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Review Article

The role of stem cell therapy in endodontics and its future

Mohammad Khaled Aljifan[1]*, Abdulrhman Ali Alshuwayi[2], Abdulaziz Saeed Almatrafi[3], Abdulelah Mohammed Shukr[2], Khalid Abdullah Alshahrani[4], Abdullah Abdulelah Almuhanna[2], Mohammed Abdullah AlMuhanna[5], Khalid Nasser Alshammari[6], Ahmed Abdullah Alghamdi[7], Mazen Dhafer Albahri[8], Muath Muhammad Benten[9]

[1]North Jeddah Specialist Dental Center, King Abdullah Medical Complex, Jeddah, Saudi Arabia
[2]College of Dentistry, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia
[3]Al Noor Specialist Hospital, Mecca, Saudi Arabia
[4]Alawn Medical Center for Specialized Dental Clinics, Mecca, Saudi Arabia
[5]College of Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia
[6]Dental Department, Rayan Al-Sharq General Medical Complex, Hail, Saudi Arabia
[7]Zain Medical Complex, Taif, Saudi Arabia
[8]Enyati Medical Center, Najran, Saudi Arabia
[9]Dentist, King Abdulaziz University Dental Hospital, Jeddah, Saudi Arabia

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***Correspondence:**
Dr. Mohammad Khaled Aljifan,
E-mail: Dentistmoh@hotmail.com

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ABSTRACT

Regenerative therapy has been introduced in the literature for a long time and is currently being practiced in different fields, including dentistry and endodontics. Many applications have been reported in the literature for stem cell therapy. However, many complications and adverse events were reported in this context. The present literature review sheds more light on the clinical applications of stem cell therapy in regenerative endodontics and the future perspectives in this field. There are no doubts that there are many questions to be answered despite the huge advances in this field. In response to tissue injury, it has been shown that stem cell therapy can strengthen the efficacy of physiological response to these events and improve tissue regeneration. They can be used for managing cases of reversible pulpitis. Moreover, evidence indicates that they can enhance the revascularization of necrotic pulp tissues. Accordingly, these outcomes can significantly change the perspectives of clinical endodontic practice, and current root canal management modalities and perhaps draws researchers into discovering further future applications for other currently untreatable conditions. However, further future investigations are still needed to understand more about the mechanisms of these modalities and improve their clinical applicability.

Keywords: Stem cell, Regenerative therapy, Endodontics, Root canal treatment

INTRODUCTION

Teeth affected by traumatic events, dental war lesions or caries are indicated for management by conventional dental pulp therapy or restorations by root canal treatment and pulp capping. However, instead of removing the pulp, researchers aimed to develop strategies to preserve these structures and maintain the vitality and functions of affected teeth. Although the efficacy of root canal treatment might be up to 90%, it has been shown that failure of restoration has been reported in many events. This might be attributed to the presence of grossly-decayed coronal structures, immature roots, and root fracture and resorption.[1-3] Accordingly, various modalities were introduced to enhance the efficacy of

tooth restoration with no adverse outcomes over the function and vitality.

Regenerative therapy has been introduced in the literature for a long time and is currently being practiced in different fields, including dentistry and endodontics. Many applications have been reported in the literature for stem cell therapy. However, many complications and adverse events were reported in this context.[4,5] In the present literature review, we will discuss the different clinical applications of stem cell therapy and future perspectives in endodontics according to the findings of relevant studies in the literature.

LITERATURE REVIEW

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases on which was performed 3rd December 2021 using the medical subject headings (MeSH) or a combination of all possible related terms, according to the database. To avoid missing poetential studies, a further manual search for papers was done through Google Scholar, while the reference lists of the initially included papers. Studies discussing the role of stem cell therapy in endodontics were screened for useful information, with no limitations posed on date, language, age of participants, or publication type.

DISCUSSION

Clinical implications

Different implications were reported for using stem cell therapy in the field of regenerative endodontics. Some of the clinically reported implications for these modalities include postnatal stem cell therapy, root canal revascularization through blood clotting, pulp implantation, injectable scaffold delivery, and other regenerative applications in permanent immature traumatized teeth. Evidence shows that injectable scaffolds include hydrogels that can be injected into the targeted tissues via syringes. The main aim of injecting these modalities is to provide a substrate for cell proliferation and promote pulp regeneration into an organized tissue structure.[6] In addition to their outcomes, it has been reported that being easy to deliver and non-invasive modalities are also other advantages of these modalities in this context. It should be noted that hydrogels were reported to have a certain limitation, which is the hypothesized poor control over tissue development and formation. However, recent technological advances in this field enabled clinicians to overcome this limitation. This has been significantly associated with an improved quality of these modalities and enhanced their efficacies in improving cell survival.

