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LITERATURE REVIEW/REVISIONE DELLA LETTERATURA

Biodentine: from biochemical and bioactive properties to clinical applications

Biodentine: dalle proprietà biochimiche e bioattive alle applicazioni cliniche

Imad About *

Aix Marseille Univ, CNRS, ISM, Inst Movement Sci, Marseille, France

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Abstract Biodentine is a tricalcium silicate-based material designed as a permanent dentin substitute. It is biocompatible and bioactive material. Its interactions with both hard and soft tissues lead to a marginal sealing preventing marginal leakage and provide protection to the underlying pulp by inducing tertiary dentin synthesis. Unlike other dentin substitutes, Biodentine application does not require any conditioning of the dentin surface and the restoration sealing is provided by micromechanical retention as Biodentine penetrates into the dentin tubules forming tag-like structures. After setting, Biodentine can be cut and reshaped like natural dentin. It can also be bonded with different types of adhesives before finishing the final restoration with composite resin. Published clinical trials, histology of human teeth and clinical cases show that Biodentine has a wide spectrum of clinical applications as a permanent bulk dentin substitute in endodontics, in restorative dentistry, and pediatric dentistry as a possible replacement material of formecresol. This review brings a comprehensive understanding of Biodentine composition, preparation properties and the mechanism of interactions with hard and soft tissues. It explains the scientific mechanisms of the induction of these specific functions and illustrates the scientific basis beyond their clinical successful use. The article provides an overview of Biodentine clinical applications summarizing published clinical trials and reporting published clinical cases with this material in restorative and pediatric dentistry as well as in endodontics.

* Correspondence to: Institut des Sciences du Mouvement (ISM), UMR 7287 CNRS & Université d'Aix-Marseille, Faculté d'Odontologie, 27 BD Jean Moulin, 13385 Marseille cedex 5, France.
E-mail: imad.about@univ-amu.fr.
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PAROLE CHIAVE
Biodentine;
Cementi a base di trisilicato di calcio;
Sostituti della dentina;
Ricerca;
Applicazioni cliniche.

Riassunto Biodentine è un materiale a base di silicato tricalcico progettato come sostituto permanente della dentina. Si tratta di un materiale biocompatibile e bioattivo. Le sue interazioni con entrambi i tessuti duri e molli portano ad una sigillatura marginale in grado di prevenire l'infiltrazione marginale e forniscono una protezione alla polpa sottostante inducendo sintesi dentina terziaria. A differenza di altri sostituti della dentina, l'applicazione di Biodentine non richiede alcun condizionamento della superficie dentinale e la tenuta della restaurazione è fornito dalla ritenzione micromeccanica in quanto Biodentine penetra nei tubuli dentinali formando strutture di simili ai resin-tag. Dopo l'indurimento, il Biodentine può essere tagliato e rimodellato come dentina naturale. Può anche essere trattato con diversi tipi di adesivi prima di terminare il restauro definitivo. Studi clinici pubblicati, istologia di denti umani estratti e casi clinici dimostrano che Biodentine ha un ampio spettro di applicazioni cliniche, come sostituto permanente della dentina in endodonzia, in odontoiatria restaurativa e odontoiatria pediatrica. Questa review si propone di descrivere in maniera completa la composizione di Biodentine, le proprietà di preparazione e il meccanismo di interazione con i tessuti duri e molli. Essa spiega i meccanismi scientifici che caratterizzano queste funzioni specifiche e illustra la base scientifica del suo successo nell'utilizzo clinico. L'articolo fornisce inoltre una panoramica delle applicazioni cliniche di Biodentine riassumendo gli studi clinici e riportando i casi clinici pubblicati con questo materiale in odontoiatria restaurativa e pediatrica, così come in endodonzia.

