



## Histologic evidence of periodontal regeneration in furcation defects: a systematic review

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### Abstract

**Objective** To systematically review the available histologic evidence on periodontal regeneration in class II and III furcations in animals and humans.

**Materials and methods** A protocol including all aspects of a systematic review methodology was developed including definition of the focused question, defined search strategy, study inclusion criteria, determination of outcome measures, screening methods, data extraction and analysis, and data synthesis. The focused question was defined as follows: “What is the regenerative effect obtained by using or not several biomaterials as adjuncts to open flap surgery in the treatment of periodontal furcation defects as evaluated in animal and human histological studies?”

**Search strategy** Using the MEDLINE database, the literature was searched for articles published up to and including September 2018: combinations of several search terms were applied to identify appropriate studies. Reference lists of review articles and of the included articles in the present review were screened. A hand search of the most important dental journals was also performed.

**Criteria for study selection and inclusion** Only articles published in English describing animal and human histological studies evaluating the effect of surgical treatment, with or without the adjunctive use of potentially regenerative materials (i.e., barrier membranes, grafting materials, growth factors/proteins, and combinations thereof) for the treatment of periodontal furcation defects were considered. Only studies reporting a minimum of 8 weeks healing following reconstructive surgery were included. The primary outcome variable was formation of periodontal supporting tissues [e.g., periodontal ligament, root cementum, and alveolar bone, given as linear measurements (in mm) or as a percentage of the instrumented root length (%)] following surgical treatment with or without regenerative materials, as determined histologically/histomorphometrically. Healing type and defect resolution (i.e., complete regeneration, long junctional epithelium, connective tissue attachment, connective tissue adhesion, or osseous repair) were also recorded.

**Results** In animals, periodontal regeneration was reported in class II and III defects with open flap debridement alone or combined with various types of bone grafts/bone substitutes, biological factors, guided tissue regeneration, and different combinations thereof. The use of biological factors and combination approaches provided the best outcomes for class II defects whereas in class III defects, the combination approaches seem to offer the highest regenerative outcomes. In human class II furcations, the best outcomes were obtained with DFDBA combined with rhPDGF-BB and with GTR. In class III furcations, evidence from two case reports indicated very limited to no periodontal regeneration.

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**Conclusions** Within their limits, the present results suggest that (a) in animals, complete periodontal regeneration has been demonstrated in class II and class III furcation defects, and (b) in humans, the evidence for substantial periodontal regeneration is limited to class II furcations.

**Clinical relevance** At present, regenerative periodontal surgery represents a valuable treatment option only for human class II furcation defects but not for class III furcations.

**Keywords** Periodontal regeneration · Furcation defects · Histology · Animal studies · Human studies

## Introduction

Furcation involvement is characterized by loss of attachment and bone in the interradicular area of multi-rooted teeth and represents one of the major complications of periodontal disease; left untreated, long-term tooth prognosis may significantly deteriorate leading ultimately to tooth loss. Substantial evidence indicates that unrelated to age, both periodontal disease severity and tooth mortality are more pronounced at molars [1–6].

Periodontal therapy at molars with furcation involvement results in less favorable outcomes compared to that at single-rooted teeth or molars without furcation involvement [7–9]. On one hand, this might be related to difficulties in self-performing adequate oral hygiene [3, 10, 11], on the other hand, to suboptimal furcation debridement due to limited accessibility and the complex tooth anatomy [12–14].

Long-term prognosis of molars with class I furcation involvement was shown to be comparable to that of molars without furcation involvement [15, 16]. Class I furcation defects can be successfully managed by non-surgical mechanical therapy [8, 9], representing no or a minor risk factor for tooth loss. However, molars with class II or III furcation involvements show a higher rate of further periodontal breakdown and tooth loss after treatment as compared to molars without furcation defects [15, 17, 18]. Over a 10-year period, molars with class III furcation involvement have been associated with a 40% mortality, despite regular supportive periodontal therapy, while the corresponding number for class II furcation defects was 25% [15].

Over the last decades, various treatment approaches including non-surgical periodontal therapy, resective or reconstructive periodontal surgery, even extraction followed by implant placement have been used to treat furcation involved teeth. Interestingly, a recent study has evaluated the cost-effectiveness of retaining furcation involved molars using various periodontal treatments (e.g., scaling and root planing, resective and reconstructive surgery) versus replacing them with implant supported crowns [19]. The study has shown that natural teeth were retained for longer periods compared to implant supported crowns irrespective of the furcation involvement, age, or smoking status. These findings are in line with those from Fardal et al. [20] who have demonstrated that in periodontitis patients, the cost of maintaining implants was

much higher than the cost of maintaining teeth. Taken together, the evidence from the literature supports the rationale to treat and maintain furcation involved molars.

The ultimate goal of furcation defects therapy is furcation closure via periodontal regeneration [i.e., formation of root cementum, periodontal ligament (PDL), and alveolar bone encompassing the entire furcation area]. Evidence from clinical studies indicates that reconstructive periodontal surgery including various types of bone grafts/bone substitutes, biologic factors, guided tissue regeneration (GTR), or various combinations thereof may indeed improve the outcomes in class II furcations [21–25]. Despite the fact that complete furcation closure was rather rare, the evidence indicates that reconstructive periodontal surgery may convert class II furcation defects to class I, thus improving long-term tooth prognosis [26, 27]. Since in clinical settings the efficacy of various regenerative materials can only be evaluated clinically or radiographically, it is still unclear which of the regenerative materials may promote periodontal regeneration in furcation type defects as demonstrated histologically. A plethora of regenerative materials have been tested on animal models and then applied clinically in patients, leaving following questions open:

1. What is the evidence for periodontal regeneration in class II and III furcation defects as evaluated histologically in animals?
2. What is the evidence for periodontal regeneration in class II and III furcation defects as evaluated histologically in humans?

Therefore, the aim of this paper was to systematically review the available histological evidence of reconstructive periodontal surgery in terms of periodontal wound healing/regeneration in animal and human furcation defects.

## Materials and methods

### Development of a protocol

A protocol including all aspects of a systematic review methodology was developed prior to commencing the review. This included definition of the focused question; a defined search strategy; study inclusion criteria; determination of outcome

measures; screening methods, data extraction, and analysis; and data synthesis.

## Defining the focused question

We defined the focused question as follows: “What is the regenerative effect (regenerated periodontal tissues) and its magnitude (amount of regenerated tissues- linear, areal, volumetric) obtained by using or not several biomaterials as adjuncts to open flap surgery in the treatment of periodontal furcation defects as evaluated in animal and human histological studies?”

## Search strategy

Using the MEDLINE database, the literature was searched for articles published up to and including September 2018: combinations of several search terms were applied to identify appropriate studies (Table 1). Reference lists of review articles and of the included articles in the present review were screened. Finally, a hand search of the major dental journals was performed.

**Table 1** Search terms used to identify the relevant studies

### Search terms

“periodontal furcation defect” OR “periodontal furcation lesion” OR “furcation osseous defect” OR “furcation lesion” OR “furcation defect” OR “furcation involvement” OR “furcation problem” OR “furcation invasion” OR “furcation”

AND

(“guided tissue regeneration” OR “GTR” OR “membrane” OR “barrier” OR “periodontal regeneration” OR “bone graft” OR “bone replacement graft” OR “bone substitute” OR “osseous graft” OR “bone transplantation” OR “bone regeneration” OR “bone matrix” OR “autograft” OR “autogenous bone graft” OR “allogenic bone graft” OR “allograft” OR “freeze dried bone allograft” OR “demineralized freeze-dried bone allograft” OR “decalcified freeze-dried bone allograft” OR “bovine bone” OR “xenograft” OR “xenogenic graft” OR “synthetic graft” OR “alloplastic graft” OR “alloplastic material” OR “polymer” OR “ceramic graft” OR “bioactive ceramic graft” OR “bioglass” OR “biomaterial” OR “bioceramic” OR “hydroxyapatite” OR “calcium phosphate” OR “tricalcium phosphate” OR “beta-tricalcium phosphate” OR “tricalcium phosphate” OR “ceramic” OR “calcium carbonate” OR “calcium sulfate” OR “Plaster of Paris” OR “Emdogain” OR “EMD” OR “enamel matrix derivative” OR “biomimetic substances” OR “growth factors” OR “graft” OR “grafting” OR “regenerative material”)

AND

“human study” OR “clinical study” OR “patient” OR “human” OR “case” OR “report” OR “preclinical study” OR “animal” OR “monkey” OR “dog” OR “pig”

AND

“histological study” OR “histology” OR “histomorphometrical study” OR “histomorphometry” OR “electron microscopy study” OR “biopsy” OR “block section” OR “histological evaluation” OR “histomorphometrical evaluation”

## Criteria for study selection and inclusion

Study selection considered only articles published in English, describing animal and human histological studies evaluating the effect of surgical treatment, with or without the adjunctive use of potentially regenerative materials (i.e., barrier membranes, grafting materials, growth factors/proteins, and combinations thereof) for the treatment of periodontal furcation defects. Only studies with minimum 8 weeks of healing following reconstructive surgery were included in the analysis.

## Outcome measure determination

The primary outcome variable was the formation of periodontal tissues following surgical treatment with or without regenerative materials as determined histologically/histomorphometrically. Formation of PDL, cementum, and alveolar bone given as linear measurements (in mm) or as a percentage of the instrumented root length (%) were extracted. Postsurgical periodontal defect size alterations, evidenced by histomorphometric measurements, were also extracted. Healing type and defect resolution were also recorded (i.e., complete regeneration, long junctional epithelium, connective tissue attachment, connective tissue adhesion, or osseous repair).

## Screening method

Titles and abstracts of the selected studies were independently screened by three reviewers (O.L., R.C., and G.N.). The screening was based on the following question: “Was the study conducted in animals or humans, and did it report histological outcomes after a healing period of at least eight weeks in periodontal furcation defects treated by means of reconstructive periodontal surgery with or without biomaterials?” Full-text articles were obtained if the response to the screening question was “yes” or “uncertain.” The level of agreement between reviewers was determined by kappa scores. Disagreement regarding inclusion was resolved by discussion between the authors. If deemed necessary, for missing data, the authors of the respective studies were also contacted.

## Data extraction and analysis

Following data were extracted: general characteristics (authors, year of publication); study characteristics (number of subjects and defects, defect characteristics, intervention strategies, evaluation period, outcome measures); methodological characteristics (study design, methodological quality); and conclusions. Because of the heterogeneity of the included studies (study design, animal type, defect type, materials used, evaluation methods, outcome measures, observation periods), no weighted mean differences could be calculated, and

consequently no quantitative data synthesis and meta-analysis could be performed. Therefore, data regarding mean and standard deviation, 95% confidence intervals, and statistical significances were extracted from the reviewed articles and summarized in separate tables based upon the various types of biomaterials/interventions employed. Results reporting percentages of regeneration with different interventions/biomaterials were combined from different studies and presented graphically.

## Results

### Data extraction after literature searching

The MEDLINE literature search resulted in 319 potentially relevant articles (Fig. 1). Based upon title and abstract screening of the identified studies, 98 articles were selected for further analysis (inter-reader agreement  $k = 0.98$ ). After further hand search, four articles were added, resulting in a total of 102 selected studies. After full-text screening, 39 articles were excluded (exclusion reasons are presented in Table 2). Finally, a total of 63 publications, completely fulfilling the inclusion criteria, were included in this review (inter-reader agreement  $k = 0.97$ ). Selected articles are presented in Table 3 and grouped according to the performed treatments.

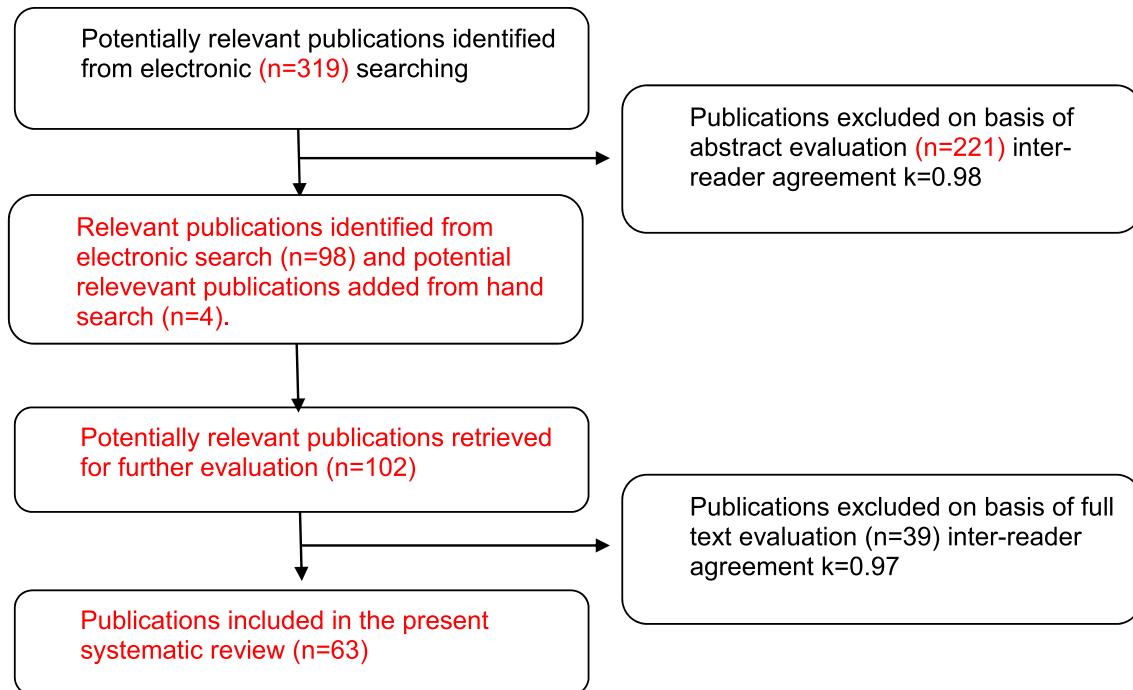
### Data analysis of the regenerative effect of each intervention in animals

Five biomaterial/intervention types (i.e., open flap debridement (OFD), bone grafts, barriers, growth factors, or other biological factors and combinations thereof) were reported for the treatment of class II furcation defects, while four biomaterial/intervention types (i.e., OFD, barriers, growth factors, or other biological factors and combinations thereof) were analyzed for class III furcation involvements.

Healing type was defined as follows: long junctional epithelium (epithelial downgrowth covering the treated tooth surface); connective tissue attachment (new cementum with inserting collagen fibers on the treated tooth surface but not connected to new bone); connective tissue adhesion (connective tissue contact to the root without apparent cementum formation); complete periodontal regeneration (new cementum with inserting fibers functionally oriented and new bone); osseous repair (bone formation opposite the tooth surface, leading to defect filling but without cementum and/or PDL formation).

For each of the selected studies, the following items were reported in tables: author name, publication date, number of animals, number of defects, defect characteristics, healing period, biomaterial type, healing type, and histological results (Tables 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20). Furthermore, histomorphometric data reporting on the amount of new cementum, bone formation, collagen

Flow chart of the screened relevant publications



**Fig. 1** Flow chart of the screened relevant publications

**Table 2** Excluded studies

No.	Study excluded	Reason for exclusion
1	Wikesjö et al. [28]	No furcation defects (supraalveolar, critical size defects were investigated).
2	Christgau et al. [29]	No histologic data available.
3	Da Silva et al. [30]	Orthodontic movement followed regenerative therapy.
4	Da Silva et al. [31]	Orthodontic intrusion followed regenerative therapy.
5	Dean et al. [32]	No furcation defects (regeneration in root perforations).
6	Klinge et al. [33]	No regenerative therapy, only OFD + (citric acid decontamination) at teeth with periodic displacement and some with splinting.
7	Koo et al. [34]	Healing period too short (4 weeks).
8	Lundgren et al. [35]	No furcation defects (recession type defects were investigated).
9	Machtei et al. [36]	No histologic data on regeneration available, Healing period too short (4–6 weeks for histological evaluation of the membrane).
10	Morris et al. [37]	No regenerative therapy, only non-surgical treatment and simvastatin injection in the defect area (no GTR).
11	Sigurdsson et al. [38]	No furcation defects, (large supraalveolar defects were included) No clear localization of the measured areas.
12	Herr et al. [39]	Healing period too short (1, 2, 3, 4 weeks).
13	Yaegashi et al. [40]	Article not in English (Japanese).
14	Mukainakano et al. [41]	Article not in English (Japanese)
15	Sculean et al. [42]	No furcation defects.
16	Crigger et al. [43]	Healing period too short (6 weeks).
17	Verino et al. [44]	Healing period too short (6 weeks).
18	Vergara et al. [45]	Healing period too short (up to 49 days).
19	Klinge et al. [46]	Healing period too short: 6 weeks.
20	Chu et al. [47]	Article not in English (Chinese).
21	Dogan et al. [48]	No baseline data (defect size) Healing period too short (7, 21, 42 days).
22	Gottlow et al. [49]	No histomorphometric analysis No furcation defects (supraalveolar defects).
23	Kim et al. [50]	No furcation defects (critical size supraalveolar periodontal defects).
24	Stoller et al. [51]	No numerical data, only descriptive.
25	Nevins et al. [52]	No numerical data, only descriptive.
26	Caffesse et al. [53]	No baseline data (defect size).
27	Caffesse et al. [54]	No baseline data (defect size).
28	Lekovic et al. [55]	No baseline data (defect size).
29	Macedo et al. [56]	No baseline data (defect size).
30	Novaes et al. [57]	No baseline data (defect size).
31	Mohammed et al. [58]	Healing period too short (2–6 weeks).
32	Tan et al. [59]	Healing period too short (6 weeks).
33	Dogan et al. [60]	Healing period too short (43 days).
34	Murakami et al. [61]	Healing period too short (6 weeks).
35	Kosen et al. [62]	Healing period too short (2–4 weeks).
36	Wohlfahrt et al. [63]	Healing period too short (6 weeks).
37	Rajnay et al. [64]	Same study as Butler et al. 1998.
38	Gkranias et al. [65]	Same study as Donos et al. 2003.
39	Baharuddin et al. [66]	Healing period too short (6 weeks).

