NEW

Your NEW dentin restoration system

Biodentine® XP

Scientific File

septodont

Agenda

01 What is Biodentine® XP

Since its launch 10 years ago, Biodentine®, based on Septodont's innovative **Active Biosilicate Technology™ platform**, has proven multiple successes and clinical benefits offering **bioactivity** and **outstanding sealing properties** to fully replace dentin, both in the crown and in the root.

Thanks to its unique features, Biodentine® has become a reference for **minimally invasive dentistry** to preserve tooth structure.

Today, Septodont introduces a new version of Biodentine®, **Biodentine® XP, a new system with an all-in-one cartridge, offering direct placement in the tooth** to facilitate practitioners' daily procedures.

Biodentine® XP, it's all Biodentine's science embedded in a new and upgraded system, designed to provide practitioners with an optimal daily experience, from product preparation to direct placement in the tooth.

02 Active BioSilicate Technology™ (ABS)

With over 15 years of research, the Active BioSilicate Technology™ from Septodont has provided safe and effective clinical solutions for the dental profession. The ABS Technology is a proprietary technology developed in a state-of-the-art pharmaceutical manufacturing environment applied to the highly biocompatible ceramic mineral chemistry. Septodont controls every step of the chemical process starting with highly pure in-coming raw materials, in order to ensure the absence of any aluminate and calcium sulfate in the final product.

The calcium silicate has the ability to interact with water leading to the setting and hardening of the material. This hydration of the tricalcium silicate (3CaO.SiO2 = C3S) produces a hydrated calcium silicate gel (CSH gel) and calcium hydroxide (Ca (OH)2), as presented hereafter.

$$2(3CaO,SiO_2) + 6H_2O \rightarrow 3CaO,2SiO_2,3H_2O+3Ca(OH)_2$$

Equation 1: Hydration reaction of tricalcium silicate with water

This hydration reaction is initiated by the physiological humidity of the root canal. It is reflected in two phenomena:

- A dissolution occurs at the surface of each grain of calcium silicate due to the solubility of this component. It releases calcium and silicate ions until the supersaturation of the medium.

- The hydrated calcium silicate gel (less soluble) tends to precipitate at the surface of each grain of calcium silicate leading to the formation of the hardened cement.

The technological challenge was to utilize calcium silicate to create a formulation with good clinical practices in both restorative and endodontic procedures. Active BioSilicate Technology™ was built on the experience from Biodentine® which possesses more than 1000 international peer-reviewed publications demonstrating the physical, biological, and clinical benefits of the ABS technology.

As Biodentine®, Biodentine® XP is now being released to the dental market with outstanding physico-chemical and biological properties demonstrating use as a bioactive dentin substitute.

03 Biodentine® XP an upgraded system

3.1 From a capsule to a cartridge

Through a continuous improvement process to evaluate user satisfaction, several studies were performed in different countries. For a significant portion of users who answered this survey, the two following improvements were suggested:

- Adaptation of the powder capsule + liquid dispensing system for an easier reproducibility of liquid dispensing leading to a better reproducibility of reconstituted product (material consistency);
- Adaptation of the system to ease the onsite application of the product as a combined mixing/delivery system.

Thus, the design objective of Biodentine® XP was to develop an all-in-one cartridge containing the powder and the liquid parts of Biodentine® in order to simplify the use of this medical device, to improve the reproducibility of the material consistency and to allow onsite product delivery. But without changing any clinical properties of Biodentine®: that's why Biodentine® and Biodentine® XP have the same composition, the same formula.

Therefore, the Biodentine® XP cartridge is composed of two compartments allowing automatic contact between the liquid and the powder, ensuring the delivery of the right amount of powder and liquid.

In order to be adequate for multiple applications, the product comes in two cartridges sizes: Biodentine® XP500 cartridges and Biodentine® XP200 cartridges for the extraction of approximately 500 mg of material and the XP200 cartridge for the extraction of approximately 200 mg. The choice of the cartridge will be determined according to the amount of material required for the treatment.

Figure 1: *Biodentine® XP500 (left) and Biodentine® XP200 (right)*

3.2 A tailor-made mixer

A specially-designed mixer holds the Biodentine® XP cartridge for mixing the powder and the liquid components. The mixer is designed with a high rotation level (6200 rpm) to ensure a perfect consistency.
During the mixing, the cartridge will follow a sinusoidal movement with a lateral amplitude about 2.5mm and a vertical amplitude about 17mm.
The mixing speed increases progressively to reach the maximum speed, about 10,000 osc/mn, after 5 seconds from the beginning of mixing with a frequency band of 90Hz.
This mixer includes a timer preset at the defined mixing time of the product for better convenience of use and to ensure the right consistency of the product. The mixer has a limited footprint thanks to its vertical design.

***Figure 2**: Biodentine® Mixer*

3.3 A dedicated gun

The Biodentine Gun has been designed to allow the practitionner to place directly Biodentine® in the tooth. The Gun fit with the specific Biodentine® cartridges (Biodentine® XP 500 and Biodentine® XP 200) in order to extrude easily dentin substitute material. A locking mechanism was designed to securely assemble Biodentine® XP cartridge's wings in the Biodentine® Gun's cartridge holder. After a quarterly clockwise turn, the cartridge is locked in the cartridge holder. A priming step has to be performed to ensure the proper placement of the cartridge and then by pushing down the lever of Biodentine® Gun, the dentin substitute is extruded directly in the dental cavity. Also, with a manually bendable cartridge nozzle, it is easier to deliver precisely the product *in-situ*.

***Figure 3**: Biodentine® Gun*

Working time

In accordance with the conditions of use of the medical device (i.e. potential cement preparation on a glass plate or by direct introduction), the working time is monitored after extraction of Biodentine® XP500 cement and Biodentine® XP200 cement. The time lapse between the end of mixing and the end of workability of the material is recorded as the working time. Overall, the working time of Biodentine® XP is demonstrated to be ≥ 1 min.

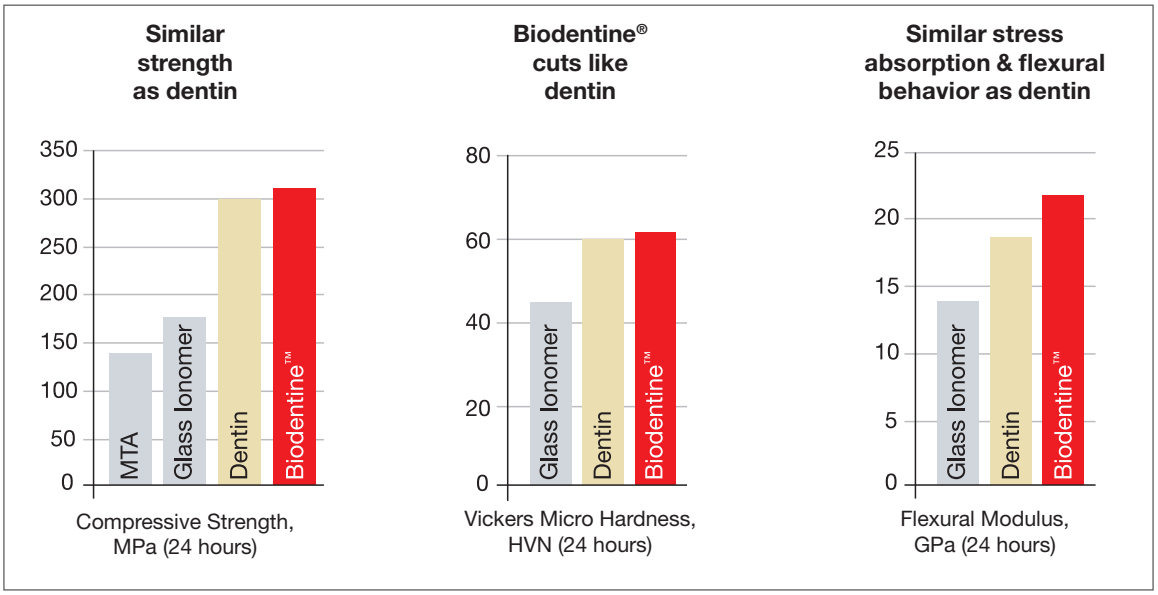
Setting time

The setting time of Biodentine® XP was defined to be suitable for the product uses: not too long for optimal use in the crown and not too short for root applications.
The setting time was evaluated with the following method: The material is dispensed into a stainless-steel ring mold that has been placed on a glass sheet. The specimen is placed into a water bath at 37°C. The initial setting time is checked with a 100g Gillmore needle and the final setting time with a 400g Gillmore needle.
By retrieving these results with others from internal tests and literature data on Biodentine® (Dawood et al. 2015; Jang et al. 2014), the setting time of Biodentine® XP is stated to range from 9 to 25 minutes.

04 Biodentine® XP: properties

4.1. Dentin like properties

Biodentine® XP is intended to replace the dentin. Therefore, the product should have similar properties to the dentin.



4.2. Compressive strength

Compressive strength is a classical mechanical evaluation of dental biomaterials (ISO 9917-1:2007), as these kind of products should resist external impact of mastication forces.

The compressive strength of Biodentine® XP was evaluated with the following method: The material is dispensed in a mold of 4 mm height and 4 mm diameter. Specimens are placed in a water bath at 37°C during 20 min to set. Then they are unmolded, placed in a test tube with water, and left in the water bath prior to be tested. Measurement is performed using a MTS testing machine.

Table 1: Biodentine® XP500, Biodentine® XP200 and Biodentine® compressive strength at 24h (n=6)

Material	Mean compressive strength at 24h (MPa)	Dentin compressive strength (MPa)
Biodentine® XP500	217	[230 – 300]
Biodentine® XP200	231	
Biodentine®	220	

Table 2: Biodentine® XP compressive strength evolution through time (n=6)

Time of setting	Compressive strength of Biodentine® XP (MPa)	Dentin compressive strength (MPa)
24h	197	[230 – 300]
48h	234	
7 days	240	
15 days	233	
28 days	264	

In addition, these results are sustained by the studies on the compressive strength from the literature (Butt et al. 2014; Vaid et al. 2019).
Hence, Biodentine® XP has a compressive strength similar to dentin. Biodentine® XP can thus replace the dentin, both in the crown and in the root, without any preliminary conditioning of mineral tissues.

4.3. Microhardness

Microhardness, plastic behavior on the surface of the material, is the property of the material that provides resistance to being permanently deformed (bent, broken, or have its shape changed), when a load is applied.
The measurement of the microhardness was carried out according to ISO 6507-1:2005. Samples are coated with an epoxy resin (EPOFIX) and polished. A 100g (HV0.1) load is applied for 15 seconds on each sample with the microhardness tester Vickers STRUERS, Duramin-1.

