Japanese Dental Science Review 59 (2023) 48–61

Contents lists available at ScienceDirect

Japanese Dental Science Review

journal homepage: www.elsevier.com/locate/jdsr

Direct pulp capping procedures – Evidence and practice☆

Rafiqul Islam [a,*], Md Refat Readul Islam [b], Toru Tanaka [a], Mohammad Khursheed Alam [c], Hany Mohamed Aly Ahmed [d], Hidehiko Sano [a]

[a] Department of Restorative Dentistry, Faculty of Dental Medicine, Hokkaido University, Kita 13, Nishi 7, Kita-ku, Sapporo 060-8586, Japan
[b] Department of Restorative Dentistry, Graduate School of Dental Medicine, Hokkaido University, Kita 13, Nishi 7, Kita-ku, Sapporo 060-8586, Japan
[c] Preventive Dentistry Department, College of Dentistry, Jouf University, 72345 Sakaka, Saudi Arabia
[d] Department of Restorative Dentistry, Faculty of Dentistry, University of Malaya, Kuala Lumpur, Malaysia

ARTICLE INFO

Article history:
Received 31 August 2022
Received in revised form 11 January 2023
Accepted 15 February 2023

Keywords:
Vital pulp therapy
Direct pulp capping
Calcium hydroxide
Mineral trioxide aggregate
Bioceramics
Pulp capping materials

ABSTRACT

The aim of direct pulp capping (DPC) is to promote pulp healing and mineralized tissue barrier formation by placing a dental biomaterial directly over the exposed pulp. Successful application of this approach avoids the need for further and more extensive treatment. In order to ensure a complete pulp healing with the placement of restorative materials, a mineralized tissue barrier must form to protect the pulp from microbial invasion. The formation of mineralized tissue barrier can only be induced when there is a significant reduction in pulp inflammation and infection. Consequently, promoting the healing of pulp inflammation may provide a favorable therapeutic opportunity to maintain the sustainability of DPC treatment. Mineralized tissue formation was observed as the favorable reaction of exposed pulp tissue against a variety of dental biomaterials utilized for DPC. This observation reveals an intrinsic capacity of pulp tissue for healing. Therefore, this review focuses on the DPC and its healing procedure as well as the materials used for DPC treatment and their mechanisms of action to promote pulpal healing. In addition, the factors that can affect the healing process of DPC, clinical considerations and future perspective has been described.

Contents

☆ Scientific field of dental Science: Restorative Dentistry, Operative Dentistry, Endodontics.

* Correspondence to: Kita 13, Nishi 7, Kita-ku, Sapporo 060-8586, Japan.
E-mail address: rony12cdc@den.hokudai.ac.jp (R. Islam).

https://doi.org/10.1016/j.jdsr.2023.02.002

1. Introduction

The vitality of the pulp is essential for the protection of the tooth structure and the maintenance of proper physiological function [1]. However, three distinct phenomena might result in vital pulp exposure, i.e., dental caries, mechanical injury, and traumatic exposure. Carious pulp exposure can be defined as pulp exposure that happens before caries removal. Mechanical pulp exposure can occur during the removal of caries when preparing a cavity or, more commonly, due to a dental procedural error. On the other hand, traumatic pulp exposure occurs when the coronal portion of the tooth is cracked or fractured due to an injury such as direct contact sports injury, motorbike accidents, and others [2]. Considering the tooth's viability, nutrition to the pulp, innervation, and immune response mechanism, preservation of the vitality of the dental pulp is crucial [3]. If the pulp exposure remains untreated, subsequent infection of the pulp occurs with more invasive treatment plans ranging from conventional root canal treatment to tooth extraction [4].

Vital pulp therapy (VPT) aims to maintain the vitality and function of pulp tissue that has been injured by carious lesion, operative protocols or iatrogenic causes, or dental trauma [5,6]. Proper diagnosis and case selection, pulp exposure site, the stage of root maturation of the tooth, and integrity of coronal restoration play a crucial role in successful VPT outcomes [5]. During this procedure, the remaining thin layer of dentin is covered with a protective biomaterial widely known as a pulp capping agent. In general, VPT can be divided according to the treatment strategy; indirect or direct pulp capping and pulpotomy which can be further subdivided as miniature, partial and complete pulpotomy. Indirect pulp capping is a treatment procedure generally used in deep cavity preparations where a thin layer of caries-free dentin remains above the pulp chamber which is covered with a biomaterial in order to prevent pulp exposure and further trauma to the pulp [6]. Indirect pulp capping can be divided into one-step and two-step approaches. In the one-step approach (partial caries removal), most of the carious dentin is removed, and a biomaterial is placed. In such a case, the biomaterial should not be in contact with the pulp, and the final restoration should be done at the same appointment. On the other hand, a two-step approach (step-wise caries removal) refers to the removal of caries in a stepwise manner, starting with the removal of soft carious dentin. A firm, discolored, deep carious dentin should remain on the floor of the cavity in such cases where there is a possibility of pulp exposure. After that, a biomaterial liner, preferably calcium hydroxide, should be placed and overlaid by a temporary restoration. After clinical observation for several months, if there are no clinical features of pain or pathology, the temporary restoration and any remaining caries should be removed, and the final restoration is placed [7]. The direct pulp capping procedure refers to the placement of a biomaterial over an exposed coronal pulp after caries excavation [4]. Miniature pulpotomy is a treatment procedure where less than 1 mm of infected dentin and damaged pulp tissue is removed from the exposed site [8]. According to the American Association of Endodontics (AAE, 2020), partial pulpotomy can be defined as the removal of a small portion of the vital coronal pulp, whereas the removal of the coronal portion of the vital pulp in order to preserve the vitality of the remaining radicular portion is known as complete pulpotomy [9].

Direct pulp capping (DPC) is considered to be one efficient, conservative treatment option [10]. During this procedure, after caries excavation, a dental biomaterial is placed directly over the exposed dental pulp. This helps to promote the mineralized tissue formation that is ubiquitously used to protect the vitality of the dental pulp [10]. Studies revealed that a tooth is more likely to survive if the exposure to the pulp is mechanical compared to dental caries [11,12]. Pulpal inflammation results from dental caries causing bacterial invasion which penetrates the pulp. Nevertheless, it is possible that the pulpal tissue remains inflamed even after the dental operative procedure has been completed. Consequently, it is more likely to have chronic, low-grade inflammation, and due to this reason, the pulp is less able to react, and healing would be delayed [13,14].

Generally, reduced pulp inflammation occurs after the elimination of infectious bacteria and the ability of the pulp immune system to neutralize intratubular diffusing substances such as intratubular immunoglobulins (IgG1, IgA1, IgA2, IgM, etc.). These two mechanisms contribute to the decreased synthesis of pro-inflammatory cytokines [15]. Eventually, following a significant reduction in inflammation, the pulp tissue starts the healing process. The freshly formed odontoblast-like cells replace the nearby odontoblasts that used to be a part of the mineralized tissue barrier or reparative dentin bridge at the exposed site [13].

However, the most challenging part of the DPC procedure is the accurate identification and removal of the severely inflamed tissue that has been damaged by prolonged contact with oral bacteria [16]. Therefore, the DPC treatment aims at the healing of the pulp as well as the maintenance of the tooth vitality. If the pulp is able to withstand this therapy and maintain its vitality, the clinical outcome can be presumed to be a success. Hence, the DPC procedure and its subsequent healing process will be discussed in this review.

2. Pulp reaction after exposure

The pulpal reactions are triggered whenever there is an exposure to the pulp, whether the exposure is caused by caries, mechanical stimuli, or traumatic injury. According to the type of exposure, the pulpal responses will significantly vary between short-term and long-term or low intensity and high intensity [17]. In the initial few minutes after exposure, nerve fibers such as large-myelinated A-δ and A-β fibers and the smaller unmyelinated C fibers in the wounded pulp are destroyed and disorganized, which is accompanied by hypersensitivity in the nerve fibers and the release of neuropeptides

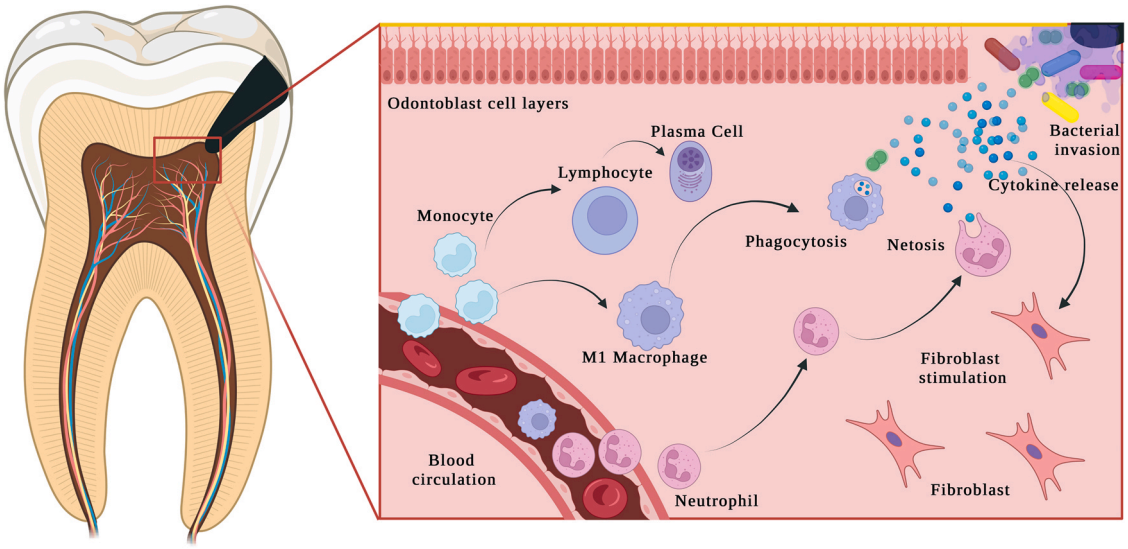

Fig. 1. Schematic representation of inflammatory response to bacterial penetration into the pulp tissue after exposure. After being exposed to carious lesions, the inflammatory response becomes more intense, and neutrophils and macrophages that have just come from blood vessels through diapedeses start to accumulate in the odontoblast layer. The layer of odontoblasts close to the infected dentine and the underlying pulp becomes necrotic, and bacteria penetrate into the pulp, causing inflammation in the entire pulp tissue.

into the pulp. Vasodilatation and a sudden elevation in vascular permeability are both symptoms of neurogenic inflammation, which is caused by these neuropeptides [18]. Also, adjacent to the exposure site, in the pulp tissue, different kinds of necrotic tissue, inflammatory cells, and extravascular and perivascular erythrocytes can be observed [19]. Lymphocytes, plasma cells, and macrophages constitute the majority of the early inflammatory cell infiltration (Fig. 1) [18]. An acute inflammation accompanied by the presence of polymorphonuclear leukocytes develops from the initial injury that results in the formation of fibrinogen and blood clots [19]. After the acute phase of inflammation, whether it is of a high or low grade, the condition progresses into a chronic state. The cell types in the immune cells are increased in number and released from neutrophils to lymphocytes and macrophages (Fig. 1). Then, the exposed pulp is then chemoattracted by neutrophils in great numbers, where they act as the initial protective mechanism [20,21]. Initially, there is a possibility of stimulation by cytokines, complement, or microorganisms in the circulation during infection, leading to enhanced lifespan at the exposure site [22]. As a consequence, neutrophils have two options for eliminating bacteria: either they can phagocytose them for intracellular destruction or they can degranulated, which releases reactive oxygen species and antimicrobial proteins [23]. Recent research has shown that a number of microorganisms related to endodontic disease can cause netosis as a defense mechanism against invasive bacteria, but it can also have potential cytotoxic and pro-inflammatory effects on infected pulp [23,24]. Netosis was first described as a kind of neutrophil death in which neutrophil extracellular traps immobilized and destroyed invading microorganisms [25]. Apparently, various bacteria within the dental pulp may employ distinct strategies to evade netosis [26]. Also, the formation of lymphocyte like-cells and the infiltration by immunocompetent cells take place in this process [27]. However, it is possible that some particles from the dentin chips may go through into the pulp tissue underneath them; as a result, hard tissue will develop around the dentinal chips [19,28]. When the inflammation is mild or moderate, the immune system often responds with a transient inflammatory response, which is then followed by reactive dentinogenesis. In addition, in the case of severe injury, odontoblastic cell death occurs. If the inflammation does not deteriorate, there is a possibility that a new generation of odontoblast-like cells may differentiate, which will ultimately result in the creation of dentin bridges at the locations of exposure, which is known as reparative dentinogenesis [17,29].