OFD, open flap debridement

fibers, and junctional epithelium on the tooth surface were reported in tables (Tables 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,

16, 17, 18, 19, 20, and 21) as linear (in mm) or surface measurements (in mm<sup>2</sup>) or percentages (in %).

**Table 3** Included studies

No.	Study included	Type of study, defect localization, defect type, therapy
1	Gottlow et al. [67]	Human, separate analysis
2	Mellonig et al. [68]	Human, separate analysis
3	Bogle et al. [69]	Animal, mandible, Class II, GTR & OFD
4	Caffesse et al. [70]	Animal, mandible, Class II, GTR
5	Cirelli et al. [71]	Animal, mandible, Class II, GTR & OFD
6	Suaid et al. [72]	Animal, mandible, maxilla, Class II GTR & Combi
7	Ripamonti et al. [73]	Animal, mandible, Class II, Factors
8	Regazzini et al. [74]	Animal, mandible, Class II, Combi & Factors
9	Deliberador et al. [39]	Animal, mandible, Class II, Combi & Bone & OFD
10	Keles et al. [75]	Animal, mandible, Class II, Combi & Factors & OFD
11	Simsek et al. [76]	Animal, mandible, Class II, Combi & Bone & Factors & OFD
12	Teare et al. [77]	Animal, mandible, Class II, Combi & Factors
13	Takayama et al. [78]	Animal, mandible, maxilla, Class II, Factors & OFD
14	Teare et al. [79]	Animal, mandible, maxilla, Class II, Combi
15	Crespi et al. [80]	Animal, mandible, Class III, GTR & OFD
16	Donos et al. [81]	Animal, mandible, Class III, GTR & Factors & Combi & OFD
17	Jiang et al. [82]	Animal, mandible, Class III, GTR & Combi
18	Lindhe et al. [83]	Animal, mandible, Class III, GTR & OFD
19	Park et al. [84]	Animal, mandible, Class III, GTR & Combi
20	Suaid et al. [85]	Animal, mandible, Class III, GTR & Combi & OFD
21	Araujo et al. [86]	Animal, mandible, Class III, GTR & Combi
22	Giannobile et al. [87]	Animal, mandible, Class III, Factors & OFD
23	Murano et al. [88]	Animal, mandible, Class III, Factors & OFD
24	De Andrade et al. [89]	Animal, mandible, Class II, GTR
25	Araujo et al. [90]	Animal, mandible, Class III, GTR
26	Araujo et al. [91]	Animal, mandible, Class III, GTR
27	Araujo et al. [92]	Animal, mandible, Class III, GTR
28	Mardas et al. [93]	Animal, mandible, Class III, Combi & OFD
29	Saito et al. [94]	Animal, mandible, Class III, Factors & Combi & OFD
30	Nagahara et al. [95]	Animal, mandible, Class III, Factors & Combi
31	Palioti et al. [96]	Animal, mandible, Class III, Factors & Combi
32	Suaid et al. [97]	Animal, mandible, Class II, Combi
33	Chen F. et al. [98]	Animal, mandible, maxilla, Class III, Factors & OFD
34	Jimbo et al. [99]	Animal, mandible, maxilla, Class II, Factors & OFD
35	Yu et al. [100]	Animal, mandible, Class III, Factors
36	Chantarawararat et al. [101]	Animal, mandible, Class II, Factors & OFD
37	Reis et al. [102]	Animal, mandible, maxilla, class II, GTR & OPD
38	Chen et al. [103]	Animal, mandible, maxilla, Class III, Combi
39	Goncalves et al. [104]	Animal, mandible, Class III, GTR
40	Klinge et al. [105]	Animal, mandible, Class III, Factors
41	Matsuura et al. [106]	Animal, mandible, Class III, GTR
42	Pontoriero et al. [107]	Animal, mandible, Class III, GTR & OFD
43	Ripamonti et al. [108]	Animal, mandible, Class III, Combi
44	Sculean et al. [109]	Animal, mandible, Class III, GTR & Factors & Combi & OFD
45	Wikesjö et al. [110]	Animal, mandible, Class III, Factors
46	Kuboki et al. [111]	Animal, mandible, Class III, GTR & Combi
47	Reis et al. [112]	Animal, mandible, Class II, GTR & OFD
48	Harris et al. [113]	Human, separate analyses
49	Stoller et al. [51]	Human, separate analyses

**Table 3** (continued)

No.	Study included	Type of study, defect localization, defect type, therapy
50	Nevins et al. [52]	Human, separate analyses
51	Camelo et al. [24]	Human, separate analyses
52	Caffesse et al. [53]	Animal, mandible, Class II, GTR & OFD
53	Caffesse et al. [54]	Animal, mandible, Class II, GTR & Combi
54	Lekovic et al. [55]	Animal, mandible, Class II, GTR & OFD
55	Macedo et al. [56]	Animal, mandible, Class II, GTR
56	Novaes et al. [57]	Animal, mandible, Class II, GTR & OFD
57	Buttler et al. [114]	Animal, andible, Class II, GTR & OFD
58	Plotzke et al. [115]	Animal, maxillary, Class II, bone & OFD
59	Fernandes et al. [116]	Animal, mandible, Class III, Combi
60	Ripamonti et al. [117]	Animal, mandibular, Class II, Bone & Factors
61	Murakami et al. [118]	Animal, mandible, Class II, Factors & OFD
62	Souza et al. [119]	Animal, mandible, Class II, GTR
63	Jimbo et al. 2018 [120]	Animal, maxilla & mandible, Class II Factors & OFD

GTR, guided tissue regeneration; OFD, open flap debridement; Combi, combined regenerative therapy; Factors, growth factors

### Animal class II furcation defects treated with OFD

Seventeen studies providing data on the effect of OFD in animal class II furcation defects were identified (Table 4) [39, 53, 55, 57, 69, 71, 75, 76, 78, 99, 101, 102, 112, 114, 115, 118, 120]. The majority of the studies (i.e., 11 out 16) showed long junctional epithelium, whereas new cementum, PDL and/or new alveolar bone were observed only in a few cases at the apical limit of the defect [28–34, 36, 38, 39, 43]. Only two studies reported periodontal regeneration [75, 76] while another three studies reported partial regeneration in combination with epithelium downgrowth [99, 101, 120]. In the study of Caffesse and coworkers [53], dentin resorption and ankylosis were often found, whereas in the studies of Delibrador et al. [39] and Cirelli et al. [71], repaired resorption lacunae were present.

Fifteen out of the 16 to 17 studies provided histomorphometrical data (Table 5). One hundred forty-nine defects in 87 animals (dogs or monkeys) were evaluated. The defect depth ranged from 1.5 to 5 mm. The new cementum averaged 0.2 mm as linear measurements and ranged from 0.2 to 14 mm<sup>2</sup> as surface measurements or ranged from 3 to 59% as percentage. Bone formation ranged from 0.1 to 2.8 mm as linear measurements, from 0.4 to 5.1 mm<sup>2</sup> as surface measurements, and from 5 to 71% as percentage.

### Animal class II furcation defects treated with OFD and bone grafts

Four studies providing data on the effect of the use of bone grafts in animal class II furcation defects were identified (Table 6) [34, 39, 42, 45]. Two studies used autogenous bone grafts and reported periodontal regeneration [39, 42]. One

study used HTR (i.e., hard tissue replacement graft, a non-resorbable, calcium-layered polymer of polymethylmethacrylate and hydroxyethyl-methacrylate) and showed long junctional epithelium with the graft particles encapsulated in connective tissue [115]. Another study applied bovine collagenous matrix and obtained long junctional epithelium with signs of limited regeneration [117]. Neither inflammation nor root resorption or ankylosis was reported.

All four studies provided histomorphometrical data (Table 7). Thirty-four defects in 16 animals (dogs or monkeys) were evaluated. The reported defect depth averaged 5 mm. The new cementum averaged 2.7 mm as linear measurements, 0.1 mm<sup>2</sup> as surface measurements and ranged from 59 to 94%. Bone formation averaged 1.7 mm<sup>2</sup> as surface measurements and from 65 to 85% as percentage of the root surface.

### Animal class II furcation defects treated with OFD and GTR

Fourteen studies providing data on the effect of the use of GTR in animal class II furcation defects were identified (Table 8). Six studies used resorbable membranes [69, 71, 72, 89, 102, 112], five studies used non-resorbable membranes [53, 54, 56, 57, 119], and three studies combined resorbable and non-resorbable membranes [55, 70, 114].

Ten studies reported periodontal regeneration describing new cementum with inserting collagen fibers observed on previously denuded surfaces [53–56, 69–71, 89, 102, 119]. Furthermore, three studies observed additional long junctional epithelium combined with periodontal regeneration [57, 72, 114] while one study referred to partial regeneration [112]. In two studies [53, 72], tooth ankylosis was present, whereas one study [55] reported that polycarbonate filter and

**Table 4** Histological results of animal type II furcation defects treated using open flap debridement (17 studies)

No.	Authors Year	Animal type No. of animals No. of defects	Furcation type Defect localization Defect nature Defect size (mm)	Treatment	Healing time	Healing type	Histological results
1	Reis et al. [102]	Dogs 10	Class II Maxilla Surgically created	60 days (5 dogs) 120 days (5 dogs) OFD	Long junctional epithelium	Defect area filled with connective tissue; cementum, alveolar bone and PDL in a few areas at the apical limit.	
2	Reis et al. [112]	Dogs 10	Class II Maxilla Surgically created	60 days (5 dogs) 120 days (5 dogs) OFD	Long junctional epithelium	Defect area filled with connective tissue; cementum, alveolar bone and PDL in a few areas at the apical limit.	
3	Caffesse et al. [53]	Dogs 6 24	Height: 5 mm Depth: 3 mm Width: 5 mm Class II Mandible Naturally occurring	3 months OFD	Limited regeneration Long junctional epithelium	Mostly modest periodontal regeneration: new bone limited adjacent to the roots; epithelium coronally. Dentin resorption and ankylosis were often found.	
4	Lekovic et al. [55]	Dogs 7 7	Class II Mandible Naturally occurring	6 months OFD	Long junctional epithelium	OF showed significantly less connective tissue and bone fill compared to GTR.	
5	Novais et al. [57]	Dogs 4 8	Class II Mandible Surgically created	2 months OFD	Long junctional epithelium	Long junctional epithelium with minimal connective tissue attachment.	
6	Buttler et al. [114]	Monkeys 5 10	Height: 5 mm Depth: 2 mm Class II Maxilla and mandible Surgically created	26 weeks Group A: OFD B: OF	Long junctional epithelium	Epithelium proliferated down the root surface to apical level of the notch.	
7	Plotzke et al. [115]	Dogs 4 12	Class II Maxilla Surgically created	4 months OFD	Long junctional epithelium	Minimal formation of new bone.	
8	Murakami et al. [118]	Monkeys n.r. n.r.	Class II Surgically created Height: 4 mm Depth: 3 mm Class II	OFD	Long junctional epithelium	Long junctional epithelium below the furcation roof with loss of connective tissue attachment; no new cementum formation but minimal bone formation.	
9	Bogle et al. [69]	Dogs 6 8	Maxilla and mandible Height: 1.92 mm Class II mandibular surgically created	6 months, OFD	Long junctional epithelium	No significant differences between OF and OFD. The connective tissue comprised nearly half of the total defect fill.	
10	Cirelli et al. [71]	Dogs 4 6	Height: 3 mm Class II	3 months OFD	Long junctional epithelium	New cementum was found only in the notches. No new attachment.	
11	Deliberador et al. [39]	Dogs		90 days	Long junctional epithelium	No signs of root resorption or ankylosis.	
						Healing by long junctional epithelium.	
						Results on OFD sites were not described.	
						A very small area of new cementum was present	
						New cementum in small amounts and limited by epithelial tissue.	
						Newly formed bone filled partially the defect.	
						Signs of resorption.	

**Table 4** (continued)

No.	Authors Year	Animal type No. of animals	Furcation type Defect localization Defect nature Defect size (mm)	Treatment	Healing time	Healing type	Histological results
12	Simssek et al. [76]	Dogs 12	Mandible Surgically created Height: 5 mm Depth: 2 mm	OFD	Regeneration	New bone was formed in the notch areas or partially filling the mid-portion of the defect. The defect was mainly filled with fibrous connective tissue. One specimen exhibited total bone fill with epithelial migration. Signs of resorption.	
13	Takayama et al. [78]	Monkeys 3 6	Class II Mandible, and maxilla, Surgically created Height: 5 mm	2 months OFD	Regeneration	New cementum with PDL and new bone in all groups. Significantly less cementum was formed in the OFD groups compared to the other treatment groups.	
14	Keles et al. [75]	Dogs 4 8	Class II Mandible and maxilla, Surgically created Height: 4 mm Depth: 3 mm	2 months OFD	Long junctional epithelium	Alveolar bone formation was similar in all groups. Limited bone and cementum regeneration. New cementum deposition was observed only at the notch level. Epithelial downgrowth and no new cementum on the root surfaces.	
15	Jimbo et al. [99]	Monkeys 8 8	Class II Mandibular and maxillary defects Surgically created Depth: 3 mm Height: 5 mm Depth: 2 mm	3 months OFD	Regeneration	New cementum with PDL and alveolar bone. Cementum formation was significantly lower in OFD compared to the platelet group.	
16	Chantarawaratit et al. [101]	Dogs 2 4	Class II defects Maxillary and mandibular Surgically created Height 5 mm Width 5 mm Depth 5 mm	12 weeks OFD	Limited regeneration Long junctional epithelium	Limited alveolar bone formation similar in all groups (mainly woven bone). New cementum was deposited over dentin, of variable thickness, composed of cells with intrinsic and extrinsic collagen.	
17	Jimbo et al. 2018 [120]	Monkeys 4 (for OFD) 8 (for OFD)	Class II defects Maxillary and mandibular Surgically created Height 5 mm	60 days OFD	Partial regeneration	Cellular, acellular and mixed cellular cementum was partially present. Full bone regeneration with partial or no cementum regeneration, along with partial or no PDL regeneration.	
				12 weeks OFD	Partial regeneration	Less periodontal regeneration (new bone, cementum and PDL) as compared to the groups treated with acemannan sponge.	
						Less periodontal regenerations (new cementum, bone, PDL) compared to groups treated with BDNF and HMW-HA	

OF, open flap; OFD, open flap debridement; PDL, periodontal ligament; BDNF, brain-derived neurotrophic factor; HMW-HA, high molecular weight hyaluronic acid; no., number; n.r., not reported

**Table 5** Histomorphometrical results (height in mm, area in mm<sup>2</sup>, volume, or area in %) of animal type II furcation defects treated using open flap debridement

n	Study	No. of furcations	Defect height mm	NB mm/mm <sup>2</sup> /% area or height	NC mm/mm <sup>2</sup> /% area or height	Collagen fibers on tooth surface mm/mm <sup>2</sup> /% area or height		Junctional epithelium mm/mm <sup>2</sup> /% area or height
						At 60 days	n.r.	
1	Reis et al. [102]	10: 5 (3 m) 5 (m)	5	At 60 days 0.08 mm	n.r.	n.r.	n.r.	n.r.
2	Reis et al. [112]	10: 5 (60 d) 5 (120 d)	5	At 60 days 0.08 ± 0.05 mm At 120 days	n.r.	n.r.	n.r.	n.r.
3	Caffesse et al. [53]	24	n.r.	0.44 ± 0.45 mm <sup>2</sup>	n.r.	1.07 ± 0.8 mm <sup>2</sup>	0.44 ± 1.09 mm <sup>2</sup>	n.r.
4	Lekovic et al. [55]	7	n.r.	0.32 ± 0.017 mm	0.24 ± 0.007 mm	n.r.	0.61 ± 0.009 mm	n.r.
5	Novaes et al. [57]	8	5	Lingual: 0.96 ± 0.19 mm Mid-portion: 1.10 ± 0.28 mm Buccal: 2.79 ± 0.40 mm	n.r.	n.r.	0.71 ± 0.28 mm	n.r.
6	Buttler et al. [114]	A: 5 B: 5	n.r.	Area: A: 17.13 ± 14.21% B: 5.56 ± 3.91%	Area: A: 9.71 ± 7.03% B: 4.28 ± 2.89%	Area: A: 35.81 ± 32.8% B: 59.11 ± 21.72%	Area: A: 37.35 ± 22.06% B: 31.06 ± 26.31%	n.r.
7	Plotzke et al. [115]	12	n.r.	5.14 ± 1.23 mm <sup>2</sup>	0.19 ± 0.1 mm <sup>2</sup>	1.86 ± 0.59 mm <sup>2</sup>	0.1 ± 0.07 mm <sup>2</sup>	n.r.
8	Murakami et al. [118]	n.r.	n.r.	Area: 42.8 ± 10.7%	Area: 34.3 ± 14.5%	n.r.	n.r.	n.r.
9	Bogle et al. [69]	8	1.47 ± 0.21	0.2 ± 0.11 mm	0.25 ± 0.14 mm	0.06 ± 0.04 mm	1.21 ± 0.25 mm	n.r.
10	Cirelli et al. [71]	6	3	Height: 14%	Height: 17%	Height: 4%	Height: 82%	n.r.
11	Deliberador et al. [39]	12	5	Area: 48.58 ± 26.91%	Area: 59.34 ± 29.43%	Area: 37.82 ± 29.69%	Area: 5.04 ± 8.05%	n.r.
12	Simsek et al. [76]	6	5	Area: 61.86 ± 9.27%	Area: 56.75 ± 23.06%	Area: 35.19 ± 17.68%	n.r.	n.r.
13	Takayama et al. [78]	8	4	Height: 31.98 ± 6.67%	Height: 3.33 ± 3.33%	Height: 3.33 ± 3.33%	n.r.	n.r.
14	Keles et al. [75]	8	5	Area: 44.7 ± 6.2%	Area: 46.7 ± 12.1%	Height: 45.60 ± 11.92%	n.r.	n.r.
15	Jimbo et al. [99]	8	5	Height: 42.44 ± 6.07%	Area: 14%	Area: 14%	n.r.	n.r.
				Complete reg.: 71%	Partial reg.: 29% Area: 69.27 ± 2.62%	Area: 54.01 ± 9.26%	Area: 58.36 ± 9.25%	n.r.
16	Chantaratwirat et al. [101]	4	5					
17	Jimbo et al. 2018 [120]	8	5	Binned %: 75% defects in lower tertile (≤ 0.37%); 25% defects in middle tertile (0.37–0.62%)	Binned %: 75% defects in lower tertile (≤ 0.37%); 25% defects in middle tertile (0.37–0.62%)	75% defects in lower tertile (≤ 0.37%); 25% defects in middle tertile (0.37–0.62%)	75% defects in lower tertile (≤ 0.37%); 25% defects in middle tertile (0.37–0.62%)	n.r.

