shorter population doubling time, and clonogenic potential. As for the expression of surface markers, these two cell types are similar, being mesenchymal and negative markers for hematopoietic markers [11].

For the collection to be possible, it is necessary to register the dental surgeon to a cryogenic center and the authorization of those responsible for the donor child. The procedure should be performed in patients aged 6 to 12 years during the dental exfoliation phase, and the elements should not present carious lesions [12]. Preceded by intra and extraoral antisepsis, the elements (s) are extracted, with the shortest time and contact with the saliva, respecting strictly the aseptic chain. After the removal of any adherent soft tissues, the elements are immersed in a DMEM culture medium maintained at 4 to 8 ° C and directed to a laboratory for isolation and culture of the stem cell [12].

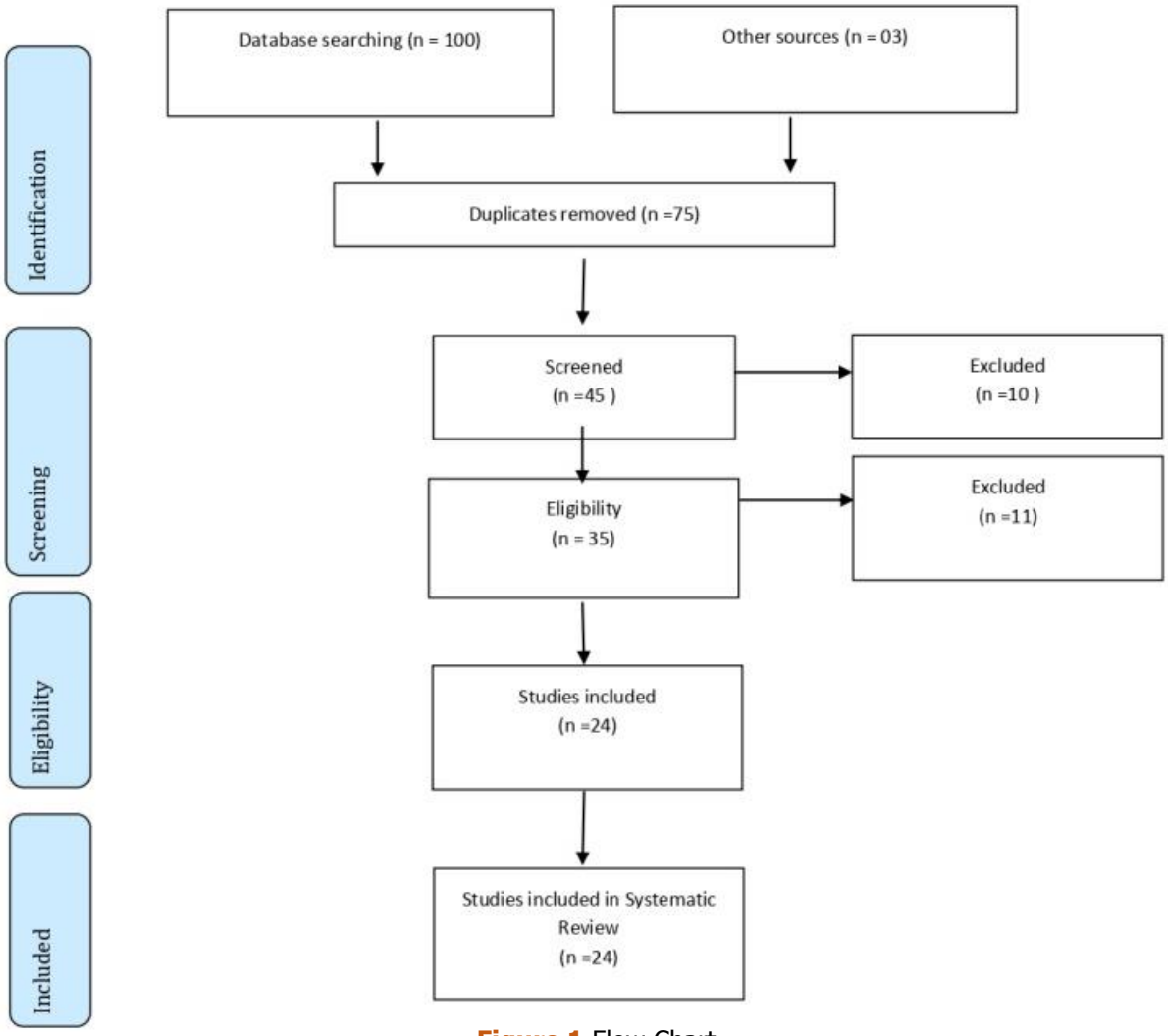

Figure 1 Flow Chart

After isolated and cultured, because they are mesenchymal stem cell, can be used for the therapy of the most diverse pathologies of the nervous system, vascular system, heart, skin, pancreas, liver, eyes, muscles, lungs, kidneys, cartilage, intestines, bones, among others [13]. The TCs acquired by this process can be stored indefinitely, being 100% compatible with the donor and relatives, making it impossible to reject them, besides allowing 20 possibilities of collection per child [13].

There is evidence that stem cells from deciduous teeth are similar to those found in the umbilical cord [14]. When compared to stem cells from the bone marrow and pulp of permanent teeth, SHED showed a higher rate of proliferation. Also, data from this study indicate that SHEDs can differentiate into functional odontoblastic cells, adipocytes, and neural cells, and stimulate osteogenesis after in vivo transplantation [15]. Research has shown that pulp stem cells require an appropriate inducing medium and a framework composed of hydroxyapatite/tricalcium phosphate to induce the formation of bone, cement, and dentin in vivo [15].

