European Archives of Paediatric Dentistry (2018) 19:1–22
https://doi.org/10.1007/s40368-018-0328-x

SYSTEMATIC REVIEW

Biodentine™ material characteristics and clinical applications: a 3 year literature review and update

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Received: 22 February 2017 / Accepted: 11 January 2018 / Published online: 25 January 2018

Abstract

Introduction Biodentine™ has frequently been acknowledged in the literature as a promising material and serves as an important representative of tricalcium silicate based cements used in dentistry.

Aim To provide an update on the physical and biological properties of Biodentine™ and to compare these properties with those of other tricalcium silicate cements namely, different variants of mineral trioxide aggregate (MTA) such as ProRoot MTA, MTA Angelus, Micro Mega MTA (MM-MTA), Retro MTA, Ortho MTA, MTA Plus, GCMTA, MTA HP and calcium enriched mixture (CEM), Endosequence and Bioaggregate™.

Study design A comprehensive literature search for publications from November 20, 2013 to November 20, 2016 was performed by two independent reviewers on Medline (PubMed), Embase, Web of Science, CENTRAL (Cochrane), SIGLE, SciELO, Scopus, Lilacs and clinicaltrials.gov. Electronic and hand search was carried out to identify randomised control trials (RCTs), case control studies, case series, case reports, as well as in vitro and animal studies published in the English language.

Conclusions The enhanced physical and biologic properties of Biodentine™ could be attributed to the presence of finer particle size, use of zirconium oxide as radiopacifier, purity of tricalcium silicate, absence of dicalcium silicate, and the addition of calcium chloride and hydrosoluble polymer. Furthermore, as Biodentine™ overcomes the major drawbacks of MTA it has great potential to revolutionise the different treatment modalities in paediatric dentistry and endodontics especially after traumatic injuries. Nevertheless, high quality long-term clinical studies are required to facilitate definitive conclusions.

Keywords Biodentine™ · Tricalcium silicate

Introduction

Biodentine™ (henceforth, referred to as Biodentine) has frequently been acknowledged in the literature as a promising material and serves as an important representative of tricalcium silicate based cements used in dentistry. Biodentine has earned positive reviews in the literature owing to its superior physical properties, better handling, increased biocompatibility and wide range of clinical applications (Malkondu et al. 2014).

The present review is a 3 year update of the previously published review (Rajasekharan et al. 2014) and aims to provide an updated analysis of the physical and biological properties of Biodentine and to compare these properties with those of other tricalcium silicate cements viz. different variants of mineral trioxide aggregate (ProRoot MTA, MTA Angelus, MM-MTA, Retro MTA, Ortho MTA, MTA Plus, GCMTA, MTA HP), calcium enriched mixture (CEM), Endosequence and Bioaggregate™.

Materials and methods

The previously published review of Biodentine (Rajasekharan et al. 2014) summarised the literature till November 20, 2013. In the present update, a comprehensive literature search for publications from November 20, 2013

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to November 20, 2016 was performed by two independent reviewers (L. M and R. C) on Medline (PubMed), Embase, Web of Science, CENTRAL (Cochrane), System for Information on Grey Literature in Europe (SIGLE), SciELO, Scopus, Lilacs and clinicaltrials.gov. The following search terms Biodentine, "tricalcium silicate", Ca_3SiO_5, "dentine substitute", "dentin substitute" and Bioceramic were used. Only randomised control trials (RCT), case control studies, case series, case reports, as well as in vitro studies and animal studies in English language were considered for this review. The search was supplemented by checking citations of relevant articles and hand searching for articles published in journals not indexed on Medline.

The electronic search resulted in 823 articles while hand search and citation search led to an additional five articles, giving a grand total of 828 articles of which 191 formed the basis of the present review, and of which the majority were in vitro studies. The detailed search methodology and selection criteria is illustrated in Fig. 1 and the physical characteristics of Biodentine compared with other materials is summarised in Table 1.

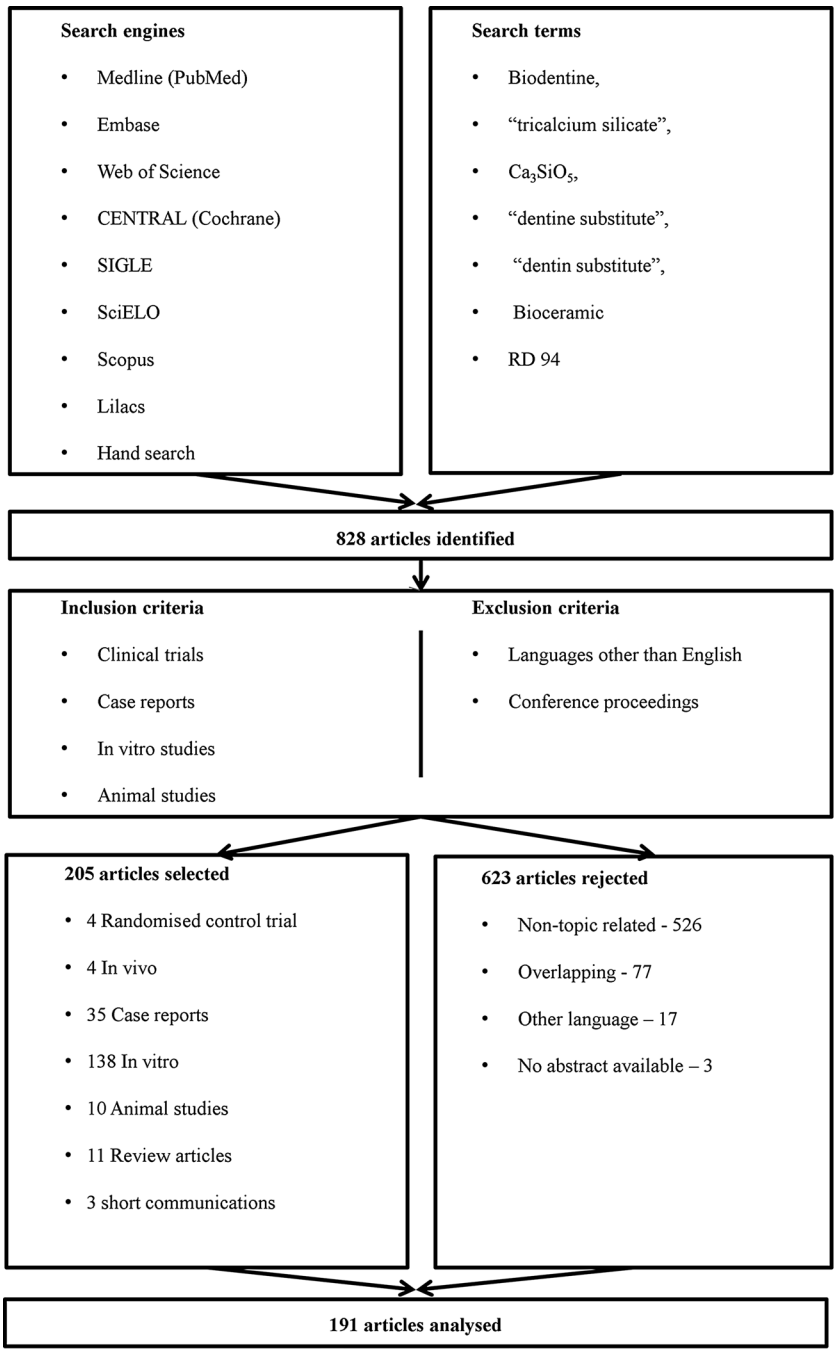

Fig. 1 Overview of the search methodology and selection criteria

Table 1 Characteristics of Biodentine compared with other tricalcium silicate materials

Material characteristics	Time period	Biodentine	Other tricalcium silicate cement groups in the study	References
Setting time				
Initial setting time (min)		6.5 ± 1.7	MTA Angelus (8.5 ± 2.4)	Butt et al. (2014)
Initial Setting time (min)		30 ± 0	Portland cement (74 ± 5.47)	Alhodiry et al. (2014)
Initial setting time in saliva (min)		31 ± 6.51	Portland cement (108 ± 4.47)	Alhodiry et al. (2014)
Initial setting time in blood (min)		46 ± 8.21	Portland cement (114 ± 5.47)	Alhodiry et al. (2014)
Final setting time (min)		85.66 ± 6.03	ProRoot MTA (228.33 ± 2.88)	Kaup et al. (2015a)
Setting time (min)		15 ± 1	MTA (275 ± 15)	Jang et al. (2014)
			Bioaggregate (385 ± 20)	
Setting time (min)		13.1 ± 1.1	MTA Angelus (20.7 ± 2.6)	Dawood et al. (2015a)
			GC MTA (233 ± 11.8)	
Radiopacity				
Radiopacity (/mmAl)		2.8 ± 0.48	MTA Angelus (4.72 ± 0.45)	Tanalp et al. (2013)
			MM-MTA (5.18 ± 0.51)	
Radiopacity (/mmAl)		1.5 ± 0.10	ProRoot MTA (6.40 ± 0.06)	Kaup et al. (2015a)
Radiopacity (/mmAl)		3.1	MTA Plus (4.5)	Camilleri et al. (2015)
			Neo MTA Plus (5.0)	
Mean value of artifact		274.7	MTA (290.3)	Helvacioglu-Yigit et al. (2016)
Colour stability				
Colour difference values (ΔE)	1 week	2.78 ± 1.13	ProRoot White MTA (10.93 ± 2.81)	Vallés et al. (2015)
	2 weeks	3.76 ± 1.48	ProRoot White MTA (14.65 ± 3.75)	
	1 month	4.08 ± 1.75	ProRoot White MTA (12.97 ± 3.15)	
	3 months	4.19 ± 1.39	ProRoot White MTA (14.27 ± 3.28)	
	6 months	5.28 ± 2.12	ProRoot White MTA (16.65 ± 4.58)	
Colour difference values (ΔE)	Immediate	6.88 ± 1.60	ProRoot MTA (5.29 ± 1.60)	Beatty et al. (2015)
	1 day	3.94 ± 1.26	ESRRM (7.44 ± 1.40)	
	7 days	3.77 ± 0.99	ProRoot MTA (2.68 ± 2.08)	
	28 days	4.48 ± 1.02	ESRRM (2.08 ± 0.66)	
	56 days	4.95 ± 1.09	ProRoot MTA (2.06 ± 1.45)	
			ESRRM (3.46 ± 0.79)	
			ProRoot MTA (2.27 ± 1.22)	
			ESRRM (4.54 ± 0.95)	
			ProRoot MTA (2.60 ± 1.26)	
			ESRRM (5.18 ± 0.98)	
Colour difference values (ΔE)	1 day	16.01 ± 7.76	MTA Angelus (18.17 ± 2.83)	Yoldas et al. (2016)
	7 days	7.11 ± 4.80	Bioaggregate (20.52 ± 7.55)	
	1 month	4.95 ± 2.78	MTA Angelus (8.01 ± 5.21)	
	3 months	3.43 ± 1.75	Bioaggregate (7.12 ± 4.65)	
	1 year	3.44 ± 2.71	MTA Angelus (11.86 ± 5.93)	
			Bioaggregate (6.23 ± 3.31)	
			MTA Angelus (6.08 ± 3.81)	
			Bioaggregate (4.92 ± 2.40)	
			MTA Angelus (3.14 ± 2.16)	
			Bioaggregate (6.62 ± 3.55)	