NC, new cementum; NB, new bone; n.r., not reported; no., number

**Table 6** Histologic results of animal type II furcation defects treated using autogenous bone or bone substitutes (4 studies)

No.	Authors Year	Animal type No. of animals No. of furcations	Furcation type Defect localization Defect nature Defect size (mm)	Healing time Graft type	Healing type	Histological results
1	Delberador et al. [39]	Dogs 6 12	Class II Mandible Surgically created Height: 5 mm Depth: 2 mm	90 days Autogenous bone graft	Partial regeneration Long junctional epithelium	Periodontal regeneration (incomplete regeneration) was similar in all treatment groups.
2	Simssek et al. [76]	Dogs 3 6	Class II Mandible and maxilla Surgically created + impression material for 3 weeks 5 mm in height 2 mm in depth	2 months Autogenous bone	Regeneration	Partial bone fill, fibrous connective tissue coronally with moderate/intense inflammatory infiltrate. Signs of resorption and ankylosis. New cementum with PDL and alveolar bone in all groups (complete filling of the defects at 8 weeks).
3	Plotzke et al. [115]	Dogs 4 12	Class II Maxilla Surgically created 5 mm in height 2 mm in depth	4 months HTR	Long junctional epithelium	Graft particles were mostly encapsulated in connective tissue, seldom alveolar bone regeneration. New cementum was found only in the notches.
4	Ripamonti et al. [117]	Monkeys 3 4	Class II Mandible Surgically created 10–12 mm in depth	60 days Bovine collagenous matrix without osteogenic proteins	Long junctional epithelium Limited regeneration	There was no evidence of new attachment. No signs of root resorption or ankylosis. Healing through long junctional epithelium. Limited regeneration, remnants of collagenous carrier, apical migration of junctional epithelium.

HTR, hard tissue replacement graft (non-resorbable, calcium-layered polymer of polymethylmethacrylate and hydroxyethyl-methacrylate); PDL, periodontal ligament; No., number

**Table 7** Histomorphometric results (height in mm, area in mm<sup>2</sup>, volume or area in %) of animal type II furcation defects treated using autogenous bone or bone substitutes (4 studies)

No.	Study	No. of furcations	Defect height mm area or height	NB mm/mm <sup>2</sup> % area or height	NC mm/mm <sup>2</sup> % area or height	Collagen fibers on tooth surface mm/mm <sup>2</sup> /% area or height	Junctional epithelium surface mm/mm <sup>2</sup> /% area or height
1	Deliberador et al. [39]	12	5	Area: 64.95 ± 15.75% Height: 84.60 ± 4.85%	Area: 58.74 ± 17.52% Height: 93.62 ± 4.09%	Area: 32.95 ± 17.11% n.r.	Area: 64.41 ± 7.67% n.r.
2	Simssek et al. [76]	6	5	1.65 ± 1.22 mm <sup>2</sup>	0.05 ± 0.04 mm <sup>2</sup>	3.68 ± 1.19 mm <sup>2</sup>	0.17 ± 0.05 mm <sup>2</sup>
3	Plotzke et al. [115]	12	n.r.	Mesial: 2.8 ± 0.1	n.r.	n.r.	n.r.
4	Ripamonti et al. [117]	4	n.r.	Distal: 2.6 ± 0.2			

NC, new cementum; NB, new bone; n.r., not reported; no., number; HTT, hard tissue replacement graft (non-resorbable, calcium-layered polymer of polymethylmethacrylate and hydroxyethyl-methacrylate)

polycaprolactone membranes led to chronic inflammatory lymphocyte response and plasma cell infiltrates.

Thirteen studies provided histomorphometrical data (Table 9). Two hundred sixty-six defects in 90 animals (dogs or monkeys) were evaluated. The defect depth ranged from 2 to 8 mm. The new cementum ranged from 1.4 to 10.9 mm as linear measurements and from 10 to 92% as percentage. New bone formation ranged from 0 to 4.6 mm as linear measurements, from 0.9 to 9.6 mm<sup>2</sup> as surface measurements, and from 7 to 83% as percentage.

### Animal class II furcation defects treated with OFD and biological factors

Twelve studies providing data on the effect of the use of biological factors (i.e., OP1, BMP2, EMD, platelet concentrates, PRP, FGF, BDNF, TGF-β, acemannan, HA, brain-derived neurotrophic factor-BDNF, high molecular weight hyaluronic acid—HMW-HA) in animal furcation defects class II were identified (Table 10) [73–79, 99, 101, 117, 118, 120].

All studies reported remarkable periodontal regeneration with the presence of new cementum along with PDL and coronal growth of alveolar bone. In nine studies, no signs of epithelial downgrowth were reported. Two studies, however, reported for EDTA [74] and for the gelatinous carrier [78] formation of long junctional epithelium. One study [99] outlined partial or no regeneration of cementum and PDL but full bone regeneration when BDNF was used in lower concentrations (50 µg/mL) or in combination with NaCl. No study evidenced the presence of inflammation nor resorption or ankylosis. A further study reported regeneration of PDL fibers inserting into new cementum and new bone to a varying extent [120].

All above mentioned studies provided histomorphometrical data (Table 11). Two hundred sixty-four defects in more than 42 animals (dogs or monkeys) were evaluated. The defect depth ranged from 4 to 9 mm. The new cementum was reported to range from 2.6 to 6.7 mm as linear measurements or from 0 to 94% as percentage. New bone formation ranged from 2.6 to 6.8 mm as linear measurements and from 15 to 94% as percentage.

### Animal class II furcation defects treated with OFD and combined techniques

Nine studies showed histological results in relation to using combined techniques for the treatment of class II animal furcation defects (Table 12) [39, 41, 42, 47, 48, 52, 54–56]. Three studies used a combination of GTR and growth factor [74, 75, 79], two studies used GTR plus bone graft [39, 48], one study used bone graft and growth factors [76], one study applied [54] GTR plus PDL cells [72], one study used a combined

**Table 8** Histologic results of animal type II furcation defects treated using guided tissue regeneration GTR (14 studies)

No.	Authors	Year	Animal type	Furcation type	Healing time	Membrane type	Healing type	Histological results
1	Bogle et al. [69]	Dogs	6 8	Class II Maxilla and mandible Naturally occurring Height: 1.92 mm (mean)	6 months, mm. (PLA in NMP)		Regeneration	Regeneration of new bone, cementum and PDL was statistically significantly higher when using a m.
2	Caffesse et al. [70]	Dogs	9 27 (9/group)	Class II Mandible Surgically created Height: 4.84 mm	A: 3 months, m. Type I B: 3 months, mm Type II C: 3 months non-mm (ePTFE) D: 6 months, mm E: 6 months, mm F: 6 months, non-mm (ePTFE)	Regeneration	Regeneration	New cementum with inserting collagen fibers Similar results were obtained with bioabsorbable barriers or non-bioabsorbable ePTFE m. No signs of root resorption or ankylosis. No apical migration of the epithelium.
3	Cirigli et al. [71]	Dogs	4 16	Class II Mandible Surgically created Height: 3 mm	3 months mm (collagen)	Regeneration	The collagen m was better than OFD in terms of newly formed cementum and epithelial migration prevention. New cementum (cellular) formed at the level of the notch and in the furcation.	
4	Suaid et al. [72]	Dogs	7 14	Class II Maxilla Surgically created Height: 8.39 mm	3 months mm (co-polymer of polylactic acid and polyglycolic acid)	Regeneration	Sharpey's fibers were inserted perpendicularly and/or obliquely along the entire area. Bone re-growth at various stages (woven bone predominantly), PDL (collagen fibers obliquely oriented to the root surface) and new cementum (cellular, mixed intrinsic and extrinsic) were observed.	
5	De Andrade et al. [89]	Dogs	6 24	Class II Mandible Surgically created + impression material for 2 weeks	3 months 1. rm (polyglycolic acid:trimethylene carbonate) 2. rm (acellular dermal matrix)	Regeneration	Ankylosis was observed in one specimen and 4 sections presented epithelial downgrowth which was restricted to the furcation formix.	
6	Reis et al. [102]	Dogs	10 10	Height: 5 mm Depth: 2 mm Class II Mandible and maxilla Surgically created + impression material	3 months 6 months mm (PLGA/CAP)	Regeneration	New cementum, cellular, mixed intrinsic and extrinsic type), PDL (collagen fibers orientated obliquely to the root surface, extending between the new cementum and newly formed bone) and alveolar bone (predominantly woven) was observed in both groups.	
7	Caffesse et al. [53]	Dogs	6 24	Height: 5 mm Width: 3 mm Class II Mandible Naturally occurring	3 months non-mm (ePTFE)	Regeneration	No signs of ankylosis. Greater periodontal regeneration as compared to the reported one by means of flexible membranes.	
8	Caffesse et al. [54]	Dogs	4 16	Class II, Mandible, Naturally occurring	4 months non-mm (ePTFE)	Regeneration	New cementum, bone and PDL (with Sharpey's fibers) in the entire defect. No newly formed acellular cementum was observed; cellular cementum along the old one along the root surface.	
9	Lekovic et al. [55]	Dogs	7	Class II Mandible	6 months GTR (4):	Regeneration	GTR showed significantly more connective tissue and bone fill as compared to surgery alone	

**Table 8** (continued)

No.	Authors	Year	Animal type	Furcation type	Healing time	Membrane type	Healing type	Histological results
			No. of animals	Defect localization				
			No. of defects	Defect nature				
			Defect size (mm)	Defect size (mm)				
28			Naturally occurring					formed cementum and bone. No significant differences were recorded regarding the gain in connective tissue attachment and new bone between the four m.
10	Macedo et al. [56]		Dogs 6 24 (12/group)	Class II Mandible Surgically created Height: 5 mm Depth: 2 mm	12 weeks non-rm (ePTFE): group A: removal after 2 weeks group B: removal after 4 weeks	Regeneration		New cementum (cellular, mixed intrinsic and extrinsic collagen fiber type) with PDL and alveolar bone in all defects (complete fill of he furation). New connective tissue attachment to cementum, with functionally oriented bundles of collagen fibers at the fornix. PDL contained collagen fibers obliquely oriented to the root surfaces.
11	Novais et al. [57]		Dogs 4 16 (8/group)	Class II Mandible Surgically created Height 5 mm Depth 2 mm	2 months group A: non-rm type I (simple ePTFE) group B: non-rm type II (modified ePTFE for better collar adaptation)	Long junctional epithelium Regeneration & minor long junctional epithelium	Long junctional epithelium Regeneration & minor long junctional epithelium	No signs of ankylosis. A: The greatest part of the defects were filled with dense connective tissue and new bone in the apical area. B: new cementum, PDL and bone formation. Minor migration of the junctional epithelium at the CEJ level
12	Butler et al. [114]		Monkeys 6 29	Class II Maxilla and mandible Surgically created	26 weeks Group A: non-rm (ePTFE) B: rm. (polylactic acid)	Limited regeneration Long junctional epithelium	None of the treatments achieved complete healing. No significant differences were found between the treated and untreated control sites.	The connective tissue comprised nearly half of the total defect fill. The non-rm became exposed at most sites. New bone formation was significantly lower than anticipated.
13	Reis et al. [112]		Dogs 10 10 (5/GTR group)	Class II defects Surgically created + impression material Height: 5 mm Width: 5 mm Depth: 3 mm	3 months (5 dogs) 6 months (5 dogs) Group A: type I (PHB matrix + 25% HA) Group B: m type II (PHB matrix + 35% HA)	Partial regeneration	3 teeth in group A and 1 tooth in group B developed from class II class III furcations.	Partial regeneration of the periodontium was observed in both GTR groups. Bone areas were present closer to the roots, central defect portions being filled with connective tissue. Cellular cementum with collagen fibers emerging into the PDL was present in the furcation. Collagen fibers were not attached to the bone. No periodontium was formed on the buccal aspect of the defect.
14	Souza et al. [119]		Dogs 5 20	Class II Mandible Surgically created Height 5 mm Depth 2 mm	12 weeks non-rm (ePTFE): A: m removal after 2 weeks B: m removal after 4 weeks	Regeneration	Bone and PDL regeneration: Bone was better organized in osteons in group B than in group A. Collagen I and III fibers were in both groups sparse and more diffuse than in the pristine sites.	

PLA in NMP, bioresorbable liquid polymer consisting of polylactic acid dissolved (PLA) in a biocompatible solvent *N*-methyl-2-pyrrolidone (NMP); CaP, calcium phosphate; NMP, *N*-methyl-2-pyrrolidone; ePTFE, expanded polytetrafluoroethylene; PHB, polyhydroxybutyrate; HA, hydroxyapatite; CEJ, cement-enamel junction; PDL, periodontal ligament; *m*, membrane; *rm*, resorbable membrane; *No.*, number

**Table 9** Histomorphometric results (height in mm, area in mm<sup>2</sup>, volume, or area in %) of animal type II furcation defects treated using guided tissue regeneration GTR

No.	Study	No. of furcations	Defect height mm	NB mm/mm <sup>2</sup> % area or height	NC mm/mm <sup>2</sup> % area or height	Collagen fibers on tooth surface mm/mm <sup>2</sup> % area or height	Junctional epithelium mm/mm <sup>2</sup> % area or height
1	Bogle et al. [69]	8	1.92 ± 0.15	1.4 ± 0.23 mm Height: 74%	1.36 ± 0.25 mm Height: 71%	0.13 ± 0.09 mm Height: 7%	0.42 ± 0.15 mm Height: 22%
2	Caffesse et al. [70]	18 (3/group)	A: 5.20 ± 0.52 B: 4.17 ± 1.60 C: 4.73 ± 0.85 D: 4.45 ± 1.08 E: 5.94 ± 0.74 F: 4.56 ± 1.21	A: 3.18 ± 1.29 mm B: 3.30 ± 0.40 mm C: 1.83 ± 0.57 mm D: 2.95 ± 1.24 mm E: 4.55 ± 1.05 mm F: 2.72 ± 1.43 mm	A: 5.20 ± 0.52 mm B: 4.16 ± 1.59 mm C: 4.54 ± 1.13 mm D: 4.42 ± 1.08 mm E: 5.80 ± 0.68 mm F: 4.42 ± 1.40 mm	A: 5.20 ± 0.52 mm B: 4.15 ± 1.57 mm C: 4.54 ± 1.13 mm D: 4.42 ± 1.08 mm E: 5.80 ± 0.68 mm F: 4.42 ± 1.40 mm	A: 2.03 ± 0.40 mm B: 2.20 ± 0.47 mm C: 2.03 ± 0.50 mm D: 2.45 ± 0.50 mm E: 2.27 ± 0.34 mm F: 1.92 ± 0.24 mm
3	Cirilli et al. [71]	8	3	Area: 56.33 ± 11.36% 3.94 ± 1.2 mm	92.35 ± 15.71% 3.94 ± 1.2 mm	n.r. 3.94 ± 1.2 mm	1.91 ± 3.54%
4	Suaid et al. [72]	7	8.39 ± 0.65	7.01 ± 0.61 mm <sup>2</sup> A: 2.86 ± 0.32 mm B: 5.12 ± 1.36 mm <sup>2</sup>	A: 8.24 ± 1.19 mm 91.94 ± 9.34% B: 8.16 ± 2.35 mm	A: 7.8 ± 0.87 mm <sup>2</sup> Area: 86.05 ± 18.16% B: 8.11 ± 11.01% Area: 70.30 ± 9.76	2.15 ± 1.92 mm A: 5.90 ± 1.67 mm <sup>2</sup> 0.03 ± 0.06 mm <sup>2</sup> Area: 0.50 ± 1.01% B: 0.05 ± 0.05 mm <sup>2</sup> Area: 29.83 ± 31.04% Are: 0.69 ± 0.8%
5	De Andrade et al. [89]	12	A: 5 B: 5	Height: 83.06 ± 11.07% Area: 70.30 ± 9.76	Height: 86.05 ± 18.16% Area: B: 2.56 ± 0.84 mm 4.09 ± 1.84 mm <sup>2</sup>	Height: 11.11 ± 11.01% Area: B: 2.80 ± 3.38 mm <sup>2</sup> Area: 29.83 ± 31.04% Are: 0.69 ± 0.8%	0.05 ± 0.05 mm <sup>2</sup> Are: 0.69 ± 0.8%
6	Reis et al. [102]	10; 5 (3 m) 5 (6 m)	5	60 days 0.28 120 days 0.33	60 days n.r. 0.28 120 days 0.33	n.r. n.r. n.r. n.r. n.r.	n.r. n.r. n.r. n.r. n.r.
7	Caffesse et al. [53]	24	n.r.	0.91 ± 0.45 mm <sup>2</sup>	n.r.	1.84 ± 0.45 mm <sup>2</sup>	0.63 ± 1.09 mm <sup>2</sup>
8	Caffesse et al. [54]	16	n.r.	0.97 ± 0.45 mm	1.37 ± 0.49 mm	1.51 ± 0.51 mm	1.62 ± 0.55 mm
9	Lekovic et al. [55]	28 (7/group)	n.r.	A: 1.18 ± 0.019 mm B: 1.44 ± 0.014 mm	A: 1.91 ± 0.031 mm B: 2.16 ± 0.01 mm	2.02 ± 0.68 mm <sup>2</sup> n.r.	0.63 ± 1.09 mm <sup>2</sup> A: 2.19 ± 0.019 mm B: 2.36 ± 0.009 mm C: 2.38 ± 0.009 mm D: 2.29 ± 0.014 mm n.r.
10	Macedo et al. [56]	24 (12/group)	5	C: 1.32 ± 0.015 mm D: 1.26 ± 0.01 mm A: 3.85 ± 1.21 mm 9.56 ± 3.77 mm <sup>2</sup>	C: 2.18 ± 0.015 mm D: 2.04 ± 0.37 mm A: 10.91 ± 1.72 mm 9.621 ± 9.69%	n.r.	n.r.
11	Novaes et al. [57]	16 (8/group)	5	Height: 8.79 ± 2.99 mm <sup>2</sup> Area: 87.49 ± 26.94% B: 4.03 ± 0.94 mm 8.79 ± 2.99 mm <sup>2</sup> Height: 81.41 ± 20.48% Area: 70.49 ± 15.6% A: 1.05 ± 0.22 mm mid: 1.23 ± 0.33 mm	Height: 66.72 ± 16.2% B: 10.59 ± 1.80 mm 91.87 ± 15.34% n.r. n.r.	n.r. n.r.	A: 0.64 ± 0.25 mm B: 0.14 ± 0.06 mm

