Abstract

Goal:

The goal of this literature review is to answer the question: "Does Biodentine™ solve the problem of dentine loss in order to maintain pulp vitality and stimulate new hard tissue formation, compared to the conventional materials?" This study, by focusing specifically on the properties and indications of Biodentine™, will attempt to provide an evidence-based insight, concerning specific features and applications of Biodentine™, the differences with other competing products, and if possible, conclusions on how this novel material can be implemented.

Methodology:

For this literature review PubMed, Web of science and Google Scholar have been used, utilising Biodentine as the main keyword. Relevancy to the topic has been the only criteria, due to the moderate number of articles, they have all been consulted and selected. Research has also been carried out concerning currently used material, selecting only review articles. “Septodont Case Studies Collection” and “Septodont Scientific file” have also been referred. The last article dates March 2014.

Results:

Biodentine™ presents distinguished mechanical properties such as high compressive strength and flexural modulus, tight sealing ability, high bond strength, low porosity and high density, and colour stability, superior to MTA. It demonstrates the same biological properties, biocompatibility and bioactivity when compared to MTA and Ca(OH)₂. An additional ease of handling due to a short setting time of 12 minutes makes it user-friendlier, compared to 165 minutes of MTA.

The only long-term randomised controlled trial, as well as the in vivo and in vitro studies on this topic, all give optimistic results and determine that Biodentine™ is a high potential material used in contact with vital tissue. The following indications for the use of Biodentine™ have been described in the literature: pulp capping, pulpotomy, apexification and apexogenesis, external, internal perforating resorptions, root and furcation perforations.
Conclusion:

When investigating on specific physical, mechanical, biological properties and the documented clinical applications of Biodentine™, the results are promising. However, dental science still lacks long-term research on the potential implementations as well as drawbacks of Biodentine™. To evaluate and apply this product in practice, the clinician must keep in vision its properties, be careful when diagnosing in order to make the right decision, until more detailed studies are carried out and published on the efficiency and safety of Biodentine™. It is prematurely and not precautiously assumed that Biodentine™ can overcome all the drawbacks of the conventional dental materials.
1. **Introduction**

The extensive field of dental materials has witnessed a long journey of breakthroughs and drawbacks. Biodentine™ (Septodont, Saint Maur des Faussés, France), the focus of study of this literature review, is a result of this evolution. Biodentine™ was launched onto the market following Food and Drug Administration (FDA) approval\(^1\) in 2009. Biodentine™ was initially developed as dentine replacement material. Applications mentioned in the literature for this material include restoration of deep and large coronal carious lesions, pulp capping and pulpotomy, apexification and apexogenesis, repair of root and furcation perforations, perforating internal and external resorptions and root-end filling in endodontic surgery.

1.1 **Materials used up to date**

Dental materials have greatly evolved in terms of characteristics, indications and limitations throughout the years. This paragraph will mostly discuss properties of conventional materials that researchers compare when investigating on Biodentine™.

**Amalgam** is used as dentine and enamel substitute and root-end filling material. It is chosen due to its low cost, ease of application, strength and durability. On the other hand, it is destructive for the biological aspect of cavity preparation, it is not aesthetic especially in the frontal zones and it is reported to release mercury vapours during chewing, which may be harmful\(^1\),\(^2\). When used as root-end filling material, failures are reported due to electrochemical corrosion\(^3\) and poor biocompatibility in the first 10-15 weeks\(^4\).

**Direct composite resin restorations** used as enamel and dentine substitute have gradually been used to replace amalgam for both anterior restorations and small to moderate-sized posterior restorations. Their advantage is the achieved micro-mechanical retention by using different bonding techniques. However, they bare their own restrictions concerning: composite resin wear resistance in high-stress situations, polymerization shrinkage, microleakage and unreacted monomer and toxic ingredient release. Monomer release may interfere with the critical step of pulp healing. This explains the need of an intermediate layer in deep cavities\(^1\),\(^5\).

\(^1\) [http://www.accessdata.fda.gov/cdrh_docs/pdf9/K092251.pdf]
**Intermediate restorative material** (IRM) is designed by the manufacturer for intermediate restorations to remain in place for no longer than one year, or used as an intermediate layer under restorative materials and cements, which should not contain resinous components. It is prohibited to use IRM as pulp capping agent. According to the literature review of Meshack et al., it can be used instead of amalgam as root-end filling material. IRM demonstrates better biocompatibility and a higher success rate compared to amalgam (3). However, this difference in outcome is not always significantly important (6).

**Glass Ionomer cements** (GIC) have a wide range of use in restorative dentistry as enamel and dentine substitute or as intermediate layer under restorative materials due to their fluoride release and chemical adhesion to tooth structure.(7) The fluoride release gives GIC bioactive cariostatic characteristics, but clinical studies present equivocal data as to whether or not these materials sufficiently prevent or inhibit secondary caries compared to non-fluoridated restorative materials. Another domain of indication of GIC is endodontic surgery. According to the literature review of De Bruyne et al., GIC proves to be successful as root-end filling material. However, contradiction remains regarding perforations or resorptions. (8)

**Calcium hydroxide** Ca(OH)\(_2\) has been the ‘gold standard’ for many years in a wide range of indications such as: vital pulp therapy, apexification, repair of root and furcation perforations, internal and external perforating resorptions. Its basic pH is the main reason for its apparent toxicity in vitro and high antibacterial effect (9). Using Ca(OH)\(_2\) to induce hard tissues formation, initiated by an inflammatory process, results in a delay of up to three months and an unsatisfactory quality of such induced hard tissues.(10) Poor bonding to dentine and mechanical properties, material resorption, adverse effects in prolonged contact with dentine (32% diminished dentine toughness), tunnel defects in the newly formed dentine explain the need for scientific research towards a material that would overcome these shortcomings (9), (10), (11). Notably, Ca(OH)\(_2\) is proved in any case as a successful short-term intracanal dressing material with a high antibacterial effect.(12)

**Mineral trioxide aggregate** (MTA) in its first formulation as ProRoot MTA, was developed in the 90’s, in attempt to overcome the drawbacks of Ca(OH)\(_2\). MTA is also indicated in situations of pulp therapy, apexification, repair of perforations and resorptions. Mainly composed of tricalcium and dicalcium silicate and tricalcium aluminate, bismuth
oxide as radiopacer, MTA presents other raw materials in small amounts. The first formulation was in grey (GMTA). To overcome tooth discoloration a white version (WMTA) was then presented with diminished amounts of iron, magnesium and aluminium. However, when researchers compare the compressive strength of GMTA and WMTA, there is contradiction in the reported results. GMTA and WMTA both have the same major components (tricalcium silicate and aluminate, calcium silicate and tetracalcium aluminoferrite) as Portland Cement (PC) used in the industry. Several literature reviews confirm that MTA is well accepted for its biocompatibility, bioactivity inducing new dentine formation and bone repair, its moisture tolerance and its sealing ability, key attributes for a material used in contact with vital tissue. During the setting reaction, MTA produces Ca(OH)$_2$ explaining its high pH and antibacterial abilities. Besides these properties, MTA presents drawbacks such as potential of tooth discoloration (especially GMTA), high cost, difficulties in handling characteristics and difficulties of removal after setting given the fact that no solvent exists. The characteristics which most limit the application of MTA are the long setting time of 2h 45 min (so it must be protected during setting) accompanied by initially reduced mechanical properties (compressive strength) (17). Other versions of MTA have been developed in the attempt to overcome the drawbacks, such as Angelus MTA (AMTA) with a setting time of 14.28 ± 0.49 minutes. However, the first formulation of MTA (ProRoot MTA) is the most used by researchers when investigating properties and indications of Biodentine™.

To a general extent, these materials are primarily site specific, substituting or dentine in the crown or dentine in the root and they can be used under specific clinical conditions. Besides substitution, the science of dental materials is shifting towards regeneration and revascularization, thus maintenance of tooth pulp vitality and promotion of dentinal tissue secretion.

1.2 Biodentine™

Many recent studies have focused on pulp-dentin complex and bone regeneration and revascularisation. Their principal aim has been designing a product that would incorporate the therapeutical properties of MTA and overcome some of its limitations such as long setting
time and low mechanical properties. It was not until 2009 that Septodont launched Biodentine™ onto the market. It is a new version of calcium-silicate cements, otherwise called “Dentine in a capsule”. The producer claims that this product is revolutionary: it can change the way of treatment offering a bioactive and biocompatible substitution for dentine. The product can used wherever dentine replacement is required and whenever pulp vitality needs to be preserved and promoted. (19) As summarised in Table 1 and 2, Biodentine™ is presented as a capsulated powder consisting of tricalcium silicate (main component), dicalcium silicate (second main component) and calcium oxide, calcium carbonate (filler material), iron oxide for colour shade and zirconium oxide as a radiopacifier. The liquid for mixing with the cement powder consists of calcium chloride (decreases the setting time) and a hydrosoluble polymer (water reducing agent) in order to keep good flowability with a low water/solid ratio. Septodont claims that Biodentine™ is produced following a new technology and it is named ‘Active Biosilicate Technology™’. (19)

### Table 1- Components of Biodentine™ (19)

<table>
<thead>
<tr>
<th>Powder (1gr)</th>
<th>Liquid (200 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricalcium silicate (3CaO·SiO₂)</td>
<td>80% Calcium chloride (CaCl₂2H₂O) 15%</td>
</tr>
<tr>
<td>Dicalcium silicate (2CaO·SiO₂)</td>
<td>Water reducing agent</td>
</tr>
<tr>
<td>Calcium carbonate &amp; oxide(CaCO₃ &amp; CaO)</td>
<td>15% Water</td>
</tr>
<tr>
<td>Iron oxide (Fe₂O₃)</td>
<td></td>
</tr>
<tr>
<td>Zirconium oxide (ZrO₂)</td>
<td>5%</td>
</tr>
</tbody>
</table>

Note: There are components, the quantity of which is not mentioned either in the producer file on Biodentine™, or in further literature publications.

### Table 2- Properties of the different components of Biodentine™ (19)

<table>
<thead>
<tr>
<th>Component</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricalcium silicate (3CaO·SiO₂)</td>
<td>Main powder component. Role- regulation of the setting reaction</td>
</tr>
<tr>
<td>Dicalcium silicate (2CaO·SiO₂)</td>
<td>Second main component. Role- Enhance the properties of material</td>
</tr>
</tbody>
</table>
Calcium carbonate (CaCO$_3$) | Traces - Role similar to filler
---|---
Iron oxide (Fe$_2$O$_3$) | Traces - Colour shade
Zirconium dioxide (ZrO$_2$) | Traces - Supplies the cement with radio-opacity
Calcium chloride (CaCl$_2$2H$_2$O) | Role – accelerator
Water reducing agent | Reducing water content, viscosity is reduced, workability is achieved

2. **Goal**

The goal of this literature study is to answer the PICO question encountered using Biodentine™, by gathering information from different databases, specifically concerning its properties and indications. The comparison between Biodentine™ and the earlier and more widely applied materials, mostly MTA, is inevitable. The producer, Septodont, gives information about composition, properties and setting, but the goal of this study is to provide an evidence-based insight for the practitioner in order answer the PICO question and succeed in material decision-making.

**PICO process**

**Problem**: to solve the problem of dentine loss from different causes in both tooth crown and root.

**Intervention**: Biodentine™ application

**Comparison**: conventional materials used up to date

**Outcome**: Maintain pulp vitality and stimulate new hard tissue formation - reparative dentine and bone tissue.

**PICO question**

"Does Biodentine™ solve the problem of dentine loss in order to maintain pulp vitality and stimulate new hard tissue formation, compared to the conventional materials?"
3. **Methodology**

For this literature review, PubMed, Web of Science and Google Scholar have been used. The principal keyword is BIODENTINE. In the advanced search other combining keywords are: tricalcium silicate, dicalcium silicate, calcium chloride. For additional information about previous used materials such as amalgam, composite restorations, GIC, IRM and MTA only literature review articles have been considered. Google machine has been used to find case reports published in the “Septodont Case Studies Collections” up to number 7- March 2014. Wikipedia has been consulted in order to clarify physical concepts.

