

Review Article

Apexogenesis and Apexification - Review

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Abstract

The role of dental pulp in the development of the teeth. Young patients with infected or damaged tooth pulp still present a challenge among practitioners due to the degree of tooth development, more specifically the permanent teeth that have not completed their root development.

At the time of eruption, only two thirds of the tooth root is developed. If there is a disruption of pulp vitality before the full root development, the root growth and dentin formation stop, resulting in reverse-tapered or flared roots and an opened apex, which will make the future root canal treatment difficult.

In these cases, we can find teeth with short roots, very thin walls and an inadequate crown-root ratio. The thin root walls increase the risk of fracture. We currently have several therapies available to treat these teeth, which we will discuss further on.

Keywords: Apexogenesis, Apexification; Root Development; Biodentine; Calcium Hydroxide; MTA

The Root Development

It begins when the formation of enamel, respectively dentin, reaches the future enamel-cementum junction. In this stage, the epithelium of the outer and inner enamel is no longer separated from the stellate reticulum and the intermediate layer, because an epithelial wall develops in two layers that leads to the formation of Hertwig's epithelial sheath. When the differentiation of the root cells into odontoblasts begins and the first layer of dentin has been deposited, Hertwig's epithelial sheath begins to disintegrate and loses its continuity and close

relationship with the root surface [1,2].

Its remains persist as an epithelial network of fibers or tubules near the external surface of the root. This Hertwig root epithelial sheath is responsible for the formation of the root or roots. The epithelial diaphragm surrounds the apical opening of the pulp, eventually becoming the apical foramen [3,4].

Pulp Lesions of The Teeth with Developing Roots

Apical closure occurs approximately 3 years after tooth eruption. Traumatic injuries of the young permanent teeth are not uncommon and is said to affect 30% of children, most incidents occur before root formation is complete and they can lead to pulpal inflammation or necrosis.

Hertwig's epithelial sheath is sensitive to trauma, but due to the degree of vascularization and the multitude of cells in the apical region, root formation continues even in the presence of pulpal inflammation and necrosis [5,6].

Because of the important role of the sheath in continued root development, after pulpal injuries, should be made every effort to maintain its viability. It is assumed to be a source of undifferentiated cells that could give rise to subsequent hard tissue formation. It may also protect against the growth of periodontal ligament cells into the root canal, which would lead to intracanal bone formation, stopping the root development [7].

Complete destruction of Hertwig's epithelial sheath results in cessation of normal development. This does not mean, however, that there is an end to hard tissue deposition in the apex region. When the sheath has been destroyed, there can be no further differentiation of odontoblasts, but the hard tissue can be formed from cementoblasts that are normally present in the apical region, and the fibroblasts of the dental follicle and periodontal ligament that undergo differentiation after injury to become hard tissue producing cells [8].

The Diagnosis

A careful evaluation of the case followed by pulpal diagnosis in the treatment of immature teeth with pulpal lesions cannot be omitted or superficial. Clinical evaluation of the pulp requires a thorough history of subjective symptoms, a careful clinical and radiographic examination, and the performance of diagnostic tests. The duration and character of the pain and the factors that aggravate it and those that relieve it must be taken into account. The duration of pain can vary, an indication of irreversible pulpitis in a tooth with vital pulp is the pain, it lasts more than a short period (a few seconds). When the pain is spontaneous and severe and long-lasting, this diagnosis is almost certain. If the pain is throbbing and the tooth is sensitive to touch, pulpal necrosis with apical periodontitis or acute abscess is likely. We can do a visual examination, percussion and thermal and electrical pulp testing. The presence of a swelling indicates pulp necrosis or acute or chronic abscess. Tenderness to percussion signifies inflammation in the periapical tissues.

Vitality testing in immature teeth is unreliable because these ones give unpredictable responses to pulp testing. Before root formation is complete, the sensory plexus of nerves in the subodontoblastic region is not well developed and the lesion itself may lead to false responses [9]. No great reliance should be placed on the results of clinical tests of pulp vitality, especially through the use of electrical testing devices. Interpreting exams imaging can be difficult. A radiolucent zone normally surrounds the developing open apex of an immature tooth with a healthy pulp, making it difficult to differentiate it from a pathologic radiolucency of a necrotic pulp. A help in this case is the comparison with the contralateral tooth [10].