Introduction

Over the past decades, search on restorative materials focused on replacing amalgams in small anterior restorations and on posterior restorations of moderate size by direct composite restorations. Opposed to amalgams, a micromechanical retention of resin composites can be achieved with these materials by applying different adhesives. However, some drawbacks have been reported with resin-based materials such as wear resistance under high stress, shrinkage upon polymerization leading to microleakage and toxic monomers release.[1,2] In order to protect the pulp from resin-based materials toxic components, Calcium hydroxide-based materials have been widely used in direct pulp capping procedures. In spite of a highly alkaline pH of this material, a dentin bridge can form within 3 months providing a protection to the underlying pulp with mild or moderate inflammation. However, several studies demonstrated a partial dissolution and that this bridge has tunnel defects.[3,4] The recent focus on biocompatible materials such as Portland led to the development of Mineral trioxide aggregate (MTA) as a root-end filling material and direct pulp capping. This material is mainly composed of tricalcium and dicalcium silicates.[5] When applied for pulp capping, it induces reparative dentin production leading to a regular tubular dentin bridge formation within 2 months with no signs of inflammation.[4] However, some shortcomings have been reported with this material. These are related to its long setting time of 2 h 45 min, weak mechanical properties and difficult handling properties.[6] Additionally, tooth discoloration has been reported when this material is used for revascularization.[7,8] Biodentine is a recently released tricalcium silicate-based material developed as a permanent dentin substitute to replace the damaged dentin.[9]

In this review, the material composition, preparation method and application, mechanical and physical properties will be described, its interactions with the soft and hard dental tissues will be explained and finally, Biodentine clinical applications based on published works will be reported.

Biodentine composition

Biodentine is a two components material. The powder is mainly composed of Tricalcium silicates. It also contains Di-Calcium Silicate as a second core material and Calcium Carbonate and Oxide as filler. The powder contains Zirconium oxide as a radio-opacifier. The liquid contains Calcium Chloride as a setting accelerator and a water reducing agent (Table 1). The presence of a setting accelerator allows the material setting in 12 min and the presence of a water reducing agent avoids the formation of cracks within the material. Such cracks are usually observed after setting of cements containing high percentage of water.[9] The material is prepared by adding 5 drops of liquid to the powder present in the capsule. These components are then triturated with an amalgamator for 30 s at 4000 rpm leading to the formation of a paste of creamy consistency. The preparation method and proportions between powder and liquid should

Table 1 Biodentine composition: two components: liquid and powder to be mixed with an amalgamator for 30 s at 4000 rpm.[9]

Powder	Role
Tri-calcium silicate (C_3S)	Main core material
Di-calcium silicate (C_2S)	Second core material
Calcium carbonate and oxide	Filler
Iron oxyde	Shade
Zirconium oxyde	Radio-opacifier
Liquid	
Calcium chloride	Setting accelerator
Hydrosoluble polymer	Water reducing agent

be respected and applied according to the manufacturer's instructions as these proportions greatly influence the material's setting and mechanical properties. This is of particular significance mainly for applications under mechanical loads such as applications in Class II cavities.

The setting reaction is a hydration reaction

When Biodentine powder and liquid are mixed with an amalgamator, the setting of the material is a hydration reaction. While Calcium silicates partially dissolve by adding the liquid, a hydrogel of hydrated silicate is produced. This will precipitate on the remaining Silicate particles' surface and in the spaces between the particles leading to a significant decrease in the material's porosity and an increase in its compressive strength over time.[9]

Biocompatibility

Like any other restorative material, Biodentine Biocompatibility was investigated to ensure its safety when applied onto the cells. Evaluation of its genotoxicity on bacteria strains by the Ames test and its effects on the formation of micronuclei by human lymphocytes demonstrated the absence of any mutagenic effect of the material. Similarly, when tested on target human pulp cells, no DNA breaks or damage was observed with the Comet assay. These results demonstrated no genotoxic effects of Biodentine *in vitro*. The biocompatibility of the material was also investigated through its direct application to human pulp cells simulating the direct pulp condition and indirectly through a dentin slice to simulate its indirect pulp capping *in vivo*. Under both conditions Biodentine was not found to affect target cell viability under *in vivo* application conditions.[9] Additionally, when Biodentine was applied onto human pulp cells to investigate its effects on their specific functions by studying expression of odontoblast specific functions such as expression of Nestin (a human odontoblast specific marker) and Dentin Sialoprotein, Biodentine was not found to inhibit the expression of these proteins but rather induce their expression and the cells mineralization capacity.[9–11] Further investigations demonstrated the absence of toxicity of Biodentine to human MG63 human osteoblast cells with the MTT assay with properties comparable to that of MTA.[12]