Table 3: Microhardness values of Biodentine® XP500, Biodentine® XP200 and Biodentine® (n=6)

Material	Microhardness (HV0.1)
Biodentine® XP500	82
Biodentine® XP200	73
Biodentine®	92
Dentine	[60 – 90]

Biodentine® XP therefore provides a microhardness similar to dentin.

4.4. Physico-chemical properties

Performance tests have been performed to ensure that Biodentine® XP is suitable for its intended use of "bioactive dentin substitute" allowing preservation of the pulp, preservation of the amelo-dentinal structure, preservation of the root canal structure and root edification and sealing ability create a favorable environment required for pulp stem cells.

4.4.1. Sealing ability

Achieving a hermetic seal by entirely filling the crown or apex of root canal spaces is important for decreasing the risk that microorganisms (oral or periapical fluids) might come in contact with the pulp and to prevent microleakage of microbial irritants into the periapical tissues.
There are no ISO standard methods nor scientific consensus on the approach to demonstrate these properties in vitro. Thus, the following method was used:
The material is dispensed in the cavity of a tooth model, three teeth are filled for the material. Specimens are placed in a water bath at 37°C for 24h and afterwards immerse in a 0.04% solution of blue methylene for 24h. After this treatment, the samples are rinsed with water, dried, and subjected to sectioning using a saw in order to observe the penetration of the solvent in the material.

Two parameters are analyzed in order to make a full interpretation of the sealing properties:
- The thickness of infiltration;
- The length of percolation.

The sealing ability of the material is checked on 3 cartridges by batch. Three samples per material (Biodentine®, Biodentine® XP 200, Biodentine® XP 500) are relevant to determine the material sealing ability and to compare the three materials.

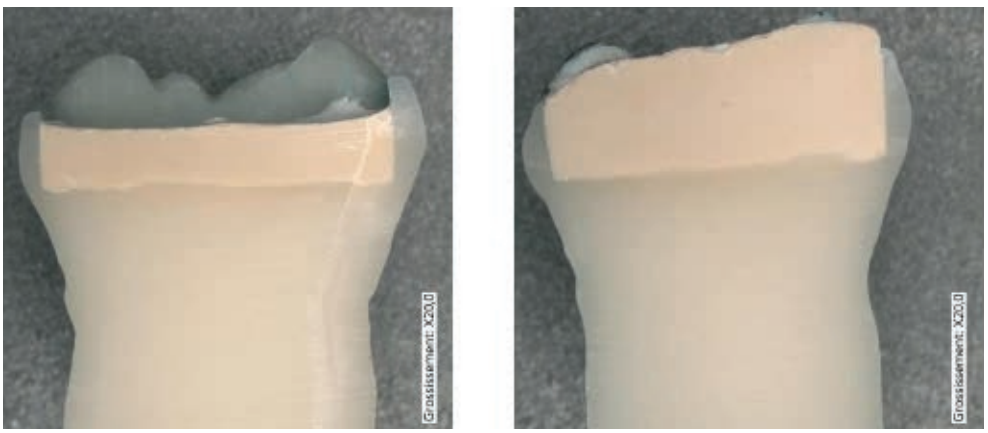


***Figure 4**: Sealing ability test with Biodentine® XP200 (left) and Biodentine® XP500 (right) (n=3).*

After 24h of setting and 24h of immersion in blue methylene, **no infiltration and no percolation** are observed for both cartridges' sizes (XP500 and XP200).
Data from the literature show similar results for the apical sealing ability (Džanković et al. 2020) and the coronary sealing ability (Makhlouf et al. 2020) of Biodentine®.
Biodentine® XP demonstrates good sealing properties and a good adherence to dentin as no percolation is observed with a smooth surface (tooth model in plastic).

4.4.2. Radiopacity

Radiopacity is obtained by adding zirconium oxide in the formula.

When compared to an aluminium step-wedge *(Figure 5)*, the following results are obtained: Biodentine® XP200 and Biodentine® XP500 have both an equivalent radiopacity of 4 mm of Al which is sufficient to differentiate them from the dentin during and after treatment.

By comparing these results with the literature for Biodentine®, a radiopacity of 2 to 4 mm of Al is demonstrated depending on the testing method used (Tanalp et al. 2013; Grech et al. 2013; Camilleri 2015). Thus, Biodentine® XP radiopacity allows good radiographic visualization.

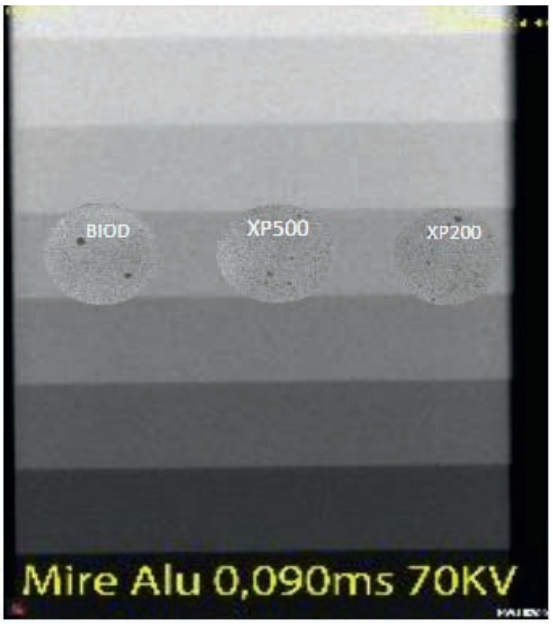


***Figure 5**: Radiopacity of Biodentine®, Biodentine® XP500 and Biodentine® XP200.*

4.4.3. Porosity

Porosity is an intrinsic characteristic of tricalcium silicate-based materials and occurs as a result of the spaces between the unhydrated material grains. The mechanical resistance is also dependant on the level of porosity. The lower the porosity, the higher the mechanical strength.
The porosity has been characterized with the Computer Tomography system Skyscan 1172 from BRUKER. The computed microtomography method is based on X-ray irradiation of a radiopaque sample. The porosity of the materials is measured on 6 cartridges by batch.

Table 6: Porosity values of Biodentine® XP500, Biodentine® XP200 and Biodentine® (n=6)

Material	Total porosity (%)
Biodentine® XP500	9.3
Biodentine® XP200	9.6
Biodentine®	9.1

The results show equivalent porosity between Biodentine® and Biodentine® XP.
In the literature, Biodentine® was studied with porosity values ranking from 4.71% (Guerrero and Berástegui 2018) to 13.44% (Camilleri et al. 2014).
Accordingly, Biodentine® XP has a low porosity, demonstrated to be between 4 - 14 %.

4.4.4. pH

As all calcium silicate-based materials, Biodentine® XP creates an alkaline environment due to the production of hydroxyl ions. This alkalization of the environment is important as it has an antibacterial effect. The production of calcium ions promotes the material's bioactivity.

The following pH values were obtained:

Table 7: pH values of Biodentine® XP500, Biodentine® XP200 and Biodentine® (n=3)

Material	Initial pH	pH at 24h
Biodentine® XP500	11.06	10.28
Biodentine® XP200	10.78	10.73
Biodentine®	11.23	10.17

The pH of Biodentine® XP was measured over 28 days and the following pH profile was obtained:

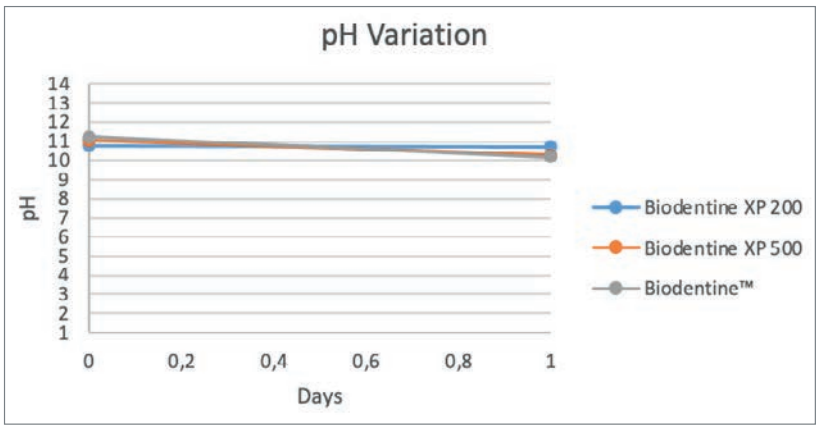


Figure 6: pH variation of Biodentine® XP200, Biodentine® XP500 and Biodentine® over 28 days (n=3)

Based on these results and data from the literature on Biodentine® (Dawood et al. 2015), Biodentine® XP environment alkalization is demonstrated through time.

Conclusion

Biodentine® XP is a bioactive dentin substitute in an all-in-one and easy-to-use cartridge. Biodentine® XP provides high performance and safety profile with an optimized system for a better user experience. Biodentine® XP demonstrated the following performance and benefits:

- Mechanical properties similar to dentin
- Effective sealing ability
- Good dentin adherence
- Alkalization of the environment
- Optimum working time and setting time

4.5. Biodentine® XP a Biocompatible product

Biodentine® & Biodentine® XP are calcium silicate-based materials, used for crown and root dentin repair treatment, involving external contact for a period of more than 30 days. The biocompatibility tests required for the preclinical evaluation of dental products followed the guidelines ISO 10993 & ISO 7405.
The following sections evaluate the compliance with these standards for the tests carried out on Biodentine® which are applicable to Biodentine® XP.
Pr. Imad About concludes in the book "Biodentine, properties and clinical applications" as such:

"Studies performed in vitro, in animals and in clinic concluded that Biodentine® can be applied safely in various restorative and endodontic therapies without compromising the target tissue/cell vitality. Beyond this, it supports the migration of tissue-resident cells such as stem cells or cells of the immune system to the site of injury. As a result, inflammatory changes are resolved, and neoangiogenesis as well as innervation is promoted in both the pulp and the tooth-surrounding tissues. Furthermore, Biodentine® induces osteogenic and odontogenic differentiation and thus lays the foundation for mineralization processes in the bone or the dental pulp, which are prerequisites for healing. Today, tricalcium silicate cements such as ***Biodentine® represents an indispensable therapeutic tool in daily restorative and endodontic practice****"*

4.5.1. Cytotoxicity

Biodentine® is not cytotoxic.
A first study was performed on human pulpal fibroblasts (human wisdom tooth), comparing Biodentine®, calcium hydroxide and MTA (Dycal®, Dentsply and ProRoot® MTA Dentsply). The cell viability was determined by MTT incorporation (About, 2003b). Results showed Biodentine® was non cytotoxic like MTA, whereas the undiluted cement Dycal® induced 22% of cytotoxicity (Table 7).
Moreover, the cell differentiation was evaluated with the expression of collagen, dentin sialoprotein (DSP) and osteonectin (OSN). Results showed the expression of the differentiation markers, underlining the safety of Biodentine® ***(Figure 7)***.