By combining the results of the history, examination and diagnostic tests, it is hoped that an accurate diagnosis will be obtained. The clinical diagnosis of pulp vitality can be made in most of the cases. When the pulp is considered vital, apexogenesis techniques can be attempted. A necrotic pulp condemns the tooth to apexification.

Apexogenesis

Apexogenesis consists in removing the inflamed pulp and placing calcium hydroxide on the remaining healthy pulp tissue. Traditionally, this method involves removing the coronal portion of the pulp. However, the depth to which the tissue is removed must be determined by the respective clinical case. Only the inflamed tissue is removed, but it is difficult to determine the level of inflammation. Several clinicians have found that after the mechanical exposure of the pulp and leaving it untreated for approximately 160 hours, the inflammation was limited to a part of 2-3 mm coronary [11]. This led to the development of superficial pulpotomy, also known as Cvek, in which only the most superficial part of the pulp is removed.

Webber states the following, as objective of apexogenesis [12]:

1. Supporting a Hertwig sheath, it so allows a continued development of a root length for a more favorable crown-root ratio
2. Maintaining pulp vitality, allowing the remaining odontoblasts to deposit dentine, producing a thicker root and decreasing the chance of fracture
3. Closing the root end, thus creating a natural apical constriction for the following obturation of the root canal

4. The formation of a dentine bridge at the pulpotomy site

Approximately, the total time to achieve the goals varies between 1 and 2 years, depending on the degree of development of the tooth at the time of procedure. The patient should be recalled every 3 months to determine the vitality of the pulp and the degree of apical maturation. If the pulp has become irreversibly inflamed or necrotic, or if internal resorption is evident, the pulp should be excised and apexification therapy initiated [12].

Apexification

Open apex management techniques in non-vital teeth were limited to customization of obturation material, paste obturation and apical surgery. Several clinicians have suggested the use of custom gutta-percha cones, but this method is not recommended because the apical portion of the root is sometimes wider than the coronal portion, making it impossible to properly condense the gutta-percha. Sufficient widening of the coronal segment so that its diameter is greater than that of the apical portion can significantly weaken the root and increase the risk of fracture [13-16].

Disadvantages of surgery include the difficulty of achieving the necessary apical seal in the young tooth with thin, fragile, irregular root apex walls. These walls may break during cavity preparation or filling material condensation. The wide foramen results in a large volume of filling material and a compromised seal. Apical resection reduces even more the length of the root, resulting in an unfavorable root-to-crown ratio. The limited success enjoyed by these procedures has led to significant interest in the phenomenon of continuous apical development or establishment of an apical barrier, first proposed in the 1060s. Several techniques have been suggested to induce the apical closure for the pulp less teeth, in order to produce the most favorable conditions for conventional obturation of the root canal [17,18].

Most techniques involve removal of necrotic tissue, followed by canal debridement and placement of a drug. However, the need for a drug to induce the formation of the apical barrier has not been conclusively demonstrated.

Nygaard-Ostby hypothesized that puncture injury to the periapical tissues until bleeding occurs may produce new vital vascular tissue in the canal. He suggested that the treatment “may lead to further development of the apex” [19].

Moller, et al., showed that infected necrotic pulp tissue induces strong inflammatory reactions in the periapical tissues. Therefore, removal of the infected pulp tissue should create an environment conducive to apical-to-apical closure without the use of a drug [20]. McCormick, et al., hypothesized that root canal debridement and removal of necrotic pulp tissue and microorganisms are the critical factors in apexification [21].

Cooke and Robotham hypothesize that the remnants of the epithelial sheath of Hertwig, under favorable conditions, can organize the apical mesodermal tissue into root components. They recommend avoiding trauma to the tissue around the apex. This theory is supported by Vojinovic and Dylewski [22,23].

Materials and Methods

Immature teeth undergoing apexification are in most cases disinfected with irrigant, including NaOCl, chlorhexidine, EDTA and potassium iodide [24]. The canal is then filled with $\text{Ca}(\text{OH})_2$ paste for further disinfection and induction of an apical barrier. $\text{Ca}(\text{OH})_2$ is antimicrobial due to its release of hydroxyl ions, which can cause damage to bacterial cellular components. The best example is the demonstration of its effect on Lipopolysaccharide (LPS). $\text{Ca}(\text{OH})_2$ chemically alters LPS which affects its various biological properties [25].