3. Healing potential after exposure

Pulpal wound healing mechanism is a dynamic interaction of different variables that have been extensively documented in past studies, such as the production of an immediate inflammatory response by the acute exposure; the recruitment and multiplication of both parenchymal and connective tissue cells; and parenchymal and connective tissue remodeling in order to restore tissue function [30]. In principle, pulp exposure is always linked with an inflammatory reaction with the following mechanism: hemostasis and blood clot formation; an inflammatory response followed by cellular accumulation and migration; and tissue regeneration [17]. Necrotic layer or tissue, blood clot development, and a cellular response accompanied by substantial infiltration of neutrophils are all features that can also be found at the site of exposure in the pulp tissue [17].

Adjacent to the pulp exposure site, cellular nutrients and oxygen circulation are both jeopardized immediately after exposure [31]. At the same time, the pulp develops new vasculature to accommodate its altered environment. These vasculatures are crucial for the transportation of metabolic waste, the maintenance of pulp homeostasis, and the migration of metabolic stem cells and progenitor cells (Fig. 2) [31,32]. In addition, angiogenesis is essential for active wound healing at the dental pulp exposure site. Dental pulp stem/progenitor cells move from the perivascular zone in the pulp tissue to the exposure site throughout the healing process. For the purposes of angiogenesis and vasculogenesis, these cells multiply and develop into endothelial cells [33].

Initially, following the placement of the pulp capping material, the inflammatory cells (such as polymorphonuclear leukocytes and macrophages) at the exposed site are replaced by granulation tissue [33]. This granulation tissue is surrounded by with many fibroblasts and endothelial cells, which are distributed in an uniform manner along the wound (Fig. 2) [34]. Starting on day three following the pulp exposure, undifferentiated mesenchymal stem cells in the perivascular region and fibroblasts in the surrounding connective tissue relocated to the wound area, reaching their highest numbers by day seven. Macrophages and lymphocyte-derived cytokines interact together to induce this response. In addition, to eliminating

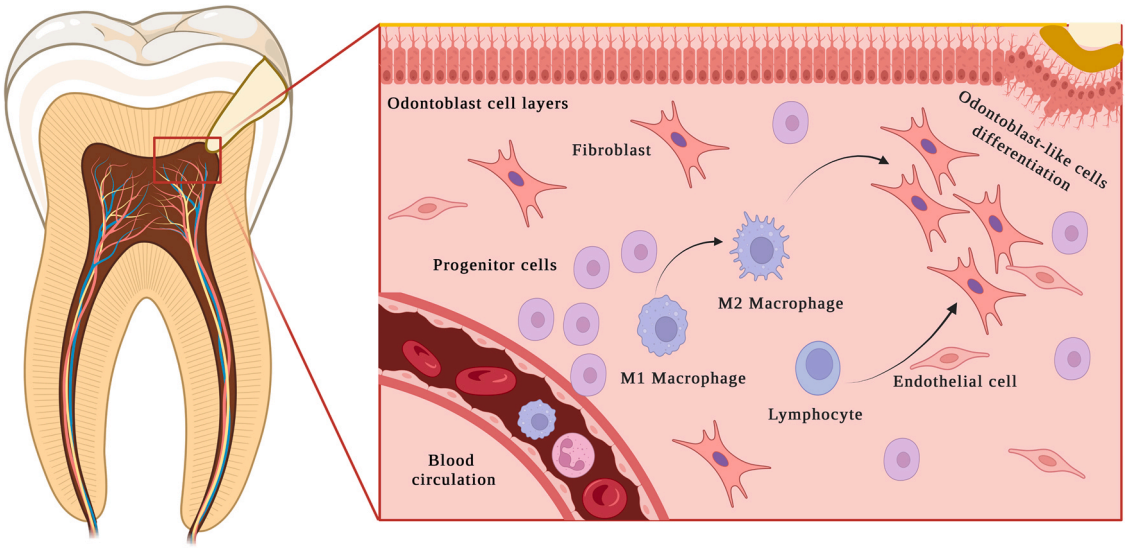

Fig. 2. Schematic representation of the healing of dental pulp after exposure. Resolution of inflammation and tissue repair are achievable after the removal of invading microorganisms. The main components in these two processes are dental pulp stem cells and M2-polarized macrophages. Both of these cells release anti-inflammatory molecules that suppress inflammation and promote tissue healing. It is generally accepted that cell polarization towards the M1 or M2 phenotype is the mechanism through which macrophages are activated. They phagocytose bacteria, release pro-inflammatory cytokines, and initiate the immunological response.

microorganisms and cell debris, recruited macrophages can help resolve inflammation by shifting from an M1 to an M2 phenotype (Fig. 2) [26]. Nevertheless, M2 phenotypic cells subsequently release anti-inflammatory cytokines like TGF- β1 and IL-10, which facilitate wound healing procedures [26]. Wounded tissue changes from granulomatous to granulation when the number of macrophages decreases, and the number of fibroblasts increases (Fig. 2) [35]. In ideal circumstances, wound healing occurs between five or seven days following the injury. This episode of healing is associated with a decrease in fibroblasts, vascular channels, and extracellular fluids [35].

There is a transition to a new extracellular matrix and mineralization nodules appears in the late stages of healing [36]. Odontoblasts are responsible for continuously synthesizing the extracellular matrix of the dentin [37]. The release of growth factors and the increase of odontoblast function are the results of an injury to the dentin, pulp, and odontoblast processes. Evidence suggests that a cascade of tissue factors or signaling molecules, primarily members of the transforming growth factor beta (TGF- β) family, are released from the dentin matrix in reaction to injury [35]. However, odontoblasts can produce those growth factors, and various irrigating solutions used in treatment procedures can flush them out of the dentin. Furthermore, TGF- β1 is released after calcium hydroxide or silicate cement (mineral trioxide aggregate or biodentine) is applied to the exposed pulp tissue [35]. Similarities between reparative dentinogenesis and the development of mantle dentin are shown by the identification of the first mineral deposits in matrix vesicles [38]. Later, cuboidal cells are encapsulated in the matrix, and a subset of these cells begins to show the indicators of odontoblast differentiation. Lastly, the cells rearrange themselves into a palisade of cells, like that found in primary or secondary dentin. A necrotic layer indicative of an inflammatory reaction is evident in the mineralized tissue barrier in the surrounding pulp tissue [34,39].

4. Mechanism of action of DPC

The mechanisms of most DPC biomaterials cause superficial necrosis after placement directly over the exposed pulp tissue. The DPC biomaterial possesses antimicrobial properties and induces mineralization [14]. With the release of hydroxyl ions by DPC biomaterials, which raised the pH of the underlying tissue, causing a thin necrotic layer between the vital pulp tissue and the DPC agent [40,41]. Due to the existence of this necrotic zone, the vital pulp cells that lie beneath it are protected from the alkaline pH of the material [42]. Additionally, it enables the underlying pulp cells to perform the repair and regeneration processes [42]. It has been suggested that the presence of such a high alkaline pH is responsible for the formation of reparative dentin by the DPC agent [43]. Furthermore, mineralization has been proven to be inhibited by pH levels above 8.0 [43]. The high pH might also have an anti-inflammatory effect through the denaturation of proinflammatory cytokines and activation of the regulatory IL-10 [44,45]. Further research is required to determine the precise effects of high pH on reparative dentin formation because it is technically challenging to measure the pH at or near the interfaces between DPC materials and pulp tissue.

Following pulp exposure and DPC, early changes include hemorrhage and moderate inflammation, resolved during the first week [19]. In turn, this might also provide a conducive environment for the formation of reparative dentin if the bacterial irritation and inflammatory reaction are successfully mitigated. Hence, such effects are indirect, the elimination of bacterial organisms does not directly contribute to the production of reparative dentin [43]. Therefore, it is unclear if the DPC materials' anti-microbial action is a molecular factor in the formation of reparative dentin [43].

The release of calcium ions from the DPC biomaterials stimulates the precipitation of calcium carbonate in the wound area and thereby contributes to the initiation of mineralization. The pulp cells then begin to differentiate; these cells have odontoblast-like behavioral traits and start to produce a collagen-rich matrix that resembles predentin [19]. Although one of the main substances released by DPC materials is calcium ions [46,47]. However, little is known about how calcium ions play a role in the formation of reparative dentin throughout the repair process. On the other hand, new data suggests that calcium ions serve essential roles in sustaining and regulating regular biological activities, as well as in the development of mineralized matrixes and the propagation of intracellular signaling pathways [43]. Furthermore, calcium ions released by pulp-capping materials may have a role in the

formation of reparative dentin, according to recent studies [42,47]. These calcium ions are thought to be one of the main mediators of the mineralization process.

5. Materials used for DPC

Through the years, many dental materials have been introduced with the goal of prompting the safest tissue response and optimizing patient outcomes [4]. New biomaterials for preserving pulp vitality through conservative and restorative dental procedures have evolved as knowledge of the dentin-pulp complex healing mechanism has grown [3,48]. Because there are so many different biomaterials that may be used for DPC, it can be challenging to determine which pulp capping material would work best in each clinical scenario [4].

The ideal DPC material would have the following characteristics: simple handling during an operative procedure; adhesion to dental substrate; antibacterial properties; excellent sealing ability; insolubility in tissue fluids; biocompatibility and bioactivity; promotion of mineralized tissue barrier formation; radiopacity and does not cause tooth discoloration [49]. However, currently there is no DPC biomaterial that possesses all of these desirable characteristics. In recent years, the market has witnessed tremendous advancements in DPC materials, which will be discussed in the following section.

5.1. Calcium hydroxide

In previous decades, calcium hydroxide (CH) has been the material of choice and gold standard for DPC [50–53]. One of the desirable properties of CH is that it has a high pH, which is responsible for the stimulation of fibroblasts [54]. It raises the pH of acidic solutions, inhibits microorganism's growth, and encourages the healing and defense mechanisms of pulp tissue [55,56]. In addition to having high solubility and poor adherence to hard tissues, it does not offer the best attainable seal. CH shows a tunnel defect like phenomenon in the dentin bridge, although there is evidence to show that the expression of these defects improves with improved dentin-bridge thickness [57–59].

According to studies that followed patients for up to 10 years, CH, as a DPC material, has shown successful clinical outcomes [11,60–62]. The development of superficial necrosis is the first consequence after CH placement on the exposed pulp [63]. The pulp is stimulated to protect and heal itself to produce a reparative dentin bridge through the processes of cellular differentiation, extracellular matrix secretion, and eventual mineralization when firm necrosis is present. This causes a very minor irritation [63]. It has been found that 89% of dentin bridges formed below CH revealed tunnel defects. This is despite the fact that the formation of a dentin bridge has been thought to be the key to the clinical effectiveness of DPC [59]. Not only are these tunnel defects in the heterogeneous dentin barrier provide inadequate durable barrier, but they are also not capable of forming a long-term effective seal against pathogenic bacteria. Another drawback of CH is dissolution [64,65]. Nevertheless, the specific mechanism for CH tissue-dissolution has not been assessed widely in the literature and would be of supreme interest for further investigation.

CH has been shown to stimulate hard tissue repair, but the exact processes behind this effect are unknown [66]. It has been hypothesized that the surface of the necrotic layer acts as a barrier between the vital tissue and the wound, allowing the pulp to heal on its own [63]. It has been speculated that the induction of hard tissue healing can be attributed to the production of a microenvironment that is supersaturated with calcium ions and is located adjacent to the pulp. However, this theory was challenged by the fact that the calcium ions integrated into the mineralized hard tissue barrier emerged from the underlying tissues instead of deriving from the pulp-capping materials itself [67,68]. In addition to this, it has been suggested that the tissue may have a favorable outcome to the high pH condition that is produced because of the release of hydroxyl ions [69].