Except the reviews about the conventional materials, publications about Biodentine™ date no further than 2008, as it was only launched into the market in 2009. The searching procedure for this review started in November 2013 and was concluded in March 2014. In the selection process, irrelevant articles for the topic have been excluded. Furthermore, no strict selection criteria have been applied concerning in vitro or in vivo studies, case series or animal studies, considering the fact that there is a lack of studies due to the novelty of this product.

A recent review of the literature with the same topic published from Paediatric Department of Ghent University has thoroughly been examined and utilised (20). The scientific file published by the manufacturer itself has also been comprehensively examined (19).

In total 70 articles from journals and 20 Publications from 7 “Septodont Case Studies Collections” are used and indicated in the reference list.

4. **Results**

The results on properties and indications of Biodentine™ are organized in subtopics: 1 composition and setting, 2 mechanical and physical properties, 3 biological properties and 4 indications.
4.1 Composition and setting

A. Composition

Based on the information given by Septodont, summarised in Table 1 and 2 further investigation on the specific components leads to these results.

- **3CaO.SiO₂ (Ca₃Si)** is the **Main Component** of Biodentine™ 80%. The so named “Active Biosilicate Technology™” manufacturing Biodentine™ produces a pure synthetic tricalcium silicate, in a standardised composition, fine particle distribution and absence of raw materials. (21) Ca₃Si has **bioactive** (induction of dentine secretion) and **biocompatible** (no cytotoxicity, creating a microenvironment that would enhance cell proliferation and differentiation) properties sustained in different studies. (1), (22), (23)
Ca₃Si is **not radiopaque** (24), has a **long setting time** above the 180 min (25), (21), (26) and has **low physical and mechanical properties** (26). All the other components, listed in Table 1, are added with the purpose of overcoming these drawbacks. (27)

- **2CaO.SiO₂ (Ca₂Si)** synthetized by sol-gel process is a **hydraulic cement** that gets into reaction when in contact with water or aqueous solution to form a hydrated phase (28). From the study of Correa et al., Ca₂Si has a **high setting time, compressive strength** comparable to human bone and is **not cytotoxic**. This material is **bioactive** in the sense that bone-like apatite spherulites in the form of hydroxyapatite (HA) can be formed after immersion in stimulated body fluid and can bond with bone(29).

- **CaCO₃** presence (15%) results in accelerated cement with better hydraulic properties (21). The calcium carbonate does not react with water to form a reaction by-product. It only acts as a nucleation site for Ca-Si-Hydrates reducing the duration of the hydration induction period.(30) As a consequence of a short induction period, the initial setting is expected after a few minutes. Enhancement of the physical properties and mechanical strength by densing the structure is specifically reported by Huan et al. (26). Pure Ca₃Si paste scores 14-16 MPa, whereas the mixture cement scores 24-27 MPa. Better bioactivity and biocompatibility are also granted by this mixing.
• ZrO$_2$, the radiopacer of Biodentine$^\text{TM}$ (5%) causes no tooth discoloration (31), such as Bi$_2$O$_3$ in MTA (14). Tanalp et al. (32) show that the radiopacity of Biodentine$^\text{TM}$ is lower (2,8 mm Al) compared to that of MTA (4,72 mm Al), but in any case not higher compared to the value of 3 mm of dentine. On the other hand, the studies of Camilleri (21) and Grench (27) confirm that the radioactivity of Biodentine$^\text{TM}$ is higher than 3 mm aluminum.

• CaCl$_2$2H$_2$O (CaCl$_2$) addition to the Ca3Si causes an acceleration of the cement setting time and compressive strength. Instead of using only water, as is the case for MTA, the liquid for Biodentine$^\text{TM}$ contains 10 up to 15% CaCl$_2$. The presence of CaCl$_2$ increases the initial quantity of reactive calcium in the chemical process, resulting in reaction acceleration. The addition of more or less than the 10-15% value of CaCl$_2$ will negatively influence the compressive strength by increasing in both cases the amount of pores in the material. In the surface of the composite cement Ca3Si/CaCl$_2$ researchers show formation of HA. This phenomenon will be further reconsidered in paragraph 4.3. (23), (33)

• Hydrosoluble polymer or otherwise called water reducing agent, is added to reduce water/cement ratio. The hydrosoluble polymer has surfactant effects, otherwise named wettability, which lowers the surface tension of the paste itself, making it easier and faster for the Ca3Si molecules to react with even lower amounts of water. This effect is expressed also in the proper wetting of the dentine. Reducing the needed water for the reaction increases the compressive strength and micro-hardness of the cement, while the workability of the cement mixture is not negatively affected.(21),(27)

The combination of CaCO$_3$, CaCl$_2$, hydrosoluble polymer and a finer particle distribution of Ca3Si decreases the setting time of Biodentine$^\text{TM}$ up to 12 minutes, as well as increases its workability, compressive strength, bioactivity and biocompatibility.² (21),(33)

² these properties will be further discussed
- **Characterisation of the un-hydrated Biodentine**<sup>TM</sup> cement is investigated in the study of Camilleri et al. (21) by X-ray diffraction analysis (XRD), X-ray fluorescence (XRF), energy dispersive analysis (EDX) and scanning electron microscopy (SEM) and compared to AMTA and radiopacified tricalcium silicate cement (TSC). It is of interest to mention the important differences in the un-hydrated pastes. Even though Biodentine<sup>TM</sup> and AMTA have Ca3Si as main component, this ingredient takes 80% in Biodentine<sup>TM</sup> and is in a triclinic form, whereas in AMTA it takes 66% and is in a monoclinic form. In Biodentine<sup>TM</sup> Ca3Si is in a finer particle size leading to a greater specific surface area. This means a higher rate of liquid-powder reaction. Opposed to AMTA, which shows remnants of raw materials namely calcium, silicon and aluminium oxide, Biodentine<sup>TM</sup> and radiopacified TSC do not contain such minor elements. This fact confirms that these products are made from pure constituents.

**B. Setting**

- During the **setting reaction** upon mixing of the liquid phase with the powder phase, the sequence of chemical events occurs:

  1. Tricalcium silicate mixed with water component generates hydrated calcium silicate gel structure and Ca(OH)<sub>2</sub>. The gel structure precipitates.
  2. Growth of gel structure further develops through nucleation and growth from the surface and fills all the spaces between tricalcium silicate grains.
  3. Further hydration of tricalcium silicate leads to further crystallisation of calcium silicate gel structure. Between the unreacted grains, CaCO<sub>3</sub> particles form crystals, which act as a nucleation site for the crystallisation of new cement grains and slowly fill the possible porosities in a period of maximum two weeks.

In other words the setting reaction of Biodentine<sup>TM</sup> leads initially to a porous structure with a time-dependent density. This process of crystallisation and gap filling gives impermeability to the structure, increases other properties such as microhardness, sealing ability, push-out bond strength that will be further investigated in paragraph 4.2.(34),(25)

- The following **chemical formula** summarises the complete hydration reaction:

\[
2(3\text{CaO}.\text{SiO}_2) + 6\text{H}_2\text{O} \rightarrow 3\text{CaO}.2\text{SiO}_2.3\text{H}_2\text{O} + 3\text{Ca(OH)}_2
\]

<table>
<thead>
<tr>
<th>Ca3Si</th>
<th>Hydrated silicate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>Gel</td>
</tr>
</tbody>
</table>
The final molecular structure of the set material is a hydrated tricalcium silicate gel matrix with CaCO₃ crystals between unreacted grains of cement. (34)

- **Characterisation of the set material** is studied by Camilleri et al. (21), (35) by the same tests as mentioned above: SEM, XRF, XRD, EDX and calorimetry. SEM shows that Biodentine™ is composed of a mixture of 5 μm round particles of CaCO₃ that act as a nucleation site embedded in a calcium silicate hydrate matrix. The particles have a reaction rim around them. The microstructure of Biodentine™ becomes dense as the production of calcium silicate hydrate around CaCO₃ leads to minimal porosity. The presence of ZrO₂ is also confirmed.

The EDX analysis shows peaks of calcium, silicon, carbon, oxygen, zirconium and chlorine. Except for zirconium, which is more concentrated in some areas, all the other elements are equally distributed. When exposed to simulated body fluids, hydroxyapatite crystals (HA) are also evident on the surface. The XRD analysis displays peaks for Ca₃Si, CaCO₃, ZrO₂ and Ca(OH)₂.

The calorimetry test during setting comparing Biodentine™ to pure tricalcium silicate cement (TSC) shows the following results: for Biodentine™ an exothermic peak after 30 min, narrower and more intense than for the pure TSC, beginning after 90 minutes and reaching a peak after 210 min. This is translated in greater kinetics of hydration and faster achieved mechanical strength for Biodentine™.

It goes without saying that researchers compare Biodentine™ to pure TCS cement to show the effect the additional elements give to Biodentine™. The demonstrated presence of Ca(OH)₂ and HA in the set material is also of importance for further evaluation of the bioactivity of the material in this literature overview.
- **Setting time** - The setting times of the cement pastes are measured by the Vicat needle\(^3\) method according to the *International Organisation for Standardization* (ISO) 9597-1987E. (26) The initial setting time is defined as the time taken from the beginning of the mixing to the time that the paste stiffens so that the needle plunges into the paste to a span of 5 ± 1mm. The final setting time is defined as the time it takes for the paste to harden since the initial mixing, so that the indenter fails to leave a print on the cement surface. The initial setting time for Biodentine\(^\text{TM}\) is reported to be 12 minutes, contrasting 165 ± 5 min of MTA. The final setting time is reported to be 45 minutes and is compared to 3 min of IRM and 290 min of TSC. (25), (27), (33)

4. 2 Mechanical and physical properties

The mechanical and physical properties are of key importance in the use of dental materials. These characteristics very often dictate the spectrum of clinical indications. *Table 4* summarises the values reported by authors in different articles concerning physical and mechanical properties, compared to MTA and IRM. This table is extracted from the review article of Rajasekharan et al. (20).

The *compressive strength* and *hardness* of Biodentine\(^\text{TM}\) are assessed in different publications. Compressive strength\(^4\) and micro-hardness\(^5\) (Vickers hardness) have both been evaluated in different moments. The values increase and after 28 days of setting they are respectively 69 VH and 70-80 MPa for Biodentine\(^\text{TM}\). These values are higher compared to TCS (attributed to the additives: CaCO\(_3\), CaCl\(_2\), hydrosoluble polymer), IRM and MTA (67 MPa). (25),(27),(17), (36).

If Biodentine\(^\text{TM}\) has to be acid-etched in order to place a definitive restorative material above it, Kayahan et al. (36) advise to delay this procedure at least one week. This way the compressive strength of Biodentine\(^\text{TM}\) is not affected.

*Flexural modulus* is an important physical property especially in the use for Class I, II and IV and is assessed as 34MPa for Biodentine\(^\text{TM}\). It is higher compared to MTA (14MPa), and

\(^3\) Needle with measured surface and weight  
\(^4\) The resistance of material against loads that tend to reduce the size  
\(^5\) The resistance of the surface of the material to plastic deformation by indentation or penetration
lower compared to composite resin (120-200MPa). This value is considered as similar when compared to dentine (20MPa), The *elastic modulus* is assessed as 22 GPa, while for dentine it is 11-20 GPa and for enamel 86 GPa. (25),(27),(37)

Table 3-Material properties of Biodentine™ compared to dentine, GIC and Composite. Table extracted from (38)

<table>
<thead>
<tr>
<th>Material</th>
<th>Compressive strength (MPa)</th>
<th>Flexural strength (MPa)</th>
<th>Elastic Modulus (MPa)</th>
<th>Micro hardness (VH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biodentine™</td>
<td>220⁶</td>
<td>34</td>
<td>22.000</td>
<td>60</td>
</tr>
<tr>
<td>Dentine</td>
<td>200-350</td>
<td>20</td>
<td>15.000-20.000</td>
<td>60-90</td>
</tr>
<tr>
<td>GIC</td>
<td>140-180</td>
<td>10-21</td>
<td>5.000-11.850</td>
<td>36</td>
</tr>
<tr>
<td>Composite</td>
<td>290-400</td>
<td>100-145</td>
<td>12.000-16.000</td>
<td>70-130</td>
</tr>
</tbody>
</table>

Biodentine™ values expressed in the journal publications and in Table 3 are comparable to dentine, higher than MTA and GIC, but lower than the values of enamel and composite materials. These results justify the indication of Biodentine™ as permanent dentine substitute and only temporal enamel substitute material.