Root canal obturation is normally achieved when the apical barrier is formed. Without the barrier, there is nothing against which the traditional gutta-percha material can be condensed. In addition to $\text{Ca}(\text{OH})_2$ functioning as a powerful disinfectant, osteo-inductive properties have also been suggested, although it has been difficult to demonstrate this effect *in-vitro* [26,27]. It has been suggested that high pH may be a factor contributing to the induction of hard tissue formation [28]. The time required for apical barrier formation in $\text{Ca}(\text{OH})_2$ apexification can be considerable, sometimes up to 20 months, and other conditions, such as age

and the presence of symptoms or periradicular radiolucency, can affect the time required for apical barrier formation. Replenishment of the $\text{Ca}(\text{OH})_2$ paste usually occurs every 3 months [24]. A number of deficiencies can be summarized for $\text{Ca}(\text{OH})_2$ apexification:

1. The long duration of the treatment
2. Multiple visits and significant unavoidable clinical costs
3. Increased risk of dental fracture in the case of using $\text{Ca}(\text{OH})_2$ as a dressing on long term for the root canal [29]. These disadvantages led to the use of Mineral Trioxide Aggregate (MTA) to fill the apical segment, without the need to form a calcified barrier

Compared to $\text{Ca}(\text{OH})_2$, some studies have shown that MTA stimulates more hard tissue production. The results were obtained based on *in-vivo* tests in dogs [30].

The use of MTA for apexification may shorten the treatment period with more favorable outcomes and improves patient compliance [31].

Many authors and clinicians suggest a single-session apexification protocol with MTA, which presents major advantages over $\text{Ca}(\text{OH})_2$ methods [32]. This rapid cleaning and shaping of the root canal system, followed by apical sealing with MTA, makes possible the rapid definitive restoration of the canals, which can prevent possible fractures.

While the advances with MTA and definitive restorations are moving towards a better result, ultimately no apexification method can produce the result obtained through apexogenesis, i.e., apical maturation with increased root thickness. As already mentioned, after the apexification of teeth with thin and weak roots, even after a successful treatment, they are very susceptible to fractures [29]. Therefore, alternative approaches that allow for increased root thickness and/or length should be pursued.

Calcium Hydroxide

Although a multitude of materials have been proposed to induce the apical barrier formation, calcium hydroxide is the most widely accepted. The use of calcium hydroxide was first introduced by Kaiser in 1964, who proposed that this material mixed with parachlorophenol camphorate (CMCP) would induce the formation of a barrier at the level of the apex [33]. This procedure was supported by Frank who emphasized the importance of reducing the contamination inside the root canal through instrumentation and medication and its temporary obturation with a resorbable paste [34]. Some studies have reported a high level of success following the use of calcium hydroxide in combination with CMCP [35-37]. Klein and Levy and others have described the successful induction of an apical barrier using calcium hydroxide and cresatin (Premier Dental Products) [38-40]. Cresatin has been shown to have minimal inflammatory potential and to be significantly less toxic than CMCP [41,42]. To further reduce the potential for cytotoxicity, the use of calcium hydroxide mixed with saline, sterile water or distilled water has been successfully investigated [43-46]. Heithersay and others used calcium hydroxide in combination with methylcellulose (Pulpdent Corporation, Watertown, MA, USA) [47-50]. Pulpdent has the advantage of low solubility in tissue fluids and a firm physical consistency [51].

Because the calcium ions in the calcium hydroxide dressing are not derived from this one but from the bloodstream, the mechanism of action of the hydroxide in inducing an apical barrier remains controversial [52,53]. Mithcell and Shankwalker studied the osteogenic potential of calcium hydroxide when implanted into the connective tissue of rats [54]. It was concluded that calcium hydroxide has a unique potential to induce heterotropic bone formation.

Holland, et al., demonstrated that the response of periapical tissues to calcium hydroxide is similar to that of pulp tissue. Calcium hydroxide produces a multilayered necrosis with underlying mineralization [55]. Scroder and Granath postulated that the layer of firm necrosis generates a low-grade irritation of the underlying tissue sufficient to produce a matrix that mineralize [56]. Calcium is attracted to the area and mineralization of the newly formed collagenous matrix is initiated from the calcified outbreaks.

