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Biodentine™ – use in dentistry. Literature review

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ABSTRACT

Introduction: The concept of "regenerative endodontics", adopted by the American Association of Endodontics in 2007 was, to an appreciable extent, connected with the introduction of bioactive materials such as Biodentine™ to dental treatment. In the field of biomedical therapeutic materials, the concept of tissue engineering is distinguishable with respect to establishing procedures and materials such as Biodentine™ aimed at replacing injured tissues with those newly developed. The use of Biodentine™ has quickly become a widespread practice in dentistry, commonly used in the biological treatment of pulp and root canal treatment.

The aim of this article is a literature review on the use of Biodentine™ in dental practice and its specific characteristics, based on the latest scientific knowledge.

Materials and methods: Articles published since the launch of the material into the market were sourced and classified according to the topic they focussed on. A total of 52 papers were chosen, encompassing those directly focusing on Biodentine™, as well as other relevant papers not mentioning Biodentine™, but pertaining to dental materials in general.

Conclusion: On the grounds of this analysis of literature on the subject, it can be concluded that bioactive materials such as Biodentine™ have a wide range of application in therapeutic dental procedures. There are numerous studies presenting the advantages of this group of materials. However, the use of Biodentine™ still requires a comprehensive and long-term analysis to unequivocally confirm its therapeutic success following use of this material.

Keywords: direct pulp capping; pulpotomy; root perforation; invasive cervical root resorption; bioceramics; apexification; regenerative endodontic procedures.

INTRODUCTION

For many years now bioactive materials have been used successfully in many dental procedures. The introduction of these materials marked a tremendous advancement in endodontic treatment. The bioceramic materials used in dentistry are classified as bioinert, bioactive and biodegradable [1, 2, 3, 4]. The shared feature of these ceramic materials is that they are specially developed to perform an intended function, as a root canal sealant, cement, or root treatment and filling. Moreover, these ceramic materials can be used in cases of exposed pulp, either from injury, caries, or other mechanical causes, in the form of direct pulp capping [1, 3].

Generally, bioceramic materials are biocompatible ceramic compounds used both *in situ* and *in vivo* in various chemical processes. They show superior biocompatible properties owing to features shared with biological hydroxyapatite. During hydration, bioceramics produce a number of compounds, e.g. hydroxyapatite, which have the ability to induce regenerative reactions in the human body. On contact with bone tissues, mineral hydroxyapatite shows osteoconductive properties, which leads to bone formation at the phase boundary. Additionally, bioceramics have the internal capability of osteoinduction, due to their documented ability to absorb osteoinductive substances near the bone healing site [1, 4]. Bioceramic materials have antibacterial properties as the result of precipitation *in situ* following the material setting time, forming porous powders containing nanocrystals of 1–3 nm in diameter which prevent bacterial adhesion. At times, fluoride ions are the constituents of apatite crystal, and the resulting nanomaterial has antibacterial properties. Moreover, bioceramics can be used jointly with synthetic hydroxyapatite [1, 5].

The aim of the present article is a literature review of the bioactive material Biodentine™ currently used in dental practice and its specific characteristics.

MATERIALS AND METHODS

This review article provides a general analysis and a summary of studies on Biodentine™, and critically evaluates existing knowledge regarding the properties of the product. A search was conducted in PubMed and the Polish Medical Bibliography using the keywords "Biodentine", "dentistry" and "endodontic repair", "direct pulp capping", "pulpotomy", "root perforation", "invasive cervical root resorption", "bioceramics". Articles that were published since the launch of the material into the market were retrieved and classified according to the topic they focussed on. A total of 52 papers were selected, encompassing those directly focusing on Biodentine™ and other relevant papers not mentioning Biodentine™ but concerning dental materials in general.