Table 8: Cell death after Dycal®, MTA and Biodentine® contact

Product	Cell Death (%)
Biodentine®	0±8
MTA	0±9
CaOH	22±10

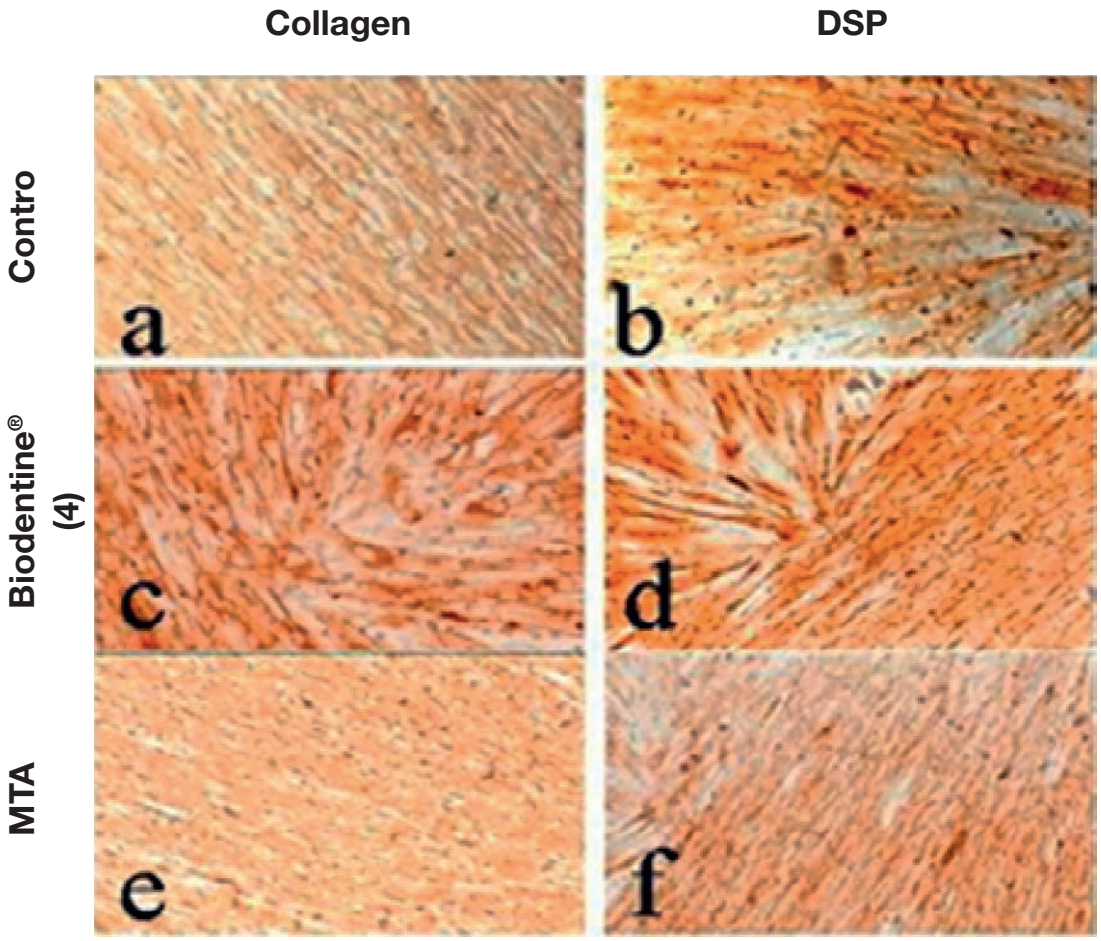


***Figure 7**: Expression of collagen and dentin sialoprotein (DSP) after contact with Biodentine® and MTA during 4 weeks.*

A second study was performed on L929 fibroblasts comparing Biodentine®, composite resin Filtek™ Z250 and MTA (Franquin, 2001). Samples were extracted 3 h, 24 h and 7 days after setting. The cell viability was determined by MTT incorporation. Results showed Biodentine® is not cytotoxic (< 10%) no matter the hardening time considered. Filtek™ Z250 resin is slightly cytotoxic (> 20%) at the 3 observation periods (Table 8).

Table 9: Cell death after Filtek™ Z250, MTA and Biodentine® contact

Product	3 hours	1 day	7 days
Filtek™ Z250	23%	25%	26%
MTA	0%	14%	8%
Biodentine®	2%	10%	9%

A third study was published in "Dental Materials" on the biological effects of Biodentine® (Laurent et al., 2008). They were compared to those induced by the materials used for pulp capping such as MTA and Dycal®. Several tests were carried out:

- A cytotoxicity test involving indirect contact through a section of dentin: none of the tested materials was cytotoxic.

- Where there is no dentin interposition, there is a significant difference in toxicity of the different materials: Biodentine® did not reveal any cytotoxicity although more marked cytotoxicity was reported for Dycal® compared to MTA.

- Differentiation of pulp fibroblasts in orthodontoblastic cells was also analyzed for contact with two materials. Pulp fibroblasts secrete a mineralized matrix and cells in contact express differentiation proteins (nestin and dentin sialoproteins). Once the cells had been in contact with Biodentine® cement or with MTA, marker expression was important in the pulp cells involving the formation of mineral nodules. Immunological marking was in all cases higher in the cells forming mineral nodules.

In 2015, Claudio Poggio et.al performed a comparative study of different pulp capping materials in which cytotoxicity was assessed by Alamar blue test and MTT assay. Biodentine® was the most biocompatible material see ***Figure 8***.

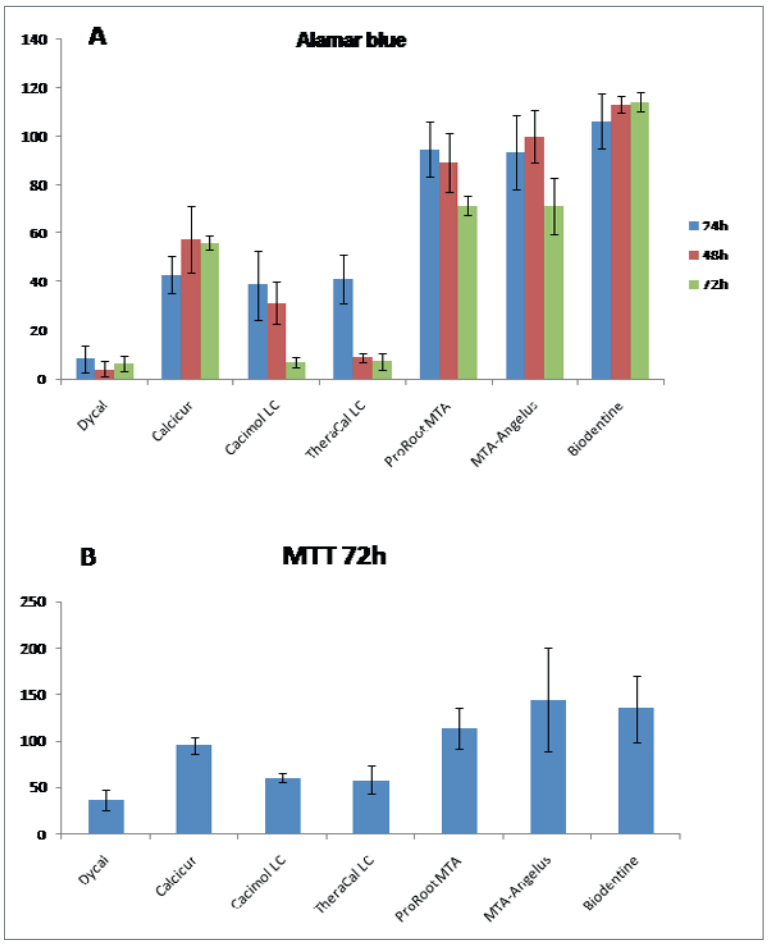


Figure 8: *MDPC-23 cells viability of the different pulp capping materials by using Transwell method. The cell viability was assessed with Alamar blue (A) and MMT (B) tests. Y-axis-percentage of cell viability referred at cells incubated in the absence of pulp capping materials set at 100% (Poggio et.al 2015).*

To conclude, these various tests demonstrate that there is no direct cytotoxic effect with Biodentine® in the form of an extract in contact with L929 fibroblast line cells and dental specialized pulp cells. Moreover, it does not affect phenotypic pulp expression of fibroblasts. Also, literature analysis demonstrates that Biodentine® is less cytotoxic than its competitors.

4.5.2. Sensitization (ISO 10993-10)

Biodentine® is not sensitizing (Gomond, 2003c).
Biodentine® was evaluated for the potential to cause delayed dermal contact sensitization in two guinea pigs studies based on ISO 10993-10.
The first sensitization test was performed according to ISO 10993-10: 2003. Ten animals received intradermal injection and epidermal application of the Biodentine® extract (100%) potentiated by the injection of Freund's Complete Adjuvant. Five control animals received the solvent by intradermal and epidermal application (0.9% NaCl). Following a recovery period of 10 to 14 days, all animals were exposed to the non-irritant challenge dose of 100%. The extent and degree of skin reaction to the challenge exposure in the test animals was compared with control animals.
Under the conditions of this study, the test material was classified as non-sensitizing by skin contact.

For the second sensitization assay with guinea pigs, Biodentine® was extracted in 0.9% sodium chloride and sesame oil. Each extract was intradermally injected and topically applied to ten guinea pigs (per extract) to induce delayed sensitization. Extraction vehicle was similarly injected and topically applied to five control blank guinea pigs (per vehicle). Following a recovery period, the test and control blank animals received a challenge patch of the appropriate test article extract and the extraction vehicle. All sites were scored at 24 and 48 hours after patch removal.
Under the conditions of this study, the topical application of both sesame oil & sodium chloride extracts did not induce delayed sensitization in the guinea pigs.

4.5.3. Genotoxicity (ISO 7405, ISO 10993-3, OCDE 471)

Biodentine® is not genotoxic.
Several genotoxicity tests were performed on the Biodentine® cement. They were carried out on extracts of the cement after complete setting.
AMES test performed on Salmonella typhimurium and Escherichia coli. Strains TA98, TA100, TA1537, TA1535, pKM101 in absence or presence of metabolism activator. Results showed that Biodentine® was not mutagenic (Harmand, 2003).
Another AMES test was performed on four strains of Salmonella typhimurium TA97A, TA98, TA100 and TA102. The results showed that Biodentine® cement does not induce reverse mutation in the presence or absence of the metabolic activator S9. Identical results were reported for the four strains of bacteria tested (Laurent et al., 2008).