Root canal necrosis and proper revascularization have been reported to be achievable with stem cell therapy. This can be done by over instrumentation to induce bleeding into the root canal system after adequate disinfection.[7-9] In this context, various advantages were reported for this approach. These include the fact that the patient's blood is used to induce regeneration of the root canal system. Accordingly, this can remarkably reduce the risk of infection transmission and immune rejection when replacing pulp tissues via an engineered tissue construct.[10] Another advantage of this method is the easy delivery and low cost of the associated procedures. It has been reported that it does not need expensive biotechnology and can be easily conducted with intracanal medicaments and available instruments.

Evidence shows that most in vitro cell cultures grow attached to the base of culture flasks as a single monolayer.[11] However, it has been shown that growing on top of a layer of feeder cells is necessary for the survival of some stem cells. In this context, theoretical evidence indicates that a biodegradable membrane filter can be used to grow pulp cells. This has been approached in cases when converting a 2D cell culture into a 3D one. Previous studies demonstrated that the main advantage of this approach is the east applicability and facilitated cell growth with favorable outcomes. However, there have been some concerns about the process of implanting sheets of culture pulp tissues. This includes the fact that sometimes specialized procedures are needed to enhance proper cell adherence to the canal wall.[10] In another context, previous studies also indicated the validity of stem cell therapy in achieving favorable outcomes regarding the regeneration of immature traumatized teeth. However, it has been reported that certain conditions and parameters are needed before achieving adequate revascularization and tissue regeneration. For instance, it has been indicated that treated teeth must be very immature and permanent with an open apex. Besides, these must also be non-suitable for apexogenesis and apexification, and nonvital. It has been furtherly shown that clinicians should also use a non-biocompatible endodontic sealer for regeneration. Besides, a thin layer of calcium hydroxide and MTA have been recommended to be placed over the targeted blood clot. Furthermore, when approaching the process of revascularization of the canal, a non-vasoconstrictor anesthetic is recommended. Finally, applying an antibiotic paste might also add to the disinfectant characteristics of sodium hypochlorite.[12]

Previous studies also reported favorable outcomes with using postnatal stem cell therapy injection. It has been shown that postnatal stem cell therapy injection is the most favorable approach to injecting stem cells with favorable regenerative abilities into the disinfected root canal system. These modalities can be obtained from different tissues, including bone, fat, buccal mucosa, and skin.[13] It should be noted that this approach is conducted after the apex has been opened. It has been shown that this approach has been associated with many advantages. For instance, it has been reported that it can effectively induce pulp tissue regeneration and autogenous cells are easy to deliver and harvest by a syringe.[14] Besides, the

approach has been reported with different fields rather than endodontics, like bone marrow transplantation practices, which indicates its validity. On the other hand, some obstacles and disadvantages were reported for this method.[15] Evidence shows that the cells have the potential to migrate to other parts of the body. Moreover, they usually have a low survival rate. Finally, reports showed that it is challenging to obtain these types of postnatal stem cells that can differentiate into different cells that are usually found in the dental pulp.[10]

It should be noted that there is small friction of multipotent cells within the dental pulp.[16] Moreover, the location of these cells in dental pulp is not adequately evident in the literature. However, it has been suggested that these modalities are present in the perivascular niches based on their characteristic phenotypes.[17] Among the different studies, evidence indicates that stem cells in human exfoliated deciduous teeth (SHED) and Permanent teeth - Dental pulp stem cells (DPSC) initially originate from within dental pulp tissues.[18] However, it has been shown that these cells usually have significant differences. For instance, studies show that DPSC cells usually have lower proliferative rates and lower levels of osteocalcin production, and levels of alkaline phosphatase activities.[19-21] In vivo studies concluded that regeneration of pulp-like and dentin tissues can be adequately achieved by DPSC and SHED cells. It is well-known that the pulp tissue is a highly innervated and vascularized tissue, enabling it to respond to different injuries and maintain tooth vitality.[19,22-24] Moreover, it has been shown that dentinogenesis is an important process that involves interaction between different tissues, including odontoblasts, nerves, and endothelial cells.[25] During caries progression and tissue invasion by bacteria, it has been reported that the first cells to respond to injury are the odontoblasts, which are defined as ecto-mesenchymal-derived cells.[26] Besides, the odontoblastic response is usually modulated by the nerve and endothelial cells, which are found in the vicinity of the carious lesion.[27-29] Primary odontoblasts also influence a dentin matrix release. During the physiological response to shallow caries, it has been shown that this matrix usually mineralizes.[30,31] Accordingly, these events can significantly maintain the integrity of dental pulp and protect it from irritants.