*Fluid uptake* values⁷ are reported to be lower for Biodentine™ compared to TCS and the same compared to IRM. *Solubility* values⁸ are negative for both Biodentine™ and TCS, indicating deposition of material in the cements’ surface. Solubility value is positive for IRM indicating possible loss of substance. There is no significant difference between Biodentine™ and TCS because of the same main component – Ca3Si, which when hydrating produces and releases Ca(OH)₂ as by-product. Ca(OH)₂ in physiologic solution deposits HA on the cement surface. According to the authors “low sorption and solubility of Biodentine™ provide evidence for dimensional stability, a very important property when used as root-end filling material”.(27)

*Alkalinity* of Biodentine™, as a result of the negative solubility mentioned above, is further studied and compared to TCS and IRM. Immersing the materials in Hank’s Balanced Salt

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⁶ 70MPa found at Grech et al.2013 and Kayahan et al. 2013, and 220 found at The scientific file of Septodont and at the review Dammanschke-Septodont Case Studies Collection Nr 2 June 2012

⁷ fluid absorbed from the surface to the body of the material

⁸ the amount of substance that will dissolve in a certain amount of solvent
Solution (HBSS)$^9$ indicates an average pH value of 12 for Biodentine™, which is similar to pH 12.2 of TCS, and higher than pH 9 of IRM. The leaching of calcium ions in HBSS measured from Biodentine™ follows a curve that grows from Day 1 to Day 14 and then hits a plateau until Day 28. The release of calcium is reported as significantly higher for Biodentine™ than TCS. In the study of Khan et al. (39), Biodentine™ is immersed in deionised water and its ability of alkalinisation is measured after 3 hours, 1 day, and 7 days and compared to MTA. The pH results for Biodentine™ are respectively 9.14±0.16, 8.88±0.27 and 8.02±0.19, with no significant difference to pH of MTA. Depending on where the set Biodentine™ is stored (HBSS or deionised water), different values of alkalinity are reported, but different articles do not compare Biodentine™ to the same control materials.

In order to evaluate the radiopacity of Biodentine™, researchers follow the standard method developed by Tagger and Katz. Radiographic images are taken when the tested material is placed next to an aluminium step-wedge (penetrometer). An endodontic cement, according to ISO 6876:2001, must have a minimum radiopacity of 3mm thickness of Al$^{10}$. The consulted literature for Biodentine™ shows a contradiction in the measured values, even though the standard ISO method is used. Tanalp et al. present a value of 2.8 mm Al, which is lower than the 3 mm Al minimum standard (32). However, the authors note that further evaluation is needed. Opposed to this, Grech et al. and Camilleri et al. present values higher than 3 mm. (27), (21)

Porosity is an important property to be considered, if a material will be in permanent contact with oral or periradicular fluids. For endodontic cements, porosity is directly linked to solubility. Through solubility of a porous material, leakage channels can be created. These can lead to passage of microorganisms, stress concentration reducing the compressive strength and push-out bond strength of the material. (40) There are three sorts of pores mentioned in the literature: closed, through and blind pores, from which the last two are considered as “open porosity”. The closed ones can affect the mechanical properties. The open ones, when in the interface with dentine, can lead to penetration of undesirable fluids into dentine. Furthermore, when evaluating pores, bubbles should be excluded. While bubbles result from problems in mixing (more formed by hand-mixing) and handling of the material, pores are directly related to the composition of the material itself (water-to-powder ratio). The

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$^9$ simulated body fluid solution  
$^{10}$ radiopacity value of dentin
study of De Souza et al. (40) observe no significant difference in porosity values between Biodentine™ and MTA. The publishers admit that in the results, bubbles have also been counted. However, they confirm that porosity decreases if the water-to-cement ratio decreases and if the cement ages. Other studies juxtapose Biodentine™ to MTA and TCS, reporting denser and less porous microstructure for Biodentine™, comparable to IRM. (21),(41) This result is attributed to a better particle size distribution when compared to TCS, and to the lack of raw materials when compared to MTA. Hydration of raw materials gives a less dense structure than the pure Ca3Si hydrates. The microstructure of the material itself and the dentine-Biodentine™ interface are jeopardised when dry stored, manifesting cracks, material shrinkage and gaps. When being in contact with periradicular fluids, these risks are avoided, making Biodentine™ applicable as root-end filling material. (41)

The interfacial layer (extensively explained later) Biodentine™ that forms between the material itself and dentine, enamel and adhesive systems, warrants for the interfacial seal\textsuperscript{11} and bond. (25)

The interfacial seal is tighter between Biodentine™-dentine, compared to Biodentine™-enamel, showed through silver nitrate penetration assessment method. (25)

- Biodentine™-Dentin Interface \textit{Day 0} - 3.23\% / \textit{Day 90} – 5\% microleakage
- Biodentine™- Enamel Interface Day 0 – 4.35\% / Day 90 – 10.72\%

Concerning the \textit{microleakage} the material will express, comparisons are made between Biodentine, MTA, and GIC/RM-GIC in different situations.

- In root-end filling scenarios, Biodentine shows significantly less microleakage compared to MTA and GIC, using 1\% methylene blue as tracing method (42).
- In sandwich restorations there is contradiction between Biodentine and Resin Modified-GIC results, probably due to variations in methodology techniques. Koubi et al. (43) using the glucose diffusion method, show no significant difference between the two materials in open sandwich technique. On the other hand, Camilleri et al. (35), using 0.5\mu m diameter tagged carboxylated-modified fluorescent microspheres, determine less microleakage for RM-GIC than Biodentine™ when covered by composite resin material.
- In cervical lining restoration (open and closed technique) there is no difference shown between Biodentine™ and RM-GiC, using the silver nitrate penetration method. Different

\textsuperscript{11} water tightness against microleakage
restorative materials can be successfully applied on top of Biodentine™ without any significant leakage between the dentine substitute and restorative material overlaid on it. (44)

The *interfacial bond with adhesive systems* is reported to be dependent on the type of adhesive system used on top of Biodentine™. Odabas et al. (45) studying the shear bond strength of different adhesive systems on top of Biodentine™ indicate the following results. If Biodentine™ has to be etched, better results are achieved if the procedure of acid etching is delayed 24 hours after mixing, instead of 12 minutes. The higher performing system is the 2-step self-etch adhesive system, in which the clinician applies primer and leaves it for 20 seconds/ dries with mild air for 5 sec/ applies bond and leaves it for 10 sec/ gently air flows/ light-cures for 10 sec. The second one is the 1-step self-etch adhesive system where the clinician directly applies bond and leaves it for 10 sec/ dries with mild air for 5 sec/ light cures for 10 sec. The lowest shear bond strength were obtained by the etch-and-rinse adhesive system where the clinician etches with 35% phosphoric acid/ rinses and dries/ applies bond/ gently air flows/ light-cures for 10 sec.

*The bond strength* of Biodentine™ to dentine is important for root and furcation perforation situations. In these cases the applied material must be resistant to dislodging forces of occlusion and condensation. Between three different tests used to assess adhesion: tensile, shear and push-out bond strength – the *push-out bond strength* test is generally selected to evaluate Biodentine™, as a practical and reliable test.

Biodentine™ shows higher values of push-out bond strength, compared to MTA, which increase with the aging of the material, as results demonstrate when collected 24 hours after mixing, as well as after 1 week, when stored in saline solution. Blood contamination or the usage of various root irrigants have no effect on the push-out bond strength of Biodentine™, contrasting the drop of push-out bond strength of MTA by both these stimulations. (33), (46) The authors Guneser et al. (46) have further investigated the causes of adhesion failure during the test, which can occur in different fashions. Failure of MTA is predominantly of adhesive origin, which means it happens at the MTA-dentine interface. On the other hand, Biodentine™ manifests a cohesive type of failure, as it happens inside the cement self. This phenomenon demonstrates a better interlocking of Biodentine™ with dentine. Nevertheless, the bonding of both materials is impaired when stored in acidic samples, simulating acidic tissue fluids in an infected area.(47)
Statistical analysis of the mean push-out bond strength of Biodentine™ compared to MTA with and without smear layer removal reveals that the bond strength of calcium silicate cements in general is negatively influenced by removal. Whether removed or not, roots filled with Biodentine™ exhibit significantly higher push-out bond strength than MTA. Smear layer, produced by root canal instrumentation, seems to be important in the formation of interfacial layer and possibly gets actively involved in the mineral interaction between the calcium silicate cements and radicular dentine. (48)

Vallés et al. state having previously observed that irradiation with a curing light or a fluorescent lamp in an oxygen-free environment causes dark discoloration in WMTA. In their recent study (31), they observe that Biodentine™ maintains colour stability, with time playing no role, with or without exposure to light or oxygen. The main cause of the discoloration of WMTA is attributed to the content of bismuth oxide (Bi₂O₃) and formation of metallic bismuth under irradiation and oxygen free conditions as a result. As listed in the composition paragraph, 4.1, the radiopacer of Biodentine™ is zirconium oxide (ZrO₂). The authors mention that further investigation should take place in this regard.