An in vitro micronucleus test was also carried out using human lymphocytes (Laurent et al., 2008). These were exposed to extracts of Biodentine® obtained either from a culture medium or DMSO. Dilutions of 1% to 5% of the extracts were used. After a culture time of 72 hours, the cells were stained and analysed. 1000 bi-nucleated lymphocytes were tested to check for a micronucleus. A toxicity index was determined, together with a ratio for the number of micronuclei in relation to the negative reference. The results showed that

after incubation of the lymphocytes with different dilutions of the extract of Biodentine®, the number of lymphocytes presenting a micronucleus was similar to that obtained with the negative reference (3.9% to 4.1%) when concentrations of 1% to 5%in an aqueous or hydrophobic medium were tested. Positive controls produced a micronucleus rate of 16%.

Biodentine®	Micronucleoted lymphocytes (%±SD)
1%	4.0±1.1
2.3%	4.0±1.1
3.7%	4.0±1.2
5%	4.2±1.2
- control	3.7±1.2
+ control	16±6.0

Table 10: Micronucleated lymphocytes after contact with Biodentine®

Biodentine®	Tail DNA mean (%±SD)
0.1%	12.59±0.96
1%	13.31±0.88
10%	14.90±1.06
Undiluted	15.58±1.08
Negative control	13.19±0.96
Positive control	46.52±1.4

Table 11: Micronucleated lymphocytes after contact with Biodentine®

Finally, the Comet test on human pulp fibroblasts was conducted (About, 2003). The extract of Biodentine® was prepared in DMSO and a culture medium, at 50 mg/ml for 24 hours and at 37°C. The cells were exposed directly to increasing dilutions of cement extracts for two hours. Following electrophoresis, the slides were analysed by fluorescent microscopy (magnification x400) and an automated analyser was used to determine DNA lesions. The results obtained showed that the percentage of tail DNA varied from 12.59 for a dilution of 0.1% to 15.58 for the undiluted medium. It was 13.19 for the negative control and 46.52 for the positive control (Table 9). In the presence of DMSO, there was no significant difference between the genotoxicity of Biodentine® and the negative control (extracted with NaCl and DMSO).

A mouse lymphoma assay (266326) was conducted according to evaluate the mutagenic potential of Biodentine® using the mouse lymphoma forward gene mutation assay in mouse lymphoma L5178Y/TK+/- cell line, heterozygous at the thymidine kinase locus.
The product was extracted either in serum-free Cell Culture medium (RPMI0) or in polyethylene glycol (PEG) 400. The assay was conducted for 4 hours in the presence and absence of metabolic activation and 24 hours in the absence of metabolic activation.
The RPMI0 extract was tested at 100%, 50%, 25%, 12.5%, 6.25% and 3.13% and was supplemented with 5% serum prior to 4 hour and 24 hour treatments. The PEG extract was diluted to a final concentration of 1% with RPMI5 for the 4 hour and 24 hour treatments. The cells were exposed to the test article extracts.
Under the condition of the study, the Biodentine® is not mutagenic.
These results are confirmed by existing data in the literature studying the genotoxicity of Biodentine® (Nai et al. 2016). The preclinical study retrieved in literature evaluating the genotoxic and mutagenic potential of Biodentine® in vivo using male rats by Comet assay and micronucleus test. The results showed that Biodentine® resulted in an increase in the frequency of micronuclei, but no genotoxicity was detected according to the Comet assay.

4.5.4. Cutaneous irritation

Biodentine® does not cause irritation.
One cutaneous irritation test was performed in the rabbit by direct application. Oedema and erythema were evaluated 1h, 24h, 48h and 72h after patch removal. Biodentine® was shown to be a non-irritant (Gomond, 2003a).
A second test was performed in hamsters by NAMSA according to ISO 10993-23 and concluded that Biodentine® is a non-irritant.

4.5.5. Acute toxicity

Two acute toxicity tests were performed according to OCDE 423 (Gomond, 2003b) and to ISO 10993-11 (NAMSA) in order to determine on a qualitative and quantitative basis the toxicity signs and their time of appearance after a unique oral administration of a dose of 2000 mg/kg of the product in rats. Rats were observed immediately after administration, 1h, 2h, 3h, 4h, and at least once a day for 14 days. The administration by oral route of the 2000 mg/kg dose of Biodentine® induced no acute toxicity in the rat. The DL50 of Biodentine® is superior to 2000 mg/kg.

4.5.6. Preclinical safety conclusions

The tests carried out on Biodentine® have shown that the Biodentine® products are biocompatible and well-tolerated. When compared to well-known dental materials such as Dycal® (calcium hydroxide) or Theracal®, Biodentine® exhibits less cytotoxicity. Moreover, when compared to ProRoot® MTA, Biodentine® demonstrates equivalent biocompatibility.

4.6. Evidence based Bioactivity

Biodentine® is a bioactive material and is characterized by:
- The formation of hydroxyapatite, creating a tight seal within the dentin tubules;
- The promotion of favorable environment to the angiogenesis and osteogenesis, isolating the root canal from the surrounding tissues and stimulating the healing process of the damaged apical tissues

The bioactivity of Biodentine® is favorable to a high success rate of restorative and endodontic treatment.
The calcium silicate interacts with water leading to the setting and hardening of the cement. This is a hydration of the tricalcium silicate (3CaO.SiO2 = C3S) which produces a hydrated calcium silicate gel (CSH gel) and calcium hydroxide (Ca(OH)2) (see Grazziotin et al. 2017). This setting reaction is characterized by an elevation of pH during the first setting hours. This phenomenon is responsible for:
- The formation of Hydroxyapatite;
- Ions exchange with the medium of the inner tooth.

Hence, based on these processes, tricalcium silicate cements are often described as bioactive (see for example Jafari et al. 2017 or Primus et al. 2019).

A) Formation of Hydroxyapatite
Several methods were used to demonstrate the formation of hydroxyapatite:
- By observation of superficial formation of hydroxyapatite deposits (see ***Figure 2*** and Kim et al. 2019);
- By studying proteins or genes activation involved in mineralization processes.

4.6.1. Evidence of Ca2+ release in the medium

Several studies demonstrate the release of high quantities of ions in the medium (Camilleri et al. 2014b; Gandolfi et al. 2014; Camilleri et al. 2014a, Chung et al. 2019; Kang et al. 2019). Hence, the chemical characterization of Biodentine® highlights up to 356 500 ppm of Ca2+ in UPW/0.9% NaCl (RDRADEVPA1507_028en). This could be attributed to the presence of tricalcium silicate, calcium chloride, increased calcium hydroxide formation and also to the high solubility of the device.
The curve hereafter shows the kinetic of Ca2+ released when Biodentine® is immersed in Eagle's medium (modified for cell culture).

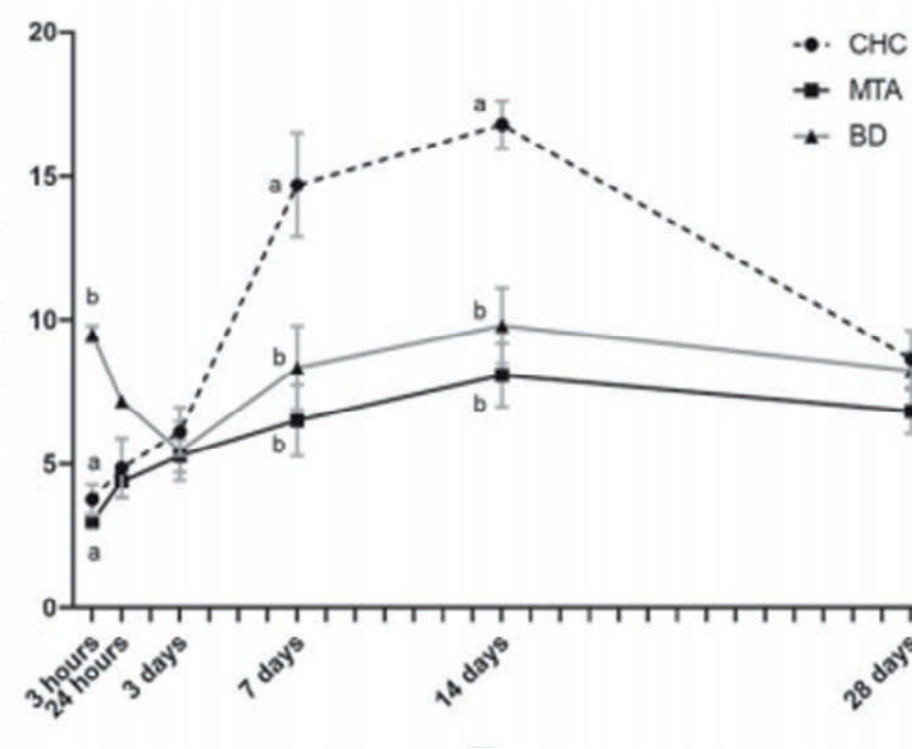


***Figure 9**: Kinetic of Ca2+ release from various cements (curve with triangle for Biodentine®) over time (excerpt from Petta et al. 2020).*

Calcium ions are mainly released in the first two weeks and seem to reach a plateau between 14 and 30 days. These results agree with those of Gandolfi et al (2014) when the cement was placed in deionized water. However, the kinetic could be different due to the medium and the methods used (for example if the medium was changed for each measurement or not):

- In NaCl the quantity of Ca2+ ions measured by Li et al. (2016a) was 225 ppm at 1 day, 241 after 1 week and 84 ppm after one month.
- In NaCl the quantity of Ca2+ ions released was 7.1 (no unit) at 24h, 23.5 after 7 days and 37.1 after 28 days. However, it seems that the medium was not changed between measurements which could explain the increase between 7 and 28 days (Kurun-Aksoy et al. 2017).

Moreover, other conditions such as the pH could influence the quantity of Ca2+ ions released. Hence, it was shown that Biodentine® released significantly more calcium at neutral pH (more close to clinical context) compared to pH at 5.5 (Natale et al. 2015).
The high release of Ca2+ is a prerequisite to the formation of hydroxyapatite and the activation of many metabolic pathways (Petta et al. 2020, Rajasekharan et al. 2018).

I. Superficial formation of hydroxyapatite deposit

Kim et al. (2019) proposed a direct observation of calcified nodule formation when hDPSC (human Dental Periodontal Stem Cells) are in contact with devices such as Biodentine®. Cells were stained with Alizarin Red S solution (ARS precipitated Calcium as red Ca-RAS salts). This dye is used to assess calcium deposits at cellular levels ***(Figure 10)***.