Interactions with hard tissues: no surface preparation is needed to apply Biodentine™

Clinical application of Biodentine in restorative dentistry implies an intimate interaction with hard and soft tissues as well as with other restorative materials. This should lead to a marginal sealing *in vivo* which provides pulp protection and marginal sealing. Thus investigating these properties in *ex vivo* is of prime importance.

An experimental work using third molar teeth was used to investigate the marginal sealing of Biodentine alone or in combination of other resin-based materials using the silver nitrate penetration method in Class II cavities. No marginal leakage was observed at the Biodentin/dentin interface or at the enamel/Biodentine interface when the whole cavity was filled with Biodentine alone as a bulk restorative material replacing dentin and enamel without any conditioning treatment. No leakage was observed when Biodentine surface was prepared with the total etch technique and resin composite application. The results of this investigation demonstrated that the results obtained with Biodentine were similar to those obtained with resin-modified glass ionomer cement (Fuji II LC) considered as a reference material in this type of indications.[13] An interesting study compared the shear bond strengths of different adhesive systems to Biodentine. Adhesive systems such as Prime & Bond NT: etch-and-rinse adhesive system, Clearfil SE Bond: 2-step self-etch adhesive system and Clearfil S3 Bond: 1-step self-etch adhesive system were applied onto Biodentine discs for 12 min and 24 h then a Composite (Clearfil Majesty) was applied. Data showed that the shear bond strengths were the same for different adhesive systems to Biodentine.[14] This confirms that the marginal sealing of Biodentine is equivalent to that of RMGIC (Fuji II LC) and that Biodentine can be etched and treated like natural dentin. Different restorative materials can be successfully applied on top of Biodentine. Whatever the surface treatment used on Biodentine, this material can be used in combination with composite resins.[13,14]

Biodentine interacts with hard tissues by micromechanical retention

Interactions of Biodentine with the dentin provided cues to understanding how this material provides a marginal sealing without any dentin surface preparation: no etching and no bonding. In an experimental work performed *ex vivo*, dentin slices were prepared and Biodentine was prepared and mixed with a fluorescent dye before its application onto the dentin surface. Confocal laser scanning electron microscopy and scanning electron microscopy were used to study the interface between Biodentine and dentin. Confocal laser scanning electron microscopy revealed that Biodentine penetrated into the dentin tubules forming tag-like structures into the dentin tubules. Scanning electron microscopy revealed that the dentin tubules appeared with plugs of mineralization crystals just beneath the interface obliterating the dentin tubules. These results explain the micromechanical retention of the material on the one side and the marginal sealing on the other side.[15]

Bioactive properties *in vitro*

An entire human tooth culture model was used to investigate both the material hydration when placed for pulp capping and its effects on the pulp response. The tooth culture model provides a useful tool to investigate the initial steps of dentin-pulp regeneration and the consequence of applying pulp capping materials. Since the teeth used are immature impacted third molars, they also have the advantage of a high regeneration potential and not to be in contact with the oral flora. Biodentine was applied into pulp cavities then an adhesive resin was applied onto Biodentine and overlayed with a composite resin. Hydration was allowed to proceed under conditions similar to those *in vivo* by incubating teeth in culture medium. After 14 days, back-scatter scanning electron micrographs revealed that the material was homogenous and appeared completely hydrated at all areas