**Table 4- Properties overview of BiodentineTM, MTA and IRM.**

*Extracted from Rajasekharan et al. 2014*

<table>
<thead>
<tr>
<th>Material Characteristics</th>
<th>Time Period</th>
<th>BIODENTINE</th>
<th>MTA</th>
<th>IRM</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Setting Time</td>
<td></td>
<td>45</td>
<td></td>
<td>3</td>
<td>Grench et al. 2013 (27)</td>
</tr>
<tr>
<td>Compressive Strength MPA</td>
<td>28 days</td>
<td>67.18</td>
<td>20.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vickers Hardness HV</td>
<td>28 days</td>
<td>48.4</td>
<td>16.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porosity % detected by Micro CT</td>
<td></td>
<td>7.09±1.87</td>
<td>6.65±1.93</td>
<td></td>
<td>De Souza et al. 2013 (40)</td>
</tr>
<tr>
<td>Porosity % after immersion in HBSS for 28 days (detected)</td>
<td></td>
<td>13.44</td>
<td>12.66</td>
<td></td>
<td>Camilleri et al. 2013 (41)</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>by Hg intrusion porosimetry)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average pore diameter</td>
<td>0.0121</td>
<td>0.0205</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total pore area m²/g</td>
<td>21.752</td>
<td>10.545</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulk density g/ml</td>
<td>2.0444</td>
<td>2.3455</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Volume of pore space</td>
<td>4.92±0.67</td>
<td>5.20±1.5</td>
<td>De Souza et al. 2013 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of closed pores</td>
<td>32.016±18.107</td>
<td>22.274±4.281</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closed Porosity %</td>
<td>5.15±0.30</td>
<td>4.60±0.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of closed pores (mm³)</td>
<td>3.86±0.13</td>
<td>3.52±0.57</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Surface of closed pores (mm²)</td>
<td>476.74±70.86</td>
<td>398.90±54.99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific surface area (m²/g)</td>
<td>2.8116</td>
<td>1.0335</td>
<td>Camilleri et al. 2013 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid uptake % (stored in HBSS)</td>
<td></td>
<td></td>
<td>Grench et al. 2013 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 day</td>
<td>0.006</td>
<td>0.003</td>
<td></td>
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<tr>
<td>7 days</td>
<td>0.011</td>
<td>0.004</td>
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<tr>
<td>14 days</td>
<td>0.011</td>
<td>0.004</td>
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<tr>
<td>21 days</td>
<td>0.010</td>
<td>0.0045</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>28 days</td>
<td>0.010</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorption % (stored in HBSS for 28 days)</td>
<td>0.007</td>
<td>0.007</td>
<td></td>
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</tr>
<tr>
<td>Weight loss % (stored in HBSS for 28 days)</td>
<td>0.002</td>
<td>0.003</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Percentage washout by mass of the test materials following 1st drop (stored in HBSS for 28 days)</td>
<td>23.3537</td>
<td>-1.4713</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage washout by mass of the test materials following 2nd drop (stored in HBSS for 28 days)</td>
<td>41.2466</td>
<td>-0.8702</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage washout by mass of the test materials following 5th drop (stored in HBSS for 28 days)</td>
<td>50.5970</td>
<td>1.3649</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>7.23±4.22</td>
<td>3.49±3.02</td>
<td>9.21±2.90</td>
<td>Guneser et al. 2013 (46)</td>
<td></td>
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<td>--------------------------</td>
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<td></td>
</tr>
<tr>
<td>Push-out bond strength</td>
<td>7.13±2.17</td>
<td>2.45±1.99</td>
<td>8.07±2.79</td>
<td></td>
<td></td>
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<tr>
<td>after immersion in</td>
<td></td>
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</tr>
<tr>
<td>NaOCL (MPa)</td>
<td></td>
<td></td>
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<tr>
<td>Push-out bond strength</td>
<td>7.22±3.14</td>
<td>6.18±3.80</td>
<td>8.18±278</td>
<td></td>
<td></td>
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<tr>
<td>after immersion in</td>
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<tr>
<td>CHX (MPa)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Push-out bond strength</td>
<td>8.79±1.55</td>
<td>7.54±1.11</td>
<td></td>
<td>El-Ma’ Aita et al. 2013</td>
<td></td>
</tr>
<tr>
<td>when smear layer is</td>
<td></td>
<td></td>
<td></td>
<td>(48)</td>
<td></td>
</tr>
<tr>
<td>preserved (MPa)</td>
<td></td>
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<tr>
<td>[Irrigation with 1%</td>
<td></td>
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<tr>
<td>NaOCL between filling]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Push-out bond strength</td>
<td>7.71±1.81</td>
<td>6.58±1.13</td>
<td></td>
<td></td>
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<tr>
<td>when smear layer is</td>
<td></td>
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<tr>
<td>removed (MPa)</td>
<td></td>
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<tr>
<td>[Irrigation with 1%</td>
<td></td>
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<tr>
<td>NaOCL between filling]</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Push-out bond strength</td>
<td>19.5 ± 0.9</td>
<td></td>
<td></td>
<td>Poplai et al. 2012 (47)</td>
<td></td>
</tr>
<tr>
<td>at pH 7.4 (MPa)</td>
<td></td>
<td></td>
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<tr>
<td>Push-out bond strength</td>
<td>19.2 ± 0.8</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>at pH 6.4</td>
<td></td>
<td></td>
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<tr>
<td>Push-out bond strength</td>
<td>17.9 ± 1.1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>at pH 5.4</td>
<td></td>
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<tr>
<td>Push-out bond strength</td>
<td>11.7 ± 0.5</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>at pH 4.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microleakage (mm)</td>
<td>0.13 ± 0.006</td>
<td>0.73 ± 0.13</td>
<td></td>
<td>Kokate &amp; Pawar 2012 (42)</td>
<td></td>
</tr>
<tr>
<td>Radiopacity (/mm Al)</td>
<td>1 day</td>
<td>4.1</td>
<td>9.6</td>
<td>Grench et al.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 days</td>
<td></td>
<td></td>
<td>2013 (27)</td>
<td></td>
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</tr>
<tr>
<td><strong>pH of leachate (deionized water)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>9.14±0.16</td>
<td>9.52±0.33</td>
<td>Khan et al. 2012 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>8.88±0.27</td>
<td>9.32±0.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>168 h</td>
<td>8.02±0.19</td>
<td>8.45±0.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>pH of leachate (HBSS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 day</td>
<td>11.7</td>
<td>9.3</td>
<td>Grench et al. 2013 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 days</td>
<td>12.1</td>
<td>9.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 days</td>
<td>12.3</td>
<td>9.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 days</td>
<td>12.4</td>
<td>8.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 days</td>
<td>12.3</td>
<td>8.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ca ion release (mg/l) [when immersed in distilled water]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 h</td>
<td>24±5.28</td>
<td>17.7±0.21</td>
<td>Han and Okiji 2013 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-24 h</td>
<td>34±3.44</td>
<td>24±0.52</td>
<td></td>
<td></td>
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<tr>
<td>24-48 h</td>
<td>27.6±1.66</td>
<td>20.2±3.44</td>
<td></td>
<td></td>
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<tr>
<td>144-168</td>
<td>14.7±2.01</td>
<td>9.7±0.26</td>
<td></td>
<td></td>
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<tr>
<td><strong>Incorporation depths of Ca into human root canal dentine (µm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 day</td>
<td>39±8.2</td>
<td>23±5.7</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7 days</td>
<td>74±18.8</td>
<td>50±19</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>30 days</td>
<td>118±11.5</td>
<td>75±22.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 days</td>
<td>166±22.5</td>
<td>133±19.2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Incorporation depths on Si into human root canal dentine (µm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1 day</td>
<td>32±14.8</td>
<td>21±6.5</td>
<td></td>
<td></td>
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<tr>
<td>7 days</td>
<td>46±12.9</td>
<td>41±9.6</td>
<td></td>
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<tr>
<td>30 days</td>
<td>86±9.6</td>
<td>62±12</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>90 days</td>
<td>130±12.7</td>
<td>107±12.5</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Cytotoxicity after indirect contact (undiluted) [%]</strong></td>
<td>0±8</td>
<td>0±9</td>
<td>Laurent et al. 2008 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytotoxicity after indirect contact (diluted) [%]</strong></td>
<td>0±8</td>
<td>0±9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Leaching of chromium in HBSS (mg/kg)</strong></td>
<td>0.06</td>
<td>0.06</td>
<td>Camilleri et al. 2012 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Leaching of arsenic in HBSS (mg/kg)</strong></td>
<td>0.19</td>
<td>0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Leaching of lead in HBSS (mg/kg)</strong></td>
<td>0.17</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acid soluble chromium concentration (mg/kg)</strong></td>
<td>4.50</td>
<td>6.25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Acid soluble arsenic concentration (mg/kg)
- **28days**: 52.25
- **35**: 35

### Acid soluble lead concentration (mg/kg)
- **28 days**: 14.50
- **0.03**: 0.03

### Flexural modulus of dentine after being in direct contact with material (MPa)
- **24 h**: 14.9 ± 2.0
- **15.7 ± 3.1**: Sawyer et al. 2012 (37)
- **1 month**: 14.6 ± 2.5
- **14.2 ± 2.3**: 1 month
- **2 months**: 13.1 ± 2.4
- **13.8 ± 3.5**: 2 months
- **3 months**: 13.8 ± 2.7
- **13.9 ± 3.2**: 3 months

### Flexural strength of dentine after being in direct contact with material (MPa)
- **24 h**: 206.8 ± 12.6
- **201.30 ± 23.5**: 24 h
- **201.30 ± 23.5**: 1 month
- **187.4 ± 18.5**: 1 month
- **187.4 ± 18.5**: 2 months
- **163.3 ± 19**: 2 months
- **178.3 ± 21.7**: 2 months
- **165.3 ± 17.8**: 3 months
- **172.5 ± 23.4**: 3 months

### Modulus of toughness of dentine after being in direct contact with material (MPa)
- **24 h**: 3.58 ± 0.1
- **3.48 ± 0.96**: Sawyer et al. 2012 (37)
- **2.22 ± 0.38**: 1 month
- **3.69 ± 1.08**: 1 month
- **2.52 ± 0.89**: 2 months
- **3.27 ± 0.82**: 2 months
- **2.15 ± 0.32**: 3 months
- **2.66 ± 0.57**: 3 months

### Mean thickness of the hard tissue dentine bridge after direct pulp capping (μm)
- **6 weeks**: 221.56
- **230.31**: Sawyer et al. 2012 (37)

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### 4.3 Biological properties

Biodentine™ is a new class of conservative material, aiming to replace dentine wherever it is damaged and at the same time preserve pulp vitality. Consequently its biocompatibility and bioactivity are questioned in this literature review and compared to the already confirmed biomaterials Ca(OH)₂ and MTA.

Generally resumed, the application of biocompatible and bioactive materials on vital tissue aim:
- To protect the pulp-dentin complex against chemical irritation by operative procedures or by the material itself
- To hermetically seal the tissue wound in order to impede bacterial penetration due to microleakage.
- To induce differentiation and proliferation of progenitor cells into odontoblast-like cells in order to stimulate dentine secretion and as a result deposition of a mineral dentinal bridge. This dentinal bridge, result of a regeneration process of dental tissue, will further enhance the hermetical seal. (51), (52).

These properties are tested in different conditions in vitro and in vivo, in certain human, animal and bacterial cell lines, all recommended by the ISO to assess biological responses to dental materials. The scientific explanation is that these selected cells are easy to culture, grow rapidly and the experiments can be comfortably repeated. Moreover, the selected cell cultures provide a similar environment to the fibroblast rich tissues such as dental pulp and periodontal ligament. (53)

**A. Biocompatibility**

The biocompatibility of Biodentine™ is questioned and thoroughly investigated, because of its direct application and contact with vital pulp tissue. It is also compared to the effect of MTA, Dycal (Ca(OH)_2) and GIC, used as control materials.

Making use of human pulp fibroblasts, lymphocytes and bacteria, Laurent et al. (1) have published a study with, currently, the highest number of performed tests concerning Biodentine™ and using MTA and Dycal as control materials. They assess genotoxicity through Ames test, Micronucleus test and Comet assay. They use MTT test to assess cytotoxicity. Effects in specific cell functions, such as differentiation, biomineralisation and protein expression, are assessed under direct and indirect contact with the materials. Direct or indirect contact means with or without the inter-positioning of a dentine slice, stimulating this way direct and indirect pulp capping scenarios. Immunohistochemistry is used to assess the specific protein expression of alkaline phosphatase, type I collagen, osteonectin and dentine sialoprotein (DSP), which are indicators of differentiated cells present in the medium.

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12 Regeneration of dentinal tissue- tertiary dentinogenesis
Such in vitro biocompatibility tests are also performed by other authors (52), (53), (54), (55), (56), (57). They assess furthermore the cell attachment to the material using different types of cells. For example, Attik et al. (54) use human MG63 osteoblast cells to compare biocompatibility of Biodentine™ to MTA. Zhou et al. (55) and Corral Nuñez et al. (53) use human gingival fibroblasts to compare cytotoxicity of Biodentine™, MTA and GIC. Zanini et al. (52) investigate immortalized murine pulp cell differentiation under effect of Biodentine™ and MTA. Perard et al. have published two papers (56), (57), both investigating biocompatibility on fibroblast and osteoblast cells, but not in the traditional two dimensional 2D monolayer study model. Instead they use a 3D spheroid study model aiming to reproduce in vivo pulp tissue and to compare Biodentine™ to Ca(OH)$_2$ (56) and to MTA. (57)

The authors, based on the outcomes of these different tests, conclude unanimously in their articles that when investigating the effects of Biodentine™ there is absence of cytotoxicity, genotoxicity or affection of normal cell functioning (differentiation, protein expression or mineralisation in the form of mineral foci) (1), (52), (53), (54), (55), (56), (57). Both in direct and indirect contact with the cells, the results show no significant difference (1). The attachment of the cells in the material is uniform, the cells show the typical morphology and build sufficient contacts between them (52), (53), (54), (55). The effect of Biodentine™ diminishes in the inner layers of the spheroid, probably due to a decline in concentration. A similar case is likely to be manifested in pulp tissue. The upper cell layer acts like a barrier to protect the underlying ones. Lower levels of cytotoxicity as a result of this phenomenon can explain the clinical positive outcomes of Ca(OH)$_2$ and MTA. (56), (57) The authors confirm no significant difference in results between Biodentine™ and MTA (1), (52), (53), (54), (55), (56), (57). Ca(OH)$_2$ results are slightly more cytotoxic (1), while GIC results show significantly more cytotoxic effects and poor attachment, spread, and cell-to-cell and cell-to-material contact when compared to Biodentine™ and MTA (53), (55).