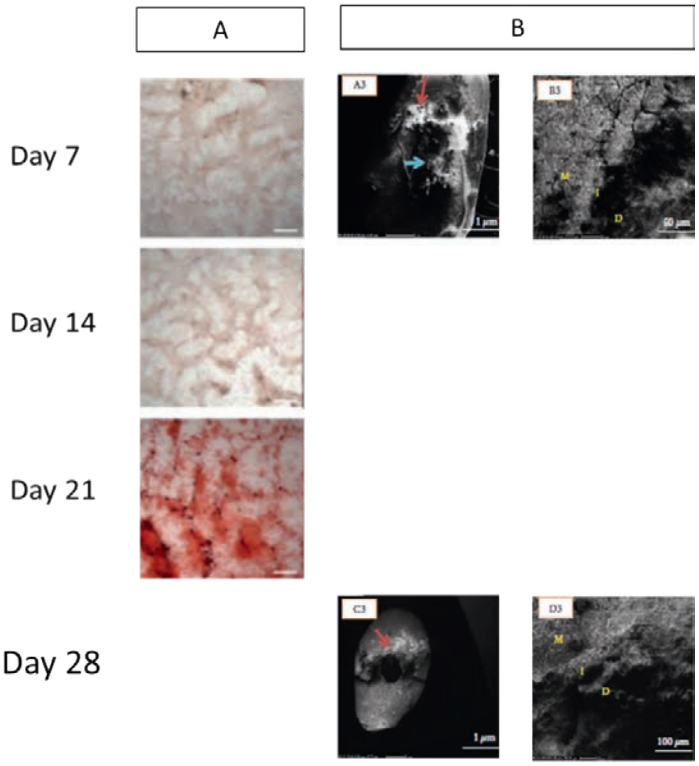


Figure 10*: (A) Observation of calcified nodule formation by Alizarin red S staining assay when hDPSC are in contact with Biodentine® (excerpt from Kim et al. 2019) (B) Scanning Electron Microscopy of Biodentine® immersed in PBS for 7 days and 28 days. On the right low power observation (100 µm) on the left high-power observation (100µm). Blue and red arrows indicate large amount of precipitated. M: Material; I: Interface and D: dentin (excerpt from Talabani et al. 2020 b)*

As seen on day 21, a presence of calcified nodules is clearly observed when cells are exposed to Biodentine® ***(Figure 10)***. This was in good agreement with results obtained with stem cells derived from dental pulp by Dahake et al. (2020) which was also confirmed by Kang et al. (2020) for the same cells model and by Paula et al. (2019) in odontoblast-like mouse cell lines.

In the same way, Talabani et al. (2020 b) showed mineralization confirmed by SEM. Formation of spherical apatite crystal was observed by this team. According to this author: "[…] interfacial zone was composed of an area devoid of larger particles but with smaller particles interspersed in the interfacial region" (Talabani et al. 2020 b).

II. Properties of Biodentine® achieved thanks to mineralization.

The table below summarizes data linking Biodentine® properties (mineralization) and the biological effects observed.

Table 12: Summary of bioactive properties of Biodentine®

Properties	Effect of Biodentine®	Reference	Study
Mineralization	Biodentine® supported extracellular mineralization after treatment of teeth from dogs. Induction of calcium phosphate mineral formation within the dentin matrix when stored in phosphate-rich media.	ortoluzzi et al. 2015, 2015; Chang et al. 2014; Daltoé et al. 2016; Rodrigues et al. 2017; Atmeh et al. 2015; Kim et al. 2015; Jung et al. 2015; Wattanapakkavong et al. 2019)	*In vitro / Ex vivo*
	Restoration of cavities. Biodentine® revealed a tag-like structure and interfacial layer due to hydroxyaptatite formation.	(Atmeh et al. 2012)	
	Root end filling. Biodentine® produce an interfacial layer and apatite crystals. Biodentine® revealed bone growth.	al. 2015; Han and Okiji 2013; Gandolfi et al. 2017; Ürkmez and Pınar Erdem 2019; Silva et al. 2019	
	Apexification. Biodentine® showed high biomineralisation capacity with interfacial layer creation. Active biomineralization processes around Biodentine®.	(Gandolfi et al. 2017; Ürkmez and Pınar Erdem 2019)	
Dentin-pulp environment	Creation of a favorable environment to pulp cells permitting differentiation of odontoblast. Viability of PDL.	(Chang, 2013; Jang et al., 2014; Jung et al., 2014; Laurent et al., 2011; Perard et al., 2013; Zanini et al., 2012) (Tran et al. 2012; Daltoé et al. 2016; Kim et al. 2016; Chang et al. 2014; Loison-Robert et al. 2018)	*In vitro / Ex vivo*
	Tricalcium silicate materials do not induce osteogenic differentiation of hBM-MSCs *in vitro.*	(Bortoluzzi et al. 2015; Costa et al. 2016; Margunato et al. 2015; Ho et al. 2017; Eid et al. 2014)	*in vitro.*
	BD improved the effects on osteoblast differentiation in mesenchymal stem cell. Useful for root-end filling material.	(Lee et al. 2014; Luo et al. 2014)	*In vitro / Ex vivo*
	Differenciation and proliferation of MSC facilitated by good apical blood supply. Creation of soft regenerative tissue including pulp-like tissue and vessels.	(Torabinejad et al. 2014; Flanagan 2014; Zhu et al. 2013; Ghoddusi et al. 2017)	*In vitro*
Healing process	Calcium silicate-based pulp capping materials induce favorable effects on reparative processes during vital pulp therapy.	(Kim et al. 2015; Han and Okiji 2013; Gandolfi et al. 2017; Ürkmez and Pınar Erdem 2019; Silva et al. 2019)	*In vivo*
	Revitalization procedure by means of revascularization of permanent immature teeth with necrotic pulp A hard tissue formation and deposition	(Nosrat et al. 2015; Torabinejad et al. 2018; Saoud et al. 2015; Zhu et al. 2013; Alrahabi and Ali 2014; Ghoddusi et al. 2017), (Tawfik et al. 2013; Flanagan 2014)	*In vivo*

As reported by the previous table, the mineralization is one of the keystones to create an environment favorable for biological tissues sustainability (cases of pulpectomy) and repairment. Mineralization was also demonstrated clinically after pulp capping and in vivo (after dental furcation perforation performed in dogs). Hence:

- Sharma et al. (2019), observed in 40 patients an average thickness of dentin deposited after 1 year of 0.25 mm. After 24 months, Holiel et al. (2021) observed with Biodentine® an average dentin bridge thickness of 1.47 in 13 patients.
- In another study, Holiel et al. (2020) observed positive effects of Biodentine as a pulp capping agent in 10 patients. Early formation of dentin synthesis was observed after 2 weeks. Thickness of dentin bridges was higher than 0.25 mm for 20% of teeth and ranging from 0.1 to 0.25 mm for 60% of teeth after 2 months (see illustration below).

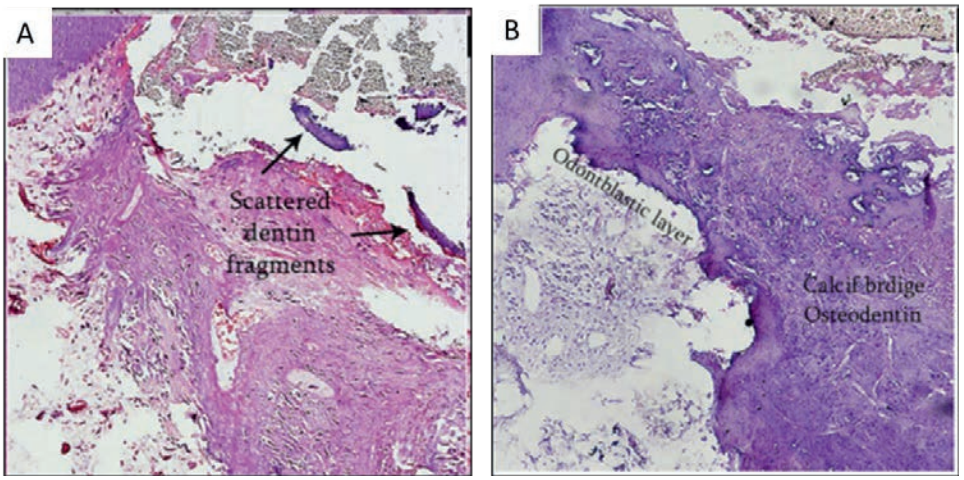


***Figure 11**: Bridge dentin formation with Biodentine® used for pulp capping after 2 weeks (A) and 2 months (B) Excerpt from Holiel et al. 2020.*

These results were also confirmed by two clinical studies:

- One performed by Hoseinifar et al. (2020) where pulp capping was performed on 30 human premolar teeth
- The other by Bui and Pham (2021) 9-12 weeks after pulp-capping with Biodentine® in 11 human premolars.

Silva et al. (2019) demonstrates that Biodentine® induced mineralization in furcation perforation in dogs.

However, it was also shown that Biodentine® could also directly interact with cells and modulate secretion of several growth factors. This will be developed in paragraphs hereafter.

4.6.2. Cells proliferation activated by Biodentine®

Cell proliferation and then wound healing is favored both by the biocompatibility of the product and the formation of the superficial apatite layer.

Concerning biocompatibility, several data showed that Biodentine® is not cytotoxic, see 5.1 Cytotoxicity.

This was also demonstrated in several other preclinical studies (Sun et al. 2019, Paula et al. 2019, Silva et al. 2019, Abuarqoub et al. 2020, Kang et al. 2020), including pulp capping context, where Biodentine® was shown to induce mainly moderate to mild inflammation (Hoseinifar et al. 2020 and Holiel et al. 2021), due to the high pH.

Some studies showed that the high biocompatibility of Biodentine® is reached by the modification (induced by the Biodentine®) of the expression of Interleukin (IL)-1ß and IL-6 both implied in the inflammatory process (Solanki et al. 2018). However, one other study observed no effect of Biodentine® on IL-6 and IL-8 production in human dental pulp stem cells stimulated with lipopolysaccharide (LPS) to induce inflammation, but rather a decrease in TGF-ß1 (Chung et al. 2019). In contrary, Wattanapakkavrong et al. (2019) observed higher quantity of TGF-ß1 elicited compared with ProRootMTA in human apical papilla cells.
Concerning cells proliferation, it was demonstrated that tricalcium silicates such as Biodentine® are able to induce cell proliferation of human dental pulp cells and stem cells (Amin et al. 2021; Weekate et al. 2021).

4.6.3. Angiogenesis & revitalization

Angiogenesis is defined as the development of new blood vessels and is a necessary step to achieve wound healing and promote neovascularization (Olcay et al. 2020).
Biodentine® has a partial angiogenesis mediation through the up-regulation of VEGFA and FIGF and the down-regulation of the ANGPT1 and the FGF2 (Sanz et al. 2020). Hence, Olcay et al. (2020) demonstrates that Biodentine® is able to increase the expression of angiogenic genes and the release of VEGF A in Human Tooth Germ Stem cells (HTGSC).

Table 13: Signaling pathways implied in angiogenesis modulated by Biodentine®

Markers	Roles/names
ANGPT1	Angiopoietins (proteins implied in angiogenesis)
FGF2	Fibroblast Growth Factors
FIGF	C-Fos Induced Growth Factor (Vascular Endothelial Growth Factor D)
VEGFA	Vascular Endothelial Growth Factor A

According to Rathinam et al (2015), angiogenesis is allowed by the release of Si4+ ions from the cement, which increases the osmolarity and, in turn, activates the differentiation of the cells via the p38 signaling pathway in hDPSC cells.