Endothelial cell survival and differentiation have been reported to be significantly enhanced by vascular endothelial growth factor (VEGF), which is the most efficacious angiogenic factor.[32-34] Furthermore, during both pathological and physiological events, it has been shown that VEGF usually has a vital role in controlling vascular permeability.[32] In vivo evidence also indicates that this modality is significantly expressed in the sub-odontoblastic layer and by odontoblasts.[35-37] Previous immunohistochemical investigations also demonstrated that VEGF is markedly expressed during caries-induced pulpitis within dental tissues of affected teeth.[38] Using biodegradable skin folds, it has been shown that seedings of various cell types can be used to generate tooth-like tissues. A common approach that has been described to achieve such outcomes has been reported in the literature. This is done through harvesting, differentiating, and expanding cells in vitro, folding them into scaffolds, and in vivo implanting them. Some evidence also shows that the jaw or an extracted tooth socket can be effectively used to reimplant these scaffolds. This has been indicated in a previous animal-based study, which reported that the authors transplanted a bioengineered tooth germ into the corresponding alveolar bone of a lost tooth. The authors reported replacing the lost tooth with a functioning one in an adult mouse.[39] Based on these findings, it has been suggested that such approaches can be effective in organ transplantation approaches.[40,41]

The approach has been demonstrated in different cases with cavities. However, some authors reported that the process could not be successfully achieved when pulp tissue compromise and extensive decays were detected. It should be noted that some studies also reported that the risk of developing cancers and tumors might be increased with stem cell therapy. For instance, during the process of stem cell expansion, evidence shows that these cells might not be capable of differentiating into the required cell types or lose the normal mechanisms controlling the process of growth and differentiation. In this context, it has been shown that embryonic cells might tend to develop tumor cells (namely teratomas) if they were not adequately directed to differentiate into more mature cells. Other complications (tissue rejections and infections) were also reported concerning stem cell transplantation procedures and the potential associated risks.[42,43]

Future perspectives

Many future challenges can be proposed for stem cell regeneration therapy in the field of endodontics. For instance, researchers should exert more effort into obtaining sufficient amounts of autogenous cells that can be applied for scaffold seeding. Besides, fabricating vascularized scaffolds might have a critical role in dental pulp tissue regeneration. Seeking modalities and innovating medications that can preferably control cell activities is also another challenge in this perspective. However, it should be noted that a better understanding of the mechanism of angiogenic response with stem cell therapy is important to innovate further approaches in this field and enhance the outcomes. However, this should be proceeded by more implications of using stem cell therapy in the daily clinical practice. The induction of regenerative growth factors should also be aimed through gene therapy to regenerate dental tissues. Research implications in this field should be strengthened and legalized because of its favorable advantages and reduced complications. Besides, developing a self-bank of cells and tissues might be adequate to overcome the ethical and immunological issues that are usually associated with using allogenic cells. In this context, it has been shown

that using stem cells or SHED from immature third molar teeth would be associated with many advantages regarding the ability to reduce traumatic injuries during permanent dentition and enhancing their abilities to proliferate.

CONCLUSION

There are no doubts that there are many questions to be answered despite the huge advances in this field. In response to tissue injury, it has been shown that stem cell therapy can strengthen the efficacy of physiological response to these events and improve tissue regeneration. They can be used for managing cases of reversible pulpitis. Moreover, evidence indicates that they can enhance the revascularization of necrotic pulp tissues. Accordingly, these outcomes can significantly change the perspectives of clinical endodontic practice, and current root canal management modalities and perhaps draws researchers into discovering further future applications for other currently untreatable conditions. However, further future investigations are still needed to understand more about the mechanisms of these modalities and improve their clinical applicability.

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