These outcomes are crucial for several reasons. Firstly, they confirm once again the acknowledged biocompatibility of MTA, and its slightly increased efficiency compared to Dycal (from cytotoxic tests (1)). Secondly, they grant the same rate of biocompatibility for Biodentine™, which besides the same Ca$_3$Si as the main component contains also additives such as: CaCO$_3$, CaCl$_2$ and hydrosoluble polymer. These additives, according to the analysis in paragraph 4.2, enhance the physical and mechanical properties, while biocompatibility remains unaffected. Direct and indirect contact test results demonstrate that Biodentine™ can
be used without preliminary conditioning of the cavity. It promotes tissue vitality whenever exposed to vital cells, without difference among pulpal, periodontal or osseous types. This attribute is of essential importance when a material has to be used in vital pulp and periapical therapy. (1)

B. Bioactivity

Resumed from literature (25), a bioactive material is one that induces a specific biological response at the interface of the material, leading to a bond formation between the tissue and the material. In order to make a connection with bone-like tissues a material should be able to produce HA crystals. It is proved that HA crystals induce in vivo and in vitro cell adhesion and differentiation, as well as bone-like tissue formation at the bone-material interface.

Another indicator of a material’s bioactivity is the leaching and incorporation of different elements from the material into the adjacent bone-like tissue. Besides of calcium (Ca) and HA, silicon (Si) is also acknowledged as essential in young bone calcification. Its release in solution can stimulate osteoblast cells to produce bone. (25)

Human dentine contains 70% mineral material, 20% organic material, 10% water. Mineral material, mainly composed of HA crystals, gives strength to dentine. The organic material mainly composed of type I collagen fibrils, gives toughness and flexibility to dentine. (37), (58)

There are many articles concerning bioactivity found in the literature. These confirm that when Biodentine™ is immersed in phosphate solutions, HBSS, it shows not only formation, but also leaching of Ca(OH)₂ and HA formation on cements’ surface (30),(49), already mentioned in the paragraphs 4.1.B (21),(35) and in the paragraph 4.2 (27),(30). Furthermore, studies demonstrate that Ca and Si ions leached from Biodentine™ integrate in the dentine interfacing Biodentine™ (25), (59), (49).

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13 characterisation of the set material
14 studying of solubility, alkalinity and leaching of Ca in solution
What happens when Biodentine™ comes in contact with dentine

During the powder-to-liquid hydration process, the cement reaches a flowable consistency. This consistency plus the fine size of Ca3Si particles produced by the “Active Biosilicate Technology™” and the wetting ability of the hydrosoluble polymer, help the cement paste penetrate through dentinal tubules when in contact with dentine (as shown in Figure 2) loading them with Ca and Si ions. During the setting process, the crystallisation growth occurs within the tubules, participating in this way in the micro-mechanical anchor (otherwise “Tag”) formation. This micro-mechanical anchor is decisive in the mechanical properties of the interface Biodentine™-dentine (sealing and push-out bond strength as already mentioned in 4.2), (25), (59), (60)

Besides this tubular diffusion of Biodentine™, reported by Han and Okiji (59), Atmeh et al. (60) demonstrate that the ion exchange process, initiated by Biodentine™, also happens in the intertubular dentine. Ca(OH)₂ is a by-product of the chemical setting reaction of Biodentine™ and is proved to be leached in the surrounding environment. (21), (27), (30), (35), (49) This Ca(OH)₂ dissolves in Ca and OH ions. The OH ions, measured in proportion to an increase in pH, are highly reactive and cause an alkaline caustic effect, or otherwise “caustic etching”, in the surrounding environment. When OH ions come in contact with dentine, the collagenous component of the intertubular dentine degrades. OH ions leave virtually intact only the highly mineralized, low organic composed peritubular dentine. The collagen degradation of
the intertubular dentine causes the formation of a porous structure. High concentrations of Ca, Si, OH, and CO$_3$ ions penetrate this way not only in the tubular dentine, but also in the porous structure in the intertubular dentine leading this way to an increased mineralisation of the dentine facing Biodentine™, called “Mineral Infiltration Zone” (MIZ). MIZ is confirmed in SEM micrographs showed in Figure 3, above the dotted line, as a band of structurally altered dentine along the interface with Biodentine™.

As illustrated in the Figure 3, mineral transfer peak is gradual near the interfacial zone, but then drops abruptly in a deeper level. Atmeh et al. explain this limited penetration in the pulp direction due to the production of CaCO$_3$ crystal nuclei (as shown in Figure 1, paragraph 4.1B), which act as a diffusion barrier. (60)

The concentration and depth of Ca and Si ions uptake in root canal dentine from Biodentine™ and MTA are measured and compared when immersed in distilled water. Results demonstrate that both these parameters are significantly higher for Biodentine™ than MTA at all time-points, suggesting different levels of bioactivity. The values both increase with the aging of the materials. (49)

\[
\text{(Ca amount): } 24 \pm 5.28 / 34 \pm 3.44 / 27.6 \pm 1.66 / 14.7 \pm 2.01 \text{ mg/l at time 5/ 5–24/ 24–48/ 144–168 hours/ Ca depth}: 39\pm 8.2 / 74\pm 18.8 / 118\pm 11.5 / 166\pm 22.5 \mu m \text{ after 1, 7, 30 and 90 days}
\]
\[
\text{Si depth}: 32 \pm 14.8 / 46 \pm 12.9 / 86 \pm 9.6 / 130 \pm 12.7 \mu m \text{ after 1/ 7/ 30 / 90 days}
\]
These results can explain the tighter interfacial seal with less microleakage found in the study of Kokate et al. (42), higher push out bond strength in the study of Aggarwal et al. (33), and the difference in adhesion failure- cohesive type for Biodentine™ and adhesive type for MTA (46).

As stated in the brief review about Ca(OH)$_2$, in paragraph 1.1, the extended exposure of dentine to Ca(OH)$_2$ shows adverse effects: 32% diminished dentine fracture resistance. (9), (11) Biodentine™ releases Ca(OH)$_2$, therefore it is equivalently important to evaluate the effect of prolonged contact of Biodentine™ on dentine flexural properties and collagen integrity.

Following studies found in the literature (37), (58), Biodentine™ decreases the \textit{modulus of toughness} \textsuperscript{15} (MOT), and the \textit{flexural strength} \textsuperscript{16} of dentine after 3 months of aging.

\textsuperscript{15} the energy absorbed form material without fracturing
\textsuperscript{16} the ability to resist deformation under load
Respectively measured as 37.3% and 17.6% reduction, these values are not significantly different from the respectively MTA values: 22.3% and 14.0%. The cause is dentine collagen integrity impairment. Quantifying the affected collagen through transmission electron microscopy, Sawyer et al. (37) and Leiendecker et al. (58) confirm that only the superficial collagen degrades when exposed to Biodentine™ or MTA. This phenomenon happens only superficially because of a diffusion gradient between the autochthonous HA and OH molecules of the dentine and those coming from Biodentine™ or MTA. The diffusion gradient impedes further penetration of OH ions, protecting the subsurface collagen fibrils. This explains the small amount of impaired collagen fibrils compared to the unaffected part. (58) Authors of these two articles (37), (58), suggest that the impairment of fracture resistance can be more jeopardising when Biodentine™ or MTA are used in full length filling of the canals and in immature teeth with very thin dentinal walls. This effect is negligible when these materials are used as apical plug, or in thin layers for pulp capping.

Additionally, leaching of trace elements: chromium (Cr), arsenic (As) and lead (Pb) from Biodentine™ and MTA are also investigated. (50) Following the ISO recommendations, samples of both materials are immersed in two different solutions, 16 hours in hydrochloric acid (HCl), 28 days in physiologic solution. Results from acid extracting solution (HCl) for Biodentine™ and MTA indicate respectively $Cr$: 4.5 and 6.25 mg/kg, $As$: 52.25 and 35 mg/kg, $Pb$: 14.5 and 0.03 mg/kg. When stored in physiologic solution the values are as follows: $Cr$: 0.06 mg/kg for both, $As$: 0.19 and 0.22 mg/kg, $Pb$: 0.17 and 0.10 mg/kg. According to the authors the leaching in physiologic solution is negligible. Although the amount of leached As in HCl is slightly above the recommendations of ISO, Biodentine™ is still considered as safe for usage.

- What happens when Biodentine™ comes in contact with vital tissue

In the previous section 4.3A when discussing Biocompatibility of Biodentine™, numerous articles confirm absence of genotoxicity, cytotoxicity and normal functioning of cells, direct or indirect in contact with Biodentine™. (1),(52),(53),(54),(55),(56),(57)

- In vitro

In this section, the focus is the interaction of Biodentine™ and its ability to induce biomineralisation when in contact with target cells. Several studies have investigated how the material precisely interacts with the injured pulp tissue, how it triggers the initiation of wound
healing process and mineralised barrier to protect the underlying pulp. (52),(61),(62) Laurent et al. (61), observing human pulp cells, sustain that in order to initiate biomineralisation, a biomaterial should stimulate the release of Transforming Growth Factor-β1 (TGF-β1) from pulp cells. One of the functions of TGF-β1 is to induce progenitor cell migration, odontoblast-like cells differentiation and biomineralisation. Zanini et al. (52) observing immortalised murine pulp cells, report that the presence of a biomaterial is associated to a down-regulation of the expression of Runx2, responsible for induction of osteoblastic differentiation and an up-regulation of osteocalcin (OC), markers of odontoblastic differentiation. Zanini et al. also distinguish a difference in Alkaline Phosphatase Activity (ALP) and Collagen I expression in different cell differentiation stadia. In an early phase of odontoblasts' differentiation in osteocytes, these two proteins are secreted in lower amounts. In a later phase these proteins start to be synthesised at higher levels, serving as markers of the secretory activity of odontocytes, the fully developed cells. According to Tran et al. (62) when observing mechanically injured rat pulp, a biomaterial should encourage a light inflammatory process and a thin necrotic layer formation as initiators of the healing process. Then, after 2-4 weeks of monitoring, they recognise the presence of polarized morphology odontoblast-like cells, secreting high amounts of DSP and osteonectin. Furthermore, they verify a newly homogenous reparative dentine, with low porosity, no cell inclusion, no interruption from the primary dentine and absence of inflammatory process in the tissue underneath (also sustaining the 3D model study of Perard et al. (56),(57)).

These authors (52),(61),(62) confirm that Biodentine™ indeed proves to be a biologic material. It stimulates TGF-β1 release from human pulp cells, without correlation between the pulp cells exposed to Biodentine™ and the released amount of TGF-β1 (61). It also exhibits a fluctuation of Runx2, OC, ALP and Collagen I expression in the prerequisite way (52). It induces a light superficial inflammatory process, thin necrotic tissue formation, differentiation of odontoblast-like cells and biomineralisation (62). All these mentioned biological effects of Biodentine™ when measured in values, are similar to MTA, slightly higher than Ca(OH)₂, but significantly higher when compared to adhesive composite resins. As mentioned in the beginning of this paragraph (4.3 B) both the Biodentine™ and MTA produce Ca(OH)₂ during setting, but once set, the release of Ca(OH)₂ decreases with aging. (52),(61),(62)
Bioactivity is tested on iatrogenically exposed pulps from caries-free human teeth scheduled for orthodontic extraction in the study of Nowicka et al. (51). It is an *in vivo* evaluation of the clinical, radiographic and histologic response of the pulp-dentin complex after 6 weeks of direct capping with Biodentine™ and MTA. The authors observe null or negligible inflammatory response plus a tubular dentine production and newly differentiated odontoblasts, as a sign of successful wound healing and tertiary dentinogenesis.