**Table 9** (continued)

No.	Study	No. of furcations	Defect height mm	NB mm/mm <sup>2</sup> % area or height	NC mm/mm <sup>2</sup> % area or height	Collagen fibers on tooth surface mm/mm <sup>2</sup> % area or height	Junctional epithelium mm/mm <sup>2</sup> % area or height
12	Buitler et al. [114]	A: 15 B: 14	n.r.	buccal: 2.60 ± 0.39 mm B: Lingual: 0.54 ± 0.03 mm mid: 0.3 ± 0.04 mm buccal: 1.06 ± 0.2 mm Area: A: 9.63 ± 8.7% B: 7.41 ± 6.63 60 d: 1: 0.027 ± 0.02 mm 2: 0.13 ± 0.09 mm 120 d: 1: 0.08 ± 0.07 mm 2: 0.16 ± 0.06 mm n.r.	A: 10.48 ± 9.49% B: 9.26 ± 5.56% n.r.	A: 40.89 ± 30.48% B: 47.13 ± 26.33% n.r.	Area: A: 39 ± 22.56% B: 36.21 ± 26.43% n.r.
13	Reis et al. [112]	10: 5 (60 d) 5 (120 d)	5				
14	Souza et al. [119]		20	5			n.r.

NC, new cementum; NB, new bone; d, days; n.r., not reported; no., number

approach of GTR, bone graft, and growth factor [97], and one applied two different growth factors [77].

All studies described regeneration [39, 41, 42, 47, 48, 52, 54–56]. In one study [54], signs of ankylosis were observed and in another one repaired root resorption lacunae and epithelial migration in the coronal part of the defects [39].

All mentioned studies provided histomorphometrical data (Table 13). Two hundred 16 defects in 44 animals (dogs or monkeys) were evaluated. The defect depth ranged from 5 to 13 mm. The new cementum ranged from 0.9 to 9.2 mm as linear measurements or from 62 to 82% as percentage. New bone formation ranged from 1.1 to 7.3 mm as linear measurements, from 7.6 to 10.3 mm<sup>2</sup> as surface measurements, and from 28 to 80% as percentage.

### Animal class III furcation defects treated with OFD

Twelve studies providing data on the effect of the use of OFD in class III furcation animal defects were identified (Table 14) [80, 81, 83, 87, 88, 93, 94, 97, 98, 107, 109, 121].

Ten out of the 12 studies showed long junctional epithelium, whereas new cementum, alveolar bone, and PDL were observed only in a few cases at the apical limit of the defect [80, 81, 83, 85, 87, 88, 94, 98, 107, 109] (Fig. 2). One study reported periodontal regeneration in two out of eight defects, whereas the rest defects showed partial regeneration in combination with epithelium downgrowth or root resorption and ankylosis [93]. Another study showed in one out of three defects limited signs of regeneration in the apical part of the defect [121].

All studies provided histomorphometrical data (Table 15). One hundred sixty-one defects in 101 animals (dogs or monkeys) were evaluated. The defect depth ranged from 3 to 14 mm. The new cementum was reported in a range from 0.2 to 4.8 mm as linear measurements and from 22 to 62% as percentage. Bone formation ranged from 0.2 to 12.2 mm as linear measurements, from 1.9 to 6.9 mm<sup>2</sup> as surface measurements, and from 21 to 64% as percentage.

### Animal class III furcation defects treated with OFD and GTR

Fourteen studies providing data on the effect of the use of GTR (both resorbable or non-resorbable membranes) in animal class III furcation defects were identified (Table 16), [80–86, 90–92, 104, 107, 109, 111].

Half of the studies (seven out of 14) reported regeneration and described presence of new cementum with inserting collagen fibers on the previously denuded root surfaces [83, 86, 90, 91, 104, 107, 109]. Five studies observed limited regeneration limited to the apical part of the defect [80–82, 84, 85]. One study found long junctional epithelium [111] while one

**Table 10** Histological results of animal type II furcation defects treated using biological factors (12 studies)

No.	Authors	Year	Animal type No. of animals No. of defects	Furcation type Defect localization Defect nature Defect size (mm)	Healing time Treatment	Healing type	Histological results
1	Ripamonti et al. [73]		Monkeys 3 12	Class II Mandible, Surgically created Width: 10–12 mm in buccolingual direction	60 days A: hOP1 B: BMP2 C: hOP1/BMP2	Regeneration	Periodontal regeneration in varying degrees in all groups. hOP1 resulted in a twofold increase of regenerated periodontal tissues. OP-1 induced substantial cementogenesis, while BMP-2 showed limited cementum formation but a temporal enhancement of alveolar bone regeneration.
2	Regazzini et al. [74]		Dogs 4 24	Class II Mandible Surgically created Height: 5 mm	2 months EDTA EDTA + EMD	Long junctional epithelium Regeneration	EDTA group showed resulted in formation of functional epithelium and limited new bone and cementum. The new cementum was acellular and with intrinsic fibers. Signs of dentin resorption were observed.
3	Keles et al. [75]		Dogs 4 24	Class II Mandible Surgically created Height: 5 mm Depth: 2 mm	3 months Platelet pellet	Regeneration	EMD showed significant bone (mainly woven) regeneration, no migration of junctional epithelium to the defect area. Regeneration of bone, cementum (variable thickness, cellular and composed of intrinsic and/or extrinsic fibers) and PDL.
4	Simssek et al. [76]		Dogs 3 30	Class II Mandible and maxilla, Surgically created Height: 5 mm	2 months PRP	Regeneration	New cementum (variable thickness, composed of cells with intrinsic and extrinsic collagen fibers distributed randomly on the root surface) with PDL and limited alveolar bone (mainly woven). The new connective tissue between the bone and the root surface was cellular and composed of collagen fiber bundles. New cementum, alveolar bone (mainly woven) and PDL. The new cementum, deposited over dentin, was of variable thickness, composed of cells with intrinsic and extrinsic collagen fibers distributed randomly on the root surface. The new connective tissue between the bone and the root surface was cellular and composed of collagen fiber bundles
5	Takayama et al. [78]		Monkeys 4 32	Class II Mandible and maxilla, Surgically created Height: 4 mm Depth: 3 mm	2 months FGF-2 1.1% FGF-2 0.4% Gelatinous carrier	Regeneration Long junctional epithelium	No root resorption or ankylosis. FGF-2 can enhance considerable periodontal regeneration (bone growth with new cementum with Sharpey's fibers on the instrumented root), PDL consisted of organized collagen fibers. No epithelial downgrowth, or resorption or ankyloses. In the carrier group, a modest amount of new bone growth was observed coronal to the old bone, and new cementum deposition was observed only along the surface of the notch. Epithelial downgrowth was also observed
6	Ripamonti et al. [117]		Monkeys 3 12	Class II Mandible Surgically created Depth 10–12 mm	60 days hOP-1 + bICBM: Test 1: 100 µg/mL Test 2: 500 µg/mL Control: BICBM	Regeneration	Striking induction of cementogenesis in both groups. The new cementum was organized and highly cellular and often extended to the forinx. Sharpey's fibers were formed and inserted into the newly formed cementum. Bone and cementum were separated by a vascular fibrous tissue resembling a PDL space.
7	Munkami et al. [118]		Monkeys 2 16 defects (8 defects/monkey)	Class II furcation defects Surgically created Height: 4 mm Depth: 3 mm	Test 1: gelatinous carrier Test 2: bFGF + gelatinous carrier	Regeneration	Substantial amounts of residual collagenous carrier were detected in the bifurcation. Statistically significant periodontal regeneration was induced by bFGF. There were no signs of epithelial downgrowth, ankylosis or root resorption in the bFGF sites.
8	Jimbo et al. [99]		Monkeys 8 56	Class II Mandible and maxilla Surgically created, with and without impression material Depth: 3 mm Height: 5 mm	12 weeks A: BDNF B: BDNF (50 µg/mL) + HMW-HA C: HMW-HA D: BDNF (500 µg/mL) + NaCl	Regeneration Limited regeneration Long junctional epithelium	No description about the carrier defects. 80% of the evaluated sites presented full bone regeneration, the others had partial or no regeneration (no statistical differences among the groups). 40% of the samples presented full cementum regeneration: Group A: full bone, cementum and PDL regeneration with inserting collagen fibers; significant higher cementum and PDL regeneration than other groups.

Table 10 (continued)

No.	Authors	Year	Animal type	Furcation type	Healing time	Healing type	Histological results
			No. of animals	Defect localization	Treatment		
			No. of defects	Defect nature			
				Defect size (mm)			
9	Chantanawaratit et al. [101]	Dogs	Class II Maxilla and mandible Surgically created Height 5 mm Width 5 mm Depth 3 mm Class II Mandible, Surgically created + silk ligature Height: 6-8 (7)mm Depth: 10-12 mm	60 days A: 10 mg acemannan sponge B: 20 mg acemannan sponge	Regeneration		Group B: full bone regeneration with partial cementum coverage and partial PDL regeneration. Group C: full bone and partial cementum and PDL regeneration. Group D: full bone with partial or no cementum regeneration along with partial PDL regeneration. Cellular, acellular, and mixed cellular cementum was present in all groups. Marked periodontal regeneration, including new bone, cementum and PDL (dense and well organized). The values of new bone, cementum and periodontal ligament were slightly higher in the 10 mg as compared to the 20 mg acemannan group.
10	Teare et al. [77]	Monkeys	Class II Mandible, Surgically created + silk ligature Height: 6-8 (7)mm Depth: 10-12 mm	60 days TGF-β3 hOP-1 hOP-1 + TGF-β3	Regeneration		Treatment (hOP-1, induced substantial periodontal tissue regeneration. TGF-β3: new cellular cementum appeared irregular and markedly thickened in some areas. TGF-β3 and hOP-1: formation of new bone and mesenchymal tissues, PDL fibers inserted into bone and cementum. The newly formed cementum was well defined.
11	Teare et al. [79]	Monkeys	Class II Mandible and maxilla Surgically created Height: 11 mm Class II defects Maxilla and mandible Surgically created Height 5 mm	60 days TGF β3 + Matrigel	Regeneration		TGF β3 in Matrigel enhanced significantly the periodontal tissue regeneration: new bone, PDL (highly vascularized) and cementum.
12	Jimbo et al. 2018 [120]	Monkeys	8 64 (groups A, B, C: 16 defects/group, groups D, E: 8 defects)	12 weeks A: BDNF (500 ng mL <sup>-1</sup> ) + HMW-HA B: BDNF(50 ng mL <sup>-1</sup> ) + HMW-HA C: HMW-HA D: BDNF(500 ng mL <sup>-1</sup> ) E: BDNF(500 ng mL <sup>-1</sup> )	Regeneration Partial regeneration		Cellular, acellular and mixed cellular and acellular new cementum were present in all groups. The greatest amount of new cementum was in BDNF (500 ng mL <sup>-1</sup> ) + HMW-HA followed by BDNF (500 ng mL <sup>-1</sup> ) alone, no significant differences betw. groups. Significantly more acellular cementum was detected for non-inflamed sites. Complete PDL regeneration was statistically significantly higher ( $p < 0.04$ ) for BDNF (500 ng mL <sup>-1</sup> ) + HMW-HA compared to the other groups.

*hOP-1*, recombinant human osteogenesis protein-1; *bFGF*, basic fibroblast growth factor; *bLCBM*, bovine insoluble collagenous matrix carrier; *BDNF*, brain-derived neurotrophic factor; *HMW-HA*, high molecular weight hyaluronic acid; *PDGF*, periodontal ligament; *BDNF*, brain-derived neurotrophic factor; *HMW-HA*, high molecular weight hyaluronic acid; *n.r.*, not reported; *no*, number

**Table 11** Histomorphometrical results (height in mm, area in  $\text{mm}^2$ , volume, or area in %) of treated animal periodontal defects by using biological factors

No.	Study	No. of furcations	Defect height mm	NB mm/mm <sup>2</sup> /%	NC mm/mm <sup>2</sup> /%	Collagen fibers on tooth surface mm/mm <sup>2</sup> /% area or height	Junctional epithelium mm/mm <sup>2</sup> /% area or height
1	Ripamonti et al. [73]	4	A: distal: 7.8±0.4 mm mesial: 8.4±0.2 mm B: distal: 8.6±0.1 mm mesial: 7.6±0.6 mm C: distal: 7.7±0.2 mm mesial: 8.6±0.3 mm	A: 4.2±0.2 mm 3.6±0.1 mm B: 3.7±0.1 mm C: 3.7±0.4 mm 2.6±0.4 mm C: 3.1±0.2 mm 3.5±0.2 mm Height: 31.65±6.06% 67.36±3.93% Height: 62.64±7.89% Height: 33.95±15.39% Area: 58.0±21.9% 71.3±13.5% 54.3±8.0% n.r.	A: 3.2±0.3 mm 3.7±0.4 mm B: 5.7±0.3 mm 5.1±0.9 mm C: 3.6±0.2 mm 5.2±0.4 mm Height: 71.95±10.86% 94.44±4.20% Height: 83.99±7.70% Height: 36.60±20.16% Area: 79.1±23.9% 72.2±14.4% 38.8±8.6% Mesial: Test 1: 6.1±0.8 mm Test 2: 6.7±0.3 mm Control: 2.8±0.1 mm Distal: Test 1: 6.2±0.5 mm Test 2: 6.2±0.3 mm Control: 2.6±0.2 mm Test 1: 38.9±9.2% Test 2: 71.2±15.2% Area: Test 1: 54.3±8.0% Test 2: 71.3±13.5%	n.r.	n.r.
2	Regazzini et al. [74]	7	5	5	5	Height: 31.65±10.86% 94.44±4.20% Height: 83.99±7.70% Height: 36.60±20.16% Area: 79.1±23.9% 72.2±14.4% 38.8±8.6% n.r.	0.04±0.01 mm <sup>2</sup> 0.00 mm <sup>2</sup>
3	Keles et al. [75]	8	5	5	5	Height: 67.36±3.93% Height: 62.64±7.89% Height: 33.95±15.39% Area: 58.0±21.9% 71.3±13.5% 54.3±8.0% n.r.	n.r.
4	Simssek et al. [76]	6	5	5	5	Height: 33.95±15.39% Area: 79.1±23.9% 72.2±14.4% 38.8±8.6% n.r.	n.r.
5	Takayama et al. [78]	8	4	4	4	71.3±13.5% 54.3±8.0% n.r.	n.r.
6	Ripamonti et al. [117]	4	6	2	2	Test 1: 6.1±0.8 mm Test 2: 6.7±0.3 mm Control: 2.8±0.1 mm Distal: Test 1: 6.2±0.5 mm Test 2: 6.2±0.3 mm Control: 2.6±0.2 mm Test 1: 38.9±9.2% Test 2: 71.2±15.2% Area: Test 1: 54.3±8.0% Test 2: 71.3±13.5%	n.r.
7	Murakami et al. [118]	16 (8/group)	4	56	5	Test 1: 6.1±0.8 mm Test 2: 6.7±0.3 mm Control: 2.8±0.1 mm Distal: Test 1: 6.2±0.5 mm Test 2: 6.2±0.3 mm Control: 2.6±0.2 mm Test 1: 38.9±9.2% Test 2: 71.2±15.2% Area: Test 1: 54.3±8.0% Test 2: 71.3±13.5%	n.r.
8	Jimbo et al. [99]	56	5	A: 16 B: 16 C: 16 D: 8	A: A: 82%/9% B: 76%/15% C: 76%/15% D: 72%/28%	Full reg/partial reg: A: 85% B: 37% C: 47% D: 28%	A: 0.69±0.109 mm Area: 69% B: 0.12±0.081 mm Area: 12% C: 0.2±0.085 mm Area: 20% D: 0.42±0.15 mm Area: 42%
9	Chantarawaratit et al. [10]	8	5	5	5	Area: 93.94±3.66% 91.70±8.83%	Area: 87.88±2.47% 83.51±3.82%
10	Teare et al. [77]	6	A: 7.37±0.56 mm B: 7.28±0.54 mm	A: 6.78±0.65 mm B: 5.93±0.92 mm	A: 5.13±0.47 mm B: 6.18±0.33 mm	88.50±6.77% 85.85±3.07%	

**Table 11** (continued)

No.	Study	No. of furcations	Defect height mm	NB mm/mm <sup>2</sup> /%	NC mm/mm <sup>2</sup> /%	Collagen fibers on tooth surface mm/mm <sup>2</sup> /% area or height	Junctional epithelium mm/mm <sup>2</sup> /% area or height
11	Tearé et al. [79]	8	11	B: 6.83 ± 0.63 mm 6.91 ± 0.61 mm C: 7.06 ± 0.32 mm 7.44 ± 0.63 mm	B: 5.60 ± 1.23 mm 5.67 ± 1.17 mm Height: 55.85 ± 9.19% C: 6.79 ± 0.35 mm 7.07 ± 0.57 mm Height: 62.67 ± 1.94%	3.44 ± 0.95 mm 3.65 ± 0.88 mm C: 5.03 ± 0.73 mm 5.45 ± 0.89 mm	n.r.
12	Jimbo et al. 2018 [120]	16	5	2.3 ± 0.4 mm Binned %: >0.63 in 76.9% defects 0.37–0.62% in 50% defects ≤0.37% in 46.7% defects 0.37–0.62% in 50% defects	4.5 ± 0.7 mm Distal 3.7 ± 0.7 mm Binned %: >0.63 in 76.9% defects 0.37–0.62% in 50% defects ≤0.37% in 46.7% defects 0.37–0.62% in 50% defects	n.r.	