BIODENTINE™ – COMPOSITION AND PROPERTIES

Biodentine™ with Active Biosilicate Technology was announced by dental material manufacturer Septodont (Saint Maur des Fosses, France) and became commercially available in 2009 [6]. Biodentine™ is a 2-component material; the powder component primarily consists of tricalcium silicate ($3CaO•SiO_2$), dicalcium silicate ($2CaO•SiO_2$) and calcium carbonate ($CaCO_3$), with zirconium dioxide (ZrO_2) as a contrast medium. The liquid component consists of calcium chloride ($CaCl_2•2H_2O$), which is used as a setting accelerator and water-reducing agent in aqueous solution with an admixture of polycarboxylate (i.e., a superplasting agent) [7, 8]. The reaction of the powder with the liquid leads to setting and hardening of the cement. Mixing is achieved using an amalgamator for 30 s at 4000–4200 rpm at a specific powder to liquid ratio to achieve a reproducible material with optimum properties. According to the manufacturer, the initial setting time is about 12 min [8]. Immediately after mixing, the calcium silicate particles of Biodentine™ react with water to form a high pH solution containing Ca^{2+}, OH^- and silicate ions. Hydration of the tricalcium silicate leads to the formation of a hydrated calcium silicate gel on the cement particles and calcium hydroxide nucleates. The hydrated calcium silicate gel then polymerizes to form a solid network, and the alkalinity of the surrounding medium increases due to the release of calcium hydroxide ions. The hydrated calcium silicate gel surrounds the unreacted tricalcium silicate particles and, due to its relatively impermeable nature to water, it helps to slow down the effects of further reactions [9]. Biodentine™ causes deposition of amorphous calcium phosphate interfacial layer with radicular dentine. The addition of bioactive glass to BiodentineTM led to a pronounced formation of apatite. Where the bioactive glass contained fluoride, the release of fluorapatite and fluoride ion was demonstrated [10]. Additionally, Biodentine™ shows odontotropic properties, it stimulates the development of reactive and reparative dentine and thus contributes to maintaining proper sensibility of the dental pulp [11, 12, 13]. As such, Biodentine™ is successfully being used in regenerative procedures, the treatment goal of which is to induce biological replacement of lost dental tissue(s). Many of these procedures have emerged from the expanding field of tissue engineering. Regenerative endodontics, such as pulp revascularization, has been defined as biologically based procedures designed to replace damaged structures such as dentine, root structures and cells of the pulp-dentin complex. Pulp revascularization has been widely achieved in the treatment of immature permanent teeth with necrotic pulp and established apical periodontitis. Successful cases exhibited thickening of the canal walls, closure of root apices and continued root development [14]. *In vivo* studies have reported that Biodentine™ exhibits low cytotoxicity in cultures of osteoblasts [15]. In pulp tissue, Biodentine™ induces cell proliferation and the expression of dentine sialoprotein and osteopontin [16]. da Fonesca et al. [17] and de Sousa Reis et al. [18] have stated that the significant regression of inflammatory reaction allows the conclusion that the bioceramic material Biodentine™ is a biocompatible material. In an odontoblast-like mouse cell line (MDPC-23), Paula et al. [19] conducted an assessment of the cytotoxicity and bioactivity of 3 different direct pulp capping materials; calcium hydroxide (Life®), mineral trioxide aggregate (WhiteProRoot®MTA) and calcium silicate (Biodentine™). The authors observed that the calcium hydroxide-based cements induced a decrease in metabolic activity and cellular viability. There was also a marked increase in cell death and some notable changes of the cell cycle. No protein synthesis or formation of calcium nodules was observed. The mineral trioxide aggregates (MTA) and tricalcium silicates materials induced an increase in metabolic activity and cell viability. Additionally, the percentage of living cells was high and there were no interferences with the cell cycle. In subsequent stages of differentiation and mineralization, the tricalcium silicate cements produced a better performance. Alkaline phosphatase expression increased significantly as did dentin sialoprotein, and formation of calcium nodules compared to the MTA cements. The study supported the advice to use tricalcium silicate together with mineral aggregate trioxide cement for pulp capping procedures [19]. In comparison to both new pulp-capping materials, MTA Repair HP (High-Plasticity) and NeoMTA Plus, Biodentine™ showed higher rates of proliferation of human dental pulp stem cells (hDPSCs) in a time-dependent manner. Additionally, Biodentine™ showed a degree of cytocompatibility with hDPSCs and good cell migration rates [20].