Table 1 (continued)

Material characteristics	Time period	Biodentine	Other tricalcium silicate cement groups in the study	References
Porosity and compressive strength				
Volume of open pores (cm^3)	1 day	0.02284 ± 0.0011	MTA Plus (0.03802 ± 0.0018)	Gandolfi et al. (2014)
			MTA Plus + gel (0.0420 ± 0.0067)	
			MTA Angelus (0.0364 ± 0.0078)	
			ProRoot MTA (0.0316 ± 0.0023)	
			Tech Biosealer capping (0.0518 ± 0.0018)	
			Theracal (0.0278 ± 0.0039)	
Volume of impervious portion (cm^3)	1 day	0.0766 ± 0.0036	MTA Plus (0.0562 ± 0.0036)	Gandolfi et al. (2014)
			MTA Plus + gel (0.06476 ± 0.0085)	
			MTA Angelus (0.0370 ± 0.0068)	
			ProRoot MTA (0.0759 ± 0.0048)	
			Tech Biosealer capping (0.0613 ± 0.0032)	
			Theracal (0.0951 ± 0.0063)	
Average pore diameter (μm)		0.012	Bioaggregate (0.0337)	Camilleri (2014)
			TCS-20-Zr (0.0508)	
Total pore area (m^2/g)		21.75	Bioaggregate (24.321)	Camilleri (2014)
			TCS-20-Zr (13.101)	
Apparent porosity (Vop/V %)	1 day	22.93 ± 0.24	MTA Plus (40.34 ± 1.07)	Gandolfi et al. (2014)
			MTA Plus + gel (39.30 ± 6.30)	
			MTA Angelus (49.47 ± 3.8)	
			ProRoot MTA (29.36 ± 0.78)	
			Tech Biosealer capping (45.80 ± 2.10)	
			Theracal (22.58 ± 2.01)	
Porosity (%)		13.44	Bioaggregate (36.86)	Camilleri et al. (2014a)
			TCS-20-Zr (30.98)	
Compressive strength (MPa) at pH 7.4	7 days	95.2 ± 9.3	White MTA Angelus (71.0 ± 6.9)	Elnaghy et al. (2014)
Compressive strength (MPa) at pH 6.4	7 days	81.4 ± 7.7	White MTA Angelus (60.1 ± 5.1)	Elnaghy et al. (2014)
Compressive strength (MPa) at pH 5.4	7 days	73.6 ± 6.6	White MTA Angelus (53.4 ± 4.7)	Elnaghy et al. (2014)
Compressive strength (MPa) at pH 4.4	7 days	58.8 ± 4.8	White MTA Angelus (31.6 ± 2.4)	Elnaghy et al. (2014)
Compressive strength (MPa)	2 days	45.1 ± 12.5	MTA Angelus (16.1 ± 5.0)	Natale et al. (Natale et al. 2015)
	7 days	49.1 ± 2.6	MTA Angelus (18.0 ± 6.5)	
Compressive strength (MPa)	1 day	61.35 ± 5.09	MTA (36.67 ± 2.95)	Jang et al. (2014)
	3 days	62.57 ± 3.75	Bioaggregate (17.65 ± 8.61)	
	7 days	62.64 ± 0.07	MTA (48.51 ± 3.63)	
			Bioaggregate (20.52 ± 3.02)	
			MTA (57.51 ± 2.16)	
			Bioaggregate (22.03 ± 0.11)	
Compressive strength (MPa)	1 h	139.5 ± 1.19	MTA Angelus (0)	Butt et al. (2014)
	1 day	170.78 ± 1.14	MTA Angelus (41.51 ± 1.41)	
	7 days	269.08 ± 1.07	MTA Angelus (91.35 ± 0.93)	
	28 days	304.78 ± 2.59	MTA Angelus (76.82 ± 2.91)	
Compressive strength (MPa)	7 days	78.5 ± 3.8	MTA Angelus (46.4 ± 2.8)	Dawood et al. (2015a)
			GC MTA (44.1 ± 2.3)	

Table 1 (continued)

Material characteristics	Time period	Biodentine	Other tricalcium silicate cement groups in the study	References
Compressive strength (MPa) after 5 min immersion in NaOCl and subsequent storage in PBS	7 days	174 ± 5.7	White ProRoot MTA (45.3 ± 1.6) NeoMTA Plus (154.6 ± 6.5) MTA Angelus (25.6 ± 5.6)	Govindaraju et al. (2016)
Compressive strength (MPa) after 5 min immersion in EDTA and subsequent storage in PBS	7 days	94 ± 2.6	White ProRoot MTA (18 ± 1.5) NeoMTA Plus (86 ± 3.1) MTA Angelus (10.2 ± 2.3)	Govindaraju et al. (2016)
Compressive strength (MPa) after immersion in PBS	7 days	194.5 ± 5.6	White ProRoot MTA (67.8 ± 3.4) NeoMTA Plus (166.5 ± 7.7) MTA Angelus (45.3 ± 1.8)	Govindaraju et al. (2016)
Hardness and flexural strength				
Vickers hardness testing at 2 mm (N/mm^2)	10 days	47.59 ± 11.55	ProRoot white MTA (87.36 ± 18.80) ESRRM (31.73 ± 9.69)	Caronna et al. (2014)
Vickers hardness testing at 4 mm (N/mm^2)	10 days	50.61 ± 12.91	ProRoot white MTA (99.82 ± 17.20) ESRRM (58.92 ± 33.54)	Caronna et al. (2014)
Microhardness (VHN) at pH 7.4	7 days	58.9 ± 3.5	White MTA Angelus (44.4 ± 3.9)	Elnaghy et al. (2014)
Microhardness (VHN) at pH 6.4	7 days	47.6 ± 3.0	White MTA Angelus (35.9 ± 2.9)	Elnaghy et al. (2014)
Microhardness (VHN) at pH 5.4	7 days	43.7 ± 2.1	White MTA Angelus (31.2 ± 1.7)	Elnaghy et al. (2014)
Microhardness (VHN) at pH 4.4	7 days	26.1 ± 1.9	White MTA Angelus (16.3 ± 1.4)	Elnaghy et al. (2014)
Vickers microhardness (HV)		62.35 ± 11.55	ProRoot MTA (26.93 ± 4.66)	Kaup et al. (2015a)
Surface microhardness (VHN, kg/mm^2)	7 days	45.4 ± 2.4	MTA Angelus (32.7 ± 1) GC MTA (32.4 ± 1.5)	Dawood et al. (2015b)
Bi-axial flexural strength (MPa)		9.49 ± 2.90	Portland cement (7.91 ± 4.08)	Alhodiry et al. (2014)
Bi-axial flexural strength (MPa) in the presence of saliva		9.10 ± 2.45	Portland cement (108 ± 4.47)	Alhodiry et al. (2014)
Bi-axial flexural strength (MPa) in the presence of blood		8.94 ± 2.44	Portland cement (114 ± 5.47)	Alhodiry et al. (2014)
Flexural strength (MPa)		24.4 ± 7.5	MTA Angelus (6.5 ± 1.3)	Natale et al. (2015)
Flexural modulus (GPa)		7.1 ± 3.1	MTA Angelus (2.4 ± 0.9)	Natale et al. (2015)
Solubility				
Solubility in distilled water (%)	1 day	11.83 ± 0.52	MTA Plus (18.55 ± 0.77) MTA Plus + gel (14.68 ± 3.62) MTA Angelus (29.55 ± 2.35) ProRoot MTA (10.89 ± 0.48) Tech Biosealer capping (27.87 ± 1.13) Theracal (2.75 ± 1.04)	Gandolfi et al. (2014)
Solubility in distilled water (%)	1 min	0.252 ± 0.100	ProRoot MTA (0.026 ± 0.017)	Kaup et al. (2015b)
	10 min	0.999 ± 0.202	ProRoot MTA (0.247 ± 0.114)	
	1 h	1.437 ± 0.426	ProRoot MTA (0.763 ± 0.235)	
	1 day	2.647 ± 0.583	ProRoot MTA (0.880 ± 0.237)	
	3 days	3.700 ± 0.782	ProRoot MTA (0.940 ± 0.516)	
	28 days	4.610 ± 1.402	ProRoot MTA (1.144 ± 0.328)	
Solubility in distilled water (%)		5.4 ± 0.6	MTA Angelus (0.6 ± 0.1) GC MTA (1.4 ± 0.1)	Dawood et al. (2015b)