Shayegan et al. (63) use *primary pig teeth* to assess the action of Biodentine™ and MTA in both pulpotomy and pulp capping procedures. After 90 days, results demonstrate a normal pulp tissue, free of inflammation, as well as normal calcified hard tissue formation, proving once more both biocompatibility and bioactivity of Biodentine™.

According to the conclusions of these articles (52),(61),(62),(51),(63) Biodentine™ leads to the same biological effects, both *in vitro* and *in vivo*. It can be safely and successfully applied for *vital pulp therapy*, stimulating tertiary dentine production in order to seal pulp against possible microleakage of bacteria and toxins. There is no proven significant difference between the effect of Biodentine™ and MTA. Because MTA is generally well accepted as a biocompatible and bioactive material, this resemblance is of great importance in establishing the indications for Biodentine™.

### 4.4 Indications

According to the extended literature analysis concerning the properties of Biodentine™, besides having Ca3Si as the same main component as MTA, Biodentine™ reveals the same *biocompatibility* (1),(52),(53),(54),(55),(56),(57) and *bioactivity* in contact with dentine (21),(25),(27),(30),(35),(59),(49),(60),(37),(58) and in contact with vital tissue both *in vitro* (52),(61),(62) and *in vivo* (51),(63). Biodentine™ is also shown to possess superior physical and mechanical properties such as: compressive strength and hardness (25),(27),(17),(36) flexural and elastic modulus (27),(37), lower porosity and higher density (21),(40),(41), less microleakage (42), higher push-out bond strength, especially when the smear layer is not removed, not affected by blood contamination and root irrigants (33),(46),(48) and colour
stability (31). For clinical applications, it is also important to mention the faster setting time of 12 minutes compared to 165 min of MTA(25),(27),(33).

These stated characteristics are substantial in specifying what the indications of Biodentine™ can be. Currently, MTA is clinically safe and considered “the material of choice” to be used in vital pulp therapy, repair of perforations and resorptions, apexification and apexogenesis, retrograde root-end filling (15). In the indications listed in the literature for Biodentine™, besides those mentioned for MTA, restoration of lost dentinal tissue is also included, due to same compressive strength, hardness, flexural and elastic modulus to dentine. (25),(27),(37)

Up to March 2014, only one randomised clinical trial can be found concerning usage of Biodentine™ as *restorative and dentine substitute* material, published by Koubi et al. (64). Absence of large numbers of long-term clinical trials may have an effect when concretely evaluating the outcomes of Biodentine™ in human population, in terms of both effectiveness and drawbacks. In this context, the trial of Koubi et al. will be summarised and emphasised later in this paper.

**A. Reviews**

Authors of two literature reviews concerning *vital pulp therapy*, Chen et al. (65) in primary teeth and Bogen et al. (66) in immature permanent teeth sustain that Biodentine™ can be a promising and a material of choice for treatment of young patients’ teeth. Meshack et al.(3) could not find clinical outcomes concerning Biodentine™ used as *root-end filling material*, apart from what the producer has published. Based only on the evaluation of the physical-mechanical and biological properties, they indicate that Biodentine™ can be a possible alternative in the periradicular surgery. The authors of these three reviews conclude in complete agreement that further investigation and long-term clinical studies are indispensable.

**B. Randomised clinical trial**

Koubi et al.17 (64) have performed the first 3-year randomised clinical trial to assess performance and safety of Biodentine™. The article presents the results of 212 adult patients, completely treated and followed-up for 1 year. The study is divided in two sections. The first section evaluates the performance and safety of Biodentine™ when functioning as posterior

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17 Three of the authors of this study do not declare any conflict of interest, four others do.
restorative material. The second one evaluates Biodentine™ when maintained as dentine substitute material and covered by composite material.

After caries excavation, 96 patients have received Biodentine™ restorations and 116 Composite restorations, class I or II cavities, placed by 10 trained clinicians. According to the authors and presented only as an observation, the Biodentine™ group requires more retentive cavities in the cavity preparation phase. During the restoration phase, no cavity pre-treatment is performed, but more matrixes are used in the Biodentine™ group, compared to the composite material group.

After the restorative treatment a radiographic photo is taken and the material performance is evaluated based on product application\(^{18}\) characteristics and restoration properties\(^{19}\). At each follow-up visit, after 15 days, 6, 12, 24 and 36 months a radiographic photo is taken and a clinical examination is performed concerning restoration properties and material safety\(^{20}\). The evaluation is based on a unified set of scores, in order to have a standardised result from each clinician. 0 is considered as the best score. Depending on which variable is being evaluated, then scores range between 1 and 4, indicating a spectrum from: clinically very satisfying, satisfying, acceptable to unacceptable variable.

-> On Day 0, product application and restoration performance of Biodentine™ achieve “satisfactory” results (reported mean scores near 0), with no significant difference compared to the composite group.

-> Used up to 6 months as restorative material, the results are as follows:

- There are significant differences for anatomic form, marginal adaptation and proximal contact. Composite material achieves “satisfying” scores while Biodentine™ achieves “acceptable” scores.
- Both materials score “satisfying” for marginal discoloration and surface roughness.
- Both materials score “excellent” in two parameters: absence of post-operative pain and secondary caries. There is one case of secondary caries presented in Biodentine™ group, due to material loss 2 months before the follow-up.

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\(^{18}\) Consistency, setting time, ease of handling and adhesion to instruments- as mentioned in the article Koubi et al. 2013

\(^{19}\) Anatomic form, marginal adaption, quality of proximal contact, marginal discoloration, surface roughness, secondary decay and post-operative pain - as mentioned in the article Koubi et al. 2013.

\(^{20}\) Based on pain as adverse effect - as mentioned in the article Koubi et al. 2013
In the period between 6 months and 1 year follow-up, some cases of Biodentine™ group (the quantity is not defined) score as:

- “Deficient” due to abrasion, lack of marginal adaptation and proximal contact.
- “Satisfying” in marginal discoloration properties

This is the reason why the authors decide to intervene (composite coverage) in the rest of the Biodentine™ cases in their 6 months follow-up.

The second section of the study is the composite covering treatment of Biodentine™. According to the clinicians, Biodentine™ is easily drilled and left as a thick layer as a dentine substitute for its sealing and biological properties. The enamel portion on top is replaced by composite material using the sandwich technique. This restorative procedure is scored as “very satisfying”.

At follow-up this second treatment is considered as “very satisfying” in all the evaluated variables.

From this study there are in total 8 cases out of 212 presented with adverse effects during follow-up visits. These are described as follows:

- 4 cases in the Composite group: one due to mouth ulcer, probably not because of the material; three cases with pain, in which two cases of post-operative pain that self-resolved after 3 days. One case needed removal of the material and was certainly due to the composite/adhesive system.
- 4 cases in the Biodentine™ group: one case presenting cold sensitivity due to material loss; three cases with pain, in which one due to initial misdiagnosis. The other two cases with pain could not be explained, probably attributed to the material. It is not reported how these patients were concretely relieved from pain.

According to the authors, Biodentine™ can be successfully applied as posterior restorative material up to 6 months. During this period of time pulp conditions can be under constant evaluation. When combined with composite materials, used as dentine substitute material, the authors assume that the restorations may present advantages such as: low risk for secondary caries, a conservative approach to the tooth structure and an increase in the lifespan of the restoration.
C. Case reports

In addition to the clinical trial, there are a few cases reported in journals and several published in the form of “Case Studies Collection” by Septodont. These are all included in Table 5.

Deep caries treatment and indirect pulp capping

Denga (72) reports treating 40 patients (with medical history of general allergy) with deep carious lesions, dividing them in two groups, 19 patients in the control group and 21 in the test group. In each group, 30 mandibular molars are treated by first performing caries lesion excavation. In the control group, Ca(OH)$_2$ is placed as liner near the pulp horn projection. The rest of the cavity is filled with composite material, this all performed in one session. In the test group, Biodentine™ is placed as both dentine and enamel substitute. The Deng study chooses to leave Biodentine™ only as dentine substitute and replace the occlusal part of the restoration after 48 hours, with direct composite restoration. Other authors report isolated clinical cases with deep caries lesions treated using Biodentine™ as a dentine substitute, with or without coverage by a definitive restoration. (67),(68),(69),(70),(71) To cover Biodentine™, in the same visit (71) or after some weeks/months (67),(68),(69),(70), these authors use different types of restorations such as: indirect composite inlay (69), indirect ceramic onlay (70) or direct composite restoration (67),(68),(69),(71).

In general, the tooth sensitivity reported a few days after the treatment with Biodentine™ resolves spontaneously. During the follow-up, as most important, the pulp vitality tests remain always positive. After 1 year of follow-up, performing radiological and calorimetry examination, Deng observes a denser mineralised hard tissue under Biodentine™ than under Ca(OH)$_2$ and composite restoration. At the same time 7 out of 30 cases from the control group present adverse effects such as secondary caries (3 cases), poor marginal adaptation (3 cases) and loss of restoration (1 case). According to all the articles taken into consideration, Biodentine™ can be successfully indicated to all patients with deep caries lesions, even in patients with allergic history. A radiographic photo is recommended after the placement of Biodentine™ in order to examine the restoration.

Direct pulp capping

Direct contact of pulp tissue with the oral cavity requires particular treatment procedures carried out by all the authors when reporting isolated cases (73),(74),(75),(69) or when
reviewing 50 cases together (76). The tooth undergoing pulp capping is judiciously diagnosed, otherwise failures are reported (2cases out of 50). In the pre-treatment examination, the tooth responds positive to cold test and negative to percussion test. The treatment is performed after rubber dam placement to prevent penetration of microorganisms from the oral cavity to the pulp. Clinically, the exposure of the pulp is moderate and easily controllable, resulting in absence of bacteria or bacterial toxins, as demonstrated through microscopic examinations. Haemostasis is achieved, in most cases using natrium hypochlorite (NaOCl), in order to avoid blood clots left behind, which can possibly be contaminated. Meticulous placement of Biodentine™ using pluggers with light pressure is advised. Additionally, during the setting time, neither contact with water must happen nor drilling must be performed, in order to conserve the crystalline structure of Biodentine™. Biodentine™ is covered during the same visit by direct composite restoration (74) or at follow-up either by direct composite restoration (73),(75),(76) or by full metal ceramic crown serving as a core material (69). The one-visit modality of Biodentine™ placement followed by composite coverage aims a more secure sealing of the pulp, a non-dependant treatment from patient’s compliance and less stress for the pulp as it avoids secondary drilling on dentine.(74) There are 2 failures documented in the 50 patients review, only because of patient’s non-compliance. (76) During the follow-up visits, authors report clinically normal teeth, positive results to sensitivity test, negative results on percussion tests and no periapical pathology in radiological examination. According to the authors, Biodentine™ gives predictable results in maintaining pulp vitality, when the diagnosis is correct from the beginning, with no symptoms of pulpitis or percussion sensitivity.

➢ **Pulpotomy**

Pulpotomy with Biodentine™ is reported in primary teeth or mature/immature permanent teeth, after extensive pulp exposure by terminal carious lesion, with or without symptoms of pulpitis, or after traumatic pulp exposure (77),(78),(75). In the case discussed in this study, partial pulpotomy21 is performed on the immature permanent teeth and pulpotomy22 on temporary teeth, both with rotary instrument, carbide or diamond burs, with low or high speed. Haemostasis is obtained with saline solution and a cotton pellet, then the pulp is covered with Biodentine™ and the rest of the cavity is filled with GIC or Biodentine™ as temporary filling.