It appears that the high pH of calcium hydroxide is an important factor in its ability to induce hard tissue formation. Javelet, et al., compared the ability of calcium hydroxide (pH 11.8) and calcium chloride (pH 4.4) to induce the formation of a hard tissue barrier in immature, pulpless monkey teeth [57]. Periapical repair and apical barrier formation occurred more readily in the presence of calcium hydroxide.

Apical barrier formation has been shown to be more successful in the absence of microorganisms and the antibacterial efficacy of calcium has been established [58-64]. Antimicrobial activity is related to the release of hydroxyl ions, which are highly oxidizing and exhibit extreme reactivity. These ions cause bacterial cytoplasmic membrane damage, protein denaturation, and bacterial DNA damage.

The hard tissue barrier was described by Ghose, et al., as a cap, bridge, or slushy wedge and may be composed of cementum, dentin, bone, or "osteodentin" [32,65]. This osteodentin appears to be formed from connective tissue at the apex. Torneck, et al., reported that a bone-like tissue was deposited on the inner walls of the canal, while Steiner and Van Hassel demonstrated apical closure by the formation of a calcium bridge that met the usual histological criteria for identification as cementum [66,67]. Study of serial sections gave the impression that cementum formation occurs from the periphery of the initial apex towards the center in descending concentric circles. Despite radiographic and clinical evidence of complete epical bridge formation, the barrier has been shown histologically to be porous [67-69]. Histological analysis of the apical barrier demonstrated that the external surface of the bridge extended over the apex of the root "like a lid", showing irregular topography, with convexities and depressions [70]. Histological sections showed distinct layers. The outer layer appeared to be composed of a dense acellular centum-like tissue. This surrounded a more central admixture of irregular dense fibrocollagens connective tissue containing foreign material with irregular fragment of intensely mineralized calcifications.

There is controversy over whether or how often the calcium hydroxide dressing should be changed. Chawla suggests that a single application is sufficient and should wait for radiographic evidence of barrier formation, while Chosack, et al., stated that no improvements were found after successive application at one or 3 months, compared to the initial application [71,72]. Proponents of a single application claim that calcium hydroxide is only necessary to initiate the healing reaction, subsequent application not guaranteeing better results. A number of authors propose that calcium hydroxide should be replaced only when symptoms worsen or when it is no longer visible on radiographs [73,74]. Abbott points out that radiographs cannot be relied upon to determine the amount of calcium hydroxide remaining in the canal or to demonstrate whether the barrier is complete or not [75]. He concludes that regular dressing replacement has a number of advantages. It allows clinical assessment of barrier formation and may increase the rate bridging [76-78]. Abbot suggests that the ideal time of dressing replacement depends on the stage of treatment and the size of the foramen opening [75].

Studies vary in the evaluation of the time required for the formation of the apical barrier in apexification when calcium hydroxide is used. In a review of ten studies, Sheehy and Roberts reported an average duration of time for the formation of the apical barrier between 5 and 20 months [79]. Finucane and Kinirons analyzed 44 immature non-vital incisors undergoing apexification with calcium hydroxide and found that the mean time to barrier formation was 34.2 weeks (range between 13 and 67 weeks) [78]. The change of calcium hydroxide and a narrower initial apical width favored faster barrier formation. Age can inversely influence the time required for barrier formation. In one study, patients of 11 years or older benefited from significantly shorter treatment [76]. Others, however, refute this Cvek reported that infection and/or the presence of periapical radiolucency at the start of treatment increased the time required for barrier formation, but other studies indicated no relationship between pretreatment infection and periapical radiolucency and barrier formation time [65,73,76,80,81]. Kleier and Barr demonstrated that in the presence of symptoms, the time to apical closure was prolonged by approximately 5 months to an average of 15.9 months [80].

In a review of 10 studies, Sheehy and Roberts reported that the use of calcium hydroxide for apical barrier formation was successful in 74-100% of cases [79]. They point out that case monitoring is necessary and information on long-term outcomes is limited. Problems such as reinfection and fracture of the cervical root can occur.

