Root canal revascularization

The beginning of a new era in endodontics

Mothanna K. Alrahabi, *MSc, PhD,* ***Mahmoud M. Ali,*** *DDS, MSc.*

ABSTRACT

تعتبر معالجة اللب المتموت للأسنان الأمامية تحدياً كبيراً وبالرغم من وجود إجراءات علاجية مختلفة للتعامل مع هذه المشكلة مثل انغلاق قمة الجذر باستخدام ماءات الكالسيوم أو بتطبيق حاجز من مادة ثلاثية الأكاسيد المعدنية وحشوة الطبرخي إلا أن النتائج لا تزال غير مرضية والجذر يبقى ضعيفا. حديثاً تم إدخال بروتوكول علاجي بإعادة التوعية لجذور الأسنان غير الناضجة والمصابة بالعدوى ومتموتة اللب وذلك لإعادة تشكل البنى السنية واكتمال نضج الجذر. ومع ذلك فإنه لقبول إعادة التوعية الدموية كأسلوب علاجي لتدبير جذور الأسنان غير الناضجة والمصابة بالعدوى فإننا نحتاج للعديد من الحالات وفترة طويلة من المتابعة. لقد حاولنا من خلال هذه المقالة تسليط الضوء على مفهوم إعادة التوعية للقناة الجذرية وآلية إعادة التوعية وكذلك بنية النسج المتولدة.

Endodontic management of immature anterior teeth with necrotic pulps is a great challenge. Although there are different treatment procedures to deal with this problem such as apexification by using calcium hydroxide dressings or applying a barrier of mineral trioxide aggregate and gutta-percha obturation, the outcomes are still unsatisfactory and the root might still be weak. Recently, a new treatment protocol by revascularization of immature non-vital, infected teeth was introduced to regenerate dental structure and complete the root maturation. However, larger case series with longer follow-up periods are required to accept revascularization as the standard protocol for management of immature non-vital, infected teeth. In this review, we discuss the concept of root canal revascularization, revascularization mechanisms, and the structure of the regenerated tissues.

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From the Department of Restorative Dental Science, College of Dentistry, Taibah University, Al Madinah AlMunawwarah, Kingdom of Saudi Arabia.

Address correspondence and reprint request to: Dr. Mothanna K. Alrahabi, Department of Restorative Dental Science, College of Dentistry, Taibah University, PO Box 2898, Al Madinah AlMunawwarah 43353, Kingdom of Saudi Arabia. Tel/Fax. +966 (14) 8384145. E-mail: dr.rahabi@gmail.com / mrahabi@taibahu.edu.sa

Traumatic dental injuries (TDI) among young children are common problems with great frequency in preschoolers, school-age children, and young adults comprising 5% of all injuries for which people seek treatment;[1,2] 25% of all school children experience dental trauma.[3] The traumatic injury of an immature permanent tooth can cause pulpal necrotic and interrupted root development. The results of arrested root development are a poor crown-root ratio, a root with very thin walls, an increased risk of fracture, and an open apex.[4] The treatment of an immature tooth with necrotic pulp and an open apex is considered a challenge to the dentist.[5] The traditional treatment of immature teeth with necrotic pulps relied on apexification procedures or the use of apical barriers.[6] In 2004, Banchs and Trope[7] published a case report describing a new treatment procedure for the management of the open apex called "revascularization," which was a great step forward, and the beginning of a new era in the endodontics world. Revascularization procedures are unlike traditional apexification or the use of apical barriers; in revascularization both the root thickness and length continue developing.[5] The purpose of this review is to discuss revascularization, the biological basis for root canal revascularization, its mechanisms, histological characterization of regenerated tissue, outcomes of root canal revascularization, and the implications for the future.

Apexification. Apexification can be defined as a method to induce a calcified barrier in a root with an open apex, or the continued apical development of an incompletely formed root in teeth with necrotic

pulps.[8] Calcium hydroxide pastes were the material of choice for apexification.[9,10] However, there are several disadvantages of apexification with calcium hydroxide. These include multiple visits over an extended time for 3-24 months,[11,12] microleakage around provisional restorations, cervical fracture, and reduction of fracture resistance of root structure.[13-15] Recently, a mineral trioxide aggregate was suggested as an alternative to calcium hydroxide, and has been used in one-step apexification procedures by creating an apical barrier on which the obturation material can be compacted.[16] Despite its good physical and biologic properties, extended setting time has been a main disadvantage. The continuity of root development (length, wall thickness, and apical closure) cannot be achieved by apexification, and the root will still be weak and highly susceptible to fracture.[17,18] Therefore, we need a new approach that can induce the maturation of the root, increasing root thickness, and length.