Finally, the study performed by Sequeira et al. (2021) did not demonstrate angiogenesis per se but shows some evidence for tissue regeneration. To note, “regenerative process” is defined by the AAE (American Association of Endodontics) as “biologically-based procedures designed to physiologically replace damaged tooth structures, including dentin and root structures, as well as cells from the pulp-dentin complex”. In this study, human apical papilla stem cells were grown in human roots and inserted in the back of rats during 4 months. Cements were used as apical barriers. In the conditions of this study, it was shown that in the group with Biodentine®, 20% of the inside root was filled with regenerated tissues, dentinal bridges, and cellular projections (connective tissues). Based on these results, authors concluded that Biodentine® was able to promote the formation of pulp-dentin complex and dentinal bridges.

Biodentine® is a perfect material for vital pulp therapy since it promotes revitalization of the damaged tissues.

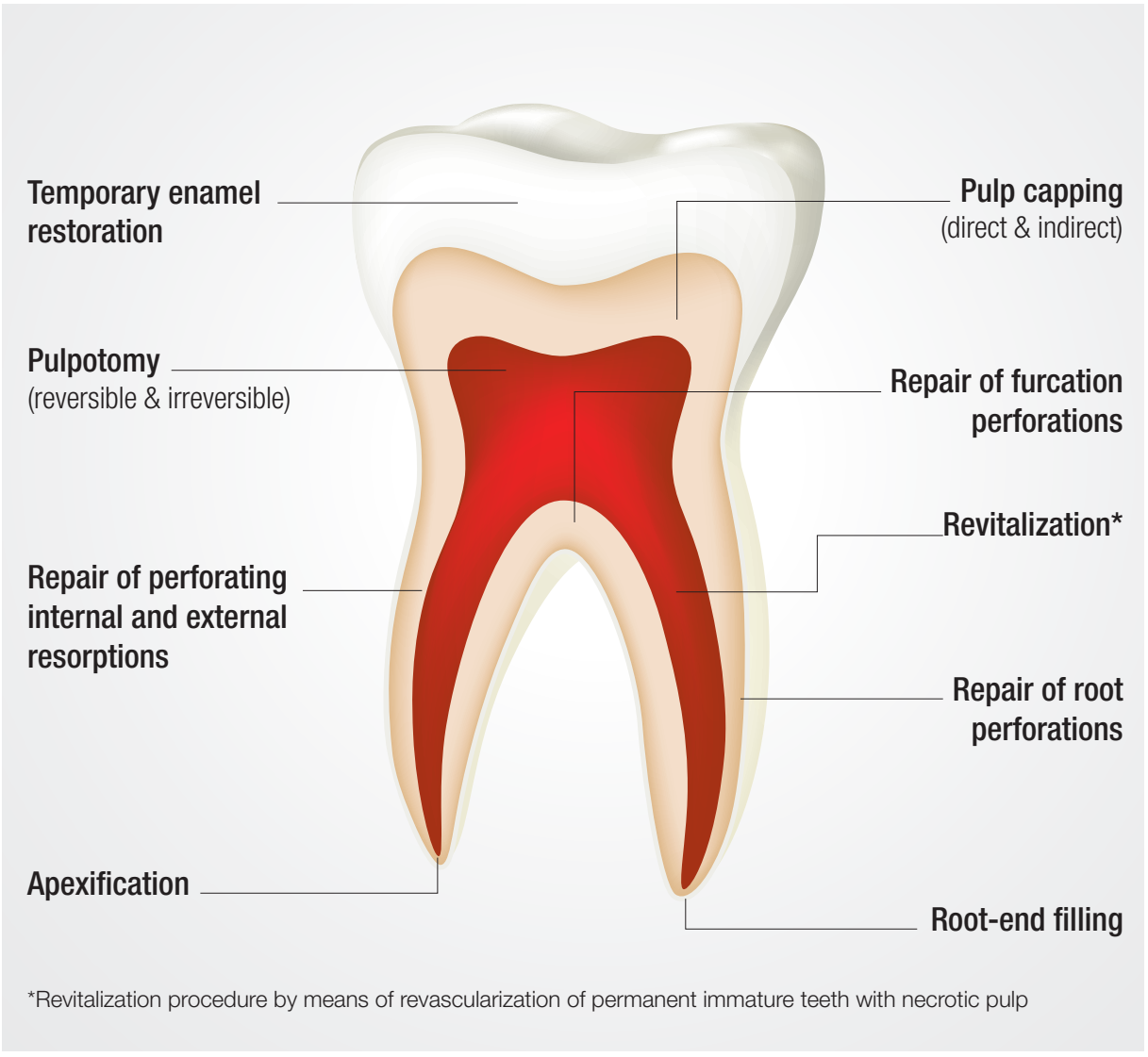
4.6.4. Overall Bioactivity

Biodentine® is able to generate hydroxyapatite and mineralized structures and the high biocompatibility of the device ensures the creation of an environment auspicious enough to induce both tissue sustainability and tissue repairment. This was demonstrated by the high success of Biodentine® when it is used as pulp capping agent. However, these effects do not seem to be limited to indirect processes. In fact, the release of ions and the high pH also directly activates some signal pathways in cells leading to their proliferation, angiogenesis or stimulating mineralization.

As a conclusion, Biodentine® is bioactive.

05 Biodentine's indications in the crown and in the root

Biodentine® XP has multiple indications both in the crown and in the root . Thanks to its biological properties, Biodentine® can save teeth even in the case of irreversible pulpitis or immature tooth necrosis.



*Revitalization procedure by means of revascularization of permanent immature teeth with necrotic pulp

5.1. Biodentine® is used in Vital Pulp Therapy (VPT)

Vital pulp therapy is defined as a treatment which aims to preserve and maintain pulp tissue that has been compromised but not destroyed by caries, trauma, or restorative procedures in a healthy state. Thanks to the bioactivity, biocompatibility and dentin-like properties, Biodentine® XP can be used for indirect pulp capping, direct pulp capping and pulpotomy.

5.1.1. Indirect pulp capping

Some authors compared Biodentine® with calcium hydroxide when used as an indirect pulp capping material on teeth diagnosed with reversible pulpitis (Hashem et al. 2015; Garrocho-Rangel et al. 2017).
Patients were followed during 12 months in these two studies. Hashem et al. obtained a clinical success rate of 83.3% after treatment of 36 teeth with Biodentine®. A failure was considered when pulp vitality was lost.

The combined clinical and radiographic success rates were 96.7% in Garrocho-Rangel et al. clinical study after treatment of 80 primary teeth.

In a randomized and controlled study, 15 primary teeth were followed for 6 months (Chauhan et al. 2018). Teeth presented active carious lesions involving either occlusal or proximal surfaces. Clinical and radiographic success rates were 100%. Despite the short-term follow-up period, those rates are predictive of long-term satisfactory outcomes.

Boddeda et al. considered that the treatment was successful when combined clinical and radiographic features were met. Success rate was 100% at 3 months, 6 months, and 12 months (Boddeda et al. 2019).

Clinical and radiographic outcomes of Biodentine® and glass ionomer cement (Fuji IX™) were compared in an indirect pulp capping procedure on 36 permanent teeth (Hashem et al. 2019). The success rate was 77.8% with Biodentine® versus 66.7% with Fuji IX™. In the Biodentine® group, 6 teeth failed to maintain vitality and with Fuji IX™ 9 teeth failed to maintain vitality.

5.1.2. Direct pulp capping

The range of success rate in teeth using Biodentine® as a direct pulp capping material was 83.3% - 100% at 12 months (Hegde et al. 2017; Brizuela et al. 2017; Katge and Patil. 2017) and 82.6% - 96.4% at 18 months (Linu et al. 2017; Lipski et al. 2018; Parinyaprom et al. 2018).

Dentin-bridge formation was also a performance parameter described several times. Dentin-bridge formation was observed in 95.2% at 12 months (Katge and Patil. 2017), and 61.5% at 18 months (Linu et al. 2017).

One study assessed which factors could influence the outcome of direct pulp capping using Biodentine®. The outcomes were not influenced by sex, initial or secondary caries treatment, occlusal or cervical caries localization, delayed placement or permanent filling, tooth position and arch type (Lipski et al. 2018). However, the patient's age did influence the outcome with failures being more prevalent in patients aged more than 40 years.

Over a 6-month period, Biodentine® showed an 83.3% success rate. In this study, the Atraumatic Restorative Treatment (ART) procedure was chosen to remove all soft caries near the pulp with spoon excavators and round carbide burs on a slow speed handpiece.

5.1.3. Pulpotomy

Eight randomized trials compared the performance of Biodentine® with that of MTA (Togaru et al. 2016; Cuadros-Fernández et al. 2016; Carti and Oznurhan 2017; Bani et al. 2017; Çelik et al. 2018; Çelik et al. 2019; Rajasekharan et al. 2016; Guven et al. 2017) on primary teeth with a follow-up between 12 and 24 months. Those 8 studies included 241 teeth that were treated with Biodentine®. Clinical success rates among those studies ranged between 95% and 100%. Those success rates were comparable to the main Biodentine® competitor, MTA.

Two clinical trials compared success rates of Biodentine® and calcium hydroxide treatment on primary teeth with follow-up between 18 and 24 months (Caruso et al. 2018; Grewal et al. 2016). The population included in those studies was children with primary teeth with caries requiring vital pulp therapy. Teeth were randomly assigned to either the control calcium hydroxide or to Biodentine®.

Patients were recruited if they had second primary molars with exposure of the pulp as a result of dental caries, no degeneration of pulp, no excessive bleeding as well as no clinical symptoms, such as pathologic mobility, swelling, or pain on percussion.
Overall, those 2 randomized and controlled studies included 220 teeth that received Biodentine® as treatment. Biodentine® revealed statistically favorable regenerative potential along with clinical success of 96.5% at 18 months (Caruso et al. 2018) and 82.75% at 24 months (Grewal et al. 2016) - compared to calcium hydroxide.

Treatment of pulpotomy with Biodentine® was described in a mix of 20 immature and mature permanent teeth (Taha et al. 2018 b). At 6 months, 100% of teeth showed clinical and radiographic success; 25% of teeth showed dentin bridge formation, and root formation continued in 3 teeth (100%). The same results were observed at 12 months.