Studies with long-term clinical follow-up of DPC with CH found success rates ranging from 37% to 81.8%, despite the fact that a number of studies have shown that CH is helpful in promoting pulp healing [61,62,70,71]. Results from studies with follow-up durations longer than five years showed a wide range of success rates: 2–6 years 77.6% [72], up to 9 years 58.7% [71], and more than ten years 72.7% [70]. According to these studies, DPC with CH is a successful treatment approach when the respective indications and restorative materials were employed [70–72]. A study on 248 teeth (186 participants) with exposed pulps showed an overall survival rate of 76.3% with an average recall period of 6.1 years when CH was used as a DPC [73]. Although, the treatment outcomes were less favorable with spontaneous tooth pain and tooth pulp may become nonvital with CH, which was significantly greater within the first 5 years of treatment [73]. It was suggested that if DPC fails, this is most likely to happen within the first 5 years after DPC. In addition, it was also presumed that all pulp tissue alterations take place during the first year after DPC. However, there is no clear explanation for this fact and requires further investigation [73]. At 5 and 10 years, the overall success rate for CH treated teeth in a study of 401 teeth with carious exposure (pulps were exposed during caries excavation) was 37% and 13%, correspondingly [62]. It has been demonstrated that the survival rate of these teeth is greatly increased by the placement of a definitive restoration within the first two days following pulp exposure [62]. All the above studies showed that failure rates increased over time. In another study, researchers found that the success rates of DPC employing CH longer recollection intervals continued to decrease [48]. Even though CH possesses a multitude of desirable characteristics, nowadays, it seems to be not the material of choice for DPC [48,74–76].

5.2. Mineral trioxide aggregate

As an alternative to CH, mineral trioxide aggregate (MTA) has gained widespread acceptance because of its potential to promote wound healing of the dentin-pulp complex [4,67,77]. MTA is mainly derived from Portland cement and the main components are tricalcium silicate, dicalcium silicate, and tricalcium aluminate, in addition to bismuth oxide for radiopacity [78]. The major benefits include excellent biocompatibility when applied to the pulp wound, superior sealing ability, which allows excellent cell/material adhesion, low solubility, inhibition of bacterial invasion, and induction for dentin bridge formation [79]. MTA possesses favorable physiochemical properties that induce reparative dentin formation by the recruitment and activation of hard tissue forming cells, contributing to matrix formation and mineralization [80]. In addition, MTA has the potential to reduce the levels of pulp inflammation, hyperemia, and necrosis and has the ability to solubilize bioactive proteins that are involved in the process of tooth repair [81–83]. Moreover, the inflammation induced by MTA is only short-term, which is less severe than CH [84]. On the other hand, MTA presents some disadvantages, such as long setting time, difficult handling characteristics, discoloration, and high cost [49,52,77]. After placing MTA material over the exposed pulp, MTA activates the progenitor cells (fibroblast) migration from the central pulp to the exposure area. This helps to promote their proliferation and differentiation into odontoblast-like cells without inducing apoptosis in the pulp cells [80]. MTA induces a time-dependent environment that is pro-inflammatory and promotes wound regeneration through upregulation of cytokines [85]. Cytokine upregulation is responsible for the induction of biomineralization by the production of collagen fibrils

or apatite-like clusters at the dentin-MTA interface. MTA releases calcium ions which exert antibacterial effects and promote mineralization beneath the pulp exposure area and has the potential to maintain the vitality of the pulp [86]. MTA prevents bacterial leakage when used with a sealed restoration and might help to protect the pulp tissue, promote healing, and maintain pulp vitality [87,88]. The main calcium ion released by the MTA reacts with phosphates in tissue fluid to form hydroxyapatite, which makes the material biocompatible and able to provide an appropriate seal [89]. This hydroxyapatite layer formation is a crucial factor for the chemical seal between the wall of the dentin and the MTA, although it cannot be considered as a true bonding process [90]. Despite this, there is a possibility of bacterial leakage when there is an inadequate seal, which could result in the DPC treatment failure [2].

Recent studies have demonstrated that MTA has a higher clinical success rate and results in less pulpal inflammatory response and more predictable mineralized tissue barrier formation than CH in DPC [57,76,91]. A study conducted on 49 teeth with carious pulp exposure of 37 patients capped with MTA showed a 97.96% overall success rate after 9 years [87]. The authors stated that MTA, when used in a two-visit treatment protocol, can be a promising pulp-capping material on direct carious exposures in permanent teeth [87]. In another study conducted on 122 teeth with carious and mechanical exposure of 108 patients was capped with MTA and CH. The overall success rate of MTA with carious and mechanical exposure was 80% and 70%, respectively, whereas the overall success rate of CH with carious and mechanical exposure was 62% and 50%, respectively, after 1–6.6 years [48]. It was stated that after DPC, MTA seems to be more successful than CH at preserving long-term pulp vitality [48]. One recent study conducted on 229 teeth with carious and mechanical exposure of 205 patients capped with MTA and CH. The overall success rate of MTA with carious and mechanical exposure was 80% and 84%, respectively, whereas the overall success rate of CH with carious and mechanical exposure was 57% and 70%, respectively, after 2–10.25 years [76]. The results of this study indicated that MTA, when used as a DPC agent, provides better long-term results compared with CH, and placing a permanent restoration immediately after the DPC was recommended [76]. Within the parameters of these studies, MTA appears to be a suitable replacement for CH used for DPC. Therefore, it seems that MTA has been shown to be a suitable capping agent with a reliable treatment option for exposed pulp with a degree of outcome predictability in DPC [5].

5.3. Biodentine

Biodentine is an innovative cement made of tricalcium silicate that also exhibits remarkable bioactive characteristics [92]. It was reported that the effectiveness of biodentine in DPC over mechanically exposed pulps was comparable to that of MTA [2]. Pure tricalcium silicate, calcium carbonate, and zirconium oxide are predominantly found in biodentine as its compositions [77]. Contrary to MTA, biodentine does not include inorganic compounds such as calcium aluminate, calcium sulfate, or bismuth oxide [93]. Bismuth oxide, which is included in MTA, is known to slow the setting process, adversely affect the biocompatibility, and cause discoloration. Nevertheless, biodentine does not contain bismuth oxide, which is a crucial factor in the characteristics of this material [94–96]. Biodentine has been shown to have superior mechanical properties, improved color stability, an easier application process, and a faster initial setting time compared to MTA [97–100]. Its main drawbacks are its limited radiopacity and the difficulty of attaining the desired or optimized consistency [93,101,102].

It has been found that the amounts of calcium that are released by biodentine are substantially higher than those released by CH cement and MTA [103–106]. An increase in the amount of calcium released is indicative of an increase in the amount of hydroxyl ions released as well. The antibacterial properties of biodentine are attributed to its high pH, which is achieved by the action of hydroxyl ions on the surrounding tissue [107,108]. A thin layer of coagulative necrosis forms between the vital pulp tissue and the pulp capping material because of the increase in pH [109]. The necrotic zone serves as a barrier between the alkaline pH of the substance and the pulp cells that lie underneath it. Furthermore, a reparative dentinal bridge will form adjacent to the necrotic zone [93]. It has additionally been observed that biodentine releases silicon ions into the surrounding dentine. It has been hypothesized that the silicon ions produced by biodentine assist in the production of dentin bridges and accelerate mineralization [93]. After DPC with biodentine, studies demonstrated that the creation of a complete dentinal bridge, a less inflammatory pulp response, and layers of well-arranged odontoblasts and odontoblast-like cells [110].

The clinical success rate of biodentine as a DPC material compared with MTA was evaluated in several investigations. In a study that was carried out over the course of six months, 24 teeth that had carious pulp exposure and had been capped with either MTA or biodentine demonstrated overall success rates of 91.7% and 83.3%, respectively [111]. MTA and biodentine exhibited overall success rates of 93.5% and 93.1%, respectively, after six months of treatment on 68 teeth with carious pulp exposure in 54 patients in a separate trial. After a period of twelve months, the MTA and biodentine treatments had a success rate of 100% and 96%, respectively. Follow up with patients for three years after treatment, the overall success rate for MTA and biodentine was found to be 96% and 91.7%, correspondingly [112]. It was revealed that when utilized as DPC materials in permanent mature teeth with carious exposure, biodentine and MTA have favorable and comparable success rates. Therefore, the long-term success of DPC may crucially depend on the amount of healthy tooth structure that remains and the durability of the coronal restoration. [112]. According to the findings of these studies, biodentine may have a high level of efficacy in the DPC of exposed pulp. Nevertheless, more evidence is needed from clinical trials of longer follow-ups.

In addition, the efficacy of the treatment and the prognosis are dependent on the age, type, exposure area, and intensity of pulp exposure. It is important to take into consideration the fact that MTA has been subjected to more extensive evaluation as a DPC material than biodentine. Moreover, as compared to studies of MTA, the current studies on biodentine had a smaller number of participants in their tested sample [93].

5.4. BioAggregate

BioAggregate, a bioinductive tricalcium cement, can induce mineralization that possesses improved performance in comparison with MTA [113]. Tricalcium silicate, dicalcium silicate, monobasic calcium phosphate, amorphous silicon dioxide, and tantalum oxide are the primary components of this material where tantalum oxide is used as a radiopacifier [114]. Evidence suggests that when used as root-end filling material, BioAggregate has superior biocompatibility than MTA and great sealing performance [114]. In terms of pulp capping, a recent study demonstrated that BioAggregate has a considerably greater ability than MTA to stimulate odontoblastic differentiation and mineralization [115].

BioAggregate is a more advanced variant of MTA. The most notable landmark is that BioAggregate does not include any aluminum, and rather than bismuth oxide and calcium phosphate, it is predominately composed of tantalum oxide [116]. It has fewer adverse effects on the inflammatory cell response, which might be due to the absence of aluminum in its chemical characteristics [114].

Nevertheless, the effects of BioAggregate on the tissues of the tooth pulp have not yet been thoroughly investigated. Current findings have shown that the MTA exhibited significantly higher levels of thicker hard tissue formation than the BioAggregate. However, the BioAggregate group also showed a thick and homogenous hard tissue barrier formation [114]. Nevertheless, further studies are required to consider whether BioAggregate could be an appropriate alternative for pulp capping materials [116].

5.5. Resin-based MTA

5.5.1. TheraCal LC

To overcome the shortcomings of the original MTA, a few modified resin-based MTAs were developed. The majority of these MTAs are intended to minimize the amount of time needed for setting by modifying the powder's composition or particle size [2]. TheraCal LC is a calcium silicate resin-based material that can be used as a pulp capping agent and as a protective liner when used with restorative materials [117]. This material is a light-curable MTA-cement and is categorized as a fourth generation of calcium silicate material [118,119]. This description has caused confusion in the literature since there is no light-initiated setting of the Portland cement [117]. TheraCal LC has shown that it can release calcium ions, which is a key factor in the proliferation and differentiation of human dental pulp cells caused by the material and the formation of new mineralized hard tissues [119–121]. The amount of calcium ions released by TheraCal LC was in the range of concentrations that could potentially stimulate the dental pulp and odontoblasts [119,122].

The clinical success rate of TheraCal LC over a shorter period of time has been investigated and compared to that of other materials [123,124]. The effectiveness of TheraCal LC, Biodentine, and MTA on carious pulp exposure in 90 permanent vital teeth was evaluated over a 6-month period. When compared to one another, TheraCal, Biodentine, and MTA did not have a statistically significant difference in their overall success rate [123]. Therefore, TheraCal LC was recommended for use as a DPC material. In another study, following up with patients for 1 month, 6 months, 1 year, and 3 years after treatment, the overall success rate for TheraCal LC was found to be 96%, 83%, 73%, and 72%, whereas Biodentine and MTA were 92%, 84%, 80%, 79%, and 93%, 86%, 86%, and 85%, respectively [124]. According to the study, TheraCal LC's short-term outcomes were promising, but its long-term efficacy is still limited. Most of the studies have recommend that TheraCal LC could be used as a DPC material [2123,124]. However, long-term clinical study is still required for this material.