NC, new cementum; NB, new bone; n.r., not reported; no., number

study reported only data on bone formation [92]. No signs of ankylosis or resorption were reported in any of the studies.

Thirteen of 14 studies provided histomorphometrical data (Table 17). Two hundred thirty-six defects in 113 animals (dogs or monkeys) were evaluated. The defect depth ranged from 2 to –11 mm. The new cementum ranged from 0.2 to 6.2 mm as linear measurements and from 3 to 89% as percentage. Bone formation ranged from 0.7 to 3.1 mm as linear measurements, from 2.4 to 3.9 mm<sup>2</sup> as surface measurements, and from 15 to 91% as percentage.

### Animal class III furcation defects treated with OFD and biological factors

Twelve studies providing data on the effect of the use of biological factors (i.e., OP1, EMD, FGF, TGF-β, PDL cells, citric acid, fibronectin, IGF, MSC cells, GMS cells) in animal class III furcation defects were identified (Table 18) [81, 87, 88, 94–96, 98, 100, 105, 109, 110, 121].

Most studies (nine out of twelve) reported periodontal regeneration with the presence of new cementum along with PDL and coronal growth of alveolar bone [81, 87, 88, 94, 95, 98, 100, 109, 121]. Two studies observed long junctional epithelium with limited signs of regeneration apically [96, 110]. One study reported mainly osseous repair [105]. Both studies using citric acid described root resorption or ankylosis [105, 110].

Ten of twelve studies provided histomorphometrical data (Table 19). Two hundred ninety-four defects in 101 animals (dogs or monkeys) were evaluated. The defect depth ranged from 3 to 15 mm. The new cementum ranged from 1.1 to 6.9 mm as linear measurements, from 3.1 to 5.4 mm<sup>2</sup> as surface measurements, or from 24 to 100% as percentage. Bone formation amounted from 1.4 to 4.9 mm as linear measurements, from 2.5 to 3.7 mm<sup>2</sup> as surface measurements, and from 10 to 92% as percentage.

### Animal class III furcation defects treated with OFD and combined techniques

Fourteen studies showed histological results following the use of combined techniques for the treatment of class III animal furcation defects (Table 20) [81, 82, 84–86, 93–95, 98, 106, 108, 109, 111, 116].

Five studies used a combination of membrane and biologic factor [81, 84, 86, 109, 111], two studies used membrane, growth factor and specified cells [82, 108], two studies used membrane, bone graft and growth factor [103, 116], three studies applied bone graft and growth factor [93–95], one study used a combination approach of membrane and specified cells [85], and one study used root conditioning and non-resorbable membrane [106].

**Table 12** Histological results of treated animal furcation II defects by using combination approaches (9 studies)

No.	Authors	Year	Animal type	Furcation type	Defect localization	Healing time	Treatment	Healing type	Histological results
1	Regazzini et al. [74]	Dogs	4	Class II Mandible, Surgically created Height: 5 mm		2 months	GTR (ePTFE) + EMD	Regeneration	EMD led to significant regeneration of the furcation lesions; the association with membranes was detrimental. Reduced new bone formation (immature); new cementum was of varying thickness, mainly cellular and with intrinsic and/or extrinsic fibers.
2	Teare et al. [79]	Monkeys	4	Class II Mandible and maxilla Surgically created Height: 11 mm		60 days	TGF $\beta$ 3 + minced muscle in Matrigel Insoluble collagenous bone matrix + Matrigel Insoluble collagenous bone matrix + Insoluble collagenous bone matrix-based induced bone	Regeneration	Pronounced periodontal regeneration in experimental defects. New alveolar bone with new cellular cementum and new, well-vascularized PDL with Sharpey's fibers. The new PDL exhibited highly organized collagenous fibers with functional insertion of Sharpey's fibers into both new alveolar bone and new cementum
3	Delibrador et al. [39]	Dogs	6	Class II Mandible, Surgically created, Height: 5 mm		90 days	Autogenous bone + rm (calcium sulfate)	Regeneration Long junctional epithelium	Periodontal healing was similar to using debridement alone, autogenous bone graft or graft with a barrier. Newly formed bone was observed and in 3 specimens total bone fill. Epithelial migration was observed in the coronal portion in some specimens. Most specimens had repaired root resorption lacunae without areas of active resorption.
4	Keles et al. [75]	Dogs	4	Class II Mandible, Surgically created Height: 5 mm		3 months	Platelet pellet + GTR (rm, i.e., polylactic acid)	Regeneration	New cementum along with PDL and alveolar bone. Cementum formation (deposited over dentin, was of variable thickness, composed of cells with intrinsic and extrinsic collagen fibers distributed randomly on the root surface) was significantly higher compared to the control group. Limited alveolar bone formation (mainly woven) was statistically similar in all groups.
5	Simsik et al. [76]	Dogs	3	Class II Mandible and maxilla Surgically created Height: 5 mm		2 months	Autogenous bone (AB) + PRP Mesenchymal stem cells (MSCs) + PRP	Regeneration	The new connective tissue between new bone and the root surface was of cellular and composed of collagen fiber bundles
			30						Periodontal regeneration with cementum (deposited over dentin, was of variable thickness, composed of cells with intrinsic and extrinsic collagen fibers distributed randomly on the root surface), alveolar bone (mainly woven), and PDL. The new connective tissue between new bone and the root surface was cellular and composed of collagen fiber bundles.

**Table 12** (continued)

No.	Authors	Year	Animal type	Furcation type	Defect localization	Healing time	Treatment	Healing type	Histological results
			No. of animals	No. of defects	Defect nature	Defect size (mm)			
6	Suaid et al. [72]		Dogs	Class II Maxilla Surgically created Height: 8.84 mm		3 months	Platelet pellet + GTR (rm, i.e., co-polymer of polylactic acid and polyglycolic acid) + PDL cells	Regeneration	PDL cells and GTR promote periodontal regeneration. New bone was predominantly woven. The newly formed cementum was of a cellular, mixed intrinsic and extrinsic collagen fiber type. Dentoalveolar ankylosis could be observed in one specimen.
7	Teare et al. [77]		Monkeys	Class II Mandible Surgically created + silk ligature, Height: 6–8 (7) mm Depth: 10–12 mm buccolingually		60 days	hOP-1 + TGF- $\beta$ 3 + MUS (morecellated autogenous muscle)	Regeneration	TGF- $\beta$ 3 & hOP-1 + MUS: New bone (marked osteoid formation) was restricted to the periphery of the furcation defects. Newly formed cementum was dense, clustered in some regions.
8	Suaid et al. [97]		Dogs	Class II Mandible and maxilla Surgically created Height: 5 mm Depth: 2 mm		90 days (mandibular) GTR (rm, i.e. co-polymer of polylactic acid and polyglycolic acid) + BG (control)	GTR (rm, i.e. co-polymer of polylactic acid and polyglycolic acid) + BG + PRP (test)	Regeneration	PRP may enhance the amount of new cementum and provide a more mineralized bone in a shorter period of time. No epithelial downgrowth, resorption or ankylosis were observed.
9	Caffesse et al. [54]		4 dogs	Class II, Mandible Naturally occurring		4 months	DFDBA + ePTFE	Regeneration	In the test group, a more evident layer of new cementum was observed in the formix region: the bone showed a more evident mineralized area with islands of highly cellular bone marrow. In the control group, the bone presented larger marrow spaces (immature bone). New connective tissue fibers (functionally oriented, very cellular, highly vascularized), cementum and bone were formed coronally to the notch. In the area with DFDBA signs of ankylosis, GTR led to an increase in connective tissue and bone regeneration. Adjunctive bone grafting did not enhance the regeneration

*BG*, bioactive glass; *PRP*, platelet-rich plasma; *DFDBA*, demineralized freeze-dried bone allograft; *ePTFE*, expanded polytetrafluoroethylene; *rm*, resorbable membrane; *TGF*  $\beta$ 3, recombinant human transforming growth factor  $\beta$ 3; *n.r.*, not reported; *no.*, number

**Table 13** Histomorphometrical results (height in mm, area in mm<sup>2</sup>, volume, or area in %) of treated animal furcation II defects by using combination approaches

No.	Study	No. of furcations	Defect height mm	NB mm/mm <sup>2</sup> /%	NC mm/mm <sup>2</sup> /%	Collagen fibers on tooth surface mm/mm <sup>2</sup> /%	Junctional epithelium mm/mm <sup>2</sup> /%
			area or height	area or height	area or height	area or height	area or height
1	Regazzini et al. [74]	8	5 mm	Height: 28.49 ± 10.32%	n.r.	n.r.	n.r.
2	Teare et al. [79]	4	11 mm	A: Mesial: 2.8 ± 0.9% Distal: 2.8 ± 0.8% B: Mesial: 4.8 ± 0.3% Distal: 4.7 ± 0.3% C: Mesial: 4.6 ± 0.4% Distal: 4.9 ± 0.5% D: Mesial: 2.6 ± 0.9% Distal: 2.8 ± 1.2% Area: 59.85 ± 20.09%	A: Mesial: 3.8 ± 0.9 mm Distal: 3.5 ± 0.6 mm B: Mesial: 6.1 ± 0.2 mm Distal: 6.1 ± 0.4 mm C: Mesial: 5.3 ± 0.4 mm Distal: 5.2 ± 0.5 mm D: Mesial: 5.1 ± 0.4 mm Distal: 4.9 ± 0.8 mm Area: 62.27 ± 15.86%	n.r.	n.r.
3	Delibrador et al. [39]	12	5 mm	Height: 61.06 ± 7.90%	Height: 81.63 ± 8.17%	n.r.	Area: 10.05 ± 9.56%
4	Keles et al. [75]	8	5 mm	Height: 68.8 ± 14.20%	Height: 66.83 ± 10.78%	n.r.	
5	Sinisek et al. [76]	6	5 mm	80.47 ± 8.23%	70.47 ± 11.75%	n.r.	
6	Suaid et al. [72]	7	8.84 ± 0.31 mm	7.28 ± 1.00 mm 9.02 ± 2.30 mm <sup>2</sup>	7.28 ± 1.00 mm	7.28 ± 1.00 mm	0.60 ± 0.99 mm 4.22 ± 0.95 mm <sup>2</sup>
7	Teare et al. [77]	6	5.31 ± 0.45 mm 6.32 ± 1.04 mm 11.14 ± 2.80 mm 12.78 ± 1.41 mm n.r.	2.70 ± 1.11 mm 4.73 ± 1.08 mm 4.33 ± 0.64 mm 5.01 ± 0.63 mm 1.09 ± 0.76 mm	0.90 ± 0.51 mm 2.69 ± 1.06 mm 9.20 ± 3.21 mm 12.45 ± 1.73 mm 1.03 ± 0.59 mm	n.r.	
8	Suaid et al. [97]	9				1.84 ± 1.87 mm 0.33 ± 0.62 mm 1.41 ± 0.63 mm	n.r.
9	Caffesse et al. [54]	4				2.38 ± 2.68 mm <sup>2</sup>	1.90 ± 0.69 mm
		16					

NC, new cementum; NB, new bone; n.r., not reported; no., number

**Table 14** Histological results of animal type III furcation defects treated using open flap debridement (12 studies)

No.	Authors Year	Animal type No. of animals No. of defects	Furcation type Defect localization Defect nature Defect size (mm)	Healing time Treatment	Healing type	Histological results
1	Pontoriero et al. [107]	Dogs Exp 1: 5 10 (9 analyzed, 1 dropout) Exp 2: 5 5 Exp. 3: 5 5	Class III Mandible Surgically created Exp 1: Height: 2 mm Width: 2 mm Exp 2: Height: 3 mm Width: 4 mm Exp. 3: Height: 5 mm Width: 4 mm Class III, Mandible Surgically created, Size n.r.	5 months Exp 1, 2, 3: OFD	Limited regeneration Long junctional epithelium.	Exp 1: new cementum with inserting collagen fibers only in the notch area and immediately coronal to the notch area. The fornix was either open or lined with epithelium. Exp 2: 1 out of 5 teeth showed new cementum. Exp 3: 1 tooth had new cementum in the notch area.
2	Sculean et al. [109]	Monkeys 3 3	Class III Mandible Surgically created Size n.r.	5 months OFD (coronally repositioned flap)	Long junctional epithelium Limited regeneration	Healing mainly by long junctional epithelium and limited new bone and attachment at the bottom of the defect. Oxytalan fibers were seen only in the apical part of the defect, together with some new cementum and PDL. 4 defects showed cementum regeneration, the others healed through long junctional epithelium.
3	Crespi et al. [80]	Dogs 6 12	Class III Mandible Surgically created Height: 6.8 mm	6 months, OFD	Long junctional epithelium Limited regeneration	All furcations were open with epithelialized inflamed connective tissue. New bone and new cementum with inserting collagen fibers was limited to the notch area.
4	Donos et al. [81]	Monkeys 3 3	Class III Mandible Surgically created Height: 3 mm Width: 4 mm Class III Mandible Surgically created Height: 3 mm Width: 4 mm	5 months OFD	Long junctional epithelium Limited regeneration	Study I: None of the teeth showed a completely regenerated attachment apparatus. The furcation fornix contained long junctional epithelium. New cementum and bone formed to a varying degree. Study II: New cementum, collagen fibers and bone were formed to a varying degree.
5	Lindhe et al. [83]	Dogs 5 and 8 (study I) 4 and 7 (study II)	Class III Mandible Surgically created + impression material, Height: 4 mm	5 months, OFD	Long junctional epithelium Limited regeneration	All defects showed incomplete filling, with inflamed connective tissue and gingival epithelium in the lower portion of the defect. New cementum with inserting collagen fibers and new bone limited to the notch area.
6	Suaid et al. [85]	Dogs 7 28	Class III Mandible Surgically created, Height: 5 mm	3 months, OFD	Long junctional epithelium	Minimal new bone, cementum and attachment were registered. Osteogenesis and cementogenesis were limited to the apical area of the defect.
7	Giannobile et al. [87]	Dogs 18 36	Class III Mandible Surgically created Height: 5 mm	2 months OFD	Minimal regeneration Long junctional epithelium	
8	Murano et al. [88]	Dogs	Class III	2 months	Long junctional epithelium	

Table 14 (continued)

No.	Authors Year	Animal type No. of animals No. of defects	Animal type No. of animals No. of defects	Furcation type Defect localization Defect nature Defect size (mm)	Healing time Treatment	Healing type	Histological results
9	Saito et al. [94]	Dogs 5 10	15 15	Mandible Surgically created + impression material Height: 4 mm Class III Mandible Surgically created + impression material Height: 4 mm Class III Maxilla and mandible Surgically created Height: 5 mm Class III Mandible Surgically created, Height: 5 mm Width: 4 mm	OFD 8 weeks OFD 8 weeks OFD 8 weeks OFD 5 months OFD	Limited Regeneration Long junctional epithelium. Minor bone formation Long junctional epithelium Minor bone formation Long junctional epithelium Regeneration Limited regeneration	All furcations were open with inflamed connective tissue covered by gingival epithelium. New cementum with inserting collagen fibers and new bone were limited to the notch level. Gingival epithelium with connective tissue in the fornix. Limited new bone at the bottom of the furcation. Limited new cementum with inserting collagen fibers at the bottom of the scaled surface. Minor new bone formation. The defects were still present after 8 weeks. No regeneration of bone, PDL and cementum was observed. Epithelium and connective tissue filled the defect to the top. Varying degrees of new attachment and bone formation. In 2 of 8 defects, the furcation was completely closed with new attachment and bone up to the fornix. New cementum was cellular with inserting collagen fibers. Ankylosis, root resorption and connective fibrotic tissue in the center of the defects in 4 defects; in 2 defects epithelial downgrowth and moderate periodontal regeneration at the notch level.
10	Chen et al. [98]	Dogs 6 8	15 15	Mandible Surgically created + impression material Height: 4 mm Class III Maxilla and mandible Surgically created Height: 5 mm Class III Mandible Surgically created, Height: 5 mm Width: 4 mm	OFD 8 weeks OFD 8 weeks OFD 5 months OFD	Long junctional epithelium Minor bone formation Long junctional epithelium Regeneration Limited regeneration	Apical migration of the junctional epithelium with varying degrees of new attachment and new bone formation. New cellular cementum with without sparse collagen fibers was seen in the lower part of the defect. One defect presented considerable new cementum and moderate new attachment.
11	Mardas et al. [93]	Dogs 9 8	15 15	Mandible Surgically created + impression material Height: 4 mm Class III Mandible Surgically created, Height: 5 mm Width: 4 mm	OFD 4 months OFD	Long junctional epithelium Limited regeneration	Plaque accumulation allowed
12	Shirakata et al. [121]	Monkeys 3 12	15 15	Mandible Surgically created Height: 5 mm Width: 5 mm Thereafter 8 weeks	Long junctional epithelium Limited regeneration		