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21 removing about 2 mm of inflamed pulp tissue
22 leaving only the radicular pulp tissue
During follow-up visits, authors report no post-operative symptoms (even in the pulpitis case reported by Villat et al.) and positive pulp vitality tests. Through radiographic examinations, authors observe dentinal bridge formation and further root maturation for the immature teeth and no periapical pathology for the temporary and the mature teeth. Goupy (78) has placed ceramic onlays (mature permanent tooth) and pedodontics metal cup (temporary tooth) to cover Biodentine™. In general, these cases demonstrate the successful application of Biodentine™ in limited coronal pulpal inflammation both in permanent teeth and primary teeth with at least 2/3 of the root not yet resorbed.

Apexogenesis and apexification

Depending on whether the pulp tissue is vital or necrotic, apexogenesis or apexification is performed in 4 traumatised immature teeth by Cauwels (Dr. University of Ghent) (79). Bronnec (84) reports apexification in two immature maxillary incisors in one patient, one of which due to failure of pulp capping after trauma and the other one due to deficient root canal obturation. After removing the root canal filling from the endodontic treated tooth, Bronnec reports rinsing with NaOCl and shaping the coronal third of both root canals. Cauwels on the other hand, reports only rinsing the necrotic pulp tissue in the canals with NaOCl, without using instruments. Bronnec reports placing Biodentine™ in the same visit, in layers only in the apical third of the root to form more than a 4 mm plug. Cauwels uses instead Ca(OH)₂ to fill the canal for one, two or up to three weeks. In a second visit, after removal of Ca(OH)₂, Biodentine™ is placed in contact with vital tissue to obturate the whole root space.

Bronnec does not provide information about the rest of the treatment, which is, in fact, later treated by another clinician. In contrast, Cauwels reports 6 up to 18 months of follow-up with no periapical pathology on the radiographic photo, no pain and no tooth discoloration. Cauwels observes similar root formation as the contralateral teeth in the apexogenesis cases and tooth discoloration only when MTA is used for apexification of a contralateral tooth.

Pulp chamber floor and lateral root perforations

The prognosis of a tooth is jeopardised when an iatrogenic perforation of pulp floor or root canal happens. Different authors report successful outcomes when using Biodentine™ to repair these perforations. Authors report different treatment

23 only a part of the canal for apexogenesis/ the whole canal for apexification
24 pulp tissue in case of apexogenesis, periodontal tissue in case of apexification
modalities depending on the time, size and position of perforations. When possible, authors choose a complete instrumentation and obturation of the canals before repairing the perforation, in one session.(67),(84),(85) If the perforation is previously made causing attachment and bone loss or if the bleeding control is difficult, an intracanal Ca(OH)₂ medication is placed. In a second visit, the perforation is repaired and then the authors proceed to a conventional root canal treatment.(84),(88) Only Cutts 2013 (86) reports repairing the perforation with Biodentine in the first visit and then performing root canal treatment in the second one. Different restorations are placed on top of Biodentine™ such as: temporary metal cup, GIC covered by direct composite restoration, bonded amalgam core, metal posts with crowns. If follow-up is reported, the teeth appear symptom-free and healing of the bone and periodontal attachment is observed on radiographic examination.

- **Root-end filling material**

Bronnec (84) and Guttierrez (89) report cases of radiologically adequate endodontic treatment or retreatment of the root canal, yet with a persisting periapical lesion. On the other hand, Pawar et al. (80) present the clinical case of a patient with previous history of trauma in the central and lateral maxillary incisors. Clinically, these two teeth demonstrate: fractured, discoloured right central incisor, non-vital central and lateral incisors and not painful soft and fluctuant swelled respective soft tissues. Radiological examination shows a well-defined periapical radiolucency of several centimetres. While Bronnec and Guttierrez opt directly for apicoectomy, Pawar et al. choose for the conventional root canal treatment of both teeth and repetitive Ca(OH)₂ filling of the canals. Observing no regression of the periapical lesion on radiographic photos, Pawar et al. schedule also apicoectomy, after definitive obturating of both canals. In general, authors report elevating a full thickness flap, osteotomy with carbide or diamond bur, curettage of the lesion and 3 mm apicoectomy. Then depending on whether traditional burs or ultrasonic tips are used, a retrograde micro-cavity is opened and 3-6 mm gutta percha is removed. After rinsing and drying, Biodentine™ retrograde filling is placed in the root canal, making sure to surface the root. During follow-ups after 1, 3, 6, 12 and 18 months, radiographic photos show complete bone formation and symptom-less teeth are reported. Biopsy of the enucleated lesion in the Pawar et al. case shows presence of cystic lesion. Usage of Biodentine™ is considered as successful by all these authors. (84),(89),(80)
Internal and external root resorptions

Nikhil et al. (81) report external root resorption induced by trauma in two different sites of a maxillary lateral incisor. The apical resorption site is considered as non-perforating, while the cervical site is considered as perforating the pulp chamber. Roubalikova (67) reports also a perforating external cervical resorption, this time of an ankylosis canine after unsuccessful orthodontic treatment. Nikhil et al. perform an endodontic treatment, irrigating with NaOCl and EDTA assisted by radiographic photos and an apex finder. They leave an impregnated cotton pellet in trichloroacetic acid (TCA) for 2 minutes in the canal against the granulation tissue and then finally obturate the canal with Ca(OH)$_2$. In a second visit Ca(OH)$_2$ is removed using NaOCl and the canal is completely obturated with Biodentine™. Roubalikova reports elevating a muco-periostal flap, placing Biodentine™ in the resorption lacuna (without stating any previous treatment of the lacuna) and then replacing the flap.

Cutts 2013 (75) reports treating a tooth with internal cervical resorption (pink spot) by opening a cavity to reach the lesion, performing pulpotomy, irrigating with NaOCl, rinsing with saline solution and drying. Finally, Cutts places Biodentine™ on top of the radicular pulpa, then covering it with GIC and restoring the rest of the cavity with resin composite material. During the follow-up, tooth vitality tests result positive.

Nikhil et al. report an asymptomatic tooth at recall visit after 7 days and after 15 months, even though Biodentine™ is extruded beyond the apex of the tooth. After 15 months in place, the occlusal part of Biodentine™ is removed and substituted with composite material. In Cone beam computed tomography (CBCT) examination, the images show a full healing of the lesions and trabecular bone formation. Roubalikova reports placing an indirect composite veneer after checking that the resorption is healed and the tooth is symptom-free for 2 months.

Palatogingival groove

Johns et al. (82) report the case of a palatogingival groove in a lateral incisor. The palatogingival groove goes up to the apex of the tooth and therefore causes a 9 mm pocket of this single tooth, resulting in a negative prognosis and needs a complex treatment in order to succeed. The authors report performing the following steps: fixation of the tooth by using wire and composite material, root canal therapy obturated with gutta percha, scaling and root planning. Then apicoectomy and sealing of the groove are both performed using Biodentine™. As last step, the clinicians accomplish bone grafting of the defect, covered by platelet-rich
fibrin membrane. A follow up of 24 months demonstrates a complete sealing of the groove and regeneration of the attachment apparatus. When compared to MTA, according to the authors, Biodentine™ is successfully applied in these complex treatments due to its short setting time, its high mechanical properties, its sealing ability and its pure composition. This can be considered as a new field of indication for Biodentine™.

➢ Peri-Implant bone substitute

Up to date Vayron et al. (83) are the first ones to have officially experimented in laboratory conditions the usage of Biodentine™ as a peri-implant bone substitute material, aiming implant stabilisation. According to the authors, the results are promising. This first experiment can be a milestone for a new indication for Biodentine™.

Table 5- Overview of the documented clinical applications of Biodentine™

Table format adapted from Rajasekharan et al. 2014 (20)

<table>
<thead>
<tr>
<th>Clinical Applications</th>
<th>Type of study</th>
<th>Number of teeth</th>
<th>Follow up (months)</th>
<th>Journal publication</th>
<th>Septodont Case Studies Collection Nr</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I and II posterior restorations</td>
<td>Randomized controlled trial</td>
<td>T96/C116&lt;sup&gt;26&lt;/sup&gt;</td>
<td>36</td>
<td>X</td>
<td></td>
<td>Koubi et al 2013 (64)</td>
</tr>
<tr>
<td>Deep carious lesion &amp; Indirect pulp capping</td>
<td>Case report</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>Roubalikova 2012 (67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case report</td>
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<td>16</td>
<td>3</td>
<td>Spirollari 2012 (68)</td>
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<tr>
<td></td>
<td>Multiple cases report- Allergic Compromised pt</td>
<td>T30/C30&lt;sup&gt;27&lt;/sup&gt;</td>
<td>12</td>
<td>4</td>
<td>Deng 2013 (72)</td>
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<tr>
<td></td>
<td>Case report</td>
<td>3</td>
<td>12</td>
<td>5</td>
<td>Bakopoulou 2013 (69)</td>
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<tr>
<td></td>
<td>Case report</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>Boutsounis 2013 (70)</td>
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<tr>
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<td>Case report</td>
<td>2</td>
<td>24</td>
<td>7</td>
<td>Banerji 2014 (71)</td>
<td></td>
</tr>
<tr>
<td>Direct pulp capping</td>
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<td>1</td>
<td>6</td>
<td>1</td>
<td>Dammanschke 2012 (73)</td>
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<td></td>
<td>Case report</td>
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<td>6</td>
<td>2</td>
<td>Dammanschke 2012 (74)</td>
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<td></td>
<td>Multiple cases report</td>
<td>50&lt;sup&gt;28&lt;/sup&gt;</td>
<td>24</td>
<td>3</td>
<td>Levin 2012 (76)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>25</sup> Obtained by 10 minutes centrifuged 12ml of the patient’s blood.
<sup>26</sup> Test group with 96 patients treated with Biodentine™/ Control group with 116 patients treated with composite.
<sup>27</sup> Test group with 21 patients - 30 teeth treated with Biodentine™/ Control group with 19 patients – 30 teeth treated with composite.
<sup>28</sup> Direct and indirect pulp capping therapy, not specified.
<table>
<thead>
<tr>
<th>Partial pulpotomy</th>
<th>Case report</th>
<th>1</th>
<th>6</th>
<th>X</th>
<th>Bakopoulou 2013 (69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case report</td>
<td>1</td>
<td>6</td>
<td></td>
<td></td>
<td>Cutts 2013 (75)</td>
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<tr>
<td>Case report</td>
<td>1</td>
<td>6</td>
<td></td>
<td>1</td>
<td>Goupy 2012 (78)</td>
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<tr>
<td>Case report</td>
<td>1</td>
<td></td>
<td>5</td>
<td></td>
<td>Cutts 2013 (75)</td>
</tr>
<tr>
<td>Pulpotomy</td>
<td>Case report-</td>
<td>1</td>
<td>6</td>
<td></td>
<td>Goupy 2012 (78)</td>
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<td>primary tooth</td>
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<tr>
<td>Apexogenesis</td>
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<td>Cauwels 2013 (79)</td>
</tr>
<tr>
<td>Pulp chamber floor perforation</td>
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<td>2</td>
<td>3</td>
<td></td>
<td>Bronnec 2012 (84)</td>
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<td>Cutts 2012 (85)</td>
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<td>Lorenzo 2014 (88)</td>
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<tr>
<td>Lateral root perforation</td>
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<td>Roubalikova 2012 (67)</td>
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<td>Root end filling</td>
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<td>X</td>
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<td>Cystic lesion</td>
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<td></td>
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<td>Bronnec 2012 (84)</td>
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<td>Guttierrez 2013 (89)</td>
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<tr>
<td>Apical external root resorption</td>
<td>Case report</td>
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<td>15</td>
<td>X</td>
<td>Nikhil 2012 (81)</td>
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<tr>
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<td>15</td>
<td>X</td>
<td>Nikhil 2012 (81)</td>
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<td>Cutts 2013 (75)</td>
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<td>Palatogingival groove</td>
<td>Case report</td>
<td>1</td>
<td>24</td>
<td>X</td>
<td>Johns et al. 2014 (82)</td>
</tr>
</tbody>
</table>


5. Discussion and conclusion

Biodentine™ (Septodont, Saint Maur des Faussés, France) was introduced onto the market approved by FDA on 2009\textsuperscript{29} as dentine substitute and pulp-dentin complex regenerating material. (19) Substantially, it consists of Ca3Si, also the main component of MTA. The high number of studies that compare Biodentine™ to MTA suggests that the main concern of researchers in this field is whether this novel material can behave similarly and in the best scenario, overcome the drawbacks of MTA. Because of MTA’s wider use and longer time on the market, since the 90-ies, more studies are carried out on its functionality, many of them confirming its high bioactivity and biocompatibility (14),(15). Hence, MTA is easily used as a relative measurement unit for the evaluation of the features of Biodentine™.