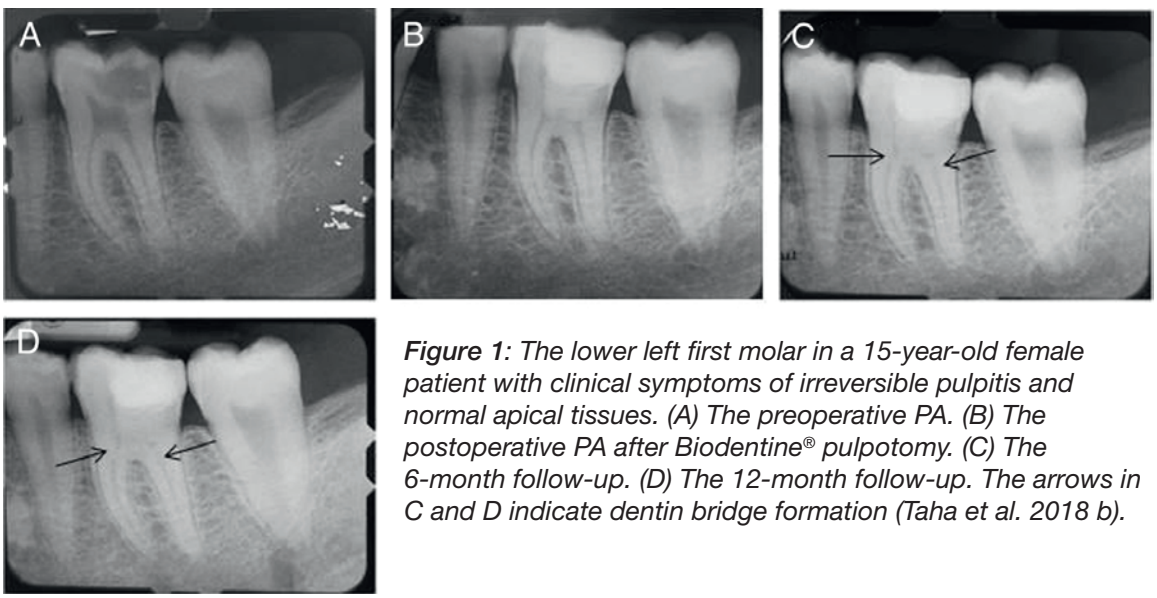


***Figure 1**: The lower left first molar in a 15-year-old female patient with clinical symptoms of irreversible pulpitis and normal apical tissues. (A) The preoperative PA. (B) The postoperative PA after Biodentine® pulpotomy. (C) The 6-month follow-up. (D) The 12-month follow-up. The arrows in C and D indicate dentin bridge formation (Taha et al. 2018 b).*

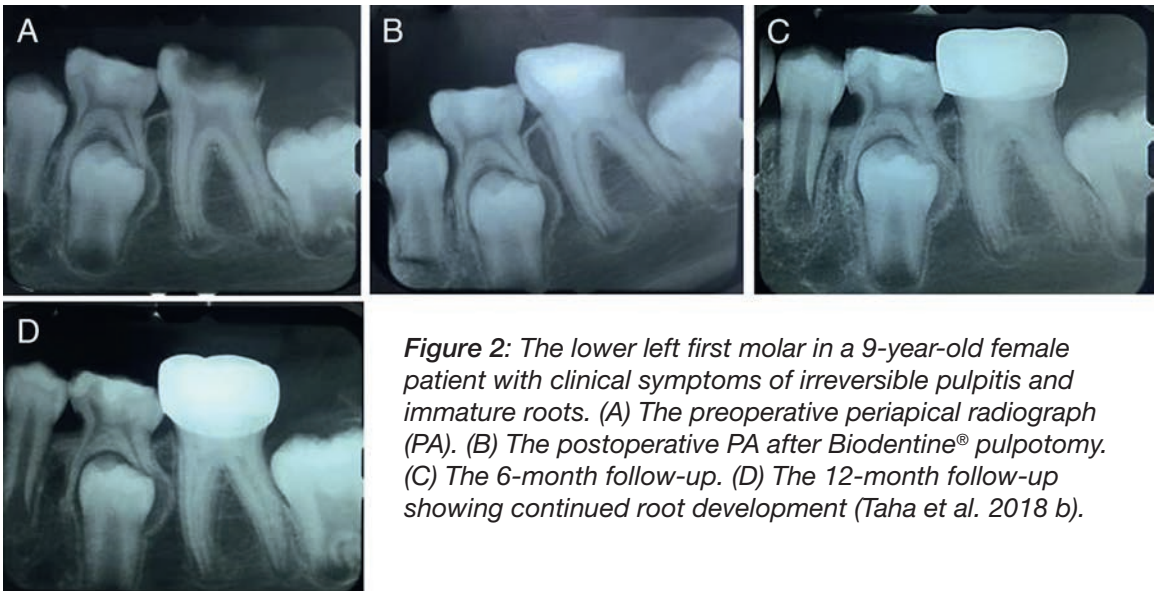


***Figure 2**: The lower left first molar in a 9-year-old female patient with clinical symptoms of irreversible pulpitis and immature roots. (A) The preoperative periapical radiograph (PA). (B) The postoperative PA after Biodentine® pulpotomy. (C) The 6-month follow-up. (D) The 12-month follow-up showing continued root development (Taha et al. 2018 b).*

In another study, Taha and colleagues described pulpotomy treatments with Biodentine® in 64 permanent teeth (Taha et al. 2018a). At 2 days, 93.8% of patients reported complete pain relief. At 6 months, clinical and radiological success rates were 98.4%. At 12 months, clinical success rate was 100% and radiological success rate was 98.4%.

Treatment of partial pulpotomy with Biodentine® was compared with ProRoot MTA in 32 permanent teeth (Uesrichai et al. 2019). Teeth were followed-up during 32±17.9 months. Clinical success rate of Biodentine® was 87% and radiographic success rate was 97%. Frequency of perceptible grey discoloration was significantly less with Biodentine® than with ProRoot MTA.

Direct pulp capping and pulpotomy using Biodentine® was described on 34 mature permanent teeth (Awawdeh et al. 2018). Success rate of treatment with Biodentine® was 91.6% at 48 months, slightly lower than with MTA (93.3%).

Finally, two cases were published, aiming to evaluate the outcome of Biodentine® during full pulpotomy in adult permanent teeth with carious exposure and clinical signs, indicative of irreversible pulpitis (Tran et al. 2021). In both cases, clinical signs and symptoms improved one month after full pulpotomy. In the first case, the apical radiolucency was improved after 6 months and completely healed after 12 months. In the second case, the periodontal ligament space was in a normal state after 6 months.

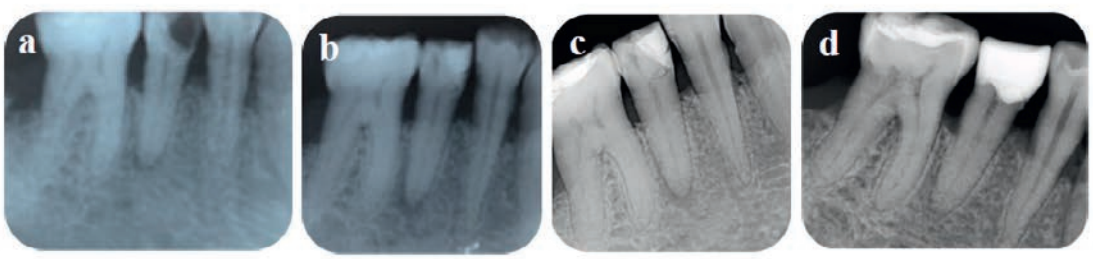


***Figure 3**: Periapical radiographs: (a) preoperative; (b) after treatment; (c) 6 months postoperative; (d) 12 months postoperative.*

5.2. Biodentine® is used as a temporary dentin-enamel restoration and a dentin substitute under composites or Inlay/Onlay

Some authors showed that Biodentine® can be used as a temporary restorative material for at least 6 months (Koubi et al. 2013). Beyond this period, a degradation of the marginal adaptation and of the interproximal contact point is observed, requiring the placement of an additional final restorative material. In this study, Biodentine® was subsequently kept as a cavity lining for 96 teeth. Biodentine® presented a good resistance to burring and a composite (Z100, 3M ESPE) was applied on the top.

One study reported the use of Biodentine® for direct pulp capping on 11 teeth scheduled for extraction. It was first used for temporary restoration by filling the entire cavity (Bio Bulk Fill), then partially removed and covered with composite 7 days later (Nowicka et al. 2015). Six weeks after application of the pulp capping material, all teeth were extracted with minimum trauma by a designated oral surgeon. After analysis, the study showed that Biodentine® actively initiated formation of reparative dentin in all teeth (100%). Dentin bridges in the Biodentine® group showed the highest average and maximum volumes compared to teeth treated with calcium hydroxide or MTA. The study concluded that the volume of reparative dentin bridges formed after direct pulp capping is dependent on the material used.

One study reported the use of Biodentine® for indirect pulp capping and temporary dentin restoration (Boddeda et al. 2019). Biodentine® was placed in the prepared cavity until the occlusal level (Bio Bulk Fill) and occlusal adjustments were performed ***(Figure 4)***. Biodentine® was partially removed to a base level at the follow-up visit that occurred 3 months after the surgery and then covered with a final restoration composite. Authors considered that treatment was successful when combined clinical and radiographic features were met. Success rate was 100% at 3, 6 and 12 months.

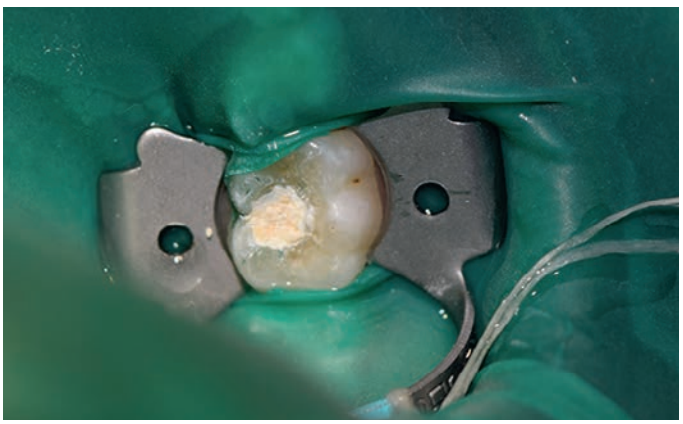


***Figure 4**: Cavity filled with Biodentine® (Boddeda et al. 2019)*

5.3. Biodentine® is used to repair furcation and root perforation

One study reported the use of Biodentine® in 3 teeth scheduled for extraction (Tirone et al. 2018). After 3 months, the root perforations appeared to be totally sealed by Biodentine® at lower-power magnification, without any visible sign of bone resorption, in the apical direction. Histomorphometry showed in average 7.9% of mineralized tissue.