*OF*, open flap; *SRP*, scaling and root planing; *OFD*, open flap debridement; *no.*, number

**Table 15** Histomorphometrical results (height in mm, area in mm<sup>2</sup>, volume, or area in %) of animal type III furcation defects treated using open flap debridement

No.	Study	No. of furcations	Defect height mm	NB mm/mm <sup>2</sup> /%	NC mm/mm <sup>2</sup> /%	Collagen fibers on tooth surface mm/mm <sup>2</sup> /% area or height	Junctional epithelium mm/mm <sup>2</sup> /% area or height
1	Pontoriero et al. [107]	Exp 1: 9 Exp 2: 9	2.7 ± 0.2 mm/4.1 ± 1.4 mm <sup>2</sup> 3.3 ± 0.2/12.8 ± 2.8 mm <sup>2</sup>	n.r. n.r. n.r.	Exp 1: 0.4–0.9 Exp 2: 1 tooth: mesial root: 0.8 mm, distal root: 1 mm Exp 3: 1 tooth: mesial root: 0.5 mm	n.r. n.r. n.r.	n.r. n.r. n.r.
2	Sculean et al. [109]	3	n.r.	n.r.	n.r.	n.r.	n.r.
3	Crespi et al. [80]	12	6.8	0.2 ± 0.5 mm	0.2 ± 0.5 mm	n.r.	n.r.
4	Donos et al. [81]	1 1 1	A: 3.16 7.70 B: 2.57 6.95 C: 3.12	A: 1.58 mm Height 50.0% B: 1.16 mm Height 54.1% C: 1.18 mm Height 37.8% 4 7.93 ± 0.75	A: 4.79 mm Height 62.2% B: 1.85 mm Height 26.2% C: 1.92 mm Height 25.4% 0.7 ± 0.6 mm 0.69 ± 0.59 mm 1.89 ± 0.95 mm <sup>2</sup>	A: 4.79 mm Height: 62.2% B: 1.85 mm Height: 26.2% C: 1.92 mm Height: 25.4% 43 ± 12% 0.69 ± 0.59 mm	n.r. n.r. n.r.
5	Lindhe et al. [83]	4	7.56	0.97 ± 0.6	1.03 ± 1.32 mm Height: 20.9 ± 25.6% 12.2 ± 1.3 mm	1.35 ± 1.13 mm Height: 27.3 ± 22.1% 22.3 ± 1.6%	n.r.
6	Suaid et al. [85]	7	4	7.93 ± 0.75	Area: 24.3 ± 9.4% 1.65 ± 0.19 mm Area: 64.24 ± 22.11%	Area: 23.4 ± 11.6% 0.99 ± 0.43 mm Area: 38.67 ± 13.87	n.r. n.r.
7	Gianmobile et al. [87]	21	4.97 ± 0.6	1.03 ± 1.32 mm Height: 20.9 ± 25.6% 12.2 ± 1.3 mm	0.94 ± 1.18 mm Height: 27.3 ± 22.1% 22.3 ± 1.6%	1.35 ± 1.13 mm Height: 27.3 ± 22.1% n.r.	n.r.
8	Murano et al. [88]	15	4	4	Area: 24.3 ± 9.4% 1.65 ± 0.19 mm Area: 64.24 ± 22.11%	Area: 23.4 ± 11.6% 0.99 ± 0.43 mm Area: 38.67 ± 13.87	n.r. n.r.
9	Saito et al. [94]	10	4	5	4.4 ± 1.3 mm 6.9 ± 3.3 mm <sup>2</sup>	2.57 ± 0.29 mm 10.8 ± 2.1 mm	2.57 ± 0.29 mm 7.6 ± 2.8 mm n.r.
10	Chen F. et al. [98]	8	5	13.9 ± 1.8 (length) 5.4 ± 0.7 (height)	13.1 ± 2.7 (area)	13.1 ± 2.7 (area)	13.1 ± 2.7 (area)
11	Mardas et al. [93]	9	13.9 ± 1.8 (length) 5.4 ± 0.7 (height)	13.1 ± 2.7 (area)	10.8 ± 2.1 mm	10.8 ± 2.1 mm	10.8 ± 2.1 mm
12	Shirakata et al. [121]	3	12.5 ± 0.5	3.5 ± 0.6 mm <sup>2</sup> 28.3 ± 5.3%	3.7 ± 1.3 mm 30.5 ± 9.8%	2.3 ± 0.9 mm 1.9 ± 0.6 mm <sup>2</sup> 19.4 ± 6.9%	4.0 ± 2.8 mm 2.4 ± 0.4 mm <sup>2</sup> 33.0 ± 22.5%

NC, new cementum; NB, new bone; n.r., not reported; no., number

**Table 16** Histological results of animal type III furcation defects treated using guided tissue regeneration (GTR) (14 studies)

No.	Authors	Year	Animal type	Furcation type	Healing time	Membrane type	Healing type	Histological results
1	Crespi et al. [80]	Dogs	6 12	Class III Mandible Surgically created Height: 6.8 mm	6 months, GTR (ePTFE)	Limited regeneration Long junctional epithelium	Incomplete formation of new PDL, cementum and bone. 4/11 specimens showed limited periodontal regeneration.	
2	Donos et al. [81]	Monkeys	3 3	Class III Mandible Surgically created Height: 3 mm Width: 4 mm	5 months, GTR (m, i.e., polyglycolic acid)	Limited regeneration (exposed m) Long junctional epithelium (exposed m) Regeneration	In 2 of 3 specimens, the membrane was exposed: limited amounts of new cementum with inserting collagen fibers within the notch area and immediate coronally to the notch. New bone limited to the notch area. The remaining part of the defect was filled with connective tissue covered by epithelium. Where the membrane was not exposed, new bone, cementum (cellular type) with inserting collagen fibers covering the entire circumference of the defect.	
3	Jiang et al. [82]	Dogs	4 24	Class III Mandible Surgically created + filled with gutta-percha, Height: 4 mm Width: 3 mm	12 weeks, GTR (ePTFE)	Regeneration Long junctional epithelium	Epithelium surrounded all regenerated tissue. New bone and cementum were formed. Newly formed cellular cementum was distributed not uniformly. Collagen fibers inserted into newly formed cementum.	
4	Lindhe et al. [83]	Dogs	5 and 8 10 and 16	Class III Mandible Surgically created + impression material Height: 4 mm Width: 3 mm	5 months, GTR (ePTFE)	Regeneration Long junctional epithelium	New connective tissue attachment, cementum and bone. Newly formed alveolar bone within the surgically produced defect in the furcations was observed adjacent to the newly formed cementum.	
5	Park et al. [84]	Dogs	6 24	Class III Mandible Surgically created + orthodontic wire Height: 5 mm (4.5–5.5 mm)	8 weeks, GTR (ePTFE)	Regeneration Long junctional epithelium	Reparation as well as regeneration. At 8 weeks new bone, new cementum and PDL (well-organized collagen fibers, oriented obliquely) in the apical half of the lesion. The coronal half of the defect was filled with dense connective tissue. The formix root surface was covered with new cellular cementum and Sharpey's fibers projected into the connective tissue.	
6	Suaid et al. [85]	Dogs	7 28	Class III Mandible Surgically created, Height: 5 mm	11 weeks, GTR (ePTFE)	Regeneration Long junctional epithelium	At 11 weeks, new alveolar bone was evident. Bone formation was frequently incomplete. 30% of the furcation area was filled with connective tissue covered by epithelium.	
7	Araujo et al. [90]	Dogs	10 12	Class III Mandible Surgically created + impression material, Height: 4 mm Depth: 3 mm	5 months GTR (m, i.e., polyglycolic acid)	Regeneration	New cementum with inserting collagen fibers and new bone were limited to the level of the notch. Cementum formation with inserting collagen fibers; bone formation was frequently incomplete. The cementum was either cellular or acellular.	
8	Araujo et al. [92]	Dogs	19 38	Class III Mandible Surgically created + impression material, Height: 4 mm Width: 3 mm	3 months, GTR (m, i.e., co-polymer of polylactic acid and polyglycolic acid)	Regeneration Long junctional epithelium	Bone formation in large "suprabony" furcation defects has 3 phases: (i) formation of a provisional connective tissue, (ii) development of a primary bone spongiosa (mainly woven bone), (iii) replacement of the spongiosa by lamellar bone and bone marrow. The newly formed trabeculae of woven bone were reinforced by the deposition of parallel-fibered bone and lamellar bone.	
9	Araujo et al. [91]	Dogs	8 16	Class III Mandible Surgically created Height: 4 mm	2 months GTR (m, i.e., polyglycolic acid)	Regeneration	Formation of new bone, cementum and PDL. Bone formation in 3 phases: (1) organization of a fibrous connective tissue, (2) differentiation of this tissue to woven bone (3) maturation of the woven bone into lamellar bone marrow.	

**Table 16** (continued)

No.	Authors	Year	Animal type	No. of animals	Furcation type	Healing time	Healing type	Histological results
			No. of defects	No. of defects	Defect localization	Membrane type		
					Defect nature			
					Defect size (mm)			
10	Araujo et al. [86]	Dogs	5		Width: 3 mm wide (key-hole defect)			Cementum formation (cellular, extrinsic and intrinsic fiber type) took place in 3 stages: 1. Assembly of collagen fibers; 2. Deposition of matrix; 3. Addition of cells and collagen fibers.
11	Goncalves et al. [104]	Dogs	9	18 (9 / group)	Class III Mandible Surgically created + impression material, Height: 4 mm Width: 3 mm Class III Mandible Ligature induced	4 months GTR (m, i.e., polyglycolic acid)	Regeneration	Histologically, new bone, new PDL and new cementum formation was observed in various degrees. The new cementum was cellular with extrinsic/intrinsic fiber type.
12	Pontorio et al. [107]	Dogs	5		Surgically created Exp 1: 10 (9 analyzed, 1 dropout) Exp. 2: 5 Exp. 3: 5	5 months (4 months after membrane removal) Exp 1, 2, 3; SRP + GTR (non-rm, ePTFE)	Partial regeneration Long junctional epithelium	Exp 1: in "key-hole" defects, GTR led to new formation of cementum with functionally oriented inserting collagen fibers and pronounced bone formation in the entire furcation area. Exp 2: in medium size defects, class III defects were present after 5 months of healing in the majority of the cases; only 1 out of 4 teeth showed newly formed cementum with collagen fibers in the entire furcation area and 1 tooth showed partial new attachment. Exp. 3: Only 1 out of 5 teeth showed signs of new cementum formation in the notch and little coronally of it (0.5–1.1 mm). The size and the defects shape influence outcomes after GTR therapy. New cementum with inserting collagen fibers and new alveolar bone were observed in all defects at a varying extent. Regenerated oxytalan fibers in apico-occlusal direction were in all defects with a new PDL.
13	Sculean et al. [109]	Monkeys	3		Class III Mandible Surgically created, Size n.r.	5 months GTR (m, i.e., polyglycolic acid)	Regeneration	
14	Kuboki et al. [111]	Monkey	3	4	Class III Mandible Surgically created, Height: 4 mm	3 months (and 6 weeks)- Not specified how many monkeys were sacrificed at 6/12 weeks. FCM (fibrous collagen membrane)	Long junctional epithelium At 12 weeks: no signs of bone formation, except for the apical area. Most of the furcation area was filled with fibrous tissue.	

*GTR*, guided tissue regeneration; *ePTFE*, expanded polytetrafluoroethylene; *rm*, resorbable membrane; *SRP*, scaling and root planning; *PDL*, periodontal ligament; *n.r.*, not reported

**Table 17** Histomorphometrical results (height in mm, area in mm<sup>2</sup>, volume, or area in %) of animal type III furcation defects treated using guided tissue regeneration (GTR)

<i>n</i>	Study	No. of furcations	Defect height (mm)	NB mm/mm <sup>2</sup> /%	NC mm/mm <sup>2</sup> /%	Junctional epithelium mm/mm <sup>2</sup> /%
1	Crespi et al. [80]	11	6.8 mm	0.7 mm	0.2 ± 0.4 mm	n.r.
2	Donos et al. [81]	1	A: 2.2 mm 5.89 mm B: 2.54 mm 6.72 mm C: 3.36 mm 8.26 mm	A: 0.97 mm Height: 44.0% B: 2.31 mm Height: 91.0% C: 0.96 mm Height: 28.6%	A: 1.84 mm Height: 31.2% B: 6.01 mm Height: 89.4% C: 4.93 mm Height: 59.7%	A: 1.84 mm Height: 31.2% B: 6.01 mm Height: 89.4% C: 4.93 mm Height: 59.7%
3	Jiang et al. [82]	4	10.83 ± 1.67 mm (height) 10.59 ± 3.52 mm (area)	2.35 ± 1.26 mm <sup>2</sup> Area: 22.62 ± 7.33%	3.37 ± 1.21 mm 31.67 ± 12.83%	1.33 ± 0.31 mm 17.7 ± 5.35% Area: 51.81 ± 5.48%
4	Lindhe et al. [83]	7	4.9 mm 9.3 mm 11.4 mm 4.9 mm 9.3 mm 11.4 mm 4 mm	1.4 ± 1.6 mm 2.2 ± 1.1 mm 2.8 ± 1.4 mm 1.2 ± 0.4 mm 2.4 ± 1.4 mm 3.1 ± 1.1 mm 1.7 ± 0.5 mm	86 ± 11% 82 ± 13% 74 ± 11%	n.r.
5	Park et al. [84]	3 (8 weeks) 4 (11 weeks)	5 mm 5 mm	Area: 14.6 ± 9.5% 60.4 ± 16.0%	Area: 4.6 ± 1.2% 14.0 ± 3.8%	Area: 26.3 ± 10.8% 4.3 ± 7.3%
6	Suaid et al. [85]	7 (GTR) 7 (GTR + sponge)	8.3 ± 0.67 mm 8.0 ± 0.65 mm	1.52 ± 0.39 mm 2.91 ± 0.56 mm <sup>2</sup> 2.33 ± 0.95 mm <sup>2</sup> 3.94 ± 1.52 mm <sup>2</sup>	1.52 ± 0.39 mm 2.33 ± 0.95 mm 2.33 ± 0.95 mm <sup>2</sup>	1.52 ± 0.39 mm 2.33 ± 0.95 mm 2.42 ± 0.26 mm 2.47 ± 1.22 mm
7	Araujo et al. [90]	12	4 mm	Area: 27.9%	Area: 29.6%	n.r.
8	Araujo et al. [92]	4	4 mm 4 mm 4 mm 4 mm	Area: 71 ± 17.6% 74 ± 1.7% 78 ± 5.1% 78 ± 4.8%	n.r.	n.r.
9	Araujo et al. [91]	4	4 mm 4 mm	Height: 4 ± 5%	Height: 3 ± 4.6% 20 ± 11.1%	n.r.
10	Araujo et al. [86]	5	4 mm	36 ± 12.6%	Area: 25 ± 8%	n.r.
11	Goncalves et al. [104]	9	Half of the root length	39 ± 7% n.r.	3.59 ± 167 mm 6.20 ± 2.26 mm	n.r.
12	Pontoriero et al. [107]	Exp 1: 9 Exp. 2: 5	2.6 ± 0.3 mm/4.8 ± 1.3 mm <sup>2</sup> 3.2 ± 0.2 mm/13.6 ± 1 mm <sup>2</sup>	Exp 1: 0.9–2.3 mm 50–100%	Exp 1: 0.9–2.3 0.9–2.3 50–100%	n.r.

**Table 17** (continued)

<i>n</i>	Study	No. of furcations	Defect height (mm)	NB mm/mm <sup>2</sup> % area or height	NC mm/mm <sup>2</sup> % area or height	Collagen fibers on tooth surface mm/mm <sup>2</sup> % area or height	Junctional epithelium mm/mm <sup>2</sup> % area or height
13	Sculean et al. [109]	3	5.1 ± 0.2 mm/22.3 ± 2.8 mm <sup>2</sup>	Exp 2: 1 tooth; mesial root: 1 mm distal root: 1.8 mm Exp. 3: n.r.	50–100% Exp 2: 1 tooth: mesial root: 1 mm distal root: 1.8 mm Exp 3: 1 tooth had: mesial root: 0.5 mm, distal root: 1.1 mm n.r.	Exp 2: 1 tooth: mesial root: 1 mm distal root: 1.8 mm n.r.	n.r.
14	Kuboki et al. [111]	3	4 mm	29%	34%	n.r.	n.r.
		14:4, 5, 5					

NC, new cementum; NB, new bone; n.m., not mentioned, no data available; PDL, periodontal ligament; Exp, experiment; SRP, scaling and root planing

In the majority of the studies (12 out of 14), periodontal regeneration was found to occur at a varying extent [81, 82, 84–86, 94, 95, 103, 106, 108, 109, 111].

One study using EMD plus bioactive glass (BG) [116] and another study applying EMD and calcium phosphate (CaP) [93] reported that the healing occurred mainly through a long junctional epithelium with limited periodontal regeneration to the apical part of the defects.

Ankylosis or root resorption was reported in four studies [85, 95, 106, 111].

Twelve of 14 studies provided histomorphometrical data (Table 21). Two hundred two defects in 78 animals (dogs or monkeys) were evaluated. The defect depth ranged from 1 to 13 mm. The new cementum was reported as a range from 0.9 to 8.6 mm as linear measurements or from 13 to 93% as percentage. Bone formation ranged from 1.1 to 4.3 mm as linear measurements, from 1.4 to 6.2 mm<sup>2</sup> as surface measurements, and from 1 to 96% as percentage.

## Data synthesis

The histological outcomes of studies employing the same methods of evaluation and similar outcome measures were summarized. Due to the fact that the results were heterogenic and mixed, and various measuring methodologies were used, data synthesis of animal studies was not possible. Based on the available data, the percentage of studies demonstrating complete or partial regeneration in treated defects was estimated and the results illustrated in Fig. 2. Expressed in percentages, periodontal regeneration ranged from 8 to 100%. Among all regenerative approaches, growth factors showed remarkable results even in class III furcation defects.