Table 1 (continued)

Material characteristics	Time period	Biodentine	Other tricalcium silicate cement groups in the study	References
Solubility in distilled water (%)	1 day	2.74 ± 0.002	ProRoot MTA (2.38 ± 0.002)	Singh et al. (2015)
	3 days	2.74 ± 0.002	ProRoot MTA (2.38 ± 0.002)	
	10 days	2.90 ± 0.004	ProRoot MTA (2.38 ± 0.002)	
	30 days	3.97 ± 0.005	ProRoot MTA (2.56 ± 0.005)	
	60 days	6.86 ± 0.002	ProRoot MTA (2.56 ± 0.005)	
Solubility in PBS buffer (%)	1 min	0.162 ± 0.170	ProRoot MTA (− 0.029 ± 0.222)	Kaup et al. (2015a)
	10 min	0.253 ± 0.144	ProRoot MTA (0.077 ± 0.074)	
	1 h	1.367 ± 0.264	ProRoot MTA (− 0.688 ± 0.098)	
	1 day	3.415 ± 0.684	ProRoot MTA (− 2.871 ± 0.256)	
	3 days	3.274 ± 1.075	ProRoot MTA (− 5.187 ± 1.019)	
	28 days	− 0.053 ± 0.669	ProRoot MTA (− 5.383 ± 0.501)	
Water sorption (%)	1 day	12.60 ± 0.15	MTA Plus (24.87 ± 1.45)	Gandolfi et al. (2014)
			MTA Plus + gel (26.46 ± 6.25)	
			MTA Angelus (37.02 ± 5.36)	
			ProRoot MTA (14.73 ± 0.52)	
			Tech Biosealer capping (36.67 ± 2.74)	
			Theracal (13.96 ± 1.56)	
Heavy metal release				
Arsenic release in water (µg/L)	7 days	9.3 ± 6.7	MTA (0.1 ± 0.2)	Jang et al. (2014)
			Bioaggregate (0.1 ± 0.2)	
Cadmium release in water (µg/L)	7 days	0.1 ± 0.1	MTA (0.1 ± 0.1)	Jang et al. (2014)
			Bioaggregate (01 ± 0.1)	
Chromium release in water (µg/L)	7 days	46.2 ± 30.8	MTA (7.0 ± 3.1)	Jang et al. (2014)
			Bioaggregate (12.5 ± 16.6)	
Copper release in water (µg/L)	7 days	31.7 ± 13.4	MTA (5.7 ± 3.5)	Jang et al. (2014)
			Bioaggregate (9.4 ± 6.1)	
Iron release in water (µg/L)	7 days	711.7 ± 267.9	MTA (171.1 ± 8.0)	Jang et al. (2014)
			Bioaggregate (189.4 + 164.3)	
Manganese release in water (µg/L)	7 days	11.1 ± 3.7	MTA (3.5 ± 0.7)	Jang et al. (2014)
			Bioaggregate (3.5 ± 2.2)	
Nickel release in water (µg/L)	7 days	59.0 ± 58.3	MTA (32.3 ± 21.2)	Jang et al. (2014)
			Bioaggregate (16.1 ± 8.9)	
Lead release in water (µg/L)	7 days	1.10.3	MTA (1.3 ± 0.5)	Jang et al. (2014)
			Bioaggregate (1.9 ± 0.8	
Zinc release in water (µg/L)	7 days	91.7 ± 17.2	MTA (88.2 ± 20.7)	Jang et al. (2014)
			Bioaggregate (31.1 ± 23.8)	
Calcium ion release				
Calcium ion concentration (mmol/L)		0.21 ± 0.03	MTA Angelus (0.22 ± 0.01)	Natale et al. (2015)
Calcium ion leaching in water (µg/g)	28 days	8.216	Theracal (3.289)	Camilleri et al. (2014b)
Calcium ion leaching in HBSS (µg/g)	28 days	10.45	Theracal (4.756)	Camilleri et al. (2014b)
Cumulative calcium ions released in deionized water (ppm) & pH of soaking water	3 h	95.3 ± 13.0 &	MTA Plus (46.6 ± 12.8) & (11.77 ± 0.34)	Gandolfi et al. (2014)
	1 day	11.60 ± 0.15	MTA Plus + gel (97.8 ± 27.8) & (12.00 ± 0.23)	
	3 days	113.4 ± 11.1 &	MTA Angelus (48.0 ± 7.3) & (11.31 ± 0.22)	

Table 1 (continued)

Material characteristics	Time period	Biodentine	Other tricalcium silicate cement groups in the study	References
	7 days	11.63 ± 0.51	ProRoot MTA (27.4 ± 5.4) & (10.99 ± 0.40)	
	14 days	135.1 ± 15.9 &	Tech Biosealer capping (162.7 ± 28.2) & (11.42 ± 0.05)	
	28 days	10.96 ± 0.72	Theracal (18.0 ± 2.3) & (9.53 ± 0.15)	
		177.8 ± 16.2 &	MTA Plus (68.1 ± 12.3) & (11.48 ± 0.59)	
		9.21 ± 0.50	MTA Plus + gel (165.8 ± 31.9) & (12.52 ± 0.27)	
		205.5 ± 17.5 &	MTA Angelus (84.9 ± 12.3) & (11.22 ± 0.11)	
		9.43 ± 0.28	ProRoot MTA (61.0 ± 14.1) & (10.53 ± 0.59)	
		245.8 ± 17.9	Tech Biosealer capping (190.1 ± 21.0) & (11.79 ± 0.25)	
		9.26 ± 0.66	Theracal (52.2 ± 3.8) & (7.89 ± 0.02)	
			MTA Plus (83.9 ± 12.9) & (10.10 ± 1.06)	
			MTA Plus + gel (183.7 ± 33.5) & (10.90 ± 1.37)	
			MTA Angelus (110.6 ± 12.3) & (11.15 ± 0.72)	
			ProRoot MTA (78.9 ± 17.3) & (9.25 ± 0.30)	
			Tech Biosealer capping (209.8 ± 20.8) & (10.65 ± 0.84)	
			Theracal (79.3 ± 6.9) & (8.54 ± 0.29)	
			MTA Plus (96.1 ± 16.4) & (8.74 ± 0.54)	
			MTA Plus + gel (196.2 ± 36.3) & (9.99 ± 1.18)	
			MTA Angelus (161.8 ± 17.5) & (11.29 ± 0.65)	
			ProRoot MTA (96.2 ± 22.0) & (8.78 ± 0.20)	
			Tech Biosealer capping (320.8 ± 24.7) & (10.14 ± 0.51)	
			Theracal (91.9 ± 8.1) & (8.00 ± 0.26)	
			MTA Plus (105.4 ± 16.4) & (8.68 ± 0.29)	
			MTA Plus + gel (207.8 ± 36.6) & (8.60 ± 0.70)	
			MTA Angelus (176.1 ± 18.9) & (10.34 ± 0.59)	
			ProRoot MTA (125.3 ± 26.8) & (7.87 ± 0.29)	
			Tech Biosealer capping (344.7 ± 24.9) & (7.95 ± 0.42)	
			Theracal (113.8 ± 12.4) & (8.43 ± 0.22)	

Table 1 (continued)

Material characteristics	Time period	Biodentine	Other tricalcium silicate cement groups in the study	References
			MTA Plus (112.6 ± 16.0) & (8.24 ± 0.45)	
			MTA Plus + gel (230.9 ± 32.4) & (7.99 ± 0.22)	
			MTA Angelus (198.1 ± 21.0) & (8.94 ± 0.73)	
			ProRoot MTA (146.1 ± 29.7) & (7.20 ± 0.12)	
			Tech Biosealer capping (370.9 ± 27.5) & (7.81 ± 0.49)	
			Theracal (137.8 ± 12.9) & (8.12 ± 0.07)	
Calcium ion concentration (μM/mm^2)	1 day	65.8 ± 2.7	MTA Angelus (27.7 ± 0.4)	Dawood et al. (2015a)
	3 days	33.9 ± 0.9	GC MTA (36.2 ± 1.7)	
	7 days	32.7 ± 0.8	MTA Angelus (24.7 ± 0.7)	
	14 days	30.8 ± 0.7	GC MTA (28.3 ± 1)	
			MTA Angelus (22.8 ± 0.9)	
			GC MTA (34.4 ± 0.8)	
			MTA Angelus (16.1 ± 1.1)	
			GC MTA (36.1 ± 0.9)	
Calcium ion release (ppm)	1 day	225	Tricalcium silicate (133.554)	Li et al. (2016)
	7 days	241.2	Tricalcium silicate + 30% zirconium oxide (173.570)	
	1 month	84.49	Tricalcium silicate + 50% zirconium oxide (156.899)	
			Tricalcium silicate (258.323)	
			Tricalcium silicate + 30% zirconium oxide (382.574)	
			Tricalcium silicate + 50% zirconium oxide (357.166)	
			Tricalcium silicate (124.028)	
			Tricalcium silicate + 30% zirconium oxide (58.673)	
			Tricalcium silicate + 50% zirconium oxide (142.183)	
Hydroxyl ion concentration (mmol/L)		0.42 ± 0.06	MTA Angelus (0.42 ± 0.02)	Natale et al. (2015)
Microleakage				
Microleakage (μm) in interface exposed to normal saline		0.50 ± 0.76	ProRoot MTA (0.81 ± 1.07)	Bolhari et al. (2015)
			CEM (1.13 ± 0.88)	
			Bioaggregate (0.66 ± 1.05)	
Microleakage (μm) in interface exposed to human blood		1.58 ± 1.31	ProRoot MTA (1.36 ± 1.17)	Bolhari et al. (2015)
			CEM (1.36 ± 1.08)	
			Bioaggregate (1.53 ± 0.94)	
Mean microleakage (μL/min/70 cm H_2O)	4 h	0.268 ± 0.0054	MTA Angelus (0.951 ± 0.064)	Butt et al. (2014)
	1 day	0.109 ± 0.0146	MTA Angelus (0.499 ± 0.0469)	
	1 week	0.052 ± 0.0236	MTA Angelus (0.070 ± 0.0035)	
	2 weeks	0.035 ± 0.0036	MTA Angelus (0.050 ± 0.0021)	
	4 weeks	0.017 ± 0.0026	MTA Angelus (0.024 ± 0.0029)	
	8 weeks	0.005 ± 0.0013	MTA Angelus (0.006 ± 0.0006)	
	12 weeks	0.005 ± 0.0005	MTA Angelus (0.005 ± 0.0013)	