Root canal revascularization. Revascularization can be defined as a restoration of blood supply.[8] The concept of treatment of pulpal necrotic teeth with an open apex by revascularization was introduced by Ostby in 1961.[19] Rule and Winter in 1966[20] published a report on the development of apical closure in cases of pulpal necrosis in children. In 1972, Ham et al[21] demonstrated the ability of apical closure in the immature pulpless teeth of monkeys. A series of reports[7,22,23] drew attention to this treatment protocol and encouraged further studies.[24-26] While several clinical methods were reported in root canal revascularization, there are common steps such as: disinfecting the root canals using either Ca(OH)2 or triple antibiotic paste, inducing intracanal bleeding through the apical foramen, and allowing endogenous mesenchymal stem cells (MSCs) to resume odontogenic differentiation and complete the root formation. Treatment considerations based on a review of case studies have been developed by The American Association of Endodontists (AAE) that are available in the AAE website (https://www.aae.org/regenerativeendo/)

Biological basis for root canal revascularization. The development of tissue engineering has seen major progression in the past years. Regenerative endodontics are an alternative treatment approach that builds on the principles of regenerative medicine. The key ingredients for tissue engineering in this field are: stem cells, growth factors, and scaffolds. A stem cell is commonly defined as a "cell that has the ability to continuously divide and produce progeny cells that differentiate (develop) into various other types of cells or tissues."[27] Four types of human dental stem cells have been identified: (i) dental pulp stem cells (DPSCs),[28] (ii) stem cells from human exfoliated deciduous teeth (SHED),[29] (iii) stem cells from apical papillae (SCAP),[30,31] and (iv) periodontal ligament stem cells (PDLSCs).[32] The second key ingredient of tissue engineering is the growth factor. Growth factors are proteins that bind to receptors on the cell and act as signals to induce cellular proliferation and/or differentiation.[33] There are several growth factors that play an important role in endodontic regeneration. These include platelet-derived growth factor, transforming growth factor β, bone morphogenetic protein, vascular endothelial growth factor, fibroblast growth factor, insulin-like growth factor, and nerve growth factor. **Table 1** summarizes growth factors that have effects in regenerative endodontics with some of their effects. The last element of tissue engineering is the scaffold. The scaffold provides a 3-dimensional microenvironment for stem cells and promotes growth and differentiation.[47] There are specific requirements that must be achieved in scaffolds. They should contain growth factors to help in stem cell proliferation and differentiation. Additionally, scaffolds should be effective for transport of nutrients, oxygen, and waste. Lastly, they should have high porosity and suitable pore size to facilitate cell seeding and diffusion throughout the whole structure of both cells and nutrients.[48,49] There

Table 1 - Summary of growth factors that effect regenerative endodontics.

Growth factor	Effects
Platelet-derived growth factor (PDGF)[34-36]	Cell proliferation Dentin matrix synthesis Odontoblastic differentiation Dentinogenesis
Transforming growth factor-β (TGF-β)[37,38]	Cell proliferation Extracellular matrix synthesis Odontoblastic differentiation Dentinogenesis Chemotaxis
Bone morphogenetic proteins (BMPS)[39,40]	Odontoblastic differentiation Dentinogenesis
Vascular endothelial growth factor (VEGF)[41,42]	Odontoblastic differentiation Cell proliferation
Fibroblast growth factor (FGF)[43,44]	Chemotaxis Cell proliferation Dentinogenesis
Insulin-like growth factor (IGFS)[45]	Cell proliferation Odontoblastic differentiation
Nerve growth factor (NGS)[46]	Odontoblastic differentiation

are 2 essential groups of scaffold materials: the biological or natural group, which contain collagen, hyaluronic acid, chitosan, and chitin, and the artificial or synthetic group which contain polylactic acid, polyglycolic acid, tricalcium phosphate, and hydroxyapatite.[50,51] Peptide hydrogel nano fibers and various fibrin gels have been investigated as new scaffolds for dental pulp tissue engineering.[52]

Mechanism of root canal revascularization. There are different explanations for the revascularization mechanism. The first of which is the possibility of vital pulp cells remaining at the apical area of the root, after which, these cells proliferate and differentiate into odontoblasts in addition to the organization of Hertwig's epithelial root sheath cells, which resist destruction.[21] These new odontoblasts form new dentin and close the apex. The second explanation behind the apical maturation following root canal revascularization is the availability of multipotent dental pulp stem cells in permanent teeth.[53] They are profusely present in teeth with incompletely developed apeces (apices). These cells might be present in the apical dentinal walls and may differentiate into odontoblasts and form dentin. The third possible mechanism that may explain the root canal revascularization is the presence of stem cells in the periodontal ligament.[54,55] These cells proliferate and form hard tissues in the apical area. The fourth hypothesis of the root canal revascularization mechanism could be attributed to stem cells from the apical papilla or the bone marrow. The over instrumentation of the immature root canal causes bleeding, which implants mesenchymal stem cells from the bone into the root canal. These cells have the ability to form bone and dentin.[56,57] The last mechanism of root canal revascularization is the growth factors that are present in abundance in blood clots and have important effects as mentioned above. The growth factors include platelet-derived growth factor, vascular endothelial growth factor (VEGF), platelet-derived epithelial growth factor, and tissue growth factor. These growth factors might stimulate the formation of fibroblasts, odontoblasts, cementoblasts, and so forth from the mesenchymal cells in the newly formed tissue matrix. Expression of VEGF has been evidenced in immature and mature permanent teeth.[58]