Mineral Trioxide Aggregate

In the last two decades, MTA has become one of the most studied endodontic materials. The 1-3 trioxide aggregate in MTA

consists of calcium, aluminum and selenium. MTA has some desirable properties in terms of biocompatibility, bioactivity, hydrophilicity, radiopacity, ability to sealing and low solubility. The most important of these are biocompatibility and sealing ability. High biocompatibility aids optimal healing. This was observed histologically in the areas of periradicular tissues and a low inflammatory response with the formation of bridges in the pulp space. The resulting barrier is due to its properties of expansion and contraction, been very similar to dentin, which results in high resistance, through the formation of the apical plug, which prevents the passage of material into the periradicular tissues and the migration of bacteria into the canal system. A stable barrier to bacterial and fluid leakage is one of the most important factors facilitating clinical success.

A very practical advantage of MTA is that it takes hold in the wet environment which is very present in dentistry, unlike other materials. When it comes in contact with moisture, calcium oxide turns into calcium hydroxide. This conversion results in a high pH microenvironment that has beneficial antibacterial effects. Unlike calcium hydroxide, however, this material has very low solubility and maintains its physical integrity after placement. MTA was first introduced to the dental literature in 1993 and received FDA approval in 1998. In 1999, Pro Root MTA (Dentsply Tulsa Dental Specialties, Johnson City, TN) was the first commercially available MTA product to be launched in United States. MTA Angelus (Angelus, Lodrina, Brazil/ Clinician's Choice, New Milford, CT) was launched in Brazil in 2001 and received FDA approval in 2011, making it available in the United States [82].

The Biodentine

It was introduced recently and was considered to bring some improvements over the MTA. Biodentine is a calcium silicate cement that was introduced as "dentin replacement" material, comparable to MTA in terms of biocompatibility and achievement of the calcified barrier.

Limited clinical data are available on the use of Biodentine. Clinical studies comparing Biodentine with MTA as pulp capping material were mostly performed on immature permanent molars with limited follow-up periods. For traumatized permanent incisors, case reports have shown the successful use of Biodentine in pulpotomy [83].

Tooth Restoration After Apexification

Due to the thin walls, after apexification, there is a high incidence of root fractures in the teeth. Restoration efforts should aim to strengthen the immature roots. A number of studies have demonstrated that new adhesive techniques can significantly increase fracture resistance as close to that of intact teeth [84]. Goldberg, et al., recently demonstrated the strengthening effect of a resin-enriched glass ionomer in the restoration of immature roots [85]. The risk of root fracture during apexification is a concern, but during this time it is essential that access to the apical portion of the canal is preserved. Katebzades, et al., described a technique in which access is restored with a composite restoration [86]. A transparent reinforcing post is inserted into the soft composite. The post is then removed, leaving a patent canal for calcium hydroxide replacement and subsequent canal obturation.

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Conflict of Interest

The authors have no conflict of interest to declare.

References

1. <https://dentagama.com/news/apexogenesis-and-apexification> [Last accessed on: February 19, 2023]
2. <https://pubmed.ncbi.nlm.nih.gov/25470507/> [Last accessed on: February 19, 2023]
3. Bhasker SN. Orban's oral histology and embryology, 11th Edn. St. Louis: Mosby-Year Book. 1991.
4. Andreasen JO, Hjorting-Hansen R. Intra-alveolar root fractures: radiographic and histologic study of 50 cases. J Oral Surg. 1967;25:414-26.
5. Pindborg JJ. Clinical, radiographic and histologic aspects of intra-alveolar fractures of upper central incisors. Acta Odontol Scand. 1956;13:41-7.