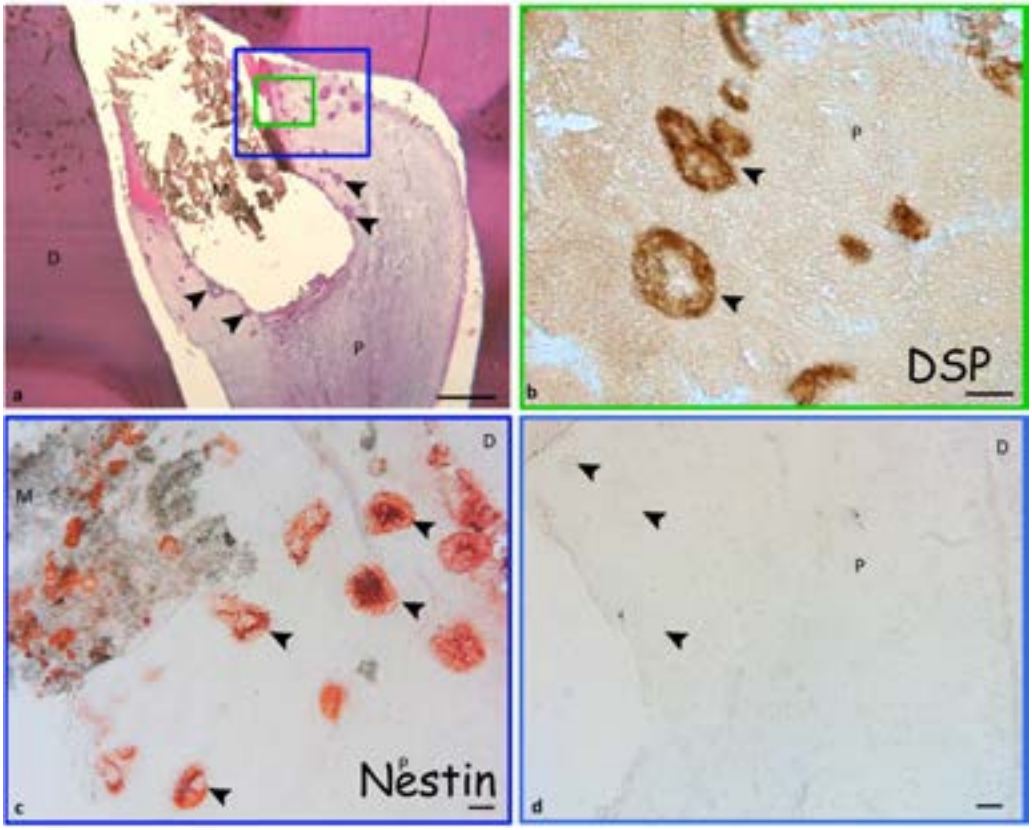

Figure 1 Biodentine direct application onto human pulp in human entire tooth culture for 4 weeks. Biodentine induced odontoblastic differentiation and reparative dentin secretion. Mineralization foci containing sequestered cells are observed in the dental pulp beneath Biodentine. The sequestered cells express odontoblast markers such as Dentin Sialoprotein (DSP) and nestin.[10]

examined: within the material, at the Biodentine/dentin interface, at Biodentine/composite resin interface and at the Biodentine/pulp interface. The hydration of this type of materials leads to the release of Calcium ions which are necessary for the mineralization. X-ray diffraction analysis of the material after setting demonstrated a significant peak of Calcium hydroxide formation which has long been used for pulp capping with a well demonstrated ability to induce dentin bridge formation.[16]

This culture model provided valuable information on the response to Biodentine application directly onto the pulp.

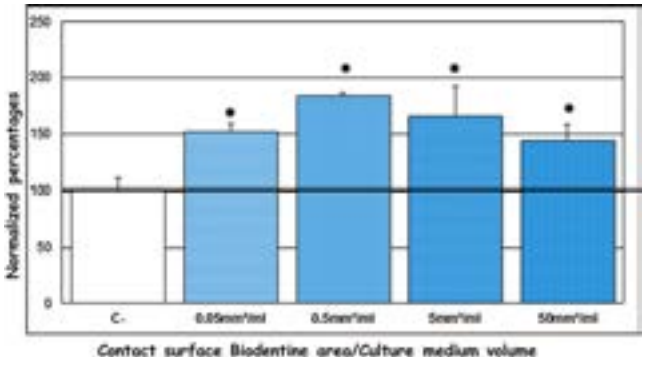

Figure 2 Effect of Biodentine on TGF-β1 release from human pulp cells. Biodentine induces release of TGF-β1 from human pulp cells. *Significant as compared to the control.[10]

Indeed, after application of Biodentine and culture for 14 days, mineralized structures appeared in the form of foci in close vicinity of the material. This mineralization seemed to be directly linked to Biodentine as some cement particles were seen within the mineralized structures but not in the neighboring pulp tissue. This mineralized tissue corresponds to an early form of reparative dentin as cells sequestered within these mineralizations express odontoblastic markers such as nestin and dentin sialoprotein (Fig. 1).