Table 1 (continued)

Material characteristics	Time period	Biodentine	Other tricalcium silicate cement groups in the study	References
Mean microleakage in permanent teeth		0.76 ± 0.83		Agrafioti et al. (2015)
Mean microleakage in primary teeth		0.60 ± 0.87		Agrafioti et al. (2015)
Microleakage (μm)	6 days		ProRoot MTA + MTAD (1.021133 ± 0.0648227)	Naik et al. (2015)
			ProRoot MTA + Saline (0.544600 ± 0.0140173)	
			Biodentine + MTAD (0.014133 ± 0.0020882)	
			Biodentine + Saline (0.327067 ± 0.0193128)	
Microleakage (μL/min)	1 day	0.54 ± 0.12	ProRoot MTA (0.59 ± 0.17)	El-Khodary et al. (2015)
	28 days	0.43 ± 0.14	Grey Portland Cement (0.61 ± 0.19)	
	6 months	0.42 ± 0.15	ProRoot MTA (0.49 ± 0.09)	
	1 year	0.42 ± 0.15	Grey Portland Cement (0.50 ± 0.13)	
			ProRoot MTA (0.47 ± 0.09)	
			Grey Portland Cement (0.50 ± 0.14)	
			ProRoot MTA (0.46 ± 0.07)	
			Grey Portland Cement (0.50 ± 0.12)	
Microleakage (mm) (endosonic tip used for preparation)	2 days	0.5650 ± 0.0728	MTA (0.9090 ± 0.1083)	Nanjappa et al. (2015)
Microleakage (mm) (Er:YAG laser used for preparation)	2 days	0.3380 ± 0.1202	MTA (0.7940 ± 0.0445)	Nanjappa et al. (2015)
Microleakage (retropreparation done with ultrasonic retrotip)		1065	MTA (321.2)	Mandava et al. (2015)
Microleakage (retropreparation done with conventional bur)		1171	MTA (490.1)	Mandava et al. (2015)
Apical leakage at 1 mm (μL cm H_2O^{-1} min^{-1})	2 days	2.03 ± 0.11	MTA (2.39 ± 0.14)	Bani et al. (2015)
Apical leakage at 2 mm (μL cm H_2O^{-1} min^{-1})	2 days	1.85 ± 0.10	MTA (1.98 ± 0.17)	Bani et al. (2015)
Apical leakage at 3 mm (μL cm H_2O^{-1} min^{-1})	2 days	0.71 ± 0.04	MTA (0.67 ± 0.05)	Bani et al. (2015)
Apical leakage at 4 mm (μL cm H_2O^{-1} min^{-1})	2 days	0.60 ± 0.05	MTA (0.56 ± 0.05)	Bani et al. (2015)
Marginal gap at dentine-retrograde filling material interface at 1 mm root section (μm)	5 days	1.345 ± 0.717	MTA (0.847 ± 0.298)	Soundappan et al. (2014)
Marginal gap at dentine-retrograde filling material interface at 2 mm root section (μm)	5 days	1.489 ± 0.459	MTA (0.738 ± 0.466)	Soundappan et al. (2014)
Marginal gap area (μm^2)	2 days	11143.42 ± 967.753	ProRoot MTA (22300.97 ± 3068.883)	Ravichandra et al. (2014)
Push-out bond strength				
Micro-push-out (MPa) at pH 7.4	7 days	9.1 ± 1.8	White MTA Angelus (7.0 ± 1.2)	Elnaghy et al. (2014)
Micro-push-out (MPa) at pH 6.4	7 days	7.2 ± 1.1	White MTA Angelus (5.2 ± 0.7)	Elnaghy et al. (2014)
Micro-push-out (MPa) at pH 5.4	7 days	5.3 ± 0.9	White MTA Angelus (3.4 ± 0.6)	Elnaghy et al. (2014)
Micro-push-out (MPa) at pH 4.4	7 days	4.3 ± 0.7	White MTA Angelus (2.5 ± 0.4)	Elnaghy et al. (2014)

Table 1 (continued)

Material characteristics	Time period	Biodentine	Other tricalcium silicate cement groups in the study	References
Push-out bond strength (MPa)	3 days	21.8578 ± 6.89735	ProRoot White MTA (23.2637 ± 5.485)	Alsubait et al. (2014)
			Bioaggregate (9.5739 ± 3.45483)	
Push-out bond strength (MPa) in dentine thickness of 0.75 mm		3.11 ± 0.86	Bioaggregate (2.72 ± 0.90)	Ulusoy et al. (2015)
Push-out bond strength (MPa) in dentine thickness of 1.50 mm		8.13 ± 1.89	Bioaggregate (3.10 ± 0.98)	Ulusoy et al. (2015)
Push-out bond strength (MPa) in dentine thickness of 2.25 mm		9.63 ± 1.58	Bioaggregate (5.73 ± 1.95)	Ulusoy et al. (2015)
Median of bond strength (MPa)	7 days	5.7	MTA Angelus (1.53)	Centenaro et al. (2016)
Push-out bond strength (MPa)	7 days	2.59 ± 0.38	ProRoot MTA (2.09 ± 0.34)	Nagas et al. (2016a)
Push-out bond strength (MPa)	30 min	1.37 ± 0.41		Cechella et al. (2015)
	1 day	8.06 ± 3.14		
	3 days	16.8 ± 7.60		
	28 days	7.77 ± 3.80		
Push-out bond strength (MPa) in PBS	30 min	0.32 ± 0.16		Cechella et al. (2015)
	1 day	9.85 ± 7.36		
	3 days	9.97 ± 4.49		
	28 days	2.84 ± 1.38		
Push-out bond strength (MPa)	14 days	3.58 ± 1.49	ProRoot MTA (7.38 ± 4.17)	Üstün et al. (2015)
			Retro MTA (7.57 ± 3.5)	
			Supra MTA (2.83 ± 1.94)	
Push-out bond strength (MPa) after contamination with blood	14 days	4.36 ± 2.55	ProRoot MTA (8.34 ± 3.9)	Üstün et al. (2015)
			Retro MTA (6.37 ± 0.82)	
			Supra MTA (2.32 ± 1.01)	
Push-out bond strength (MPa) after manual compaction	4 days	9.40 ± 3.04	MTA (6.82 ± 2.13)	Küçükkaya et al. (2016)
			MTA + $CaCl_2$ (5.30 ± 2.32)	
Push-out bond strength (MPa) after ultrasonic activation	4 days	11.12 ± 2.66	MTA (8.50 ± 2.30)	Küçükkaya et al. (2016)
			MTA + $CaCl_2$ (7.72 ± 3.42)	
Shear bond strength				
Shear bond strength (MPa)	12 min	1.600 ± 0.512	Biodentine + Prime & Bond NT (9.127 ± 3.161)	Odabas et al. (2013)
	24 h	1.737 ± 0.434	Biodentine + Clearfil SE Bond (16.903 ± 8.112)	
			Biodentine + Clearfil S^3 Bond (11.057 ± 3.850)	
			Biodentine + Prime & Bond NT (15.990 ± 3.409)	
			Biodentine + Clearfil SE Bond (19.559 ± 7.582)	
			Biodentine + Clearfil S^3 Bond (15.193 ± 3.344)	
Shear bond strength (MPa)	2 days	3.14 ± 1.09	ProRoot MTA (0.0)	Kaup et al. (2015b)
	7 days	9.75 ± 2.19	ProRoot MTA (0.85 ± 1.42)	
	14 days	9.34 ± 1.01	ProRoot MTA (4.96 ± 4.54)	
Mean shear bond strength (MPa) in permanent teeth		3.441 ± 1.953		Agrafioti et al. (2015)
Mean shear bond strength (MPa) in primary teeth		2.485 ± 1.151		Agrafioti et al. (2015)
Fracture resistance				
Fracture resistance		814.54 ± 138.54		Topcuoglu and Topcuoglu (2016)

Table 1 (continued)

Material characteristics	Time period	Biodentine	Other tricalcium silicate cement groups in the study	References
Root fracture resistance (kN)	3 days	2.22 ± 0.54		Di Fiore et al. (2016)
Fracture resistance (MPa)	1 year	38.29 ± 4.58	White MTA Angelus (36.72 ± 6.09)	Elnaghy et al. (2014)
Fracture resistance (N)		529.0284 ± 90.73658	MTA (568.3618 ± 91.78048)	Bayram et al. (2016)
			Bioaggregate (481.6923 ± 126.77524)	
Fracture resistance (N)		1130.61 ± 223.46	MTA (1238.58 ± 142.16)	Ok et al. (2016)
			CEM (1309.46 ± 177.65)	

MTA mineral trioxide aggregate, *MM-MTA* micro mega MTA, *NT* nano-technology, *SE* self etch, *CEM* calcium enriched mixture, *ESRRM* endosequence root repair material, *PBS* phosphate buffered saline, *TCS-20-Zr* tricalcium silicate, zirconium oxide and water, *NaOCl* sodium hypochlorite, *EDTA* ethylenediamenetetraacetic acid, $CaCl_2$ calcium chloride

To facilitate a simple work flow the present paper is organised into four sections as follows. Section I: composition and setting, Section II: physical and mechanical properties, Section III: biological properties, and Section IV: potential clinical applications.