Histological characterization of regenerated tissue in root canal revascularization. What is the type of regenerated tissue after root canal revascularization? Is there any difference in histological structure of the regenerated tissues between necrotic cases and irreversible pulpitis cases? These questions puzzled clinicians as the histological structure of regenerated tissue is poorly investigated. The available studies were conducted on immature teeth of animals with pulp necrosis and apical periodontitis. Based on the histological examination reported in these studies,[25,59,60] mainly 3 types of tissue were generated in the canal space: (1) cementum-like tissue termed herein "intracanal cementum" (IC) along the dentinal walls causing the thickening of the root, (2) bone or bone-like tissue: observed in the canal space in many cases and termed "intracanal bone" (IB), and (3) connective tissue similar to periodontal ligament (PDL-like tissue) was also present in the canal space surrounding the IC and/or IB. These tissues do not function like pulp tissues and are not pulp parenchymal tissue; therefore, revascularization in these cases is not due to tissue regeneration but rather wound repair. An immunohistological investigation performed to determine the nature of newly formed tissues after revascularization procedures carried out on immature dog teeth showed that new mineralized tissues were formed in the canal space but the nature of these tissues were not clear.[61] These regenerated tissues were 2 types of mineralized tissues, dentin-associated mineralized tissue (DAMT), and bony islands (BIs). Based on both Picro Sirius Red staining protocol staining patterns and immunohistochemical analysis, DAMT was clearly different from dentin and bone, and the Picro Sirius Red staining protocol staining pattern for BIs was similar to a woven bone-like structure. Revascularization is a histological process and cannot be observed radiographically; therefore, the histological structure of regenerated tissues in human revascularized immature permanent teeth is guesswork because there are no available histological studies. However, a recently published case reports[62-64] of an extracted immature human teeth with a chronic apical abscess and apical periodontitis revealed that the tissues formed in the root canal of this previously revascularized human tooth are similar to cementum- or bone-like tissue and fibrous connective tissue. In another 2 studies,[65,66] and based on the histologic observation of a human immature permanent teeth with irreversible pulpitis, there was regeneration of pulp-like tissue because, both the apical papilla and the Hertwig's epithelial root sheath survived.

Outcomes of root canal revascularization. There is no definitive description of the outcomes of root canal revascularization.[67-69] The evaluation criteria of the outcome should consist of clinical and radiographic examinations. In the clinical examination there should be no pain to percussion/palpation, and no soft-tissue swelling or sinus tract formation. The radiographic findings should reveal resolution of an apical radiolucency if it were present before treatment,

an increased width of root walls, and an increased root length.[70] Many human case reports show good clinical outcomes (absence of clinical signs and symptoms, radiographic evidence of apical pathosis healed, continued root development, and increased canal wall thickness) for immature permanent teeth with pulpal necrosis following root canal revascularization procedures.[71-74] A recent report on revascularization outcomes[75] showed 90.3% resolution of the periapical radiolucency. Apical closure was assessed as incomplete in 47.2% and complete apical closure in 19.4% of cases. Quantitative assessment showed change in root length varying from -2.7% to 25.3%, and change in root dentin thickness of -1.9% to 72.6%.

What does the future hold? Treatment of immature teeth is undergoing dramatic changes. The conventional endodontic treatment can control infection, while the root development usually remains impaired. Therefore, a regenerative endodontic procedure, the revascularization method, can now control the infection, and enable such teeth to continue root development. Future studies could focus on the applications of using scaffolding as a drug delivery system by incorporating different antibiotics, individually and combined, into the scaffold along with bioactive molecules such as growth factors to improve the scaffold's tissue regenerative capacity.[76,77] Another research area could be that the irrigation regimen for regenerative endodontics should be considered not only for antimicrobial effectiveness, but also for the ability to promote stem cell survival.[78] Dental pulp stem cells are another area of innovation in regenerative endodontics;[79] however, one must recognize the presence of substantial barriers in terms of clinical applications of dental stem cells, and those include scientific, ethical, and commercial barriers. Future directions involve the fabrication of scaffolds that are able to have a sustained release of growth factors and stem cells with the aim of complete and true biological regeneration to restore the original tissues.

In conclusion, regenerative endodontics is a promising and innovative trend in treatment, and may change many of our concepts in root canal treatment. Regenerative endodontics proposes to stimulate the self-healing ability of the body, modulating the immune-inflammatory response of tissues and enabling a regeneration of the root system, with a minimally invasive therapeutic technique. Although there are still significant scientific challenges to overcome, the continued growth of knowledge and understanding of regenerative therapy will help to make the regenerative endodontic concept a routinely applied clinical procedure.

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