This mineralization seems to be due to the release of a growth factor, namely Transforming factor beta 1 (TGF-β1) from pulp cells incubated with Biodentine (Fig. 2). This factor has been shown to be involved in odontoblastic differentiation and recent investigations revealed that this factor is involved in the recruitment of pulp stem cells to TGF-β1production site[17] which is related to Biodentine application. Interestingly, increase in TGF-β1 was significant whatever the ratio between the Biodentine surface area and cell culture volume.[10] This has a clinical significance as it indicates that this cement can be applied onto the pulp whatever the injured pulp surface area (Fig. 2).

Biodentine interactions with soft tissues induce tertiary dentin synthesis

When Biodentine was used for vital pulp therapy *in vivo*, investigations carrier out on different animal models showed

that this material can be applied for both pulp capping and pulpotomy. Indeed, Biodentine induced tertiary dentin synthesis when applied as direct or indirect pulp capping material in rat teeth.[18,19] After direct pulp capping, the dentin bridge observed after 4 weeks in rat teeth was tubular and its porosity was similar to that of MTA.[19] Similar results demonstrated in miniature swine teeth. Indeed, after pulp capping with Biodentine, no pulp inflammation was observed while a thick dentin bridge formed after 3 and 8 weeks.[20] Similar results were reported in primary pig teeth after 4 weeks and 90 days. Application of Biodentine in pulpotomy was also investigated in primary pig teeth and compared to formecresol and white MTA (WMTA). The results with Biodentine showed no inflammation and a thick dentin bridge formed in 90% of the cases.[21] These data were comparable to the results obtained with WMTA and indicate the biocompatibility of these materials and their suitability for pulp capping and pulpotomy.

Clinical applications

Although Biodentine is a recently developed material as it has been released by the end of the year 2010 in Europe, different clinical applications have been so far published with this material. These include applications in restorative dentistry, pediatric dentistry and endodontics. Although it can be used as a temporary enamel substitute for upto 6 months, Biodentine is mainly used as a permanent dentin substitute. It can be used to replace the missing/damaged bulk dentin volume. It can also be used as an alternative to Formecresol in pulpotomy. The major clinical trials and histological studies in human teeth are detailed below and reported (Table 2) while the clinical case reports are only listed in the same table.

Table 2 Biodentine clinical applications and type of clinical works published on each application. Biodentine can be used in restorative dentistry, pediatric dentistry and endodontics as a permanent dentin substitute. It can be used to replace the missing/damaged whole dentin volume. It can also be used as an alternative to formecresol in pulpotomy.

Application	Type of investigations/ references
Crown	
Temporary enamel restoration	Clinical trials[22]
Permanent dentin substitute in	
Deep/large carious lesions	Clinical trials[22]
Deep cervical/radicular lesions	Case reports[36–38]
Indirect pulp capping	Clinical trials[22,23]
Direct pulp capping	Clinical and histological studies[25,26]
Pulpotomy	Clinical trials[27,39]
Root	
Root canal/furcation perforations	Case reports[40]
External resorption	Case reports[41]
Internal resorption	Case reports[42]
Regenerative endodontics	Case reports[43]
Apexogenesis after traumatic exposure	Case reports[33,44]
Apexification	Case reports[45–48]
Retrograde root canal obturation	Case reports[49,50]