5.5.2. Super MTA Paste

Recently, a resin-based MTA material has been introduced named Super MTA Paste. Super MTA Paste is a resin-modified MTA that contains Portland cement, which is incorporated with TBB (tributylborane) as a polymerization initiator that does not require light curing. Super MTA Paste also possesses high biocompatibility as a pulp capping material and can promote a homogenous dentin bridge formation [125]. The tissue reaction of Super MTA Paste in the exposed pulp where the therapeutic effectiveness is similar to that of TheraCal LC [126]. Clinical trials are needed to support its effectiveness in short and long term clinical outcomes.

5.6. Other DPC materials

A number of DPC materials, such as zinc oxide eugenol, glass ionomer or resin modified glass ionomer, and adhesive resin, have been reported. Zinc oxide eugenol (ZOE) possesses bactericidal effects which are similar to CH and calcium silicate cements [14]. On the other hand, eugenol released from this material is highly cytotoxic [127]. A study demonstrated that after DPC with this material, there was no pulpal healing with chronic inflammation and no dentin bridge formation after 12 weeks [14]. Therefore, ZOE is not recommended as a DPC agent [14,128].

While CH and calcium silicate-based cements are alkaline in nature, glass ionomer (GI) or resin modified glass ionomer (RMGI) are acidic and do not have the antibacterial properties [128]. In addition to the cytotoxicity of other components, the initial acidity of this material persists at a low pH for a prolonged period, which may cause a damaging effect on the pulp tissue [128]. When compared to CH and GI/RMGI, it was reported that CH showed significantly better pulpal healing, whereas GI/RMGI showed chronic inflammation with no sign of dentin bridge formation after 10 months [129]. Therefore, GI/RMGIs should not be used for DPC [11,128].

Adhesive resin materials were recommended for DPC more than 20 years ago due to their excellent bonding ability [128]. Although adhesive resins are acidic in nature and do not have bactericidal properties, which is similar to GI/RMGI [128]. Studies reported that when compared with CH, adhesive resin showed poor pulpal healing with chronic inflammation and a lack of dentin bridge formation [130–133]. It is interesting to note that pulp capped directly with non-acidic bonding resin or resin composite showed a trend towards better pulp response than the ones capped with acidic primers or adhesives [128]. Therefore, dental adhesive should be avoided for DPC [11,128].

Adhesive resin, GI/RMGI all demonstrated favorable outcomes in the early stages after DPC with nonhuman subjects [134,135]. In addition, use of these materials in human subjects demonstrated a lack of biocompatibility or a consistent formation of reparative dentin [133,136,137]. The use of resin-based materials after DPC in human teeth showed unfavorable pulpal responses with inflammatory cell infiltration that are consistent with pulp cell cytotoxicity, adhesive failures at the pulp interface, and a complete lack of biocompatibility [129,136,138–140].

6. Mineralized tissue formation ability

In contrast to the formation of reparative or reactionary dentin, the formation of mineralized tissue following the loss of the odontoblast is a more complicated process [141,142]. Without odontoblasts, dentin formation would not be possible [142]. The formation of mineralized tissue is mainly characterized by heterogeneity, amorphousness, and tubular architecture [141]. However, it is debatable as to whether it can be referred to as a dentin bridge. If dentin were to be formed further, a different kind of cell would have to replace the initial odontoblast that had been destroyed already. It is remained unknown where these initial cells derived from or how they differentiated [35].

After the DPC on the human teeth with either CH or MTA, recent studies have found no histological evidence for the formation of replaced odontoblasts or new odontoblast-like cells [48,72,73,76]. Because of this, secondary odontoblasts or cells that behave similarly to odontoblasts which cannot be identified histologically [141]. It is also currently unknown if the hard tissue development is replicated in the dentin or just a hypoplastic intrapulpal mineralization as a reaction to inflammation [35]. However, it is significant to highlight how the mineralized tissue and reactive dentin can be formed by primary odontoblast or sequentially in the same wound.

7. Factors that affect the healing after DPC

7.1. Pulpal bleeding

One of the major factors that can affect the success of DPC is the extent of pulpal bleeding after exposure of pulp and before placing the DPC material. Excessive bleeding after exposure of pulp is generally associated with increased inflammation, which consequently

reduces the repair capacity at the exposure area [14]. Bleeding at the exposure area increases the moisture level of dentin surfaces, which leads to increased contamination where an adequate seal is difficult to obtain, and the possibility of bacterial infection is greater [14,143]. It was reported that pulpal bleeding should stop within a few minutes [144]. Moreover, the time to stop pulpal bleeding demonstrated no effect on the results of treatment outcome. Notably, depending on the type of exposure, the time to stop bleeding varies from 1 to 2 min up to 10 min [144].

Bleeding can be controlled by pressing a sterile cotton pellet soaked in a solution onto the exposed pulp. Saline or hemostatic agents' application has been recommended to stop pulpal bleeding after pulp exposure. A variety of hemostatic solutions have been used to control the bleeding, such as sodium hypochlorite, hydrogen peroxide, and ferric sulfate [145]. In addition, sodium hypochlorite is the most commonly used solution and demonstrated a moderate to high rate of pulp survival with a concentration level of 0.12–5.25% [146].

A successful outcome following DPC depends on controlling bleeding and preventing the formation of blood clots between the material and pulp tissue. Even though it might be challenging to apply a DPC material to a moist surface like a blood clot and the presence of blood clot might lead to an increased risk of post-operative infection [147]. If the DPC agent could not adhere to the exposed pulp tissue due to uncontrolled bleeding, a gap could form between the DPC agent and exposed pulp tissue. As a result, it was speculated that pulp tissue hyperplasia into the gap could result in a pulp tissue projection resembling a polyp [148].

7.2. Bacterial infection

Bacterial infection is another factor that can interfere with the healing process of the exposed dental pulp. Bacteria have the potential to penetrate the exposed pulp through caries, cracks, or fractures in the tooth, and as a result, marginal breakdown occurs at the interface between the restoration and the tooth [18]. At the time of DPC treatment, the exposed pulpal area might be at risk of being contaminated by bacteria. During caries excavation, dentin chips containing bacteria can be displaced into the exposed pulp tissue and this can cause chronic inflammation. Bacteria can also penetrate the pulp wound through leakage around the restoration and DPC agent [149]. Bacterial infections of the pulp tissue consist of mixed microbial and predominantly anaerobic flora [18]. Studies have found that pulpal inflammation induced by bacteria is mainly *Streptococcus mutans*, but other different bacterial species are also responsible for inducing pulp inflammation [150,151]. Bacterial infection of the exposed pulp may cause odontoblast cell death and the odontoblast cell processes become dislodged from the dentinal tubules that turn into dead tracts. These tracts are highly permeable, and therefore they are a potential threat to the integrity of the pulp [18]. The pulpal inflammation is caused by bacteria that impedes the reparative process, which can be prevented after appropriate resolution of inflammation, which likely occurs after disinfecting the inflamed area [13].

The success of DPC depends on the prevention of bacterial penetration into the cavity preparation. This will increase the longevity of the restorations of the cavity. The complications of a bacterial infection include postoperative sensitivity, marginal discoloration, inflammation, recurrent caries, and ultimately the requirement for further endodontic treatment [152]. Even though the wound area was contaminated with bacteria, pulpal healing might have been possible. This may depend on a number of factors. The bacterial mass that accumulated during the exposure might be reduced by a considerable amount by the debridement of the wound area and the irrigation of the cavity preparation using solutions such as sodium hypochlorite [153]. It has been demonstrated that the key factor in healing after pulpal exposure is the absence of microorganisms and infection [154].

7.3. Operative debris

Operative debris includes dentin fragments from the cavity preparation and foreign particles that are mixed with the capping materials (Fig. 3). When the operative debris is present in the exposed pulp, it can interrupt the dentin bridge integrity, which in turn weakens the structure of the bridge, and as a result, the odontoblast cells are unable to secrete dentin [152]. The presence of operative debris has also been associated with an increase in the activity of pulpal inflammatory cells. It is possible that the operative debris might be contaminated with bacteria. These bacteria can enter the pulp tissue and provoke an immunological reaction. In the most severe cases, this can lead to necrosis of the pulp and an inhibition of the formation of the dentin bridge [155]. Frequently, operative debris migrates deep into the pulp tissue from the exposure area [152].

After the pulp exposure, the presence of operative debris, such as dentin chips, might be considered a benefit because they can stimulate the formation of dentin bridge [156]. Although it has been stated that there might be a direct correlation between the area of operative debris and dentin bridge formation, where the operative debris does not appear to have any benefits, only healing complications [156].

7.4. Tunnel defects in dentin bridge

The success of DPC is considered to be negatively affected by a tunnel-like defect within the dentin bridge. This defect can result in microleakage, which leads to the loss of tooth vitality and calcification [2,10]. The tunnel defect can be caused by the intensity of the pulp injury and the number of vessels damaged during exposure, which can lead to dystrophic calcification and incomplete dentin bridge formation [49]. A tunnel defect is an open tunnel from the exposure area through the dentin bridge to the pulp tissue, and this defect may contain fibroblasts and capillaries (Fig. 3) [14]. These tunnels favor bacteria communication and recontamination, which allow the penetration of bacteria or microorganisms into the pulp tissue and not only fail to provide a permanent barrier, but also fail to provide a long-term biological seal against bacterial infection [2,152,157]. More than likely, this is the reason for the failure of DPC after a short period of time because the tunnel defects are committed to developing secondary infection in pulp tissue [157]. Consequently, the incidence and severity of these defects influence pulp healing and treatment outcomes [152].

In an ideal situation, the creation of tunnel defects should be minimized to prevent the complications that can occur during the healing process of pulp tissue. Although there might be a strong correlation between operative debris and tunnel defects [152]. The presence of tunnel defects in the dentin bridge seems to have the possibility of causing more complications than the presence of operative debris. Further investigation is necessary to determine the correlation between tunnel defects and operative debris. Although the presence of operative debris might inhibit the odontoblast cell's ability to secrete a uniform dentin bridge. This finding implies that the tunnel defects can be prevented by eliminating the operative debris associated during cavity preparation and thoroughly cleaning the exposure area before placing a DPC material. Investigation have found that after DPC with CH and RMGI had 82% and 42% tunnel defects in the dentin bridge, respectively. Whereas DPC with MTA showed no tunnel defects in the dentin bridge [152]. It has been reported that the tunnels contain blood vessels or pulp tissue that can provide calcium supply to the affected pulp tissue [49].