6. Andreasen JO, Borum MK, Andreasen FM. Replantation of 400 avulsed permanent incisors. *Endod Dent Trauma*. 1992;8:45-55.
7. Torneck CD. Effects of trauma to the developing permanent dentition. *Dent Clin N Am*. 1982;26:481-504.
8. Klein H. Pulp response to an electric pulp stimulator in the developing permanent anterior dentition. *J Dent Child*. 1978;45:23-5.
9. Jacobsen I, Kerekcs K. Long-term prognosis of traumatized permanent anterior teeth showing calcifying processes in the pulp cavity. *Scand J Dent Res*. 1975;83:355-64.
10. Cvek M, Cleaton-Jones PE. Pulp reactions to exposure after experimental crown fracture or grinding in the adult monkey. *J Endod*. 1982;8:391-7.
11. Webber RT. Apexogenesis versus apexification. *Dent Clin N Am*. 1984;28:669-97.
12. Stewart DJ. Root canal therapy in incisor teeth with open apices. *Br Dent J*. 1963;114:249-54.
13. Friend LA. The root treatment of teeth with open apices. *Proc R Soc Med*. 1966;19:1035-6.
14. Friend LA. Treatment of immature teeth and non-vital pulps. *J Br Endod Soc*. 1967;1:28-33.
15. Ingle JJ. *Endodontics*. Philadelphia: Lea and Febiger. 1965:504.
16. Kaiser HJ. Management of wide-open apex canals with calcium hydroxide. Presented at the 21st Annual Meeting of the American Association of Endodontists, Washington DC. 1964.
17. Frank AL. Therapy for the divergent pulpless tooth by continued apical formation. *J Am Dent Assoc*. 1966;72:87- 93.
18. Nygaard-Ostby B. The role of the blood clot in endodontic therapy. *Acta Odontol Scand*. 1961;19:323-46.
19. Moller AJ, Fabricius L, Dahlen G, Ohman AE, Heyden G. Influence on periapical tissues of indigenous oral bacteria and necrotic pulp tissue in monkeys. *Scand J Dent Res*. 1981;89:475-84.
20. McCormick JE, Weine FS, Maggio JD. Tissue pH of developing periapical lesions in dogs. *J Endod*. 1983;9:47- 51.
21. Chawla HS, Tewari A, Ramakrishnan E. A study of apexification without a catalyst paste. *J Dent Child*. 1980;47:431-4.
22. Vojinovic O. Induction of apical formation in immature teeth by different endodontic methods of treatment. Experimental pathohistological study. *J Oral Rehab*. 1974;1:85-97.
23. Dylewski JJ. Apical closure of non-vital teeth. *Oral Surg*. 1971;32:82-9.
24. Rafter M. Apexification: a review. *Dental Traumatology*. 2025.
25. Safavi KE, Nichols FC. Alteration of biological properties of bacterial lipopolysaccharide by calcium hydroxide treatment. *J Endod*. 1994;20:127-9.
26. Mitchell DF, Shankwalker GB. Osteogenic potential of calcium hydroxide and other materials in soft tissue and bone wounds. *J Dental Research*. 1985;37:1157-63.
27. Da Silva RA, Leonardo MR, da Silva LA, de Castro LM, Rosa AL, de Oliveira PT. Effects of the association between a calcium hydroxide paste and 0.4% chlorhexidine on the development of the osteogenic phenotype *in-vitro*. *J Endod*. 2008;34(12):1485-9.
28. Javelet J, Torabinejad M, Bakland LK. Comparison of two pH levels for the induction of apical barriers in immature teeth of monkeys. *J Endod*. 1985;11:375-8.
29. Cvek M. Prognosis of luxated non-vital maxillary incisors treated with calcium hydroxide and filled with gutta-percha. A retrospective clinical study. *Endodontics and Dental Traumatol*. 1992;8:45-55.
30. Shabahang S, Torabinejad M, Boyne PP, Abedi H, McMillan P. A comparative study of root-end induction using osteogenic protein-1, calcium hydroxide, and mineral trioxide aggregate in dogs. *J Endod*. 1999;25:1-5.
31. Maroto M, Barberia E, Planells P, Vera V. Treatment of a non-vital immature incisor with Mineral Trioxide Aggregate (MTA). *Dental Traumatol*. 2003;19:165-9.
32. Witherspoon DE, Ham K. One-visit apexification: technique for inducing root-end barrier formation in apical closures. *Practical Procedures and Aesthetic Dentistry*. 2001;13:455-60.
33. Kaiser HJ. Management of wide-open apex canals with calcium hydroxide. Presented at the 21st Annual Meeting of the American Association of Endodontists, Washington DC. 1964.
34. Frank AL. Therapy for the divergent pulpless tooth by continued apical formation. *J Am Dent Assoc*. 1966;72:87- 93.
35. Dylewski JJ. Apical closure of non-vital teeth. *Oral Surg*. 1971;32:82-9.
36. Steiner JC, Dow PR, Cathey GM. Inducing root end closure of non-vital permanent teeth. *J Dent Child*. 1968;35:47-54.
37. Van Hassel HJ, Natkin E. Induction of root end closure. *J Dent Child*. 1970;37:57-9.