Biodentine™ stimulates the formation and mineralisation of a tissue barrier in the dental pulp following a pulpotomy [21]. Apart from the chemical parameters of Biodentine™, an equally important facet is its so-called biocompatibility, as from the clinician's perspective, each material used to fill a tooth, even those showing optimal chemical parameters, is in fact a foreign body [11]. The host's response to the substances released by the biomaterials interferes with the intensity and duration of the inflammatory process. A regression of the inflammatory process, accompanied by the formation of collagen-rich capsules surrounding the implanted materials, is indicative of biocompatibility [22].

Specific properties of Biodentine™ make it favourable for use as a dentine substitute; such as an elastic modulus of 22.0 GPa – similar to that of dentine at around 18.5 GPa; a compressive strength of about 220 MPa – similar to dentine at about 290 MPa; and a microhardness of 60 HVN (Hardness Vickers Number) – the same as natural dentine. Biodentine™ is a promising restorative material (increased compressive strength, pushout bond strength, density, and porosity), offering a lower cost and better handling properties, allowing it to be sculpted into a desired form within the adequate setting time. It also possesses high wash out, low fluid uptake and resorption values, as well as superior mechanical properties [23]. However, Biodentine™ does not satisfy the requirements to be used as an ideal core material [24]. The study by Subash et al. [24] investigated the fracture resistance of Biodentine™ as a core material in comparison with resin modified glass ionomer (GIC) and composite resins. The results showed a significant difference in fracture load. The fracture resistance of a root

post-core assembly is of paramount importance for the long-term stability of the restoration. Stress is generated within the core opposing the external forces, to prevent fracturing. When this force exceeds the internal stress, a fracture occurs. Therefore, when the stress exceeds the cohesive strength of the object, the object breaks. In that study, Biodentine™ showed a significantly lower fracture resistance than resin-modified GIC and composite. It seems that the compressive forces applied on the restorations with Biodentine™ created enough stress to exceed the cohesive strength and lead to an earlier failure at lower load values than compared to the other materials [24]. A complete root canal obturation with Biodentine™ has shown a significantly higher fracture resistance ($p < 0.05$) than only apexification with Biodentine™ [25]. The bond strength between calcium silicate-based and restorative materials is one of the main factors for the success of the restoration. The results by Tulumbaci et al. showed that even though Biodentine™ has many advantages over MTA, it still had a lower shear bond strength to copolymer and composite resin materials [26]. Considering that acid etching is one of the steps following application of Biodentine™ to provide mechanical adhesion, an assessment was made whether any compressive strength was lost following the etching procedure, concluding that the acid etching procedure after 7 days did not reduce the compressive strength of ProRoot MTA and Biodentine™ [6].

THE USE OF BIODENTINE™ IN DIRECT PULP CAPPING AND PULPOTOMY

Direct pulp capping is a procedure in which a medication, dressing, or dental material is placed directly over the exposed dental pulp to preserve its vitality. However, it must be emphasized that the success of vital pulp therapy depends on the complete removal of any disintegrated tissue, and controlling infection is crucial for the success of the procedure. The formation of a dentine-bridge is key in the final healing and long-term success, as it protects the exposed pulp from further attacks by oral bacteria which may result in pulp degeneration, atrophy, and shrinkage [27]. Inducing reparative tertiary dentine formation by pulp cells has been widely accepted as the ultimate goal of using capping materials [28]. For many decades, calcium hydroxide was the material of choice among the various available pulp-capping agents [8]. However, there are shortcomings when using this material, such as dissolution in tissue fluids and degradation on tooth flexure, the formation of tunnel defects beneath dentine bridges, and poor sealing. The use of calcium silicate-based cements (biomaterials with calcium oxide and carbonate filler additives) in dentistry is now a method of choice for developing a dentine bridge in direct pulp capping [28]. Studies have shown that MTA may be used as an alternative to $Ca(OH)_2$ for treating pulp wounds. Mineral trioxide aggregate stimulates the formation of dentine bridges faster than calcium hydroxide. However, MTA is reportedly difficult to use because of its long setting time, poor handling properties, high material costs and the discoloration potential of dental tissue [29]. Biodentine™ presents an adequate biological response *in vivo* similar to MTA [13]. Particles of Biodentine™ were entrapped in the newly formed foci, and mineralization appeared as osteodentin, suggesting that the physicochemical properties of the material might promote the mineralization process, as shown with MTA-based cements. Stimulation of cell proliferation and differentiation might be related to the tricalcium silicate itself, which is one of the main components of Biodentine™, and the presence of both calcium and silicon ions [12]. Moreover, the use of 3% sodium hypochlorite to control haemorrhaging provides an additional advantage of disinfection, and the placement of a well-sealed restoration immediately after pulp capping also provides protection against ongoing leakage and bacterial contamination [8]. The success of the treatment is unaffected by such parameters as gender, initial or secondary caries treatment, occlusal or cervical caries localization, delayed placement of permanent filling, tooth position, and arch type. However, the patients' age did negatively influence the outcome. The success rate is higher in younger patients compared to older patients [8]. In comparison with Biodentine™, MTA placement is more time consuming and technically difficult. It is necessary to use a dental triturator for the preparation of Biodentine™, while MTA does not require any additional equipment [12]. Biodentine™ appears to be a suitable material for direct pulp capping under clinical conditions. Long-term follow-up studies and controlled trials involving a large sample size are warranted [7].