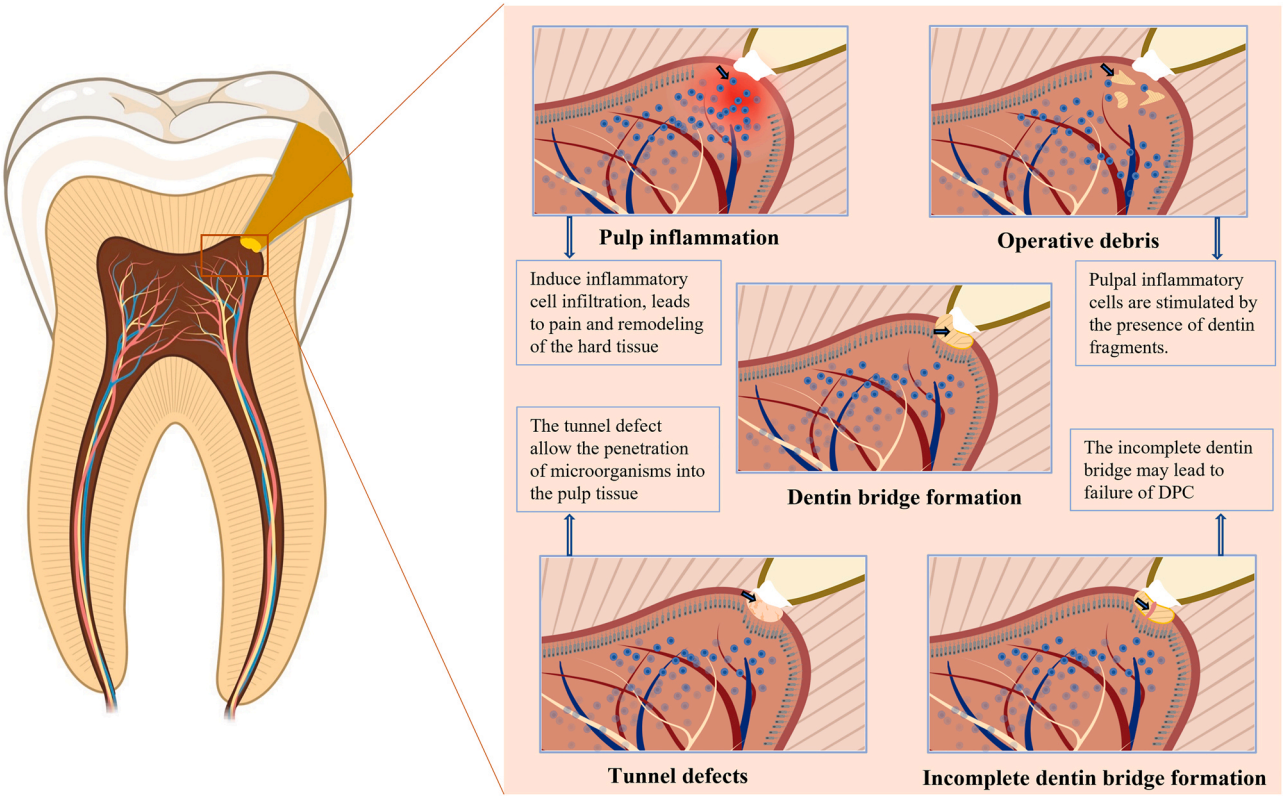

Fig. 3. Schematic presentation of factors affecting DPC healing process. Pulp inflammation: various phases of inflammation of the pulp have been described, including mild, moderate, and severe inflammation; Operative debris: operative debris includes dentinal chips and foreign particles that can increase the activity of pulpal inflammatory cells and interrupt the dentin bridge integrity; Tunnel defects: the number of vessels injured during exposure and the severity of the pulp injury can both contribute to the tunnel defect, which can lead to microleakage that facilitates bacterial communication and recontamination. Incomplete dentin bridge formation: it might contain pulp tissue and can penetrate microorganisms.

7.5. Pulpal inflammation

Inflammation after exposure of the dental pulp can be caused by a number of factors, including mechanical irritation during cavity preparation, penetration of microorganisms through caries into the exposed pulp, and mechanical irritation caused by the DPC material. All these factors are responsible for inducing inflammatory cell infiltration, which then leads to pain and the remodeling of the hard tissue [158]. Various stages of inflammation to the pulp have been investigated after DPC, including mild to moderate, or severe inflammation which can lead to necrosis to the pulp (Fig. 3) [157]. In severe cases, this might lead to hypersensitivity that has been caused by a greater extent of bacterial leakage, leading to cytotoxicity and therefore might lead to failure of DPC treatment [159].

Even though inflammation is a destructive process to the pulp tissue, but immune response that it triggers is required to accelerate the healing process. In fact, the initial stage of inflammation is the recovery process of damaged pulp tissue. On the other hand, if the pulp tissue is severely inflamed and irreversibly damaged, pulpotomy, or complete removal of the inflamed pulp tissue, is the required treatment option [147,160].

8. Clinical considerations of DPC

8.1. Diagnosis

DPC treatment is recommended and carried out after a proper diagnosis has been made [161]. However, it can be more challenging to accurately assess the pulpal condition prior to treatment [162]. To accurately assess the caries and fracture extension on the involved tooth, intraoral radiographs must be taken, which is considered acceptable diagnostic quality [161]. Patients' medical history and reports, radiographic evidence, clinical evaluation, and sensibility testing should all be carefully considered by the clinician before making treatment decisions [35].

After clinical evaluation and confirmation of the pulp exposure, the preliminary pulpal diagnosis can be confirmed. If there is no sign of bleeding at the exposure area, the pulp tissue is most likely necrotic. This necrotic tissue has to be removed with a high-speed diamond bur until there is evidence of bleeding. If it is not possible to control the bleeding, the pulp has been irreparably damaged. In this case, a pulpotomy or root canal treatment is the preferred option.

8.2. Removal of caries

When pulpal exposures occur, complete caries removal is needed to eliminate infected tissues. The presence of residual caries impedes observations of pulpal inflammation and necrosis [161]. Demineralized enamel and infected dentin must be removed for DPC management. If the infected tissue remains, chronic inflammatory cell infiltrates and subclinical pulp inflammation have been observed, which compromise pulp vitality [163].

Caries detectors can be helpful adjuncts during caries removal, especially near the pulp cavity [164,165]. The use of detectors can establish an objective standard during the removal of caries. On the other hand, it must be understood that detectors can cause excessive and unnecessary removal of healthy tooth structure [166,167]. In order to improve pulpal repair, the clinician should concentrate on completely removing demineralized infected dentin rather than avoiding pulp exposure.

8.3. Use of hemostatic agent

To control bleeding from the exposed pulp, a variety of hemostatic solutions and methods are recommended. These include sodium hypochlorite (NaOCl), chlorhexidine, hydrogen peroxide, ferric sulfate, and others. 2.5% NaOCl is the most effective hemostatic solution for direct pulp exposure in dentistry [145]. It is an antimicrobial solution that promotes hemostasis, disinfects the dentin-pulp interface, eliminates biofilm, removes blood clots and fibrin chemically, and clears dentinal chips and damaged cells from the mechanical exposure site [161]. Direct passive irrigation or NaOCl-soaked cotton pellets have been recommended to achieve hemostasis on the exposed pulp [168]. Even though there are several different hemostatic options, NaOCl can be used directly on pulp tissue at different concentrations without jeopardizing pulp integrity [169]. Bleeding must be controlled before the placement of an appropriate biomaterial, which can allow clinical assessment of the inflammatory levels and identify the potential necrotic tissue.

8.4. Use of biomaterials

The biomaterial placed directly on the exposed pulp is the most important goal in successful DPC treatment. The use of calcium-silicate based materials in DPC procedures has gained popularity [2,3,51,52,72,73]. These materials have shown persistent clinical efficacy, and MTA is one of the most widely utilized and investigated materials in DPC [72,74–76]. Calcium silicate-based materials formed into mineralized tissue barriers are of higher quality than CH-based materials [2,3,52]. The choice of a biomaterials must be based on evidence and must include considerations for patient-centered outcomes, consistent mineralized tissue formation, and prolonged pulp vitality [161].

8.5. Final restoration

An essential step in DPC procedures is the final tooth restoration. Teeth treated with DPC using calcium silicate-based cements and immediately restored have a higher success rate [48,75,170]. Advantages of immediate restoration include preventing microleakage, protecting the biomaterial layer, reducing post-operative sensitivity and thermal conductivity. Notably, the immediate restoration of the teeth has not been shown to have any adverse effects [161].

9. Future perspective for DPC

Discovering a DPC material that is biocompatible, accelerates the natural healing process to the pulp and provide more benefits than currently available biomaterials. To develop an ideal DPC material, manufacturers are always changing the composition of the materials to improve their efficacy. Currently available DPC materials have been investigated extensively, but little investigation has been done to modify them for further improvement. The current trends indicate that CH-based materials were extensively used in the past as a DPC agent, followed by resin-based materials, and finally the use of MTA, bioactive materials, or bioceramics, has become increasingly popular in recent years.

The lack of effectiveness of the currently available DPC materials is due to leakage at the interface between the dentin and the material as well as final restorative materials. For the development of an ideal DPC material, manufacturers or researchers should focus on adding the bioactive molecules to the materials for further development where the material will be bioactive and biocompatible, non-cytotoxic, and should adhere to the dentin, which can prevent external leakage, promote faster healing, and form a homogenous mineralized tissue barrier at the exposure area (Fig. 4) [4]. Encouragement and further development of therapeutically beneficial strategies to maximize the release of these bioactive molecules, such

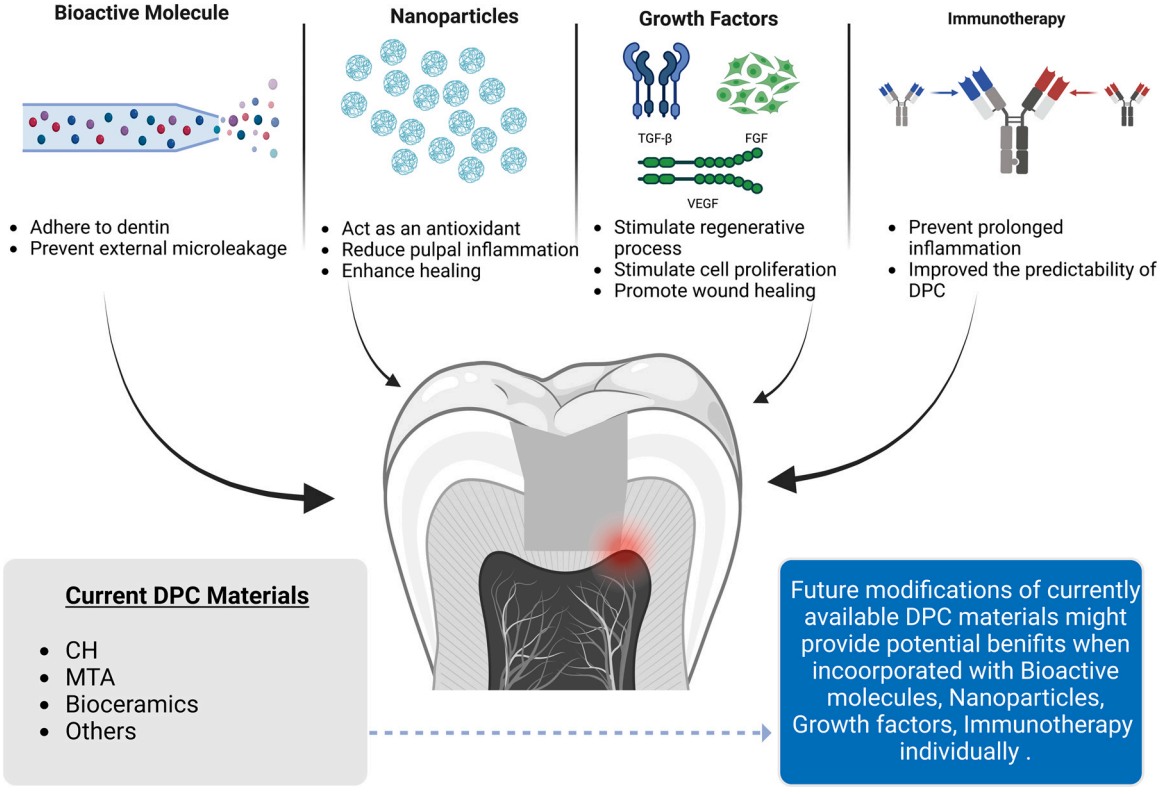

Fig. 4. Graphical illustration of future perspective of DPC materials. Potential benefits might be obtained from combining bioactive molecules, or nanoparticles, or growth factors, or immunotherapy with future developments of currently existing DPC materials.

as irrigation with EDTA, ultrasonication, or the direct administration of extracted dentin matrix components, should be carried out [171].

DPC refers to an overarching concept that incorporates a variety of procedures that stimulate the pulp's natural wound-healing [171]. Even though the inflammatory state of the pulp is thought to be the most important factor in determining whether the DPC procedure will be effective [12]. However, other factors that are within the control of the operator, such as the choice of DPC materials, working under an endodontic microscope, and the application of antimicrobial wound lavage, can also affect the outcome of treatment [76,147]. Currently, the DPC concept is still dominated by a technical rather than a biological standpoint, but even minor alterations to current practice might support a change toward a more biologically grounded perspective [171].