## Data analysis of the regenerative effect of each intervention in humans for class II and III furcation type defects

Regarding human histological data, six studies were identified (Tables 22 and 23) [24, 51, 52, 67, 68, 113]. Four studies investigated class II furcation defects [24, 51, 52, 113], one study class III [68] while one presented mixed data from class II and III furcation defects [67].

Once again, the nature of healing in the treated defects following regenerative therapy was defined as follows: long junctional epithelium (epithelial downgrowth covering the treated tooth surface); connective tissue attachment (new cementum with inserting collagen fibers on the treated tooth surface but not connected to new bone); connective tissue adhesion (connective tissue contact to the root without apparent cementum formation); regeneration (new cementum with inserting fibers functionally oriented and new bone); and osseous repair (bone formation opposite the tooth surface, leading to defect filling but without apparent PDL formation).

**Table 18** Histological results of animal type III furcation defects treated using biological factors (12 studies)

No.	Authors	Year	Animal type	No. of animals	No. of defects	Furcation type	Defect localization	Defect nature	Defect size (mm)	Healing time	Treatment	Healing type	Histological results
1	Donos et al. [81]		Monkeys	3		Class III Mandible Surgically created, Height: 3 mm Width: 4 mm			5 months	EMD	Regeneration Limited regeneration		In the lower portion of the defects new cementum (facicular type) and in the coronal portion, a mixed cellular and acellular type of cementum was observed. The formix of the furcation did not present new cementum in any of the specimens. OP-1 in class III regenerative surgery shows periodontal regeneration: newly formed cementum was cellular with collagen-like fibrils which anchored into the adjacent alveolar bone. Tooth ankylosis was elseon.
2	Giannobile et al. [87]		Dogs	18		Class III Mandible Surgically created Height: 5 mm			2 months	OP-1: 0.75 mg/g OP-1: 2.5 mg/g OP-1: 7.5 mg/g	Regeneration		
3	Murano et al. [88]		Dogs	15		Class III Mandible surgically created + impression material, Height: 4 mm			2 months	PDL	Regeneration		In the PDL treatment group, new cementum, new PDL and bone fill could be observed in most of the defect.
4	Nagahara et al. [95]		Dogs	12		Class III Mandible Surgically created + impression material Height: 4 mm			8 weeks	A: MSC + Col B: Col	Regeneration		In group B, alveolar bone regeneration was incomplete. In group A connective tissue fibers inserted into newly formed cementum.
5	Saito et al. [94]		Dogs	5		Class III Mandible Surgically created + impression material Height: 4 mm			8 weeks	EDTA + bFGF-2	Regeneration Long junctional epithelium		There was no ankylosis in both groups Gingival epithelium was observed in the formix of the furcation in all specimens together with new bone had formed in 2/3 of the furcation, new cementum with inserting collagen fibers, new connective tissue fibers (oriented parallel/inclined to the root surface).
6.	Palioioti et al. [96]		Dogs	6		Class III Mandible Surgically created + impression material Height: 3 mm			12 weeks	A: EDTA+propylene glycol alginate B: EMD C: TGF-β1 + propylene glycol alginate D: EMD + TGF-β1	Limited regeneration Long junctional epithelium		EDM and TGF-β present do not bring additional advantages in periodontal bone formation in class III furcation in dogs. All furcations were open with epithelialized tissue in the lower portion of the defect. New cementum (reparative cellular tissue that presented irregular distribution and variable thickness) with inserting collagen fibers (predominantly intrinsic collagen fibers but also included areas with extrinsic (Sharpey) fibers) and new bone was limited to the notch area. Inflammatory connective tissue was present in a great portion of the defect. The formix of the furcation did not present new cementum in any of the specimens. The new bone, under polarized light, seemed to be immature (woven bone)
7.	Sculean et al. [109]		Monkeys	3		Class III Mandible Surgically created, Size nr.			5 months	EMP	Regeneration		New cementum with inserting collagen fibers and new alveolar bone was observed in all defects at a varying extent. Regenerated oxytalan fibers, mainly oriented in apico-occlusal direction, were observed in all defects with a new PDL.
8	Klinge et al. [105]		Dogs	12		Class III Mandible Surgically created: Height: 2–5 mm Study I: 2–5 mm (13 study I, 26 study II) Study II: 3–9 mm			Study I: 10 weeks Study II: 9 weeks Therapy: OF + SRP + citric acid + wound closure: (a) CAF (b) repositioned flaps at CEJ	Bone regeneration		Bone formation more advanced adjacent to the roots than in the mid-portion of the interradicular area. Ankyloses were more frequent in large than in small defects; no differences between study I and II, or between splinting vs. displacement regarding bone formation pattern or ankyloses. Root resorptions were observed, some filled with	

**Table 18** (continued)

No.	Authors	Year	Animal type	No. of animals	Furcation type	Defect localization	Healing time	Treatment	Healing type	Histological results
9	Wiksjö et al. [110]		Dogs	1: 8 dogs, 47 defects II: 6 dogs, 36 defects	Class III Mandible Surgically created Height: I: 4.5–5.5 mm II: 4–5 mm		12 weeks	Some teeth subjected to periodic displacement, some were spinted I: a. OF + SRP + citric acid b. OF + SRP + citric acid + fibronectin c. OF + SRP + tetracycline d. OF + SRP + tetracycline + fibronectin II: a. OF + SRP + citric acid b. OF + SRP + tetracycline c. OF + SRP + tetracycline + fibronectin	Regeneration Long junctional epithelium	cementum-like materia, others with bone, ankylosed to the root surfaces.
10	Chen F. et al. [98]		Dogs	6 20	Class III Maxilla and mandible Surgically created Height: 5 mm		8 weeks	A: DG-MP control B: 100 µ IGF C: 100 µ IGF + DG-MP <sup>7,8</sup> D: 100 µ IGF + DG-MP <sup>6,3</sup> E: 100 µ IGF + DG-MP <sup>4,7</sup>	A: Long junctional epithelium B: partial regeneration C, D, E: regeneration	A: Little bone formation; at the top of the furcation area no new bone formation. Lack of bone, PDL and cementum regeneration was observed. B: Partial bone regeneration and other tissues; at the top of the furcation no completed regeneration and PDL tissues. C, D, E: New cementum with PDL and coronal growth of bone was observed.
11	Yu et al. [100]		Dogs	4 16	Class III Mandible Surgically created Height: 5 mm		8 weeks	EDTA EDTA + GMSCs	Regeneration	Group C: complete furcation filling with regenerative tissues. Alveolar bone regeneration was in both groups. GMSCs exhibiting enhanced bone formation compared to EDTA. In the GSCM group, newly formed Sharpey's fibers were anchored into the newly formed cementum, arranged perpendicularly to the root surface. In the EDTA group, the fibers were oriented parallel to the root.
12	Shirakata et al. [121]		Monkeys	3 12	Class III Mandible Surgically created Height: 5 mm Width: 5 mm Thereafter 8 weeks plaque accumulation allowed		4 months	ACS ACS + EDTA + EMP ACS + EDTA + Osteogain	Limited periodontal regeneration Regeneration	ACS: Limited periodontal regeneration, junctional epithelium migration; small amount of new bone in the lower part of the defect. One defect had minimal formation of new cementum and new attachment, in the other 2 reached the mid-portion of the defect. Moderate cellular cementum +/- oblique collagen fibers. ACS + EMP: less migration of junctional epithelium, more new cementum than in ACS group. New bone extended up to the coronal part of the defect. Acellular and cellular cementum with oblique dense collagen fibers. ACS + Osteogain: Similar healing to ACS + EMP group. Less apical migration of junctional epithelium, new attachment and new bone up to the coronal part of the defect in all defects. Acellular and cellular new cementum with oblique and/or perpendicular dense collagen fibers was observed with highly vascularized new PDL-like tissue.

OF, open flap; SRP, scaling and root planing; CAF, coronally positioned flap; CEJ, cement-enamel-junction; EMP, enamel matrix proteins; *IGF-I*, insulin-like growth factor I; *DG-MP*, dextran-co-gelatin hydrogel microspheres;  $\beta$ -TCP,  $\beta$  tricalcium phosphate; MSC, mesenchimal stem cells; Col, atelocollagen; GMSCs, gingiva-derived mesenchimal stromal cells; *n.r.*, not reported; ACS, porcine absorbable collagen sponge type I and III

**Table 19** Histomorphometrical results (height in mm, area in mm<sup>2</sup>, volume, or area in %) of treated animal furcation III defects by using biological factors

No.	Study	No. of furcations	Defect height (mm)	NB mm/mm <sup>2</sup> /%	NC mm/mm <sup>2</sup> /%	Collagen fibers on tooth surface mm/mm <sup>2</sup> /% area or height	Junctional epithelium mm/mm <sup>2</sup> /% area or height
1	Donos et al. [81]	1	A: 3.14 mm 7.88 mm B: 2.69 mm 6.96 mm C: 3.07 mm 8.02 mm	A: 2.90 mm Height: 92.4% B: 2.21 mm Height: 82.1% C: 1.58 mm Height: 51.5% A: 2.26 ± 1.66 mm B: 5.19 ± 0.19 mm C: 5.18 ± 0.92 mm	A: 6.89 mm Height: 87.4% B: 2.95 mm Height: 42.4% C: 3.7 mm Height: 46.1% A: 1.80 ± 1.47 mm Height: 47.2 ± 32.9% B: 2.35 ± 1.97 mm Height: 44.0 ± 33.2% C: 3.91 ± 1.70 mm Height: 77.8 ± 34.7% Height: 84.8 ± 3.9%	A: 6.89 mm Height: 87.4% B: 2.95 mm Height: 42.4% C: 3.7 mm Height: 46.1% A: 2.38 ± 1.65 mm Height: 49.5 ± 32.3% B: 2.07 ± 1.34 mm Height: 41.2 ± 28.6% C: 3.40 ± 1.65 mm Height: 77.4 ± 26.9% Height: 98.1 ± 2.3%	n.r. n.r.
		1					
2	Gianmobile et al. [87]	18					
		16					
		14					
3	Murano et al. [88]	15					
	Nagahara et al. [95]	6	4 mm 4 mm	Area: 65.6 ± 19.9% 31.1 ± 4.3% Area: 51.5 ± 11.0%	Area: 89.1 ± 15.1% 56.9 ± 16.3% Area: 71.8 ± 3.6%	n.r. n.r.	Area: 12.9 ± 3.5%
4		3					
5	Saito et al. [94]	10	4 mm	Height: A: 4.62 ± 0.12 mm 11.79 ± 1.79 mm 5 6	Height: A: 1.69 ± 0.57 mm 3.66 ± 1.87 mm <sup>2</sup> B: 1.51 ± 0.69 mm 10.95 ± 1.01 mm B: 5.30 ± 0.22 mm 15.33 ± 1.98 mm 12.58 ± 1.04 mm C: 4.87 ± 0.39 mm 13.41 ± 2.60 mm 11.45 ± 0.92 mm 4.76 ± 0.3 mm D: 4.76 ± 0.37 mm 11.85 ± 2.23 mm 11.10 ± 1.2 mm	Height: A: 4.27 ± 0.91 mm 3.13 ± 0.91 mm <sup>2</sup> B: 4.08 ± 0.61 mm 5.36 ± 2.86 mm <sup>2</sup> C: 4.55 ± 0.7 mm 3.69 ± 1.37 mm <sup>2</sup> D: 4.19 ± 0.59 mm 4.53 ± 2.14 mm <sup>2</sup>	Height: A: 3.53 ± 0.45 mm B: 3.82 ± 0.62 mm C: 3.78 ± 0.63 mm D: 3.65 ± 0.50 mm
6	Palioti et al. [96]	6	Height: A: 4.62 ± 0.12 mm 11.79 ± 1.79 mm 5 6	Height: A: 1.69 ± 0.57 mm 3.66 ± 1.87 mm <sup>2</sup> B: 1.51 ± 0.69 mm 10.95 ± 1.01 mm B: 5.30 ± 0.22 mm 15.33 ± 1.98 mm 12.58 ± 1.04 mm C: 4.87 ± 0.39 mm 13.41 ± 2.60 mm 11.45 ± 0.92 mm 4.76 ± 0.3 mm D: 4.76 ± 0.37 mm 11.85 ± 2.23 mm 11.10 ± 1.2 mm	Height: A: 4.27 ± 0.91 mm 3.13 ± 0.91 mm <sup>2</sup> B: 4.08 ± 0.61 mm 5.36 ± 2.86 mm <sup>2</sup> C: 4.55 ± 0.7 mm 3.69 ± 1.37 mm <sup>2</sup> D: 4.19 ± 0.59 mm 4.53 ± 2.14 mm <sup>2</sup>	Height: A: 3.53 ± 0.45 mm B: 3.82 ± 0.62 mm C: 3.78 ± 0.63 mm D: 3.65 ± 0.50 mm	
7	Sculean et al. [109]	3					
8	Klinge et al. [105]	I: 13 II: 26	I: 2–5 mm II: 3–9 mm	n.r. n.r.	n.r. n.r.	n.r. n.r.	n.r. n.r.
9	Wiklesjö et al. [110]	I: 47 a: 12 b: 11 c: 12 d: 12 II: 36	I: a. 5.7 ± 0.5 mm b. 5.3 ± 0.7 mm c. 4.9 ± 0.6 mm d. 5.1 ± 0.4 mm II: a. 4.1 ± 0.5 mm b. 4.7 ± 0.3 mm	Height (%): I: a. 58 ± 34 56 ± 35 47 ± 39 b. 57 ± 37 64 ± 35 53 ± 40	Height (%): I: a. 81 ± 27% b. 75 ± 26% c. 53 ± 37% d. 44 ± 31%	Height (%): I: a. 81 ± 27% b. 75 ± 26% c. 53 ± 37% d. 44 ± 31%	Height (%): I: a. 81 ± 27% b. 75 ± 26% c. 53 ± 37% d. 44 ± 31%

**Table 19** (continued)

No.	Study	No. of furcations	Defect height (mm)	NB mm/mm <sup>2</sup> /%	NC mm/mm <sup>2</sup> /%	Collagen fibers on tooth surface mm/mm <sup>2</sup> /% area or height	Junctional epithelium mm/mm <sup>2</sup> /% area or height
10	Chen. et al. [98]	c. 12	c. 4.4±0.6 mm	c. 40±39 33±35 26±36 d. 27±34 26±32 16±29 II. a. 76±34 81±28 62±47 b. 69±36 70±39 64±45 c. 28±33 46±42 26±39	a. 100±00% b. 83±23% c. 66±30%	a. 100±00% b. 83±23% c. 66±30%	a.0 b.42 c.7
11	Yu et al. [100]			5 mm			n.r.
12	Shirakata et al. [121]	3	8 (GMSCs) 8 (EDTA)	A: 1.76±0.25 mm Area: 62.33±23.65% B: 4.97±0.29 mm Area: 99.84±7.63% C: 4.15±0.28 mm Area: 92.36±6.38% D: 4.10±0.19 mm Area: 88.54±7.43& E: 3.29±0.32 mm Area: 85.35±12.47% Height: 47.11±7.91%	A: 1.13±0.32 mm Area: 39.64±10.27% B: 4.42±0.26 mm Area: 89.27±11.28% C: 3.31±0.25 mm Area: 80.67±10.87% D: 3.32±0.24 mm Area: 78.33±9.87% E: 1.96±0.54 mm Area: 68.47±9.67% Height: 68%	A: 2.68±0.37 mm B: 4.39±0.37 mm C: 3.64±0.37 mm D: 3.66±0.33 mm E: 2.73±0.22 mm	n.r.
				10.37±9.53%			
				A: 3.2±0.5 mm <sup>2</sup> 26.3±8.7% B: 4.4±0.9 mm <sup>2</sup> 33.8±3.0% C: 5.8±0.9 mm <sup>2</sup> 39.9±8.8	A: 2.2±0.5 mm 19.4±7.5% B: 4.0±0.3 mm 34.1±5.1% C: 5.4±0.4 mm 40.5±7.2%	A: 1.5±0.9 mm 2.4±1.2 mm <sup>2</sup> 14.1±9.6% B: 3.0±0.2 mm 2.2±0.8 mm <sup>2</sup> 25.0±1.8% C: 5.0±0.3 mm 2.1±1.0 mm <sup>2</sup>	A: 3.2±1.5 mm 2.9±1.2 mm <sup>2</sup> 26.4±7.0% B: 3.3±1.2 mm 1.9±0.5 mm <sup>2</sup> 19.9±12.1% C: 2.2±1.2 mm 2.2±0.6 mm <sup>2</sup> 15.7±5.5%
				24%			

NC, new cementum; NB: new bone; n, mesial; d, distal; mid, mid-portion of the defect; n.r., not reported; no., number

**Table 20** Histological results of animal type III furcation defects treated using a combination approach (14 studies)

No.	Authors	Year	Animal type	No. of animals	Furcation type	Healing time	Treatment type	Healing type	Histological results
			No. of defects	No. of defects	Defect localization				
				Defect size (mm)	Defect nature				
1	Donos et al. [81]		Monkeys	3	Class III Mandible Surgically created, Height: 3 mm	5 months	GTR (m, polymer of polyglycolic acid) + EMD	Regeneration Partial regeneration (exposed membrane) Long junctional epithelium (exposed membrane)	One specimen: the membrane was exposed; new cementum up to the fornix (one root) and new cementum restricted to the notch level and the coronal part was covered by epithelium (other root). Inserting collagen fibers were in the new cementum and trabecular bone was in most of the defect.
2	Jiang et al. [82]		Dogs	4	Class III Mandible Surgically created + gutta-percha, Height: 4 mm	3 months	GTR (ePTFE) + periost cells + $\beta$ -TCP GTR (ePTFE) + $\beta$ -TCP	Regeneration Long junctional epithelium	The unexposed membrane specimens showed formation of new bone, cementum (acellular and mixed cellular) and PDL along the entire circumference of the defect.
3	Park et al. [84]		Dogs	8	Class III Mandible mandible, Surgically created + orthodontic wire	8 weeks, 11 weeks	GTR (ePTFE) + PDGF	Regeneration	Epithelium surrounded all regenerated tissue. New bone and cementum were formed. Obvious boundary between new and old bone. Not uniformly distributed cellular cement.
4	Suaïd et al. [85]		Dogs	6	Height: 5 mm (4.5–5.5 mm)	3 months	GTR (m, i.e., co-polymer of polyactic acid and polyglycolic acid)	Reparation and regeneration.	Complete regeneration after 8 weeks, with new cementum, alveolar bone fibers, numerous fibroblasts and blood vessels.
				24	Class III Mandible Surgically created Height: 5 mm		+ carrier (collagen sponge) GTR (m, i.e., co-polymer of polyactic acid and polyglycolic acid) + carrier + PDL		No signs of ankylosis or root resorption.
									Sponge group: greater formation of new cementum compared to GTR alone, however no formation along the entire root surface.
									PDL cells + GTR: 2 defects presented complete filling with cementum with inserting collagen fibers along the entire root surface. New cementum with inserted collagen fibers and new bone were limited to the level of the notch.
									Bone ankylosis and root resorption were observed in two sites in each group.
									GFG-2 + TCP enhances connective tissue attachment.
									No downgrowth of epithelium in 9/10 specimens. Extensive bone formation up to the furcation formix; new cementum the entire root surface near the top of the furcation; new connective tissue fibers oriented parallel/inclined to the root surface and embedded into new cementum and bone.
									Group A: new bone, new cementum, new PDL with inserting Sharpey's fibers in the entire furcation area
									Group B: partial regeneration of bone and other tissues without regeneration in the top of the furcation area.
									Group C: lack of bone and cementum regeneration, with formation of connective tissue and epithelial cells.
									Group A: large amounts alveolar bone associated with PDL and cementum were newly formed.
									Group B: The treatment led to cementogenesis with the regeneration of alveolar bone to a varying degree.
									In group A significantly higher bone and cementum formation were recorded as compared to group B.
									New cementum with inserting collagen fibers and new alveolar bone in all defects at a varying extent. Regenerated oxytalan fibers, mainly oriented in apico-occlusal direction were observed in all defects with a new PDL.
									At 12 weeks:
									Group I: newly formed bone in almost entire furcation area; often ankylosis was observed.