Review update

Section I: composition and setting

Composition

Two studies (Setbon et al. 2014; Gandolfi et al. 2014) employed an environmental scanning electron microscope—energy dispersive X-ray (ESEM-EDX) to analyse the elemental composition (wt%) of unhydrated Biodentine powder and reported the presence of carbon (4.34 and 9.7), oxygen (42 and 38.5), silicon (7.3 and 7.7), calcium (39 and 41.9) and zirconium (2.2 and 2.2), respectively.

Recent studies based on X-ray Energy Dispersive Analysis (EDX) suggest the absence of dicalcium silicate in Biodentine (Camilleri 2014; Setbon et al. 2014). This confirms previous study data (Camilleri et al. 2013) that used XRD to define that Biodentine is mainly composed of tricalcium silicate cement, which facilitates better purification during the fabrication process and may explain the more homogenous particle size. The difference in the chemical composition between Biodentine and ProRoot MTA does not affect the surface topography and both materials exhibited similar levels of surface roughness (Attik et al. 2014). The short setting time of Biodentine compared to all other materials is explained by the absence of dicalcium silicate, which is associated with a slower hydration reaction (Darvell and Wu 2011).

Setting time

The initial setting time of Biodentine as indicated by its manufacturer is about 12 min. However, some studies have reported the initial setting time of Biodentine to be 6.5 ± 1.7 min (Butt et al. 2014) and 30 ± 0 min (Alhodiry et al. 2014). These differences in the setting time may be explained by the different ISO standards used. According to the International Organisation for Standardisation guidelines, ISO 9917-1:2007, the setting time of Biodentine was assessed as 15 ± 1 min (Jang et al. 2014) and 13.1 ± 1.1 min (Dawood et al. 2015c). In the study by Kaup et al., the final setting time of Biodentine was 85.66 ± 6.03 min (Kaup et al. 2015b). Nevertheless, all the studies reported a shorter setting time for Biodentine when compared to ProRoot MTA.

Both saliva and blood contamination, increased the setting time of Biodentine by 1 ± 6.51 min and 16 ± 8.21 min respectively. While, the blood-contaminated group showed a significantly longer setting time compared to the non-contaminated Biodentine group ($p < 0.01$), there was no significant difference in the saliva-contaminated group ($p > 0.05$).

Section II: physical and mechanical properties

Radiopacity

The radiopacity of Biodentine was found to be significantly lower than ProRoot MTA (Kaup et al. 2015b), MTA Angelus, Micro Mega MTA (Tanalp et al. 2013), MTA Plus and Neo MTA Plus (Camilleri 2015). Furthermore, the radiopacity of Biodentine varied between studies with some studies reporting the radiopacity to be lower than the ISO 6876:2001 requirement (Tanalp et al. 2013; Kaup et al. 2015b). In a cone-beam computer tomography (CBCT) study, Biodentine and MTA generated fewer artefacts than amalgam. Therefore, it was concluded that the use of 84 or 96 kVp with

metal artefact reduction (MAR) and low resolution reduced the artefacts and generated the lowest effective dose (Demirturk Kocasarac et al. 2016; Helvacioglu-Yigit et al. 2016).

Colour stability

Biodentine maintained colour stability up to 6 months and exhibited significantly less discolouration compared with ProRoot MTA (Valles et al. 2015; Marconyak et al. 2016), Ortho MTA (Shokouhinejad et al. 2016), gray MTA and white MTA (Kohli et al. 2015), Bioaggregate and MTA Angelus (Yoldas et al. 2016). The presence of bismuth oxide and uptake of blood components in the porosities of various Portland cement based products were considered to be a possible factor to induce discolouration (Lenherr et al. 2012; Marconyak et al. 2016). Conversely, Beatty et al. concluded that Biodentine discoloured significantly more than ProRoot MTA (Beatty and Svec 2015). Clinically perceptible discolouration was observed with Biodentine in the presence of sodium hypochlorite (Camilleri 2015; Keskin et al. 2015), chlorhexidine gluconate (Keskin et al. 2015) and blood (Shokouhinejad et al. 2016). Delayed tooth discolouration was detected in both ProRoot MTA and Biodentine at the one-year evaluation, but it was more evident for ProRoot MTA than Biodentine (Ramos et al. 2016).

Porosity and compressive strength

Biodentine and ProRoot MTA demonstrated lower average pore diameter, porosity, total pore area and higher bulk density when compared to Bioaggregate™, MTA Angelus and MTA Plus (Camilleri et al. 2014a; Gandolfi et al. 2014). Compressive strength of Biodentine was found to be significantly higher than MTA-Angelus, trial MTA (GCMTA) and calcium-enriched mixture (Kayahan et al. 2013; Butt et al. 2014; Dawood et al. 2015c; Natale et al. 2015). Biodentine did not show a significant reduction in its compressive strength when exposed to sodium hypochlorite (NaOCl) while ethylenediamenetetraacetic acid (EDTA) reduced the compressive strength of Biodentine (Govindaraju et al. 2016). Exposure to different pH (4.4, 5.4, 6.4 and 7.4) environments for 7 days led to Biodentine displaying significantly higher compressive strength than white MTA (Elnaghy 2014). In this study, white MTA appeared to be more sensitive to acidic pH than Biodentine. Conversely, another study reported that acid etching procedures after 7 days did not reduce Biodentine's compressive strength (Kayahan et al. 2013), which supports the manufacturer's recommendations to delay the placement of the final restoration for at least one week to obtain mature crystalline formation.

Hardness and flexural strength Biodentine exhibited significantly higher hardness, flexural strength and elastic modulus than ProRoot MTA, Angelus MTA and GCMTA (Dawood et al. 2015c; Kaup et al. 2015b; Natale et al. 2015). Vickers microhardness of Biodentine was identical to sound human dentine but 2-fold higher than that of ProRoot MTA (Kaup et al. 2015b). Surface hardness of Biodentine was not affected by moist or dry storage environment (Caronna et al. 2014) but decreased significantly in the presence of acidic pH of 6.4, 5.4 and 4.4 (Elnaghy 2014). Saliva and blood caused no significant difference in the bi-axial flexural strength of either Biodentine or Portland cement (Alhodiry et al. 2014).

Solubility

According to ISO 6876:2001, studies confirmed that Biodentine displayed solubility similar to ProRoot MTA up to 10-day exposure times. After 10 days, Biodentine demonstrated a marked increase in its solubility (Dawood et al. 2015c; Kaup et al. 2015b; Singh et al. 2015) which could be explained by the higher dissolution of calcium and silicon ions (Singh et al. 2015). Though Biodentine solubility values were higher than ProRoot MTA, this solubility occurred only at the surface which is exposed to the solution and caused negligible dimensional change (Singh et al. 2015). The solubility of Biodentine was higher in distilled water than in phosphate buffered saline (Kaup et al. 2015b). The increased solubility of Biodentine has been attributed to the use of water soluble polycarboxylate in the liquid component. This hydrosoluble polymer has a surfactant effect and thus leads to increased dissolution by applying a charge on it's surfaces (Dawood et al. 2015c). Conflicting results were obtained in the study by Gandolfi et al. with significantly lower solubility values for Biodentine compared to ProRoot MTA, MTA Angelus and MTA Plus (Gandolfi et al. 2014).

Heavy metal release

Nine heavy metal ions released in distilled water (μg/L) were evaluated after 7 days in the study by Jang et al. Arsenic (9.3 ± 6.7), copper (31.7 ± 13.4), iron (711.7 ± 267.9), manganese (11.1 ± 3.7) and zinc (91.7 ± 17.2) were released significantly higher in Biodentine than MTA and Bioaggregate™. Cadmium (0.1 ± 01), chromium (46.2 ± 30.8), nickel (59.0 ± 58.3) and lead (1.1 ± 0.3) release was also higher in Biodentine but without any significant difference in comparison to Bioaggregate™ and MTA (Jang et al. 2014). This increased heavy metal release could be correlated to increased solubility.

Arsenic and lead released from Biodentine was well below the ISO (International Standardisation Organisation) recommendations of < 2 and 100 ppm, respectively. As there are no standards on other trace metals,

the maximum allowable levels in drinking water as put forward by the United States Environmental Protection Agency (USEPA) may be compared. The overall concentration of heavy metals leached out from Biodentine in distilled water was below toxic levels and did not exceed 0.1 ppm in all materials, except for iron. USEPA also set the guidelines of the maximum allowable levels of iron to be 0.3 ppm (Kum et al. 2014).