38. Klein SH, Levy BA. Histologic evaluation of induced apical closure of a human pulpless tooth. *Oral Surg.* 1974;38:954-9.
39. Stewart GG. Calcium hydroxide induced root healing. *J Am Dent Assoc.* 1975;90:793-800.
40. West NM, Lieb RJ. Biologic root-end closure on a traumatized and surgically resected maxillary central incisor: an alternative method of treatment. *Endod Dent Traumatol.* 1985;1:146-9.
41. Schilder H, Amsterdam M. Inflammatory potential of root canal medicaments: Preliminary report including non-specific drugs. *Oral Surg.* 1959;12:211-21.
42. Vander Wall GL, Dowson J, Shipman C. Antibacterial efficacy and cytotoxicity of three endodontic drugs. *Oral Surg.* 1972;33:230-41.
43. Citrome GP, Kaminski EJ, Heuer MA. A comparative study of tooth apexification in the dog. *J Endod.* 1979;5:290-7.
44. Michanowicz J, Michanowicz A. A conservative approach and procedure to fill an incompletely formed root using calcium hydroxide as an adjunct. *J Dent Child.* 1967;32:42-7.
45. Wechsler SM, Fishelberg G, Opderbeck WR. Apexification: a valuable and effective clinical procedure. *Gen Dent.* 1978;26:40-3.
46. Binnie WH, Rowe AHR. A histologic study of the periapical tissues of incompletely formed pulp less teeth filled with calcium hydroxide. *J Dent Res.* 1973;52:1110-6.
47. Heithersay GS. Periapical repair following conservative endodontic therapy. *Aus Dent J.* 1970;15:511-8.
48. Heithersay GS. Stimulation of root formation in incom- pletely developed pulpless teeth. *Oral Surg.* 1970;29:620-30.
49. Anthony DR, Senia ES. The use of calcium hydroxide as a paste fill. *Tex Dent J.* 1981;99:6-10.
50. Feiglin B. Differences in apex formation during apexifica- tion with calcium hydroxide paste. *Endod Dent Traumatol.* 1985;1:195-9.
51. Heithersay GS. Calcium hydroxide in the treatment of pulp less teeth with associated pathology. *J Br Endod Soc.* 1975;8:74-93.
52. Sciaky I, Pisanti S. Localization of calcium placed over amputated pulps in dog's teeth. *J Dent Res.* 1960;39:1128-32.
53. Pisanti S, Sciaky I. Origin of calcium in the repair wall after pulp exposure in the dog. *J Dent Res.* 1964;43:641-44.
54. Mitchell DF, Shankwalker GB. Osteogenic potential of calcium hydroxide and other materials in soft tissue and bone wounds. *J Dent Res.* 1958;37:1157-63.
55. Holland R, de Mello W, Nery MJ. Reaction of human periapical tissue to pulp extirpation and immediate root canal filling with calcium hydroxide. *J Endod.* 1977;3:63-7.
56. Schroder U, Granath L. Early reaction of intact human teeth to calcium hydroxide following experimental pulp- otomy and its significance to the development of hard tissue barrier. *Odontol Revy.* 1971;22:379-95.
57. Javelet J, Torabinejad M, Bakland L. Comparison of two pH levels for the induction of apical barriers in immature teeth of monkeys. *J Endod.* 1985;11:375-8.
58. Ham JW, Patterson SS, Mitchell DF. Induced apical closure of immature pulpless teeth in monkeys. *Oral Surg.* 1972;33:438-49.
59. Barthel CR, Levin LG, Reisner HM, Trope M. TNF- alpha release in monocytes after exposure to calcium hydroxide treated *E. coli* LPS. *Int Endod J.* 1997;30:155-9.
60. Bystrom RH, Claesson R, Sundqvist G. The antibacterial effect of calcium hydroxide in the treatment of infected root canals. *Endod Dent Traumatol.* 1985;1:170-5.
61. Estrela C, Pimento FC, Ito IY, Bammann LL. *In-vitro* determination of direct antimicrobial effect of calcium hydroxide. *J Endod.* 1998;24:15-7.
62. Jiang J, Zuo J, Chen SH, Holliday LS. Calcium hydroxide reduces lipopolysaccharide-stimulated osteoclast forma- tion. *Oral Surg.* 2003;95:348-54.
63. Kontakiotis E, Nakou M, Georgopoulou M. *In-vitro* study of the indirect action of calcium hydroxide on the anaerobic flora of the root canal. *Int Endod J.* 1995;28:285-9.
64. Safavi KE, Nicholls FC. Alteration of biological properties of bacterial lipopolysaccharide by calcium hydroxide. *J Endod.* 1994;20:127-9.
65. Ghose LJ, Bagdady VS, Hikmat BYM. Apexification of immature apices of pulpless permanent anterior teeth with calcium hydroxide. *J Endod.* 1987;13:285-90.
66. Torneck CD, Smith JS, Grindall P. Biological effects of endodontic procedures on developing incisor teeth. IV Effect of