There are reports on the use of Biodentine™ in pulpotomy procedures. Pulpotomy is a procedure that involves removal of the pulp from the pulp chamber of the primary tooth without the removal of the canal pulp, as well as the application of medication at the entrance of the root canal to fix or stimulate the repair of the vital remaining pulp [30]. Pulpotomy is indicated in cases of exposed vital pulp by the caries process, by accident during cavity preparation, or as a result of injury and fracture of the tooth in primary teeth. However, it is not indicated for primary teeth with internal resorption, furcal perforation, insufficient root structure, and periradicular pathosis that may alter permanent successor eruption [30]. Preserving pulp vitality after carious or traumatic injuries remains a challenge in immature permanent teeth because this vitality is important for complete root formation. To this end, vital pulp therapy should be considered in teeth with reversible injury [31].

Vital pulpotomy treatment of primary teeth is performed when the caries removal procedure results in exposure with the presence of a healthy radicular pulp [32]. Full pulpotomy using Biodentine™ appears to have a high success rate in young permanent teeth with carious exposure and could be considered an alternative to root canal treatment in vital cases [31, 33]. Bakhtiar et al. investigated human pulp responses to partial pulpotomy treatment with Biodentine™ and ProRoot MTA. In both groups, ProRoot MTA and Biodentine™, a complete dentine bridge was developed by differentiated cells similar to odontoblasts. The dentine bridge developed in teeth using Biodentine™ was thicker than in those on which MTA was used [31].

Biodentine™ shows characteristics similar to natural dentine and enables the stimulation of growth factors that activate dentineogenesis and differentiation of odontoblasts. It has been stated that Biodentine™ has bioactive properties, encourages hard tissue regeneration, and provokes no signs of moderate or severe pulp inflammation response [30]. However, beyond the clinical results, Biodentine™ has disadvantages, such as higher costs and longer setting time compared to calcium hydroxide. Clinical and radiographic evaluations should be performed carefully by the paediatric dentist to achieve correct diagnosis, and both materials (calcium hydroxide and Biodentine™) can be used successfully for pulpotomy in primary molars [30].

Full pulpotomy using Biodentine™ was a successful treatment option for carious exposed pulps in mature permanent molar teeth with clinical signs and symptoms indicative of irreversible pulpitis, up to 1 year. Clinical signs and symptoms indicative of partial irreversible pulpitis are not a contraindication and full pulpotomy might be considered as an alternative treatment approach to root canal treatment [33].