It is important to take into consideration other translational breakthroughs that can decrease pulpal inflammation and enhance healing. The use of biomarkers provides the possibility of measuring pulpal inflammation. This can be accomplished while conserving the vitality of the pulp, maintaining the integrity of the tooth, and increasing the predictability of the treatment [171]. On the other hand, regeneration processes can be enhanced if the balance is altered in a certain direction. Therefore, strategies should be developed to target the inflammatory processes in the pulp, such as pharmacological inhibitors or immunotherapy, in order to prevent more protracted and severe inflammation [171]. Therefore, better scientific and clinical outcomes may be achieved in the near future if DPC materials evolve to target biological processes such as specific miRNA, epigenetic processes, antioxidants, or the direct administration of growth factors (Fig. 4) [171]. This might lead to the stimulation of regenerative rather than reparative responses in the dentin-pulp complex.

10. Conclusion

Based on this review, different stages of pulpal inflammation following DPC therapy have been identified, and these stages are associated with mild to moderate, or severe inflammation, including necrosis of the pulp. Inflammation has always been viewed as nothing more than a negative side effect, but recent research suggests that it plays a crucial role in the pulpal healing process. There is now evidence to suggest that inflammation is necessary for the pulpal healing process. During the inflammatory process, proliferation of pulp cells occurs and increases numerously and differentiates into odontoblast-like cells to promote mineralized tissue formation at the exposure site.

According to the discussion of this review, CH has been the most extensively studied biomaterial with favorable clinical outcomes. However, calcium silicate-based materials appear to be the most effective type of biomaterial currently employed for DPC. Furthermore, MTA and biodentine showed superior clinical performance than other DPC materials. Additionally, long-term clinical investigations could confirm the acceptability of DPC material among several biomaterials.

Conflict of interest

None

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research number 22K09994 and 21K21028 from the Ministry of Education, Science, and Culture, Japan. All the figures created with BioRender.com.

References

[1] Cobanoglu N, Alptekin T, Kitagawa H, Blatz MB, Imazato S, Ozer F. Evaluation of human pulp tissue response following direct pulp capping with a self-etching adhesive system containing MDPB. Dent Mater J 2021;40:689–96.
[2] Komabayashi T, Zhu Q, Eberhart R, Imai Y. Current status of direct pulp-capping materials for permanent teeth. Dent Mater J 2016;35:1–12.
[3] Nie E, Yu J, Jiang R, Liu X, Li X, Islam R, et al. Effectiveness of direct pulp capping bioactive materials in dentin regeneration: a systematic review. Mater 2021;14:6811.
[4] da Rosa WL, Cocco AR, Silva TMD, Mesquita LC, Galarca AD, Silva AFD, et al. Current trends and future perspectives of dental pulp capping materials: a systematic review. J Biomed Mater Res B Appl Biomater 2018;106:1358–68.
[5] Sun HH, Jin T, Yu Q, Chen FM. Biological approaches toward dental pulp regeneration by tissue engineering. J Tissue Eng Regen Med 2011;5:1–16.
[6] Hanna SN, Alfayate RP, Prichard J. Vital pulp therapy an insight over the available literature and future expectations. Eur Endod J 2020;5:46–53.
[7] Alex G. Direct and indirect pulp capping: a brief history, material innovations, and clinical case report. Compend Contin Educ Dent 2018;2018(39):182–9.
[8] Asgary S, Nourzadeh M, Eghbal MJ. Miniature pulpotomy of symptomatic mature permanent teeth: a report of two cases. Iran Endod J 2016;2016(11):75–8.
[9] Glossary of Endodontic Terms. American Association of Endodontists 2020.
[10] Okamoto M, Takahashi Y, Komichi S, Ali M, Yoneda N, Ishimoto T, et al. Novel evaluation method of dentin repair by direct pulp capping using high-resolution micro-computed tomography. Clin Oral Invest 2018;22:2879–87.
[11] Baume L, Holz J. Long-term clinical assessment of direct pulp capping. Int Dent J 1981;31:251–60.
[12] Al-Hiyasat A, Barrieshi-Nusair K, Al-Mari M. The radiographic outcomes of direct pulp-capping procedures performed by dental students. J Am Dent Assoc 2006;137:1699–705.
[13] Farges JC, Alliot-Licht B, Renard E, Ducret M, Gaudin A, Smith AJ, et al. Dental pulp defence and repair mechanisms in dental caries. Mediat Inflamm 2015;2015:230251.
[14] Hilton TJ. Keys to clinical success with pulp capping: a review of the literature. Oper Dent 2009;34:615–25.
[15] Hahn CL, Liewehr FR. Innate immune responses of the dental pulp to caries. J Endod 2007;33:643–51.
[16] Marchi J, de Araujo F, Fröner A, Straffon L, Nör J. Indirect pulp capping in the primary dentition: a 4-year follow-up study. J Clin Pedia Dent 2007;31:68–71.
[17] Simon S, Smith AJ, Lumley PJ, Cooper PR, Berdal A. The pulp healing process: from generation to regeneration. Endod Top 2012;26:41–56.
[18] Yu C, Abbott PV. An overview of the dental pulp: its functions and responses to injury. Aust Dent J 2007;52:4–6.
[19] Asgary S, Ahmadyar M. Vital pulp therapy using calcium-enriched mixture: an evidence-based review. J Conserv Dent 2013;16:92–8.
[20] Gaudin A, Renard E, Hill M, Bouchet-Delbos L, Bienvenu-Louvet G, Farges JC, et al. Phenotypic analysis of immunocompetent cells in healthy human dental pulp. J Endod 2015;41:621–7.
[21] Renard E, Gaudin A, Bienvenu G, Amiaud J, Farges JC, Cuturi MC, et al. Immune cells and molecular networks in experimentally induced pulpitis. J Dent Res 2016;95:196–205.
[22] Metcalf D. Control of granulocytes and macrophages: molecular, cellular, and clinical aspects. Science 1991;254:529–33.
[23] Holder MJ, Wright HJ, Couve E, Milward MR, Cooper PR. Neutrophil extracellular traps exert potential cytotoxic and proinflammatory effects in the dental pulp. J Endod 2019;45:513–20.
[24] Cooper PR, Chicca IJ, Holder MJ, Milward MR. Inflammation and regeneration in the dentin-pulp complex: net gain or net loss? J Endod 2017;43:87–94.
[25] Huang M, Zhan C, Yang X, Hou J. Regulated cell death in pulpitis. J Endod 2020;46:1403–13.
[26] Duncan HF, Cooper PR. Pulp innate immune defense: translational opportunities. J Endod 2020;46:10–8.
[27] Leprince JG, Zeitlin BD, Tolar M, Peters OA. Interactions between immune system and mesenchymal stem cells in dental pulp and periapical tissues. Int Endod J 2012;45:689–701.
[28] Hørsted P, El Attar K, Langeland K. Capping of monkey pulps with Dycal and a Ca-eugenol cement. Oral Surg Oral Med Oral Pathol 1981;52:531–53.
[29] Cooper PR, Takahashi Y, Graham LW, Simon S, Imazato S, Smith AJ. Inflammation–regeneration interplay in the dentine–pulp complex. J Dent 2010;2010(38):687–97.
[30] Alacam ALEV, Tulunoglu Ö, Oygür T, Bilici S. Effects of topical Catalase application on dental pulp tissue: a histopathological evaluation. J Dent 2000;28:333–9.
[31] Caviedes Bucheli J, Gomez Sosa JF, Azuero Holguin MM, Ormeño Gomez M, Pinto Pascual V, Munoz HR. Angiogenic mechanisms of human dental pulp and their relationship with substance P expression in response to occlusal trauma. Int Endod J 2017;50:339–51.
[32] Nakashima M, Akamine A. The application of tissue engineering to regeneration of pulp and dentin in endodontics. J Endod 2005;31:711–8.
[33] Yamamura T. Differentiation of pulpal cells and inductive influences of various matrices with reference to pulpal wound healing. J Dent Res 1985;64:530–40.
[34] Fitzgerald M. Cellular mechanics of dentinal bridge repair using 3H-thymidine. J Dent Res 1979;58:2198–206.