Indirect pulp capping

A randomized clinical study was performed in the restoration of posterior teeth with Biodentine. 397 cases were included with a three years follow-up. Biodentine was applied as a bulk restorative material in deep dentin cavities in replacement of both dentin and enamel. The scoring scales included consistency, working time, adhesion to instruments, ease of handling, anatomic form, marginal adaption, quality of proximal contact, marginal discoloration, surface roughness, secondary caries and post-operative pain. The results of this trial reported that Biodentine was easy to handle, showed, a, excellent anatomic form, marginal adaptation and very good interproximal contact. During the follow-up, the restoration with Biodentine™ in comparison to the composite resin Z100 was well tolerated in all cases with no post-operative pain. The anatomic form, marginal adaptation and interproximal contact started to deteriorate only after 6 months. Due to the deterioration, a complementary treatment was performed. Biodentine was kept as dentin substitute as the pulp vitality test was positive. Biodentine presented a good resistance to burring and the composite Z100 was applied onto Biodentine surface and evaluated for up to 3 years. The conclusions of this study is that Biodentine can be used as a posterior restoration material for up to 6 months as a temporary enamel substitute. When covered with Z100®, it is a well-tolerated permanent dentin substitute. Additionally, Biodentine can be cut and shaped like the natural dentin.[22] In another clinical study, the efficacy of Biodentine as an indirect pulp capping material was evaluated and compared to a glass ionomer cement (Fuji IX) in irreversible pulpitis. 36 restorations with Biodentine and 36 Fuji IX were placed randomly in 53 patients. The clinical efficacy at 12 months revealed no statistically significant differences in clinical efficacy between Biodentine and Fuji IX.[23]

The reported absence of post-operative pain and post-operative sensitivity in the clinical trial[22] may be due at least to 2 factors:

1) The infiltration of Biodentine into the dentin tubules[15] due to the precipitation of crystals within the tubules decreases the dentin tubule permeability and fluid movement which may decrease post-operative sensitivity.
2) The reduction odontoblast pain receptor expression and function and the reduction of the secretion of pro-inflammatory cytokines. Indeed, odontoblasts express pain receptors of the transient receptor potential family of ion channels (TRP) namely TRPA1. These receptors play a significant role in nociception and neurogenic inflammation. When extracts of Biodentine were applied on odontoblast-like cells, expression of these receptors decreased together with their functional activity as measured by an intracellular calcium level increase. Additionally, Application of Biodentine decreased the pro-inflammatory tumor necrosis factor secretion (TNF-α) from odontoblast like cells[24] as measured by Enzyme-linked immunosorbent assay (ELISA).

Direct pulp capping

Pulps of 28 non-carious molars scheduled for orthodontic treatment were exposed mechanically and pulps capped directly with Biodentine or MTA in class I cavities. 7 patients complained from mild pain on the day of surgery. 4 of these patients were treated with Biodentine and 3 with MTA. No symptoms were reported in the other patients. Teeth were tested before extraction for cold and electro-sensitivity and all confirmed the pulp vitality. The absence of periapical pathology was confirmed radiographically before the treatment and just before the tooth extraction. The histological examination of the pulp state and response after direct pulp capping with Biodentine as compared to MTA in human teeth revealed an absence of pulp inflammation and the formation of a complete dentin bridge beneath both materials after 6 weeks.[25] Tomographic data evaluating the density and volume of reparative dentin revealed that these values were higher for Biodentine.[26] These results indicate that Biodentine can be safely applied directly onto the human vital pulp.

Pulpotomy

Clinical application of Biodentine in pulpotomy has been investigated in few clinical studies as a pulpotomy medicament. A randomized clinical study was performed in children of 4—9 years of age. 84 pulpotomies were performed and attributed to MTA or Biodentine. All teeth were restored with stainless steel crowns. Clinical and radiographic evaluations were performed after 6 and 12 months. Data showed that one molar of the MTA group had an internal resorption while 1 molar of Biodentine treated group had internal resorption and another showed a radiographic radiolucency. Over all, both materials had a very high clinical success rate[27] and the overall clinical success after 12 months is reported (Table 3). Another study evaluated Biodentine and compared it to MTA in a short term clinical study. Biodentine was applied in pulpotomy in 20 teeth followed by restoration with stainless steel crowns. At 3 and 6 months, patients were recalled and Biodentine was shown as equally efficient as MTA with similar radiographic success.[28] A similar study was performed comparing Biodentine to MTA and Propolis as pulpotomy medicaments. After 9 months, Biodentine and MTA showed comparable results with a high radiographic success rate and more favorable than Propolis.[29] Finally, a confirmation of all these data reported no significant differences between MTA and Biodentine used as pulpotomy medicaments even after 18 months with clinical success higher than 95% for both materials.[30] Taken together, although longer term clinical evaluations are required, these data indicate that Biodentine has the potential to be used as a substitute for formocresol in primary molar pulpotomies.