Calcium ion release

Biodentine released significantly more calcium ions than MTA Angelus and GCMTA after 1, 3, 7 and 14 days (Dawood et al. 2015c). In a similar study, Biodentine showed significantly higher calcium ion release at short-term (3 h) than ProRoot MTA, MTA Angelus and MTA Plus. However, in the long-term (28 days) calcium ion release from Biodentine was significantly higher than MTA Plus alone (Gandolfi et al. 2014). Biodentine released more calcium ions in the early stages and the calcium ion release at 30 days was significantly lower than at day one (Li et al. 2016). The higher calcium ion release from Biodentine could be attributed to the presence of pure tricalcium silicate, calcium chloride, increased calcium hydroxide formation and high solubility (Camilleri 2014; Camilleri et al. 2014b; Gandolfi et al. 2014). When comparing calcium ion release in pH 5.5 and 7.0, Biodentine released significantly more calcium at neutral pH (Natale et al. 2015). In an attempt to compare the effect of leaching in different soaking solutions, it was found that Biodentine leached more calcium ions in Hank's Balanced Salt Solution (HBSS) than in distilled water (Camilleri 2014). Also, Biodentine induced a rise in pH of the soaking water indicating alkalization (Gandolfi et al. 2014).

Microleakage

In an analysis of the sealing ability by fluid-filtration technique, Biodentine provided a valid and stable apical seal for the entire 12-week period tested. At 4- and 24-h period Biodentine provided a seal similar to ProRoot MTA, grey Portland cement and Tech Biosealer (Bani et al. 2015; El-Khodary et al. 2015) but significantly superior than MTA Angelus (Butt et al. 2014). Better adhesion of Biodentine to dentine may result from the physical process of crystal growth within the dentinal tubules leading to micromechanical bonding (Naik et al. 2015). Using the dye penetration technique, it was reported that Biodentine exhibited significantly lesser microleakage than MTA (Soundappan et al. 2014; Agrafioti et al. 2015; Mandava et al. 2015; Nanjappa et al. 2015) but significantly higher than ProRoot MTA, MM-MTA, Glass ionomer cement (Fuji IX GP) and Endosequence (Jeevani et al. 2014; Raju et al. 2014; Vemisetty et al. 2014). When the materials were stored in an acidic environment, no statistical significant difference was found between Biodentine and ProRoot MTA after 3 months (Agrafioti et al. 2015).

Also, in a comparison of various root-end cavity preparation techniques, Er:YAG laser preparation showed better sealing ability with Biodentine than ultrasonic preparation (Nanjappa et al. 2015). The removal of smear layer with MTAD™ irrigation significantly improved the apical seal of Biodentine (Naik et al. 2015). Upon assessing various manipulation techniques, increased microleakage was evident when Biodentine was manually manipulated as compared to machine trituration. This could be explained by the more homogenous mix obtained by mechanical trituration (Gupta et al. 2015). When different storage environments were tested, dry storage of Biodentine resulted in microstructural changes and cracks at the root dentine to Biodentine interface (Camilleri et al. 2014a). Biodentine samples stored in phosphate buffer solution (PBS) produced larger amounts of calcium phosphate precipitates and showed a higher percentage of marginal adaptation than MTA Angelus (Aggarwal et al. 2015). In the presence of simulated body fluid, Biodentine demonstrated the presence of an interfacial layer formation on root canal dentine indicating bioactivity (Kim et al. 2015). However, the thickness of the interfacial layer formed was significantly less than that of white ProRoot MTA. Furthermore, blood contamination did not affect the marginal adaptation of Biodentine, Bioaggregate™, MTA and CEM (Bolhari et al. 2015). In addition, it has also been established that Biodentine exhibited greater dentine mineralisation in totally demineralised dentine than Fuji IX glass ionomer cement (Atmeh et al. 2015).

Push-out bond strength

The capacity of Biodentine to resist dislodgement was greater than Bioaggregate™ (Alsubait et al. 2014; Ulusoy et al. 2015), ProRoot MTA (Nagas et al. 2016a), MTA Angelus (Elnaghy 2014; Dawood et al. 2015b; Centenaro et al. 2016; De-Deus et al. 2016; Silva et al. 2016), GCMTA (Dawood et al. 2015b) and MTA HP (high plasticity). The higher dislodgement resistance of Biodentine is speculated to be a result from smaller particle size that has the potential to enhance penetration of cement into dentinal tubules. This effect is further reinforced through formation of 'mineral tags' leading to increased micromechanical retention (Han and Okiji 2011; Nagas et al. 2016a). The micromechanical anchorage is also partly due to increased calcium and hydroxyl ion release responsible for improved apatite formation at the Biodentine-dentine interface (Silva et al. 2016a). Biodentine and ProRoot MTA were found to fill

gaps between dentine and cement by calcium phosphate deposition without any chemical changes to the adjacent dentine. The thickness of the transition zone as measured by micro Raman spectroscopy was 7.5 ± 4.2 µm for Biodentine compared to 6.2 ± 5.4 µm for ProRoot MTA with no significant difference between the groups (Li et al. 2015). On the contrary, one study concluded that Biodentine showed significantly lower bond strength than ProRoot MTA and Retro MTA (Ustun et al. 2015).

Micro-push-out bond strength of Biodentine decreased significantly with decreasing pH form 7.4, 6.4, 5.4 to 4.4 (Elnaghy 2014). Conversely, blood contamination did not affect the dislocation resistance of Biodentine (Ustun et al. 2015). Conflicting results have been published regarding the effect of PBS on the push-out bond strength of Biodentine. Long-term PBS immersion (60 days) was found to positively influence the resistance to dislodgement in the study by De-Deus et al. whereas the study by Cechella et al., showed that the bond strength of Biodentine increased up to 3 days but reduced significantly after 28 days when exposed to PBS (Cechella et al. 2015; De-Deus et al. 2016). Regardless of the placement technique used (manual compaction or ultrasonic activation), Biodentine exhibited significantly higher bond strength values when compared with MTA or MTA + $CaCl_2$ (calcium chloride) groups (Kucukkaya Eren et al. 2016).

Shear bond strength

Biodentine exhibited lower shear bond strength than MTA Angelus (Altunsoy et al. 2015), CEM (Altunsoy et al. 2015) and Fuji IX GP (Raju et al. 2014) but higher shear bond strength than ProRoot MTA (Cantekin and Avci 2014; Kaup et al. 2015a). Biodentine presented significantly lower shear bond strength values when immediately bonded to resin composite. Cohesive failure within Biodentine indicated a weak material in its early setting phase (Deepa et al. 2016). Therefore, several authors have concluded that a final resin composite restoration should best be delayed for more than 2 weeks to allow adequate setting and sufficient intrinsic maturation of Biodentine for withstanding contraction forces from the resin composite (Hashem et al. 2014; Deepa et al. 2016). Also, the placement of glass ionomer cement based materials prior to composite resin restorations decreased the shear bond strength (Cengiz and Ulusoy 2016). For immediate permanent restoration, a stainless steel crown loaded with glass ionomer cement could be seated on unset Biodentine after the third minute of mixing in pulpotomy cases (Dawood et al. 2015a).

No statistically significant differences were evident between different adhesive systems (Colak et al. 2016) but the 2-step self-etch adhesives exhibited higher shear bond strength to Biodentine in comparison to 1-step self-etch adhesives and etch-and-rinse adhesives (Odabas et al. 2013).

Fracture resistance

For the treatment of simulated immature teeth with open apices, Biodentine, White MTA Angelus, Calcium-enriched mixture (CEM) and Bioaggregate did not show any significant difference regarding root fracture resistance (Bayram and Bayram 2016; Elnaghy and Elsaka 2016; Evren et al. 2016). Subsequent inspection of the fractured tooth revealed fracture along the same plane as surrounding dentine and no areas of material de-bonding from dentine (Di Fiore et al. 2016). In the study by Zhabuawala et al. the fracture resistance of immature teeth with an apical plug of Biodentine followed by obturation with gutta-percha, composite resin, or Biodentine was similar when tested immediately. In the same study, after 3 months of aging, teeth obturated completely with Biodentine showed a drastic reduction in the fracture resistance whereas there was no significant reduction in fracture strength in teeth with an apical plug of Biodentine backfilled with gutta-percha and composite resin (Zhabuawala et al. 2016).

Alterations to the composition To improve the properties of Biodentine, CPP-ACP has been added to the original composition in varying concentrations (0.5, 1, 2 and 3%). The addition of up to 1% CPP-ACP did not affect the physical properties of Biodentine except for a significant increase in the setting time, calcium and phosphate ion release (Dawood et al. 2015c) and push-out bond strength (Dawood et al. 2015b). The incorporation of 3% CPP-ACP into Biodentine increased solubility but reduced the compressive strength and surface microhardness by 36 and 31% respectively. In another study by Nagas et al., addition of 5 wt% alkali resistant glass fibre powder to Biodentine resulted in higher compressive and diametrical tensile strength than Biodentine, ProRoot MTA or fibre-reinforced ProRoot MTA (Nagas et al. 2016b).

Section III: biological properties

Antimicrobial activity

Biodentine's antibacterial activity was strongest against the *Streptococcus sanguis* strains, which was significantly higher than MTA Angelus, ProRoot MTA and intermediate restorative material (Poggio et al. 2014a, 2015a; Ceci et al. 2015). The weakest antibacterial activity of Biodentine was seen against *Streptococcus mutans* with Biodentine exhibiting minimal or almost no antibacterial activity (Poggio et al. 2014a; Ceci et al. 2015; Poggio et al. 2015a). Against *Streptococcus salivarius,* MTA Angelus and ProRoot MTA showed significantly higher antibacterial activity than Biodentine (Poggio et al. 2014a, 2015a; Ceci et al. 2015). Furthermore, Biodentine's antibacterial activity was similar to MTA Angelus but significantly higher than ProRoot MTA

and MTA Plus against *Enterococcus faecalis (Bhavana* et al. 2015*; Hiremath* et al. 2015*; Koruyucu* et al. 2015*)* and *Escherichia coli (Bhavana* et al. 2015*)*. Antifungal activity of Biodentine against *Candida albicans* was similar to MTA Angelus and MTA Plus (Hiremath et al. 2015) but significantly higher than ProRoot MTA (Bhavana et al. 2015).