[35] Hargreaves KM, Berman LH. Cohen's Pathways of the Pulp. fourteenth ed. St Louis, MO: Elsevier Saunders; 2021.
[36] Schroder U. Scanning electron microscopy of hard tissue barrier following experimental pulpotomy of intact human teeth and capping with calcium hydroxide. Odontol Rev 1972;23:211–20.
[37] Farges JC, Keller JF, Carrouel F, Durand SH, Romeas A, Bleicher F, et al. Odontoblasts in the dental pulp immune response. J Exp Zool B Mol Dev Evol 2009;312:425–36.
[38] Hayashi Y. Ultrastructure of initial calcification in wound healing following pulpotomy. J Oral Pathol Med 1982;11:174–80.
[39] Mjör IA, Dah E, Cox CF. Healing of pulp exposures: an ultrastructural study. J Oral Pathol Med 1991;20:496–501.
[40] Aeinehchi M, Eslami B, Ghanbariha M, Saffar AS. Mineral trioxide aggregate (MTA) and calcium hydroxide as pulp-capping agents in human teeth: a preliminary report. Int Endod J 2003;36:225–35.
[41] Téclès O, Laurent P, Aubut V, About I. Human tooth culture: a study model for reparative dentinogenesis and direct pulp capping materials biocompatibility. J Biomed Mater Res B Appl Biomater 2008;85:180–7.
[42] Sangwan P, Sangwan A, Duhan J, Rohilla A. Tertiary dentinogenesis with calcium hydroxide: a review of proposed mechanisms. Int Endod J 2013;46:3–19.
[43] Song M, Yu B, Kim S, Hayashi M, Smith C, Sohn S, et al. Clinical and molecular perspectives of reparative dentin formation: lessons learned from pulp-capping materials and the emerging roles of calcium. Dent Clin North Am 2017;61:93–110.
[44] Khan AA, Sun X, Hargreaves KM. Effect of calcium hydroxide on proinflammatory cytokines and neuropeptides. J Endod 2008;34:1360–3.
[45] Reyes-Carmona JF, Santos AR, Figueiredo CP, Felippe MS, Felippe WT, Cordeiro MM. In vivo host interactions with mineral trioxide aggregate and calcium hydroxide: inflammatory molecular signaling assessment. J Endod 2011;37:1225–35.
[46] Tanomaru-Filho M, Chaves Faleiros FB, Sacaki JN, Hungaro Duarte MA, Guerreiro-Tanomaru JM. Evaluation of pH and calcium ion release of root-end filling materials containing calcium hydroxide or mineral trioxide aggregate. J Endod 2009;35:1418–21.
[47] Duarte MA, Martins CS, de Oliveira Cardoso Demarchi AC, de Godoy LF, Kuga MC, Yamashita JC. Calcium and hydroxide release from different pulp-capping materials. Oral Surg Oral Med Oral Pathol Oral Radio Endod 2007;104:66–9.
[48] Mente J, Geletneky B, Ohle M, Koch MJ, Ding PGF, Wolff D, et al. Mineral trioxide aggregate or calcium hydroxide direct pulp capping: an analysis of the clinical treatment outcome. J Endod 2010;36:806–13.
[49] Islam R, Toida Y, Chen F, Tanaka T, Inoue S, Kitamura T, et al. Histological evaluation of a novel phosphorylated pullulan based pulp capping material: an in vivo study on rat molars. Int Endod J 2021;54:1902–14.
[50] Ba-Hattab R, Al-Jamie M, Aldreib H, Alessa L, Alonazi M. Calcium hydroxide in endodontics: an overview. Open J Stomatol 2016;6:274–89.
[51] Andrei M, Vacaru RP, Coricovac A, Ilinca R, Didilescu AC, Demetrescu I. The effect of calcium-silicate cements on reparative dentinogenesis following direct pulp capping on animal models. Molecules 2021;26:2725.
[52] Toida Y, Kawano S, Islam R, Jiale F, Chowdhury AA, Hoshika S, et al. Pulpal response to mineral trioxide aggregate containing phosphorylated pullulan-based capping material. Dent Mater J 2021;41:126–33.
[53] Matsuura T, Kawata-Matsuura VK, Yamada S. Long-term clinical and radiographic evaluation of the effectiveness of direct pulp-capping materials. J Oral Sci 2019;61:1–12.
[54] Modena KCDS, Calvo AM, Sipert CR, Colombini-Ishikiriama BL, Dionísio TJ, Navarro MFDL, et al. Molecular response of pulp fibroblasts after stimulation with pulp capping materials. Braz Dent J 2020;31:244–51.
[55] Barthel CR, Levin LG, Reisner HM, Trope M. TNF-alpha release in monocytes after exposure to calcium hydroxide treated Escherichia coli LPS. Int Endod J 1997;30:155–9.
[56] Stuart KG, Miller CH, Brown Jr CE, Newton CW. The comparative antimicrobial effect of calcium hydroxide. Oral Surg Oral Med Oral Pathol 1991;72:101–4.
[57] Li Z, Cao L, Fan M, Xu Q. Direct pulp capping with calcium hydroxide or mineral trioxide aggregate: a meta-analysis. J Endod 2015;41:1412–7.
[58] Al-Hezaimi K, Salameh Z, Al-Fouzan K, Al Rejaie M, Tay FR. Histomorphometric and micro–computed tomography analysis of pulpal response to three different pulp capping materials. J Endod 2011;37:507–12.
[59] Cox CF, Sübay RK, Ostro E, Suzuki S, Suzuki SH. Tunnel defects in dentin bridges: their formation following direct pulp capping. Oper Dent 1996;21:4–11.
[60] Matsuo T, Nakanishi T, Shimizu H, Ebisu S. A clinical study of direct pulp capping applied to carious-exposed pulps. J Endod 1996;22:551–6.
[61] Auschill TM, Arweiler NB, Hellwig E, Zamani-Alaei A, Sculean A. Success rate of direct pulp capping with calcium hydroxide. Schweiz Mon Zahnmed 2003;113:946–52.
[62] Barthel CR, Rosenkranz B, Leuenberg A, Roulet JF. Pulp capping of carious exposures: treatment outcome after 5 and 10 years: a retrospective study. J Endod 2000;26:525–8.
[63] Schröder U. Effects of calcium hydroxide-containing pulp-capping agents on pulp cell migration, proliferation, and differentiation. J Dent Res 1985;64:541–8.
[64] Cox CF, Suzuki S. Re-evaluating pulp protection: calcium hydroxide liners vs. cohesive hybridization. J Am Dent Assoc 1994;125:823–31.
[65] Taira Y, Shinkai K, Suzuki M, Kato C, Katoh Y. Direct pulp capping effect with experimentally developed adhesive resin systems containing reparative dentin-promoting agents on rat pulp: mixed amounts of additives and their effect on wound healing. Odontology 2011;99:135–47.
[66] Smith AJ. Pulpal responses to caries and dental repair. Caries Res 2002;36:223–32.
[67] Pisanti S, Sciaky I. Origin of calcium in the repair wall after pulp exposure in the dog. J Dent Res 1964;43:641–4.
[68] Sciaky I, Pisanti S. Localization of calcium placed over amputated pulps in dogs' teeth. J Dent Res 1960;39:1128–32.
[69] Kardos TB, Hunter AR, Hanlin SM, Kirk EEJ. Odontoblast differentiation: a response to environmental calcium? Dent Trauma 1998;14:105–11.
[70] Hørsted P, Søndergaard B, Thylstrup A, El Attar K, Fejerskov O. A retrospective study of direct pulp capping with calcium hydroxide compounds. Dent Trauma 1985;1:29–34.
[71] Willershausen B, Willershausen I, Ross A, Velikonja S, Kasaj A, Blettner M. Retrospective study on direct pulp capping with calcium hydroxide. Quintessence Int 2011;42:165–71.
[72] Çalışkan MK, Güneri P. Prognostic factors in direct pulp capping with mineral trioxide aggregate or calcium hydroxide: 2-to 6-year follow-up. Clin Oral Invest 2017;21:357–67.
[73] Dammaschke T, Leidinger J, Schäfer E. Long-term evaluation of direct pulp capping—treatment outcomes over an average period of 6.1 years. Clin Oral Invest 2010;14:559–67.
[74] Eskandarizadeh A, Shahpasandzadeh MH, Shahpasandzadeh M, Torabi M, Parirokh M. A comparative study on dental pulp response to calcium hydroxide, white and grey mineral trioxide aggregate as pulp capping agents. J Conserv Dent 2011;14:351–5.
[75] Hilton TJ, Ferracane JL, Mancl L. Comparison of CaOH with MTA for direct pulp capping: a PBRN randomized clinical trial. J Dent Res 2013;92:16S–22S.
[76] Mente J, Hufnagel S, Leo M, Michel A, Gehrig H, Panagidis D, et al. Treatment outcome of mineral trioxide aggregate or calcium hydroxide direct pulp capping: long-term results. J Endod 2014;40:1746–51.
[77] Lipski M, Nowicka A, Kot K, Postek-Stefańska L, Wysoczańska-Jankowicz I, Borkowski L, et al. Factors affecting the outcomes of direct pulp capping using Biodentine. Clin Oral Invest 2018;22:2021–9.
[78] Camilleri J. Characterization of hydration products of mineral trioxide aggregate. Int Endod J 2008;41:408–17.
[79] Tawil PZ, Duggan DJ, Galicia JC. Mineral trioxide aggregate (MTA): its history, composition, and clinical applications. Compend Contin Educ Dent 2015;36:247–52.
[80] Okiji T, Yoshiba K. Reparative dentinogenesis induced by mineral trioxide aggregate: a review from the biological and physicochemical points of view. Int J Dent 2009;2009:464280.
[81] Marques MS, Wesselink PR, Shemesh H. Outcome of direct pulp capping with mineral trioxide aggregate: a prospective study. J Endod 2015;41:1026–31.
[82] Nair PNR, Duncan HF, Pitt Ford TR, Luder HU. Histological, ultrastructural and quantitative investigations on the response of healthy human pulps to experimental capping with mineral trioxide aggregate: a randomized controlled trial. Int Endod J 2008;2008(41):128–50.
[83] Tomson PL, Grover LM, Lumley PJ, Sloan AJ, Smith AJ, Cooper PR. Dissolution of bio-active dentine matrix components by mineral trioxide aggregate. J Dent 2007;35:636–42.
[84] Schwendicke F, Brouwer F, Schwendicke A, Paris S. Different materials for direct pulp capping: systematic review and meta-analysis and trial sequential analysis. Clin Oral Invest 2016;20:1121–32.
[85] Reyes-Carmona JF, Santos AS, Figueiredo CP, Baggio CH, Felippe MC, Felippe WT, et al. Host–mineral trioxide aggregate inflammatory molecular signaling and biomineralization ability. J Endod 2010;36:1347–53.
[86] Kunert M, Lukomska-Szymanska M. Bio-inductive materials in direct and indirect pulp capping—a review article. Mater 2020;13:1204.
[87] Bogen G, Kim JS, Bakland LK. Direct pulp capping with mineral trioxide aggregate: an observational study. J Am Dent Assoc 2008;139:305–15.
[88] Kuratate M, Yoshiba K, Shigetani Y, Yoshiba N, Ohshima H, Okiji T. Immunohistochemical analysis of nestin, osteopontin, and proliferating cells in the reparative process of exposed dental pulp capped with mineral trioxide aggregate. J Endod 2008;34:970–4.
[89] Sarkar NK, Caicedo R, Ritwik P, Moiseyeva R, Kawashima I. Physicochemical basis of the biologic properties of mineral trioxide aggregate. J Endod 2005;31:97–100.
[90] Parirokh M, Torabinejad M. Mineral trioxide aggregate: a comprehensive literature review-part III: clinical applications, drawbacks, and mechanism of action. J Endod 2010;2010(36):400–13.
[91] Zhu C, Ju B, Ni R. Clinical outcome of direct pulp capping with MTA or calcium hydroxide: a systematic review and meta-analysis. Int J Clin Exp Med 2015;8:17055–60.
[92] About I. Recent trends in tricalcium silicates for vital pulp therapy. Curr Oral Health Rep 2017;5:178–85.
[93] Arandi NZ, Thabet M. Minimal intervention in dentistry: a literature review on Biodentine as a bioactive pulp capping material. BioMed Res Int 2021;2021:5569313.
[94] Marciano MA, Costa RM, Camilleri J, Mondelli RFL, Guimarães BM, Duarte MAH. Assessment of color stability of white mineral trioxide aggregate angelus and bismuth oxide in contact with tooth structure. J Endod 2014;2014(40):1235–40.
[95] Formosa LM, Mallia B, Camilleri J. The effect of curing conditions on the physical properties of tricalcium silicate cement for use as a dental biomaterial. Int Endod J 2012;45:326–36.