The biological properties of Biodentine™ are mostly attributed to Ca3Si, its main component. Ca3Si, being the same in both MTA and Biodentine™, shows, in fact, similar levels of bioactivity and biocompatibility. Biodentine™ is demonstrated to be biocompatible by inducing no cytotoxicity, no genotoxicity, leading to differentiation, biomineralisation and protein expression, stimulating a satisfactory attachment of normal functioning cells, no matter in direct or indirect contact.\textsuperscript{(1),(52),(53),(54),(55),(56),(57)} Due to its bioactivity, Biodentine™ induces creation of MIZ (21),(25),(27),(30),(35),(59),(49),(60),(37), (58), with infiltration of more Ca and Si ions compared to MTA \textsuperscript{(49)} and creating this way a denser zone in the interfacing dentine, leading to less microleakage (42) and higher push-out bond strength (33). Bioactivity of Biodentine™ is also proved by the increased expression\textsuperscript{30} of specific genes (52),(61) and its induction of light inflammatory process that acts as a trigger for wound healing (62). Both \textit{in vitro} (52),(61),(62) and \textit{in vivo} (51),(63) observations have demonstrated normal cells and homogenous hard tissue formation under the material. In unison, these authors conclude that Biodentine™ does promote tissue vitality. It is a remarkable property when a material has to be applied in vital pulp therapies such as direct and indirect pulp capping, pulpotomy and apexogenesis, as well as in apexitification and retrograde root-end filling and perforations context.

\textsuperscript{29} http://www.accessdata.fda.gov/cdrh_docs/pdf9/K092251.pdf
\textsuperscript{30} such as TGF-β1, Runx2 and OC
However, Ca3Si when used alone, in the form of pure TCS, demonstrates several drawbacks such as long setting time (180min), low mechanical properties (25),(21),(26), no radiopacity (24), which are not satisfactory for the clinician. These facts explain why in this literature review, the table of contents of Biodentine™ requires much attention. The additive components, CaCO₃, CaCl₂ and the hydrosoluble polymer, are equally important in determining the properties of Biodentine™. When added together, they have a synergetic effect.(21),(27) They accelerate the setting reaction up to 12 minutes. (25),(27),(30),(33) By decreasing the water/cement ratio (21),(27) and porosity (21),(26),(41) of Biodentine™ they enhance the compressive strength and hardness (25),(27),(17),(33),(36), but do not affect workability (21),(27),(33) ensure good wetting of dentine resulting in tight sealing ability. They influence positively in the creating of a biomimetic environment for vital cells (23),(26).

Biodentine™ is produced according to a new technology called “Active Biosilicate Technology” (19), also leading to enhanced mechanical and physical properties (21), when compared to MTA (17),(36). Biodentine™ proves to have compressive strength and micro-hardness (25),(27),(17),(36), flexural and elastic modulus superior to MTA (25),(27), (37), comparable to human bone and dentine and significantly lower than enamel (19),(90). Based on these results and the clinical proved sensitivity to abrasion (64), Biodentine™ is indicated as a permanent dentine and temporary enamel replacing material.

Biodentine™ absorbs moderate quantities of fluid, has a negative solubility (27), alkaline pH (30),(39), adequate radiopacity (27),(21), low porosity (40),(21),(41), tighter interfacial seal (42) and higher bond strength, not affected by blood contamination or root irrigants, (33),(46),(48) when compared to MTA. According to researchers, possessing these mentioned characteristics, plus the same biocompatibility and bioactivity as MTA and additionally the short setting time, Biodentine™ can be applied safely and successfully in permanent contact with periradicular fluids in the context of root-end filling, apexification and perforation treatments.

Given its colour stability and no documented tooth discoloration (31), clinicians can use Biodentine™ in both posterior and anterior tooth treatment. A new field of research is the application of Biodentine™ as bone substitute around implants, triggered by its mechanical properties comparable to osseous tissue. Up to now, only one experimental research is documented, reporting promising results. (83)
The current published applications of Biodentine™, reported in paragraph 4.4 and configured in Table 5, outline a wide field of possible implementations of Biodentine™, in root and crown. The successful clinical outcomes reported corroborate the positive findings of researchers when investigating the properties of Biodentine™. In the conclusion of several of these case reports, the authors express their opinion based on their personal experience (72),(76),(77),(78),(67),(80),(81),(82) (by other authors also mentioned). They admit having previously used other materials, such as Ca(OH)2 or MTA, but they consider Biodentine™ as user-friendlier and clinically superior because of the higher mechanical properties, shorter setting time and no tooth discoloration. Surprisingly, these authors do not mention either the cost price of Biodentine™ or a comparison to the cost of conventional materials or a possible financial influence on treatment modalities. Consequently, it cannot be further discussed about this topic.

After all, this review cannot be concluded without discussing the potential limitations of Biodentine™. Despite being thoroughly discussed or implied, some of the limitations can be deduced based on the literature review concerning the properties of Biodentine™ as well as on the clinical experience of the randomised clinical trial and the reported clinical cases.

- In general authors mention that during handling procedures they follow the producer’s instructions. However, in the clinical trial, there are trained clinicians who place Biodentine™ (64). It is not clear whether every clinician can easily perform the material handling or if it seeks any additional training. Admittedly, it is reported that the handling of Biodentine™ follows a learning curve and besides the instructions of the producer, some advises are given by different authors. (76)

- The reported need for more matrix placement for Biodentine™, when compared to composite, can be time-consuming. However, one of the main challenges is establishing whether Biodentine™ is biologically threatening for the tooth structure, as the clinicians observe that Biodentine™ requires a more retentive form of cavity when used as a restorative material. However, this fact is only reported as an observation, without further explanation. (64)

- Biodentine™ is reported to give satisfactory results as restorative material up to 6 months. At the same time clinicians attest considerable amount of abrasion (25%) before the 6-month-period. In case of Biodentine™ restoration loss, the emergence of secondary caries...
and cold sensitivity is inevitable (64), (76) As a result, the need to intervene earlier than 6 months cannot be excluded.

- It becomes apparent that Biodentine™ promotes tissue vitality if contact with vital tissue is provided. Biodentine™ is successfully implemented when the diagnose is correct (pulpitis or not, inflamed necrotic tissue or not) and the treatment accurately designated and performed, as in the reported cases of deep caries (72), pulp capping (76), pulpotomy (77),(78), apexogenesis and apexification (79). Nevertheless, there are failures mentioned, possibly because of misdiagnosing. (64), (76) It is not sure whether it is due to the inability or the clinician’s deliberate decision to give the pulp a chance to recuperate.

- There is no information provided by the authors of the clinical trial regarding the solution for the adverse results in the Biodentine™ group (64). For Levin (76) root canal treatment is the option. Intervening in the failure cases and switching from vital pulp therapy to root canal treatment can be an achievable solution.

- What happens in cases of apexogenesis, apexification, retrograde root-end filling treatments, if failures and misdiagnoses occur and Biodentine™ comes in contact with non-vital tissue? There is no such failure mentioned in the literature yet. However, once Biodentine™ is placed in the root canal, there is no product or method mentioned in the literature to remove it. It becomes then obvious why the authors (79),(80),(81) use in such cases Ca(OH)₂ as an inter-appointment canal dressing material, prior to the Biodentine™ application. Ca(OH)₂ is proved in any case a successful short-term intracanal dressing material because of its high antibacterial effect (12) even when in contact with inflammatory and necrotic tissue. As reported, the routinely used endodontic irrigant NaOCl can remove Ca(OH)₂. (79),(80),(81)

- In an acidic inflammatory environment the level of As leaching from Biodentine™ immersed in HCl is reported as increased, exceeding the ISO recommended levels. Nevertheless, the material is considered as safe. (50)

- The impairment of collagen fibrils in the interfacing dentine, by the caustic effect of Biodentine™ is considered as superficial. Regardless of that, the authors advise the clinicians to reconsider the application of Biodentine™ in cases of immature permanent teeth with thin dentinal walls and the obturation of the whole canal with Biodentine™. (37),(58) However, authors report no adverse effect obturating with Biodentine™ the
whole canal in immature teeth by Cauwels (79) and external resorbed teeth by Nikhil et al. (81) after respectively 18 and 15 months of follow-up.

- According to literature (36),(45), researchers advice postponing the acid-etching of Biodentine™ 24 hours up to 1 week after setting, in order to not affect the compressive strength of Biodentine™ and establish a higher interfacial bond with the composite restoration. Furthermore, the 2 step self-etch adhesive system is highly recommended. These facts may be restrictive for the treatment modality. On the other hand, authors of case reports aim with the one-visit modality of Biodentine™ placement followed by composite coverage a more secure sealing of the pulp, less stress for the pulp as a secondary drilling on dentine is avoided and a non-dependant treatment from patient’s compliance. (74),(76)

This literature review has encountered limitations on its journey. There is a lack of long-term clinical studies on Biodentine™. This restricts and concentrates the discussion mainly to its properties. It becomes an issue when reviewing the possible indications. It must be mentioned that some of the authors of the randomised clinical trial admit having conflict of interest with Septodont.(64) When concretely discussing this article and the possible limitations of Biodentine™, many found facts are only stated with no further explanation or investigation by the authors (such as the two unexplained failures, the higher number of matrixes needed and the requirement of more retentive cavity form in the Biodentine™ group). In the majority of the publications and the "Septodont Case Studies Collections" only isolated clinical cases are presented, most of which have obtained successful end results. Given these facts, when considering possible failures and adverse effects, few possible alternatives and solutions can be provided. When specifically evaluating the outcomes of Biodentine™ in human population in terms of effectiveness and drawbacks, no long-term conclusions can be drawn. All the authors unanimously conclude that further long-term investigations in different fields of applications should be carried out.

In conclusion, it is the goal of this literature review to introduce to the clinician an evidence-based information related to Biodentine™. It is a material that demonstrates biological properties similar to MTA, but with a much shorter setting time, higher mechanical properties and ease of handling. Biodentine™ proves to be a promising material, with successful outcomes documented in the clinical trial and case reports, giving a positive answer to the
PICO question posed when using Biodentine™. However, more studies are expected to be published in the future. Until more information is provided, it is advised to the clinician to diagnose careful each case before applying Biodentine™.

6. Bibliography


86. Cutts G. Repair of perforation of the floor of the pulp chamber with BiodentineTM. Septodont Case studies Collection Nr 4. March 2013:14-5.


7. Appendix

❖ Source Indications for figures

Figure 1 – Camilleri et al 2013 - with approved permission from the authors

“Investigation of Biodentine as dentine replacement material” (35)

Figure 2 – Goldberg et al 2009 - no available contact found to ask permission

“Emerging trends in Biomaterials”. (25)

Figure 3 – Atmeh et al 2012 - with approved permission from the authors

“Dentin-cement interfacial interaction: calcium silicates and polyalkenoates.” (60)