Some authors have demonstrated the formation of autologous fibrous bone tissue from stem cells from pulps of individuals over the age of 30 years, as well as the differentiation of these cells into odontoblasts [16]. The markers for the stem cells are of extreme importance because these cells reside in different places inside the tissue. Further studies are needed on specific markers that can identify niches of stem cells present in the dental pulp in situ and on how the development of these niches occurs [16]. Stem cells from the human pulp and periodontal ligament may be associated with the microvasculature [16].

The following microvascular markers are currently used for the localization of such cells: STRO-1 (stromal cell marker), Von Willebrand Factor and CD146 (endothelial cell surface molecule). The

expression of cellular telomerase in normal tissues seems to be associated with the presence of stem cells. In situ detection techniques of this ribonucleoprotein have the possibility to act as cellular markers [16].

In addition, researchers cultivated bone marrow and human pulp stem cells from impacted third molars and analyzed the gene expression of these cells through the Microarray cDNA method [17]. A highly similar gene pattern has been demonstrated between these two cell types, with the exception of a few genes, including IGF-2 (insulin-like growth factor-2) and type XVIII collagen 1, however, the expression of this difference is unknown [17].

Dental morphogenesis involves a series of dynamic and reciprocal interactions between the ectoderm and the mesenchyme. Growth factors are extracellularly secreted proteins that govern morphogenesis during such interactions and comprise five protein families: bone morphogenetic protein (BMP); growth factors for fibroblasts (FGFs); Hedgehog proteins (Hhs), wingless and int-related proteins (Wnts), and tumor necrosis factor (TNF) [17, 18].

Although these distinct families are involved in dental development, BMPs are sufficient for the formation of tertiary dentin. Some authors have further demonstrated that calcium-hydroxide-induced pulp regeneration is mediated by Notch cell-cell signaling. The results were consistent to affirm that this signaling controls the fate of stem cells from the pulp during its regeneration [19].

BMPs are also expressed in the starry enamel organ epithelium during the hood phase and are associated with the differentiation of ameloblasts and odontoblasts. Growth hormone may induce the expression of these BMPs during tooth formation. At the onset of dental morphogenesis, BMP-2, BMP4 and BMP-7 act as important epithelial flags that regulate differentiation of neural crest-derived mesenchyme in an odontogenic lineage. Such flags still determine the number and position of the tooth cusps [20, 21].

In this sense, a study identified and isolated stem cells from healthy and inflamed dental pulp and to characterize their differentiation potential in multiple strains. The study was carried out on dental pulp tissues obtained from children aged 5 to 14 years. Tissue samples were collected from teeth indicated for pulp therapy and extractions for orthodontic purposes. There was no statistical difference found in the expression of various surface markers between inflamed dental pulp and bone marrow. The healthy pulp of primary teeth was not enough to be used as a source for harvesting stem cells, also, the healthy tissue obtained from permanent teeth did not produce any results [22].

Still, a narrative review study investigated the implication of mesenchymal stem cells harvested from human dental pulp in bone tissue regeneration in vivo. A total of 1,021 studies were identified; after assessing eligibility, only 39 studies were included in the review. The main general evidence highlighted in the analysis is that stem cells from dental pulp and stem cells from human exfoliated primary teeth supported by an appropriate structure should be considered a valuable source for bone tissue regeneration.

The analysis evaluated studies focused on the functions of dental pulp stem cells DPSCs and SHEDs in bone tissue engineering (TE), to estimate the effectiveness of using permanent and primary teeth DPSCs for repair of bone defects. The main general evidence highlighted that DPSCs and SHEDs supported by an adequate scaffold should be considered a valuable source for the bone regeneration process.

The importance of improving the quality of life is also emphasized, therefore, future studies should focus more on the human being with the highest number of patients in the investigations and consider longer periods of evaluation [23].

4. Future perspectives

Investigations into the dental pulp as a source of stem cells for ET began in the last decade. Several studies involving different scaffolds, biomaterials, and in vivo models have been conducted. Even though in different ways, each of them demonstrated the ability of DPSCs to regenerate bone and repair the defect in vivo. However, each study used different strategies and methodologies including different sources of stem cells, the isolation method, scaffolding, bone defect, and animal model in vivo, basically affecting the resulting entity that makes it slightly variable between comments [24].

A reliable and meaningful conclusion about the implications of DPSC for bone regeneration must be postponed until the various factors that influence in vitro and in vivo results are limited as much as possible. For more practical and clinically applicable results, a standardization of the scientific methodology must be developed in order to be able to compare the results derived from different studies and, finally, open

the possibility of promoting the use of DPSCs / SHEDs for TE from the bench to the local bed [24].

5. Conclusion

DPSCs and SHEDs have very promising properties and potential for bone TE; however, based on these findings and the well-known restrictions in stem cell research, it may be beneficial to at least standardize the methods currently used in animal models based on the bone defect to heal, in order to achieve a higher level of reliability results, enabling safe clinical use.

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Authors Contribution

Data collection, analysis and preparation of initial draft (GCdSSS & ENK); Designing the study, data collection, analysis, preparation and finalising the manuscript (IJZF).

Data sharing statement

No additional data are available

Ethics Approval

Not Applicable

Informed consent

Informed written consent obtained from the participant

Conflict of interest

The authors declare no conflict of interest.

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