[96] Gomes Cornélio AL, Rodrigues EM, Salles LP, Mestieri LB, Faria G, Guerreiro Tanomaru JM, et al. Bioactivity of MTA Plus, Biodentine and an experimental calcium silicate-based cement on human osteoblast-like cells. Int Endod J 2017;50:39–47.
[97] Camilleri J, Sorrentino F, Damidot D. Investigation of the hydration and bioactivity of radiopacified tricalcium silicate cement, Biodentine and MTA Angelus. Dent Mater 2013;29:580–93.
[98] Grech L, Mallia B, Camilleri J. Investigation of the physical properties of tricalcium silicate cement-based root-end filling materials. Dent Mater 2013;29:20–8.
[99] Kaur M, Singh H, Dhillon JS, Batra M, Saini M. MTA versus Biodentine: review of literature with a comparative analysis. J Clin Diagn Res 2017;11:ZG01–5.
[100] Butt N, Talwar S, Chaudhry S, Nawal RR, Yadav S, Bali A. Comparison of physical and mechanical properties of mineral trioxide aggregate and Biodentine. Indian J Dent Res 2014;25:692–7.
[101] Duarte MAH, Marciano MA, Vivan RR, Tanomaru Filho M, Tanomaru JMG, Camilleri J. Tricalcium silicate-based cements: properties and modifications. Braz Oral Res 2018;32:e70.
[102] Tanalp J, Karapınar-Kazandağ M, Dölekoğlu S, Kayahan MB. Comparison of the radiopacities of different root-end filling and repair materials. Sci World J 2013;2013:594950. [84].
[103] Li X, Yoshihara K, De Munck J, Cokic S, Pongprueksa P, Putzeys E, et al. Modified tricalcium silicate cement formulations with added zirconium oxide. Clin Oral Invest 2017;21:895–905.
[104] Natale LC, Rodrigues MC, Xavier TA, Simões A, De Souza DN, Braga RR. Ion release and mechanical properties of calcium silicate and calcium hydroxide materials used for pulp capping. Int Endod J 2015;48:89–94.
[105] Al-Sherbiny IM, Farid MH, Abu-Seida AM, Motawea IT, Bastawy HA. Chemico-physical and mechanical evaluation of three calcium silicate-based pulp capping materials. Saudi Dent J 2021;33:207–14.
[106] Gandolfi MG, Siboni F, Botero T, Bossù M, Riccitiello F, Prati C. Calcium silicate and calcium hydroxide materials for pulp capping: biointeractivity, porosity, solubility and bioactivity of current formulations. J Appl Biomater Func Mater 2015;13:43–60.
[107] Poggio C, Arciola CR, Beltrami R, Monaco A, Dagna A, Lombardini M, et al. Cytocompatibility and antibacterial properties of capping materials. Sci World J 2014;2014:181945.
[108] Bhavana V, Chaitanya KP, Gandi P, Patil J, Dola B, Reddy RB. Evaluation of antibacterial and antifungal activity of new calcium-based cement (Biodentine) compared to MTA and glass ionomer cement. J Conserv Dent 2015;18:44–6.
[109] Giraud T, Jeanneau C, Rombouts C, Bakhtiar H, Laurent P, About I. Pulp capping materials modulate the balance between inflammation and regeneration. Dent Mater 2019;35:24–35.
[110] Nowicka A, Lipski M, Parafiniuk M, Sporniak-Tutak K, Lichota D, Kosierkiewicz A, et al. Response of human dental pulp capped with biodentine and mineral trioxide aggregate. J Endod 2013;39:743–7.
[111] Hegde S, Sowmya B, Mathew S, Bhandi SH, Nagaraja S, Dinesh K. Clinical evaluation of mineral trioxide aggregate and biodentine as direct pulp capping agents in carious teeth. J Conserv Dent 2017;20:91–5.
[112] Awawdeh L, Al-Qudah A, Hamouri H, Chakra RJ. Outcomes of vital pulp therapy using mineral trioxide aggregate or biodentine: a prospective randomized clinical trial. J Endod 2018;44:1603–9.
[113] Davaie S, Hooshmand T, Ansarifard S. Different types of bioceramics as dental pulp capping materials: a systematic review. Ceram Int 2021;47:20781–92.
[114] Kim J, Song YS, Min KS, Kim SH, Koh JT, Lee BN, et al. Evaluation of reparative dentin formation of ProRoot MTA, Biodentine and BioAggregate using micro-CT and immunohistochemistry. Restor Dent Endod 2016;41:29–36.
[115] Zhang S, Yang X, Fan M. BioAggregate and iR oot BP Plus optimize the proliferation and mineralization ability of human dental pulp cells. Int Endod J 2013;46:923–9.
[116] Zhu L, Yang J, Zhang J, Peng B. A comparative study of BioAggregate and ProRoot MTA on adhesion, migration, and attachment of human dental pulp cells. J Endod 2014;40:1118–23.
[117] Arandi NZ, Rabi T. TheraCal LC: from biochemical and bioactive properties to clinical applications. Int J Dent 2018;2018:3484653.
[118] Dutta A, Saunders WP. Calcium silicate materials in endodontics. Dent Update 2014;41:708–22.
[119] Gandolfi MG, Siboni F, Prati C. Chemical-physical properties of TheraCal, a novel light-curable MTA-like material for pulp capping. Int Endod J 2012;45:571–9.
[120] Camilleri J. Hydration characteristics of Biodentine and Theracal used as pulp capping materials. Dent Mater 2014;30:709–15.
[121] Camilleri J, Laurent P, About I. Hydration of biodentine, theracal lc, and a prototype tricalcium silicate–based dentin replacement material after pulp capping in entire tooth cultures. J Endod 2014;40:1846–54.
[122] Dawood AE, Parashos P, Wong RH, Reynolds EC, Manton DJ. Calcium silicate-based cements: composition, properties, and clinical applications. J Invest Clin Dent 2017;8:12195.
[123] Iyer JV, Kanodia SK, Parmar GJ, Parmar AP, Asthana G, Dhanak NR. Comparative evaluation of different direct pulp capping agents in carious tooth: An in vivo study. J Conserv Dent 2021;24:283–7.
[124] Peskersoy C, Lukarcanin J, Turkun M. Efficacy of different calcium silicate materials as pulp-capping agents: randomized clinical trial. J Dent Sci 2021;16:723–31.
[125] Inami C, Iwasaki S, Tsuchikawa M. Resin-modified MTA-based material "Super MTA Paste" using TBB as a polymerization initiator. J Jpn Assoc Regen Dent 2020;18:9–13.
[126] Inami C, Endoh C, Ichinohe H, Itsuno S. Effect of direct pulp capping with a novel chemically curable mineral trioxide aggregate material using tri-butylborane as a polymerization initiator. J Hard Tissue Biol 2019;28:383–90.
[127] Ho YC, Huang FM, Chang YC. Mechanisms of cytotoxicity of eugenol in human osteoblastic cells in vitro. Int Endod J 2006;39:389–93.
[128] Chen L, Suh BI. Cytotoxicity and biocompatibility of resin-free and resin-modified direct pulp capping materials: a state-of-the-art review. Dent Mater J 2017;36:1–7.
[129] Do Nascimento AB, Fontana UF, Teixeira HM, Costa CA. Biocompatibility of a resin-modified glass-ionomer cement applied as pulp capping in human teeth. Am J Dent 2000;13:28–34.
[130] Sübay RK, Demirci M. Pulp tissue reactions to a dentin bonding agent as a direct capping agent. J Endod 2005;31:201–4.
[131] Lu Y, Liu T, Li X, Li H, Pi G. Histologic evaluation of direct pulp capping with a self-etching adhesive and calcium hydroxide in beagles. Oral Surg Oral Med Oral Pathol Oral Radio Endod 2006;102:78–84.
[132] Cui C, Zhou X, Chen X, Fan M, Bian Z, Chen Z. The adverse effect of self-etching adhesive systems on dental pulp after direct pulp capping. Quintessence Int 2009;40:26–34.
[133] Hebling J, Giro EMA, de Souza, Costa CA. Biocompatibility of an adhesive system applied to exposed human dental pulp. J Endod 1999;25:676–82.
[134] Cox CF, Hafez AA, Akimoto N, Otsuki M, Suzuki S, Tarim B. Biocompatibility of primer, adhesive and resin composite systems on non-exposed and exposed pulps of non-human primate teeth. Am J Dent 1998;11:55–63.
[135] Tarim B, Hafez AA, Cox CF. Pulpal response to a resin-modified glass-ionomer material on nonexposed and exposed monkey pulps. Quintessence Int 1998;1998(29):535–42.
[136] Accorinte MDLR, Loguercio AD, Reis A, Muench A, de Araújo VC. Adverse effects of human pulps after direct pulp capping with the different components from a total-etch, three-step adhesive system. Dent Mater 2005;21:599–607.
[137] Hörsted-Bindslev P, Vilkinis V, Sidlauskas A. Direct capping of human pulps with a dentin bonding system or with calcium hydroxide cement. Oral Surg Oral Med Oral Pathol Oral Radio Endod 2003;96:591–600.
[138] Modena KCDS, Casas-Apayco LC, Atta MT, Costa CADS, Hebling J, Sipert CR, et al. Cytotoxicity and biocompatibility of direct and indirect pulp capping materials. J Appl Oral Sci 2009;17:544–54.
[139] Nowicka A, Parafiniuk M, Lipski M, Lichota D, Buczkowska-Radlinska J. Pulpo-dentin complex response after direct capping with self-etch adhesive systems. Folia Histochem Cytobiol 2012;50:565–73.
[140] Silva GAB, Gava E, Lanza LD, Estrela C, Alves JB. Subclinical failures of direct pulp capping of human teeth by using a dentin bonding system. J Endod 2013;39:182–9.
[141] Ricucci D, Loghin S, Lin LM, Spångberg LS, Tay FR. Is hard tissue formation in the dental pulp after the death of the primary odontoblasts a regenerative or a reparative process? J Dent 2014;42:1156–70.
[142] Cooper PR, Takahashi Y, Graham LW, Simon S, Imazato S, Smith AJ. Inflammation-regeneration interplay in the dentine-pulp complex. J Dent 2010;38:687–97.
[143] Zakaria MN. Save the pulp is the essential issues on pulp capping treatment. J Dentomaxillofac Sci 2016;1:73–6.
[144] Asgary S, Parhizkar A. Importance of "time" on "haemostasis" in vital pulp therapy. Eur Endod J 2021;2021(6):128–9.
[145] Ballal NV, Duncan HF, Rai N, Jalan P, Zehnder M. Sodium hypochlorite reduces postoperative discomfort and painful early failure after carious exposure and direct pulp capping—initial findings of a randomized controlled trial. J Clin Med 2020;9:2408.
[146] Accorinte MDLR, Loguercio AD, Reis A, Muench A, Araujo VC. Response of human pulp capped with a bonding agent after bleeding control with hemostatic agents. Oper Dent 2005;30:147–55.
[147] Bjørndal L, Simon S, Tomson PL, Duncan HF. Management of deep caries and the exposed pulp. Int Endod J 2019;52:949–73.
[148] Ogisu T, Suzuki M, Shinkai K, Katoh Y. Effect on pulp healing of CO_2 laser irradiation and direct pulp capping with experimentally developed adhesive resin systems containing reparative dentin-promoting agents. J Oral Laser Appl 2008;8:257–78.
[149] Cox CF, Bergenholtz G, Fitzgerald M, Heys DR, Heys RJ, Avery JK, et al. Capping of the dental pulp mechanically exposed to the oral microflora–a 5 week observation of wound healing in the monkey. J Oral Pathol 1982;11:327–39.
[150] Paterson RC, Pountney SK. Pulp response to Streptococcus mutans. Oral Surg Oral Med Oral Pathol 1987;64:339–47.
[151] Paterson RC, Pountney SK. Pulp response to dental caries induced by Streptococcus mutans. Oral Surg Oral Med Oral Pathol 1982;53:88–92.
[152] Murray PE, Garcia-Godoy F. The incidence of pulp healing defects with direct capping materials. Am J Dent 2006;19:171–7.
[153] Cox CF, Bergenholtz G. Healing sequence in capped inflamed dental pulps of Rhesus monkeys (Macaca mulatta). Int Endod J 1986;19:113–20.
[154] Duncan HF, Ramachandran Nair PN, Pitt Ford TR. Vital pulp treatment: a review. Endo 2008;2:247–58.
[155] Kitasako Y, Shibata S, Pereira PR, Tagami J. Short-term dentin bridging of mechanically-exposed pulps capped with adhesive resin systems. Oper Dent 2000;25:155–62.
[156] Stanley HR. Pulp capping: conserving the dental pulp-can it be done? Is it worth it? Oral Surg Oral Med Oral Pathol 1989;68:628–39.

[157] Goldberg M, Njeh A, Uzunoglu E. Is pulp inflammation a prerequisite for pulp healing and regeneration? Mediat Inflamm 2015;2015:347649.
[158] Park SH, Ye L, Love RM, Farges JC, Yumoto H. Inflammation of the dental pulp. Mediat Inflamm 2015;2015:980196.
[159] About I, Murray PE, Franquin JC, Remusat M, Smith AJ. Pulpal inflammatory responses following non-carious Class V restorations. Oper Dent 2001;26:336–42.
[160] Bjørndal L, Reit C, Bruun G, Markvart M, Kjaeldgaard M, Näsman P, et al. Treatment of deep caries lesions in adults: randomized clinical trials comparing stepwise vs. direct complete excavation, and direct pulp capping vs. partial pulpotomy. Eur J Oral Sci 2010;2010(118):290–7.
[161] AAE position statement on vital pulp therapy. J Endod 2021;47:1340–1344.
[162] Souza RA, Gomes SCN, Dantas JDCP, Silva-Sousa YT, Pécora JD. Importance of the diagnosis in the pulpotomy of immature permanent teeth. Braz Dent J 2007;18:244–7. 2007.
[163] Ricucci D, Siqueira Jr JF, Rôças IN, Lipski M, Shiban A, Tay FR. Pulp and dentine responses to selective caries excavation: a histological and histobacteriological human study. J Dent 2020;100:103430.
[164] Hosoya Y, Taguchi T, Tay FR. Evaluation of a new caries detecting dye for primary and permanent carious dentin. J Dent 2007;35:137–43.
[165] Neves Ade A, Coutinho E, De Munck J, Van Meerbeek B. Caries-removal effectiveness and minimal-invasiveness potential of caries-excavation techniques: a micro-CT investigation. J Dent 2011;39:154–62.
[166] Banerjee A, Kidd EA, Watson TF. In vitro validation of carious dentin removed using different excavation criteria. Am J Dent 2003;16:228–30.
[167] Dorothy McComb BDS. Caries-detector dyes—how accurate and useful are they? J Can Dent Assoc 2000;66:195–8.
[168] Cho SY, Seo DG, Lee SJ, Lee J, Lee SJ, Jung IY. Prognostic factors for clinical outcomes according to time after direct pulp capping. J Endod 2013;39:327–31.
[169] Suhag K, Duhan J, Tewari S, Sangwan P. Success of direct pulp capping using mineral trioxide aggregate and calcium hydroxide in mature permanent molars with pulps exposed during carious tissue removal: 1-year follow-up. J Endod 2019;45:840–7.
[170] Brizuela C, Ormeño A, Cabrera C, Cabezas R, Silva CI, Ramírez V, et al. Direct pulp capping with calcium hydroxide, mineral trioxide aggregate, and bio-dentine in permanent young teeth with caries: a randomized clinical trial. J Endod 2017;43:1776–80.
[171] Duncan HF. Present status and future directions—vital pulp treatment and pulp preservation strategies. Int Endod J 2022;55:497–511.