Gene expression

Biodentine exhibited the capacity to induce odontoblastic differentiation of human dental pulp stem cells (hDPSCs) obtained from impacted third molars via heme oxygenase-1 (HO-1), reactive oxygen species (ROS), nuclear factor-E2-related factor-2 (Nrf2), mitogen-activated protein kinase (MAPK) and calmodulin-dependent protein kinase (CAMKII) pathways (Chang et al. 2014; Luo et al. 2014b; Jung et al. 2015). Biodentine increased phosphorylation of extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (Jung et al. 2015). Like ProRoot MTA, Biodentine also induced the up-regulation of osteocalcin (OCN), dentine sialophosphoprotein (DSPP), dentine matrix acidic phosphoprotein 1(DMP1), collagen type I (COL1A1), runt related transcription factor (Runx2) and bone sialoprotein (BSP) upon exposure to hDPSCs (Chang et al. 2014; Luo et al. 2014b; Widbiller et al. 2016). Although Biodentine stimulated similar markers as MTA, the staining was more intense and spread over a larger area of the pulp tissue (Daltoe et al. 2016). Exposure of hDPSCs to Biodentine (0.2 mg/ml) for 24 hours showed a significantly increased mRNA expression of chemokines such as CXC chemokine receptor type 4 (CSCR4), monocyte chemoattractant protein 1 (MCP-1), stromal cell-derived factor-1 (SDF-1) and adhesion molecules such as fibronectin (FN), intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and Integrinβ1 (Luo et al. 2014a). Osteogenic differentiation of hDPSCs were increased after elution of cytotoxic components from Biodentine.

Exposure to MTA and Biodentine stimulated expression of angiogenic genes such as vascular endothelial growth factor (VEGFA) and c-fos induced growth factor (FIGF/VEGFD) but significantly decreased the mRNA levels of angiopoietin 1, ANGPT1 and fibroblast growth factor 2 (FGF2). Based on these findings, Biodentine might enhance angiogenesis when used in direct contact with SCAP (Peters et al. 2015). Biodentine also elicited a favourable response on human mesenchymal stem cells (hMSCs) and human umbilical vein endothelial cells (HUVECs) but the osteogenic and angiogenic outcome was slightly lower than ProRoot MTA and MTA Plus (Costa et al. 2016). Biodentine induced mRNA expression of alkaline phosphatase (ALP), osteocalcin (OC) and bone sialoprotein (BSP) in hMSCs (Lee et al. 2014).

Cytotoxicity

After 24 h, cytotoxicity was in the order of CEM > Biodentine > ProRoot MTA on human stem cells from apical papilla (SCAP). At 48- and 72-h, the cytotoxicity was reported to be MTA > Biodentine > CEM (Saberi et al. 2016). Stem cells from apical papilla in contact with Biodentine exhibited increased cell viability than control group at day one but not at days 3 and 7. Biodentine showed significantly less cell viability (73%) after 24 h of incubation, whereas more than 90% cell viability was evident after 48- and 72-h of incubation with human periodontal ligament fibroblasts (Kucukkaya et al. 2016). In comparison to ProRoot MTA, Biodentine demonstrated significantly better results regarding cell survival and proliferation of periodontal ligament cells (Jung et al. 2014; Escobar-Garcia et al. 2016). The presence of a less toxic radiopacifier (zirconium oxide) in Biodentine could be responsible for these results (Kucukkaya et al. 2016). Contrasting results with ProRoot MTA exhibiting better human periodontal ligament cell viability than Biodentine and Endosequence has also been reported (Samyuktha et al. 2014). Biodentine and ProRoot MTA showed similar effects in terms of cytotoxicity and cytokine expression (interleukin-1α and interleukin-6) level in mouse embryonic fibroblast cells (Corral Nunez et al. 2014) and primary mouse embryonic Balb/c 3T3 fibroblasts (Silva et al. 2016b). The cytotoxic effect of Biodentine on hDPSCs were time and concentration dependent. The initial cytotoxicity of Biodentine could be attributed to the high pH values (Bortoluzzi et al. 2015), and when used in direct contact with the pulp can positively influence healing by enhancing proliferation, migration and adhesion of hDPSCs (Luo et al. 2014a).

Biodentine and ProRoot MTA showed lower cytotoxicity towards MDPC-23 murine odontoblasts cells (Poggio et al. 2015b). In other studies, with MDPC-23 cells, at 24- and 48-h, Biodentine, MTA Angelus and ProRoot MTA did not show any significant differences in the cytocompatibility but at 72 h, Biodentine demonstrated significantly higher cytocompatibility than MTA Angelus (Poggio et al. 2014a, b; Ceci et al. 2015). TRPA1 is an ion channel responsible for pain and inflammation. Its expression was induced in cultured odontoblast like cells by tumour necrosis factor alpha (TNF-α) and this expression was significantly reduced in the presence of Biodentine (El Karim et al. 2016).

Biodentine, ProRoot MTA and MTA Plus revealed dose-dependent cytotoxicity and time dependent cell viability of osteoblasts (Cornelio et al. 2015). There was no significant difference in the osteoblast cell viability between ProRoot MTA and Biodentine (Jung et al. 2014; Cornelio et al. 2015).

Animal model

Subcutaneous implantation of endodontic materials in 60 Holtzman adult male rats (da Fonseca et al. 2016), 45 white female Wistar rats (Simsek et al. 2015) and 15 male Wistar rats (Mori et al. 2014) concluded that Biodentine showed an initial inflammatory response that was quickly followed by acceptance of Biodentine by the tissue in contact. The reduction in inflammatory process and lymphocyte infiltration from 7 to 14 and 30 days was statistically significant (Mori et al. 2014). This process was coupled with the formation of collagen fibre bundles in the capsules of Biodentine and not harmful to the connective tissue after prolonged implantation in subcutaneous tissue (da Fonseca et al. 2016). Biodentine could be considered to be biocompatible as it allows for reduction in the inflammatory response over time (Mori et al. 2014) and the decline in inflammation is more rapid in Biodentine when compared to MM-MTA and Bioaggregate™ (Simsek et al. 2015).

In a pulp capping study performed in 18 Sprague–Dawley rats (9 weeks old), micro CT analysis revealed that Biodentine and ProRoot MTA showed significantly thicker hard tissue formation than Bioaggregate™. Hematoxylin and eosin staining illustrated formation of complete dentine bridge with normal pulp histology. In comparison to ProRoot MTA, Biodentine showed an irregular, heterogeneous distribution of mineralization nodules within a uniform thickness of hard tissue barrier. This could be a result of rapid initial disorganised formation of the reparative dentine (Kim et al. 2016). Similar results were obtained in the human model, with tomographic evaluation of direct pulp capping executed in 44 caries-free human third molars indicated for extraction. The dentine bridges in the Biodentine group were found to have highest average and maximum volumes in comparison to ProRoot white MTA (Nowicka et al. 2015).

Pulp capping study by Tziafa et al. on 34 teeth of three miniature swine revealed that the thickness of hard tissue bridges were significantly higher with Biodentine when compared to white MTA Angelus. In the Biodentine group, a thick zone of new osteodentinal matrix with cellular inclusions was consistently observed after 3 and 8 weeks. Ectopic formation of osteodentine far from the capping materials was also noted to be significantly higher in Biodentine than in white MTA Angelus (Tziafa et al. 2014). Pulpotomy performed in 30 teeth of 3 beagle dogs (12 months old) demonstrated mineralised tissue bridge formation in significantly more specimens treated with Biodentine (96.8%) than with ProRoot white MTA (72.2%). Radiographic visualisation of more bridges in Biodentine was related to the sensitivity of radiographic techniques to detect bridges thinner than 0.5 mm. The tissue bridges formed by both the cements had similar morphology but the thickness was significantly more in the Biodentine group (De Rossi et al. 2014).

The analyses of magnesium, aluminium, calcium, chromium, arsenic and lead accumulation in the brain, kidney and liver of 18 Wistar albino rats (3–5 months old) was detected after subcutaneous implantation of endodontic materials by inductively coupled plasma mass spectrometry (ICP-MS) with a sensitivity of 0.2 parts per billion (ppb). Elevated levels of these trace elements were identified in the different organs but they were below the toxic levels in all cases. Furthermore, there was no significant difference between the control groups and Biodentine, MM-MTA and Bioaggregate™ based on the concentration of aluminium, calcium, arsenic and lead in the rat organs (Simsek et al. 2016).

Section IV: clinical applications

A total of 43 clinical studies were identified, of which four were RCTs, three were case control studies and 36 were case reports. Very few high quality clinical trials with long follow-up periods were identified. Only seven clinical studies were based on treatment of the primary dentition and all of them evaluated Biodentine as a pulpotomy medicament. As case reports are considered to be of low evidence, the results of this section have to be interpreted with caution. However, the case reports included provided an overview of the possible clinical indications in which Biodentine™ could be used. In addition, 11 ongoing clinical trials were identified in the database of clinicaltrials.gov of which six were newly registered in the past 3 years and 5 were still in their recruitment phase.