THE USE OF BIODENTINE™ IN ROOT PERFORATION REPAIR, TREATMENT OF INVASIVE CERVICAL ROOT RESORPTION AND SURGICAL ENDODONTICS

Biodentine™ is also used for sealing root perforations. Furcation perforations are iatrogenic artificial connections between the pulp chamber and the periodontal ligament. This is one of the most usual complications of endodontic treatment. When a pulp chamber floor perforation occurs, the periodontal ligament and the bone tissue are destroyed in varying degrees and an inflammatory process is established [13]. The teeth with perforations treated with Biodentine™ may contribute to regression of the inflammatory process and a reduction in bone resorption over time. Concomitantly, Biodentine™ may also stimulate the expression of cell differentiation factors including osterix, promoting the osteoblast differentiation and, consequently, bone neoformation. Furthermore, Biodentine™ participates in inflammatory reaction modulation and promotes fibroblast and osteoblast differentiation, stimulating the formation of collagen bundles of the periodontal ligament and bone matrix of the alveolar process, respectively, favouring periodontal tissue repair. The diameter of the perforation was found to have an impact on microleakage and the perforation [13]. Micromechanical adhesion of Biodentine™ allows superior adaptation of Biodentine™ crystals to basic dentine. However, in comparison to other materials such as MTA and Intermediate Restorative Material (IRM), the marginal adaptation of Biodentine™ was found to be inferior to both MTA and IRM when used as the basic material for root filling [9, 34]. Additionally, de Sousa Reis et al. [18] stated that Biodentine™ and MTA promoted similar responses when used to seal furcation perforations, and should therefore be regarded as a promising alternative. Sixty male Wistar rats were used (n = 6 per group/period). The mandibular 1st molars had a furcation mechanically exposed and sealed with either MTA or Biodentine™ and restored with silver amalgam. In an additional test group, the teeth were sealed with just Biodentine™. Furcation sealing with gutta-percha and silver amalgam restoration served as the positive control, and healthy untreated teeth were the negative control. Histological evaluation was performed after 14 or 21 days. Biodentine™ and MTA presented satisfactory results, showing a milder inflammatory response when compared to the control, regardless of the material used for coronal sealing and of the evaluated experimental period [18].

One of the dental pathologies which can result in tooth loss is root resorption, where dentine is substituted with resorptive granulation tissue or, in extreme cases, with a tissue showing structural similarities to bone. The use of Biodentine™ in filling cavities due to invasive cervical root resorption (ICR) is documented. However, the studies concerning this issue are mainly based on analyses of individual clinical cases. Invasive cervical root resorption is the reversible/irreversible loss of a tooth structure in the connective tissue attachment zone with unclear aetiology. Biodentine™ shows a setting time of less than 12 min and high mechanical properties with excellent sealing ability. Its ability to release calcium ions and enhancing the alkaline environment makes Biodentine™ more conducive for osteoblastic activity. Also, calcium and hydroxide ions stimulate the release of pyrophosphatase, alkaline phosphatase, and BMP-2, which contributes to the mineralization process [35]. The teeth treated with Biodentine™ were completely asymptomatic, and probing depth was within normal limits at each follow-up time point, indicating that negating resorption was successfully performed with Biodentine™ [36]. However, it must be noted that the remnants of calcium hydroxide may affect the bonding of Biodentine™ to dentin; hence, its complete removal is necessary. Considering the thin and weakened tooth structure in a resorptive defect, a bioactive material (ProRoot MTA, Biodentine™) was needed to reinforce the tooth and thereby enhance the prognosis of the tooth. Biodentine™ is used because it has some features which are superior to MTA; for example, its consistency is better suited to clinical use than is MTA, additionally Biodentine™ does not require 2-step obturation as in the case of MTA [37]. Pruthi et al. reported surgical endodontic management of a trauma--induced perforating external root resorption [38]. Following root canal treatment, intentional replantation of the tooth was performed so as to expose the opening of the resorption defect to allow for complete debridement and closure with Biotentine™. The 18 month follow-up showed the arrest of root resorption, and progressive healing of the defect [38]. General publications on the use of Biodentine™ in resorption treatment, concern studies of individual cases [35, 36, 37, 38, 39].