- debridement procedures and calcium hydroxide CPCP paste in the treatment of experimentally induced pulp and periapical disease. *Oral Surg.* 1973;35:541-54.
67. Steiner JC, Van Hassel HJ. Experimental root apexification in primates. *Oral Surg.* 1971;31:409-15.
 68. Walia T, Chawla HS, Gauba K. Management of wide open apices in non-vital permanent teeth with calcium hydroxide paste. *J Clin Pediatr Dent.* 2000;25:51-6.
 69. Lieberman J, Trowbridge H. Apical closure of non vital permanent incisor teeth where no treatment was performed: a case report. *J Endod.* 1987;9:257-60.
 70. Baldassari-Cruz LA, Walton RE, Johnson WT. Scanning electron microscopy and histologic analysis of an apexification 'cap'. *Oral Surg.* 1998;86:465-8.
 71. Chawla HS. Apical closure in a non-vital permanent tooth using one calcium hydroxide dressing. *J Dent Child.* 1986;53:44-7.
 72. Chosack A, Sela J, Cleaton-Jones P. A histological and quantitative histomorphometric study of apexification of nonvital permanent incisors of vervet monkeys after repeated root filling with a calcium hydroxide paste. *Endod Dent Traumatol.* 1997;13:211-7.
 73. Cvek M. Treatment of non-vital permanent incisors with calcium hydroxide I. Follow-up of periapical repair and apical closure of immature roots. *Odonotol Rev.* 1972;23:27-44.
 74. Feiglin B. Differences in apex formation during apexification with calcium hydroxide paste. *Endod Dent Traumatol.* 1985;1:195-9.
 75. Abbot P. Apexification with calcium hydroxide - when should the dressing be changed? The case for regular dressing changes. *Aust Endod J.* 1998;24:27-32.
 76. Mackie IC, Bentley EM, Worthington HV. The closure of open apices in non-vital immature teeth. *Brit Dent J.* 1988;165:169-73.
 77. Kinirons MJ, Srinivasan V, Welbury RR, Finucane D. A study in two centers of variations in the time of apical barrier detection and barrier position in nonvital immature permanent incisors. *Int J Pediatr Dent.* 2001;11:447-51.
 78. Finucane D, Kinirons MJ. Non-vital immature permanent incisors: factors that may influence treatment outcome. *Endod Dent Traumatol.* 1999;15:273-7.
 79. Sheehy EC, Roberts GJ. Use of calcium hydroxide for apical barrier formation and healing in non-vital immature permanent teeth: a review. *Br Dent J.* 1997;183:241-6.
 80. Kleier DJ, Barr ES. A study of endodontically apexified teeth. *Endod Dent Traumatol.* 1991;7:112-7.
 81. Yates JA. Barrier formation time in non-vital teeth with open apices. *Int Endod J.* 1988;21:313-9.
 82. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4962539/> [Last accessed on: February 19, 2023]
 83. <https://sci-hub.se/10.1111/edt.12553> [Last accessed on: February 19, 2023]
 84. Hernandez R, Bader S, Boston D, Trope M. Resistance to fracture of endodontically treated premolars restored with new generation dentin bonding systems. *Int Endod J.* 1994;27:281-4.
 85. Goldberg F, Kaplan A, Roitman M, Monfre S, Picca M. Reinforcing effect of a resin glass ionomer in the restoration of immature roots *in-vitro*. *Dent Traumatol.* 2002;18:70-2.
 86. Katebzadeh N, Dalton C, Trope M. Strengthening immature teeth during and after apexification. *J Endod.* 1998;24:256-9.

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