Randomised controlled trial

A RCT evaluating Biodentine as a pulpotomy agent in 41 primary molars in children aged 4 to 9 years (Cuadros-Fernandez et al. 2015) and reported a 100% clinical and 94.9% radiographic success after 12 months. Similarly, another RCT of 25 primary molars treated with Biodentine, reported 95.2% clinical and 94.4% radiographic success after 18 months (Rajasekharan et al. 2016). In both RCTs, clinical and radiographic findings did not show any significant difference between Biodentine and MTA. However, another randomised, split-mouth, double blind, controlled clinical trial carried out in 56 primary molars showed 100% clinical and radiographic success with Biodentine after 6 months (Meligy et al. 2016).

A RCT evaluated the efficacy of Biodentine as an indirect pulp capping material was assessed in 18 to 76 year old

adults (Hashem et al. 2015). Thirty-six teeth with reversible pulpitis were used in each group with 85% of the restorations placed in molars. After 12 months follow up, clinical success rates for Biodentine and Fuji IX GIC were 83.3%. Statistically, there was no significant difference in the dentine-pulp response between Biodentine and Fuji IX GIC.

Case–control studies

Three case–control studies evaluated Biodentine as a pulpotomy medicament in primary molars. In the study by Kusum et al. 25 primary molars in 3 to 10 year old children were treated with Biodentine (Kusum et al. 2015). MTA and Biodentine showed 92 and 80% radiographic success respectively after 9 months follow-up and 100% clinical success was observed in both the groups. Similarly, in the study by Niranjani et al., no statistically significant difference was observed between MTA and Biodentine as a pulpotomy medicament after 6 months follow-up (Niranjani et al. 2015). In this study, 25 primary molars in 5–9 year old children were treated with Biodentine. The study by Togaru et al., evaluated 90 decayed primary molars that required pulpotomy treatment with either Biodentine or MTA. Both the groups showed a 95.5% success rate at the end of 12 months (Togaru et al. 2016).

Case reports

A total of 36 case reports were published in the past 3 years and the use of Biodentine in various therapies such as direct pulp capping (Bhat et al. 2014), partial pulpotomy (Villat et al. 2013; Martens et al. 2015), pulpotomy (Borkar and Ataide 2015; Kenchappa et al. 2015; Martens et al. 2015; Soni 2016), palatogingival groove (Johns et al. 2014; Sharma et al. 2015), palatoradicular groove (Naik et al. 2014; Nadig et al. 2016), apexification (Khetarpal et al. 2014; Nayak and Hasan 2014; Sinha et al. 2014; Bajwa et al. 2015; Kenchappa et al. 2015; Martens et al. 2016; Niranjan et al. 2016; Vidal et al. 2016), apexogenesis (Kenchappa et al. 2015), single-visit pulp revascularization/regeneration (Aldakak et al. 2016; Topcuoglu and Topcuoglu 2016), internal resorption (Umashetty et al. 2015), invasive cervical resorption (Salzano and Tirone 2015; Baranwal 2016; Karypidou et al. 2016), perforation repair (Borkar and de Noronha de Ataide 2015; Kenchappa et al. 2015; Pruthi et al. 2015), incomplete vertical root fracture (Hadrossek and Dammaschke 2014), endodontic surgery (Caron et al. 2014) and retrograde restoration (Pawar et al. 2013) have been reported. All reported case reports have advocated the use of Biodentine as they demonstrated successful healing without adverse clinical and/or radiographic symptoms.

A summary of the treatment, type of study, number of teeth used, age of the patient and follow up period is listed in Table 2. The use of Biodentine has been reported to be successful in certain unconventional circumstances which include pulpotomy after several days of traumatic pulp exposure, single visit apexification, massive resorptive lesion with multiple perforations, combined endodontic-periodontic lesion and incomplete vertical root fracture. Although Biodentine has demonstrated successful outcomes in a variety of treatment scenarios, high quality clinical trials are still scarce.

Conclusion

In summary, recent studies have confirmed the absence of dicalcium silicate in Biodentine. The initial setting time times range between 6 and 30 min in various studies. Radiopacity of Biodentine was significantly lower than other tricalcium silicate based cements. Contrasting reports were published on whether the radiopacity values were in accordance with the ISO limits. Similarly, conflicting results were observed regarding the colour stability of Biodentine. The conflicting results could be due to the heterogeneity in the methodology used in respective studies.

On a positive note, Biodentine exhibited significantly superior compressive strength, microhardness, flexural strength, sealing ability, push-out bond strength and calcium ion release in comparison to other tricalcium silicate based cements. On the other hand, increased long-term solubility, higher heavy metal release and decreased shear bond strength were also observed with Biodentine.

Antimicrobial activity of Biodentine was significantly higher against certain strains such as *Streptococcus sanguis, Enterococcus faecalis, Escherichia coli* and *Candida albicans* whereas significantly lower antibacterial activity was observed against *Streptococcus mutans* and *Streptococcus salivarius.* Similair to other tricalcum silicate based cements, cytotoxicity of Biodentine was dose and time dependent.

In animal model studies, pulp capping experiments showed thicker hard tissue bridges and increased mineralised tissue bridge formation was observed in pulpotomy experiments. Randomised controlled trials and case control studies showed Biodentine to be a suitable alternative to MTA. A wide range of clinical indications have been published as case reports regarding the use of Biodentine but clinical studies of long term efficiency and high evidence are still lacking and that precludes a definitive conclusion.

The enhanced physical and biologic properties of Biodentine have been repeatedly emphasised in the literature. Due to its ability to overcome the drawbacks of MTA, Biodentine has great potential to revolutionise the different treatment modalities in paediatric dentistry and endodontics especially after traumatic injuries.

Table 2 Overview of reported clinical applications of Biodentine

Clinical applications	Type of study	Number of teeth	Age of patient (years)	Dentition	Follow up (months)	Authors
Indirect pulp capping	Randomized Controlled Trial	36	18–76	Permanent	12	Hashem et al. (2015)
Direct pulp capping	Case report	1	8	Permanent	12	Bhat et al. (2014)
Partial pulpotomy	Case report	1	12	Permanent	6	Villat et al. (2013)
	Case report	3	18, 19 & 25	Permanent	18	Borkar and Ataide (2015)
	Case report	2	8	Permanent	36	Martens et al. (2015)
	Case report	1	12	Permanent	18	Soni et al. (2016)
Pulpotomy	Case report	1	7	Permanent	48	Martens et al. (2015)
	Case report	1	26	Permanent	18	Borkar and Ataide (2015)
	Case report	1	5	Primary	–	Kenchappa et al. (2015)
	Case control study	25	3–10	Primary	9	Kusum et al. (2015)
	Case control study	20	5–9	Primary	6	Niranjani et al. (2015)
	Case control study	45	4–9	Primary	12	Togaru et al. (2016)
	Randomized Controlled Trial	41	4 - 9	Primary	12	Cuadros-Fernández et al. (2015)
	Randomized Controlled Trial	56	4–8	Primary	6	El Meligy et al. (2016)
	Randomized Controlled Trial	25	3–8	Primary	18	Rajasekharan et al. (2016)
Palatogingival groove	Case report	1	24	Permanent	24	Johns et al. (2014)
	Case report	1	25	Permanent	12	Sharma et al. (2015)
Palatoradicular groove	Case report	1	22	Permanent	6	Naik et al. (2014)
	Case report	1	35	Permanent	12	Nadig et al. (2016)
Single visit apexification	Case report	1	20	Permanent	12	Nayak et al. (2013)
	Case report	1	18	Permanent	12	Sinha et al. (2014)
	Case report	1	10	Permanent	1	Bajwa et al. (2015)
	Case report	1	11	Permanent	24	Aldakak et al. (2016)
	Case report	2	8	Permanent	12	Niranjan et al. (2016)
Apexification	Case report	1	9	Permanent	18	Vidal et al. (2016)
	Case report	1	11	Permanent	6	Kenchappa et al. (2015)
Root end apexification	Case report	1	15	Permanent	18	Khetarpal et al. (2014)
Apexogenesis	Case report	2	9	Permanent	18	Kenchappa et al. (2015)
	Case report	3	8 & 9	Permanent	6–24	Rajasekharan et al. (2016)
Retrograde restoration	Case report	2	24	Permanent	18	Pawar et al. (2013)
Internal resorption	Case report	1	25	Permanent	43	Borkar and Ataide (2015)
	Case report	1	30	Permanent	10	Umashetty et al. (2015)
Invasive cervical resorption	Case report	1	46	Permanent	18	Salzano and Tirone (2015)
	Case report	1	22	Permanent	12	Salzano and Tirone (2015)
	Case report	1	61	Permanent	10	Salzano and Tirone (2015)
	Case report	1	14	Permanent	4	Salzano and Tirone (2015)
	Case report	2	–	Permanent	24	Karypidou et al. (2016)
	Case report	2	23	Permanent	11	Baranwal (2016)
Root perforation repair	Case report	1	14	Permanent	–	Kenchappa et al. (2015)
External perforating root resorption	Case report	1	28	Permanent	18	Pruthi et al. (2015)
Incomplete vertical root fracture	Case report	1	78	Permanent	24	Hadrossek and Dammaschke (2014)
Endodontic surgery	Case report	2	48 & 50	Permanent	24	Caron et al. (2014)
Regenerative endodontic therapy	Case report	3	8 & 9	Permanent	18	Topcuoglu and Topcuoglu (2016)

Funding The authors declare that no funding was received for this review.

Compliance with ethical standards

Conflict of interest The research group received material support from Septodont, Paris, France for educational programmes intended for general dentists.

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