Biodentine™ is a promising material which is suitable for surgical endodontics, demonstrating excellent biological properties and fast clinical setting time, but with poor radiopacity. The good sealing ability of Biodentine™, along with its favorable biological properties, show that this material can be used competently in clinical practice as a retrograde filling material [40]. The degree of clinical success observed in 2 cases presented after a 2-year follow-up, indicates that this

calcium silicate cement can be used successfully in this indication. These results confirm biological observations of the lack of toxicity and genotoxicity. In addition to the lack of toxicity, Biodentine™ displayed bioactivity, i.e., activation of angiogenesis and activation of progenitor pulpal cells promoting healing and remineralization [41]. Pawar et al. presented a case report of surgical management of a large cystic lesion using Biodentine™ as a retrograde filling material. The 18 month radiographic follow-up examination revealed a completely healed cystic lesion [42].

THE USE OF BIODENTINE™ IN APEXIFICATION AND REGENERETIVE ENDODONTICS

Apexification is defined as a procedure used to induce a calcified barrier in a root with an open apex, or the continued apical development of an incomplete root in teeth with necrotic pulp. Recently, attention has been paid to the development of materials which do more than simply replace the lost tooth tissue, but rather seek to induce repair and regeneration [43]. Biodentine™ is set in a hydration reaction which consists in dissolving the calcium silicate granules to obtain calcium hydroxide and hydrates of calcium silicate. The formation of calcium silicate hydrate gel is the result of permanent hydration of tricalcium silicate, which gradually fills the spaces between the granules of tricalcium silicate and improves impermeability [44]. Improved sealing properties between the dentine and Biodentine™ can be attributed to an increase in surface crystals in dentinal tubules which may lead to ion exchange between the cement and the biological structure of dentine [44]. At the material-dentine contact site, Biodentine™ induces the formation of structures similar to markers along the interphase layer, named "the zone of infiltration mineralisation". An interphase layer abundant in Ca and Si can be observed with magnification, and can result in a greater resistance to acids as well as greater physical durability. In 6 and 12 month long observation periods, Biodentine™ showed better root apex closing properties and dentine thickness than MTA [44]. Moreover, it was found that Biodentine™ at 4 mm thickness applied in the apical area of the root shows good impermeability, though less than that of MTA [45, 46]. Revitalization procedures, being a part of regenerative endodontics, became an alternative to apexification in immature teeth after pulp necrosis.

The current American Association of Endodontists (AAE) "Glossary of Endodontic Terms", defines regenerative endodontics as "biologically-based procedures designed to physiologically replace damaged tooth structures, such as dentin and root structures, as well as cells of the pulp-dentin complex" [14, 47, 48, 49]. The new tissue within the pulp space, although not necessarily pulp, does not comprise just blood vessels, but also vital cells that are required to deposit the new tissue [47]. Therefore, the pulp space is filled with connective tissue of some type, and this tissue is vital. This conservative 2-step procedure consists of the use of a combination of antimicrobials to reduce the infection, no canal wall instrumentation, and induced apical bleeding to form a blood clot tightly sealed into the root canal to promote healing [47]. It can be performed in cases of pulp necrosis secondary to the trauma, decay or dental anomalies [14, 47]. The guidelines advise the use of a bacteria--tight sealing material on top of the barrier to obtain the desired sealing after the intentional evoked-bleeding step in root canal. It was found that Biodentine™ stimulates odontoblastic differentiation and nodule formation during mineralisation [50]. Biodentine™ can be used as an intracanal barrier over the blood clot and has been shown to stain teeth less than MTA [48]. Also, an *in vitro* study assessing the bond strength of a filling placed immediately after the application of MTA and BECs (bioactive endodontic cements), advises a delayed definitive filling for MTA and the possibility of a same-session filling for Biodentine™, waiting just 12 min between the cement application and composite restoration [47]. However, according to Kot et al., 15 min after preparation, Biodentine™ does not bond to a degree in which its use as a primer is safe, i.e. without the possibility of interaction, in a procedure of applying the bonding system to dentin and enamel. Postponing crown restoration for 24 h seems perfectly adequate. Moreover, assessment of the effect of contamination on the restoration adhesion to tooth tissue needs additional studies [51].

CONCLUSIONS

On the grounds of this analysis of literature on the subject, it can be concluded that bioactive materials such as Biodentine™ have a wide range of application in therapeutic dental procedures. There are numerous studies presenting the advantages of this group of materials. However, the use of Biodentine™ still requires a comprehensive and long-term analysis to unequivocally confirm its therapeutic success following use of this material.

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