Another study reported the use of Biodentine® in 51 teeth for reparation of root perforation (Mancino et al. 2018). Perforation was classified as healed when all the following findings were not observed: pain or discomfort, presence of a sinus tract infection or swelling, positive probing and radiolucency. Complete healing was observed in 46 teeth after 12 months (90.2%) and in 48 teeth at 24 months (94%). Healing rate depends on perforation size, with a lower rate (91%) for larger perforations (>3mm) compared to 100% for small ones (<1mm).

5.4. Biodentine® is used in internal and external resorption treatment

Four case reports and one case series including 4 teeth reported use of Biodentine® as a material for internal and external resorption, totalizing 8 teeth (Pruthi et al. 2015; Karypidou et al. 2016; Patni et al. 2018; Salzano and Tirone 2015; Borkar and Noronha 2015).
There was no case of failure. Also, there was no case of pain on percussion, and radiographically there was no sign of replacement resorption.

Although data are limited, follow-up is long, between 18 months and 5 years. Nevertheless, an additional clinical study is being conducted (NCT05084742), which will provide additional clinical performance and safety data. It should be noted that the recruitment of patients with root resorption may be difficult to obtain because the prevalence is rather low.

5.5. Biodentine® is used for retrograde filling after endodontic surgery

Three studies described the use of Biodentine® for root end filling in a total of 23 teeth (Caron et al. 2014; Pawar et al. 2013; Boucher et al. 2021). Furthermore, a clinical study is being conducted (NCT05084742) to provide additional clinical performance and safety data.

Caron et al. reported two cases of adults aged 48 and 50 years old with a periapical lesion and suspicion of an apical isthmus (Caron et al. 2014). Patients no longer presented clinical symptoms 24 months after treatment with Biodentine® and radiographic evidence of regeneration of the periapical tissues could be observed ***(Figure 5)***.

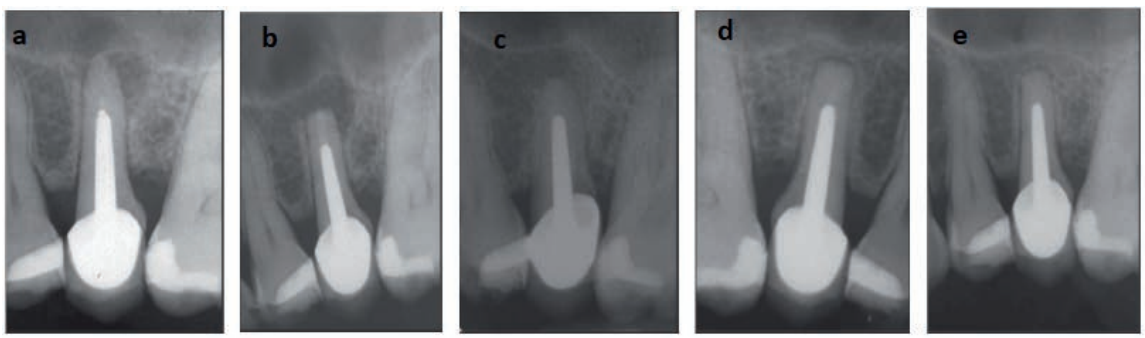


Figure 5*: Case 1. (a) Orthocentric preoperative view. (b) Immediate postoperative view. (c) Three months after surgery. (d) One year after surgery. (e) Two years after surgery (Caron et al 2014).*

Pawar et al. reported one case of a patient with an injury of the anterior teeth due to cystic lesion, and with apical periodontitis (Pawar et al. 2013). Patient's cystic lesion was completely healed 18 months after treatment.

Finally, Boucher et al. reported 10 cases of adults who presented with an endodontic failure (Boucher et al. 2021). Patients no longer presented clinical symptoms 24 months after treatment with Biodentine® and radiographic evidence of regeneration of the periapical tissues could be observed ***(Figure 6)***.

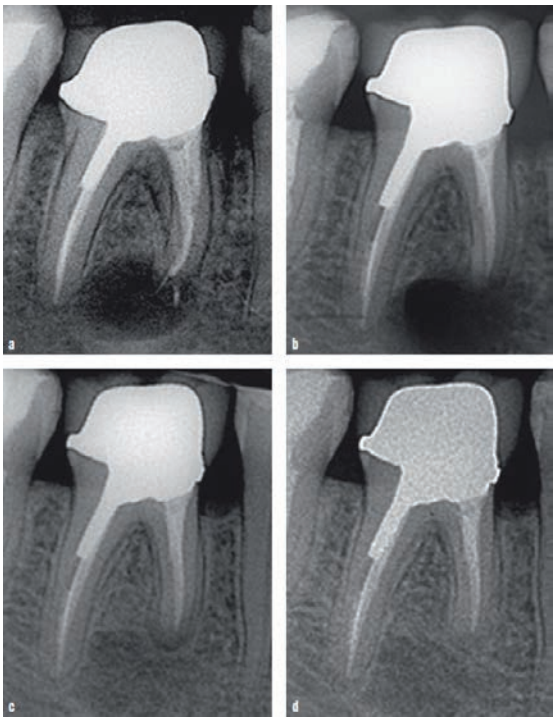


Figure 6*: Example of periapical healing after endodontic surgery with Biodentine® placement during retrograde filling of the mesial root of 46. (a) Preoperative vie. (b) Immediate postoperative view. (c) One year after surgery. (d) Two years after surgery (Boucher et al. 2021)*

5.6. Biodentine® is used in apexification

Biodentine® is indicated for apexification in immature permanent teeth. A clinical trial and four case series reported the use of Biodentine® for apexification, totaling 17 teeth (Tolibah et al. 2022 ; Bajwa et al. 2015; Kenchappa et al. 2015; Niranjan et al. 2016; Ashraf et al. 2017).

Tolibah and colleagues compared the use of Biodentine® as an apical plug in a single visit to MTA used in two visits on necrotic immature permanent molars, 11 molars (15 roots) and 13 molars (15 roots) respectively (Tolibah et al. 2022). No cases showed treatment failure in either group. At 12 months, the formation of a calcified barrier was noted in four cases of the Biodentine® group, while it was absent in the MTA group ***(Figure 7)***.

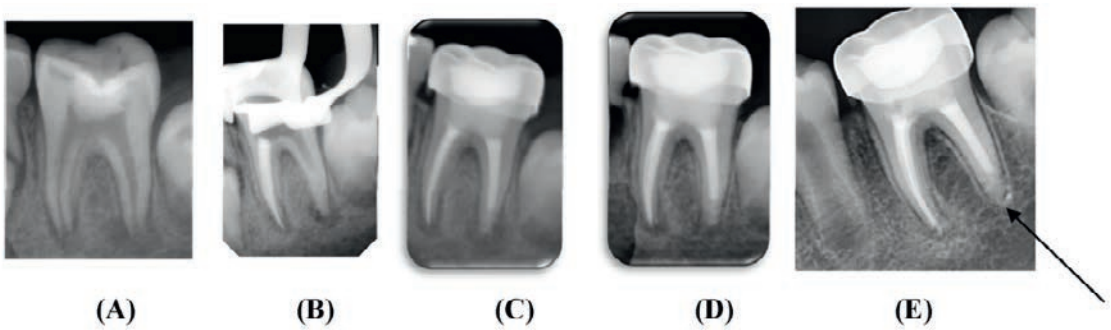


Figure 7*: Apexification using Biodentine® as an apical plug: (A) preoperative; (B) after placement of the apical plug; (C) postoperative; (D) 6 months follow-up; (E) 12 months follow-up. The arrow demonstrates the formation of an apical barrier (Tolibah et al. 2022).*

All (6) teeth were successfully treated in case series (Bajwa et al. 2015; Kenchappa et al. 2015; Niranjan et al. 2016; Ashraf et al. 2017).

5.7. Biodentine® is used in the revitalization procedure

Three studies (one of which is pending publication) described the use of Biodentine® for revitalization, totaling 47 teeth.

Aly and colleagues showed that Biodentine® used as a material for revitalization of 13 non-vital immature teeth had a 100% success rate at 12 months versus 91.66% for MTA (Aly et al. 2019). Regarding the distribution of discoloration among both groups, there was a significant difference (7.69% in Biodentine® group vs. 58.33% in MTA group).

In a case report, a patient requiring pulp revitalization of a non-vital immature tooth was included (Aldakak et al. 2016). Revitalization procedure steps were carried out following steps described in the AAE recommendations (AAE, 2018). The patient was followed for 24 months.
Clinical and radiographic outcomes measured were: responses to cold thermal pulp and electric pulp tests, tenderness to percussion, tooth mobility, pain on palpation, swelling, sinus tract, coronal discoloration, apical closure and root thickening.
Clinical and radiographic examinations showed complete root maturation, with intact supporting soft tissues, without a sinus tract, pain, or swelling at the recall appointments (6, 12 and 24 months). Radiographs revealed further root development and apical closure.

In order to supplement this limited data, a clinical study was recently conducted in collaboration with the University of Reisenburg in Germany. Its coordinating investigator, Kerstin Galler (D.D.S; Ph.D.), participated in the elaboration of the guideline “European Society of Endodontology position statement: Revitalization procedures (ESE, 2016)”.
Preliminary results have been reported by the investigator and are pending publication.
In this study, there are a total 56 necrotic immature teeth for which revitalization was carried out, of which 33 had been treated with Biodentine® and 23 with MTA.
These immature teeth became necrotic as a result of traumatic injury including, concussion, lateral luxation, intrusion, or crown fracture.
Consequently, these teeth have stopped their root development at different stages (from 2 to 5 according to the classification of Cvek, 1992).

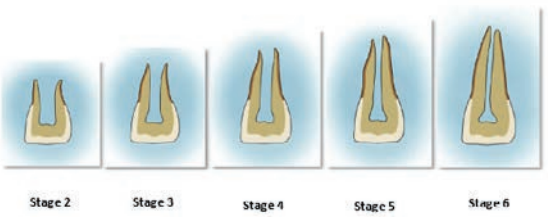


***Figure 8**: Stages of root development according to Cvek.*

The objective of this study was to evaluate whether an increase of root length and/or thickness had taken place over the observation period.
According to the results, revitalization procedures led to an increase of root length and thickness and to a reduction of the root canal space in 58% and 66 % for Biodentine® and MTA cases, respectively.
Periapical lesions were present preoperatively in 20 (35.7%) patients and healing was observed in all cases both in the Biodentine® and in the MTA group.

A distinct advantage of Biodentine® was noted in terms of tooth discoloration, which occurred in many fewer cases than with MTA (18% versus 74%).

06 Conclusion

Biodentine® is a unique bioactive dentin substitute to be used both in the crown and in the root that allows to keep the pulp vital in deep cavities and pulp exposures.

Biodentine® XP can be applied in the tooth from the pulp to the top of the cavity, regardless of how deep: with Biodentine® XP, the procedure is made easier & faster because it can also be used as a Bio-Bulk Fill procedure.

The ease of use and multiple indications of Biodentine® XP will help practitioners treat their patients every day.

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