Table 3 Evaluation of Biodentine as compared to MTA in pulpotomy after 12 months. Clinical success rates are reported in number of cases and percentage showing a high clinical success rate of both MTA and Biodentine in pulpotomy after 12 months.[27]

	Success/total number of cases	Success (%)
MTA	36/39	92
Biodentine	38/39	97

Case reports on the other clinical applications

In addition to the above detailed indications, many case reports have been published with Biodentine in different clinical indications. These include deep cervical/radicular lesions, root canal/furcation perforations, external/internal resorption, regenerative endodontics, apexogenesis after traumatic exposure, apexification and retrograde root canal obturation. These applications are listed and corresponding case report references are provided (Table 2).

Discussion

Although Biodentine is among the most recently developed tricalcium silicate-based materials, a significant and increasing number of investigations have been published on this material. While many studies reported its biocompatibility and Bioactivity *in vitro* and *in vivo*, preclinical investigations shed the light on the mechanisms of its interaction with the dental hard tissue. Indeed, many investigations performed both *in vitro* and *in vivo* demonstrated that the interactions of Biodentine with both hard and soft tissues provide a hermetic seal protecting the dental pulp by preventing bacterial infiltration. These studies demonstrated that, through its interactions with the hard tissues, Biodentine provides a micro-mechanical retention by infiltrating the dentin tubules. On the other hand it induces the target tissue specific functions by inducing tertiary dentin synthesis which provides further protection to the pulp. These two combined effects might be responsible, at least in part, for the absence of post-operative pain and hypersensitivity. Another important investigation reported that the application of Biodentine reduces both TRPA1 pain receptor expression and function. More importantly, when applied on odontoblast-like cells Biodentine decreases pro-inflammatory TNF-α secretion. This indicates that, in addition to the abovementioned roles of Biodentine, its application onto the dentin/pulp reduces the inflammation and consequently the post-operative pain.

How does Biodentine compare to other widely used and common pulp capping materials

When compared to Calcium Hydroxide, Biodentine is stronger mechanically due to its composition and low porosity. It is less soluble and the produced dentin bridge shows no tunnel defects as compared to that under Calcium hydroxide thus it has a better sealing ability than Calcium hydroxide.[19,31] When Compared to MTA, Biodentine is easier to handle,[22] stronger mechanically and has a shorter setting time.[6] It can be used as a temporary enamel substitute up to 6 months and in different applications as a permanent dentin substitute without any surface treatment. Additionally, while discoloration with MTA[32] and its derivatives have been reported in regenerative endodontics and seem to be mainly due to the

presence of Bismuth oxide as a radio-opacifier,[7] no discoloration of tooth crown has been reported after 48 months with Biodentine which does not contain Bismuth oxide but Zirconium oxide as a radio-opacifier.[33–35]

Conclusions

Taken together, through *in vitro*, *in vivo*, clinical trials/reports, this review shows that Biodentine is biocompatible, has strong mechanical properties and can safely be applied in restorative dentistry, in pediatric dentistry (as a possible alternative to formecresol) and in endodontics. It is important to know that Biodentine does not require any surface conditioning treatment. It can be cut and reshaped like natural dentin. It can be used as a bulk permanent dentin substitute to replace the whole damaged/lost dentin and not only as a pulp capping material. Biodentine surface can be bonded like the natural dentin with different adhesives before final composite resins application.

Conflict of interest

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