**Table 20** (continued)

No.	Authors	Year	Animal type	Furcation type	Healing time	Treatment type	Healing type	Histological results
			No. of animals	Defect localization				
			No. of defects	Defect nature				
				Defect size (mm)				
5/5								
10	Fernandes et al. Braz. [116]	Dogs 5 20 (3 defects were not analyzed)		Class III Mandible Surgically created Height: 4–5 mm	3 months Test group 1: EMD + BG + (rn. i.e., co-polymer of polylactic acid and polyglycolic acid) Test group 2: EMD + m Control: BG + m	Long junctional epithelium Regeneration		Group II: BMP + FCM (single/double layer technique)
11	Araujo et al. [86]	Dogs 5 10		Class III Mandible Surgically created + impression material, Height: 4 mm Width: 3 mm	4 months EMD + phosphoric acid gel + (rn. polymer of polyglycolic acid)	Regeneration		Group II: the double layer technique resulted in regeneration of the alveolar bone, the cementum and the PDL, with perpendicular oriented collagen fibers along the entire treated dentin surface; no signs of ankylosis.
12	Mardas et al. [93]	Dogs 9 17		Class III Mandible Surgically created, 5 mm in height 4 mm in width	5 months EDTA + EMD + biphasic CP	Long junctional epithelium Regeneration		All 3 treatment modalities showed partial filling of the furcations with bone, cementum regeneration was limited to the apical portion of the defects.
13	Nagahara et al. [95]	Dogs 12 21		Class III Mandible Surgically created + impression material Height: 4 mm	8 weeks A: MSC+ $\beta$ -TCP + Col B: $\beta$ -TCP + Col	Regeneration		New cementum with inserting collagen fibers was formed in the notch area, extended coronally to various degrees. New bone formation (in some teeth) was limited to the notch area.
14	Matsuura et al. [106]	Dogs 2 8		Class III Mandible Surgically created Depth: 4.5–5.5 mm	8 weeks citric acid + non-rn (ePTFE)	Regeneration		In the mid-portion of the apical half of the defect, the new cementum was of acellular with extrinsic/intrinsic fiber type, and in the mid-portion of the coronal half of the defect, the cementum was cellular with extrinsic/intrinsic fiber.
								The study failed to show higher amounts of newly formed cementum and bone after EMD Plus compared with CAF.
								A thick mixture of cellular and acellular cementum with inserting collagen fibers perpendicular or parallel to the root surface and alveolar bone was observed.
								No signs of ankylosis.
								TCP and MSC help augment alveolar bone without impairing regeneration of cementum.
								In group B, alveolar bone regeneration was incomplete. Newly formed cementum and PDL was similar in groups A and B.
								A short length of ankylosis was found in group A.
								Almost complete periodontal regeneration in the furcation defects: fibrous connective tissue was replaced with new bone and PDL. New cementum was formed on the root surfaces and in the resorption lacunae (already at 4 weeks).
								In the fornix area, thick collagen fibers extended coronally into the root surface.

CPC, calcium phosphate ceramic; CP, calcium phosphate; n.r., not reported; EMP, enamel matrix proteins; EMD, enamel matrix derivative; BG, bioactive glass; m, membrane; fm, functionalized collagen membrane; rm, resorbable membrane; MSC, mesenchimal stem cells;  $\beta$ -TCP,  $\beta$  tricalcium phosphate; Col, atelocollagen; CAF, coronally advanced flap

**Table 21** Histomorphometrical results (height in mm, area in mm<sup>2</sup>, volume, or area in %) of animal type III furcation defects treated using a combination approach

No.	Study	No. of furcations	Defect height (mm)	NB mm/mm <sup>2</sup> /%	NC mm/mm <sup>2</sup> /%	Collagen fibers on tooth surface mm/mm <sup>2</sup> /% area or height	Junctional epithelium mm/mm <sup>2</sup> /% area or height
1	Donos et al. [81]	1	A: 1.38 mm 4.44 mm B: 2.06 mm 5.75 mm C: 2.55 mm 6.19 mm A: 10.81±1.04 mm <sup>2</sup> 10.38±1.79 mm <sup>2</sup> (area) B: 10.21±1.33 (height) 10.11±2.05 mm <sup>2</sup> (area)	A: 1.13 mm Height: 81.9% B: 1.80 mm Height: 87.4% C: 1.65 mm Height: 64.7% A: 6.21±2.18 mm <sup>2</sup> Area: 60.23±18.16% B: 3.71±2.00 mm <sup>2</sup> Area: 34.77±15.38% 5 mm 5 mm	A: 4.13 mm Height: 93% B: 4.72 mm Height: 82% C: 3.78 mm Height: 61% A: 5.53±1.34 mm Area: 50.77±8.19% B: 4.71±1.47 mm Area: 43.02±8.08% Area: 20.0±2.4% 13.3±2.9%	A: 4.13 mm Height: 93% B: 4.72 mm Height: 82% C: 3.78 mm Height: 61% A: 3.71±1.82 mm Area: 33.64±13.83% B: 2.34±0.47 mm Area: 22.18±5.19% Area: 20.0±2.4% 13.3±2.9%	n.r. n.r.
2	Jiang et al. [82]	8	A: 10.21±1.33 (height) 10.11±2.05 mm <sup>2</sup> (area)	A: 6.21±2.18 mm <sup>2</sup> Area: 60.23±18.16% B: 3.71±2.00 mm <sup>2</sup> Area: 34.77±15.38% 80.0±6.3% 87.2±3.5%	A: 5.53±1.34 mm Area: 50.77±8.19% B: 4.71±1.47 mm Area: 43.02±8.08% 3.43±1.44 mm 5.45±1.58 mm <sup>2</sup> Area: 75.8±6.3% A: 4.94±0.28 mm <sup>2</sup> Area: 96.7±5.29% B: 3.67±0.27 mm <sup>2</sup> 85.3±12.4% C: 1.40±0.11 mm <sup>2</sup> 70.4±20.11	A: 3.71±1.82 mm Area: 33.64±13.83% B: 2.34±0.47 mm Area: 22.18±5.19% Area: 20.0±2.4% 13.3±2.9%	A: 3.37±2.35 mm Area: 32.59±17.33% B: 4.85±1.28 mm <sup>2</sup> Area: 50.11±13.57% Area: 20.0±2.4% 0%
3	Park et al. [84]	4 (8 weeks) 4 (11 weeks)	5 mm 5 mm	8.2±1.29 mm	3.43±1.44 mm	3.43±1.44 mm	1.53±10.8 mm
4	Suaide et al. [85]	7	4 mm	5.45±1.58 mm <sup>2</sup> Area: 75.8±6.3% A: 4.94±0.28 mm <sup>2</sup> Area: 96.7±5.29% B: 3.67±0.27 mm <sup>2</sup> 85.3±12.4% C: 0.92±0.43 mm C: 1.40±0.11 mm <sup>2</sup> 70.4±20.11	Area: 84.1±8.9%	n.r.	Area: 2.0±2.3%
5	Saito et al. [94]	10	4 mm	5.45±1.58 mm <sup>2</sup> Area: 75.8±6.3% A: 4.94±0.28 mm <sup>2</sup> Area: 96.7±5.29% B: 3.67±0.27 mm <sup>2</sup> 85.3±12.4% C: 0.92±0.43 mm C: 1.40±0.11 mm <sup>2</sup> 70.4±20.11	Area: 84.1±8.9%	n.r.	Area: 2.0±2.3%
6	Chen et al. [103]	A: 34 B: 32 C: 33	A: 5.34±0.32 mm B: 5.31±0.24 mm C: 5.30±0.34 mm	A: 4.35±0.25 mm 84.3±10.5% B: 1.67±0.11 mm 68.7±9.7% C: 0.92±0.43 mm C: 1.40±0.11 mm <sup>2</sup> 70.4±20.11	A: 4.35±0.25 mm 84.3±10.5% B: 1.67±0.11 mm 68.7±9.7% C: 0.92±0.43 mm C: 1.40±0.11 mm <sup>2</sup> 70.4±20.11	A: 3.94±0.36 mm B: 1.73±0.12 mm C: 1.62±0.31 mm	
7	Ripamonti et al. [108]	A: 4 B: 4	n.r.	Height: Animal 1: 1st molar: 55% 25% 2nd: molar: 67% 28% Animal 2: 1st molar: 68% 32% 2nd molar: 69% 20% n.r.	Height: Animal 1: 1st molar: 3.7 mm 2.5 mm 2nd: molar 3.6 mm 2.3 mm Animal 2: 1st molar: 3.4 mm 2.6 mm 2nd molar: 3.9 mm 2.6 mm n.r.	n.r.	n.r.
8	Sculean et al. [109]	3	n.r.	Height: 74% 86%	Height: 62% 87%	n.r.	n.r.
9	Kuboki et al. [111]	3 I: 5 II: 5	4 mm	Area: 2.0±2.9% 0.1±0.3%	Area: 24.2±9.2% 1.5±3.1%	Height: 70% Area: 6.3±6.4% 1.0±2.5% 1.5±3.1%	Height: 23.2±8.5% 24.8±13.7%
10	Fernandes et al. [116]	Test 1: 7 Test 2: 6 Control: 4	4.5 mm				

**Table 21** (continued)

No.	Study	No. of furcations	Defect height (mm)	NB mm/mm <sup>2</sup> /%	NC mm/mm <sup>2</sup> /%	Collagen fibers on tooth surface mm/mm <sup>2</sup> /% area or height	Junctional epithelium mm/mm <sup>2</sup> /% area or height
11	Araujo et al. [86]	5	4	0.8 ± 1.7%	4.2 ± 9.0%	Area: 46 ± 3% 4.3 ± 1.6 mm 4.5 ± 2.5 mm <sup>2</sup>	22.1 ± 8.5% Area: 71.5 ± 13.7% 64.8 ± 13.2% 53.7 ± 16.4%
12	Mardas et al. [93]	8	12.3 ± 1.5 (length) 5.5 ± 0.9 (height) 13.0 ± 3.5 (area)	4 mm	Area: 76.6 ± 10.3% 49.8 ± 11.4%	21 ± 1% 8.6 ± 3.2 mm	21 ± 1% 8.1 ± 4.0 mm n.r.
13	Nagahara et al. [95]	9	4 mm	n.r.	Area: 89.2 ± 10.3% 45.4 ± 19.0%	n.r.	n.r.
14	Matsuura et al. [106]	3	n.r.	n.r.	n.r.	n.r.	n.r.

NC, new cementum; NB, new bone; n.r., not reported (no data available)

Histological data were included in one table reporting for each selected study the following items: author name, publication date, number of patients, number of defects, defect characteristics, healing period, biomaterial type, healing type, and histological results (Table 22). Additionally, histomorphometric data were analyzed (Table 23) by reporting the amount of new cementum and bone formation, and also collagen fibers and junctional epithelium on the tooth surface, as linear measurements (in mm) or surface measurements (in mm<sup>2</sup>) or percentage of them (in %).

Regarding class II defects, all five studies reported regeneration of the periodontal tissues but not in the entire defect [24, 51, 52, 67, 113]. Two studies used DFDBA combined with rhPDGF-BB following root conditioning and reported formation of bone, cementum, and PDL coronally to the notch, however, without reporting any histomorphometric measurements [24, 52]. Two other studies used GTR and reported formation of cementum, PDL, and bone, again without providing histomorphometric data [51, 67]. Another study [113] that applied a combined technique (DFDBA + PHA + tetracycline + polylactic acid membrane) reported partial defect closure with new bone, cementum, and connective tissue attachment coronal or limited to the notch area with scattered graft particles throughout the defects. Epithelial proliferation (i.e., long junctional epithelium) and signs of ankylosis were also visible. No histomorphometrical data were reported.

The two studies evaluating class III defects reported only partial regeneration [67, 68]. The first study [67] using GTR has demonstrated 2.8 mm new cementum with inserting collagen fibers in a 7-mm furcation defect. The second study [68] used a combined technique (rhPDGF + β-TCP + collagen membrane) and described partial closure in three out of the four defects. The fourth defect presented an impaired healing probably caused by membrane exposure. The histomorphometric data revealed new cementum ranging from 0.0 to 5.5 mm, while the length of new bone and new collagen fibers ranged from 0.0 to 2.0 mm.

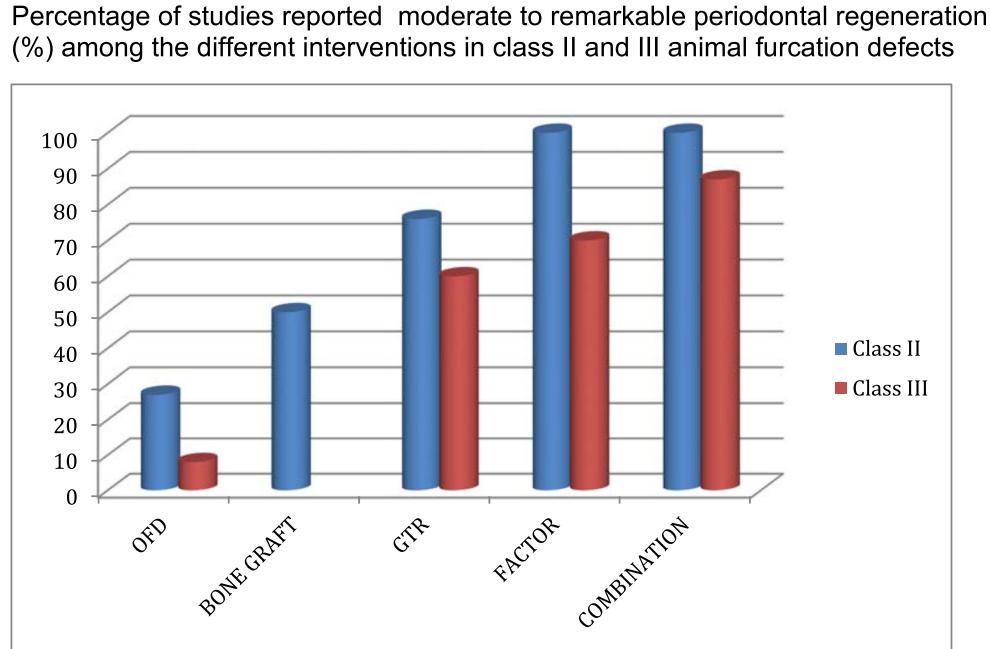
## Discussion

The findings of the present systematic review revealed that in animals, periodontal regeneration can be accomplished in class II and class III furcations to a varying extent by means of OFD in conjunction with different biomaterial materials including various types of bone grafts/bone substitutes, biological factors, GTR, and various combinations thereof.

In animals, the use of biological factors alone and different combinations involving biologics and bone grafts with or without GTR yielded the best outcomes in class II and even in class III defects.

In human class II furcations, the complete regeneration was obtained following combination of bone grafts (i.e., DFDBA)

**Fig. 2** Percentage of studies reported moderate to remarkable periodontal regeneration (%) among the different interventions in class II and III animal furcation defects



and a biologic agent (i.e., rhPDGF-BB) and with GTR. In contrast, in human class III furcations, the histologic evidence is very limited (i.e., two case reports) and indicates minimal (i.e., limited to the apical part of the defects) or no periodontal regeneration.

An interesting aspect that needs to be considered when interpreting the results is related to the fact that for many of the used biomaterials in furcation reconstructive/regenerative surgery, only histologic evidence from animal models is available while human histologic evidence is limited to case reports involving only very few biomaterials. While in animals, periodontal regeneration has been demonstrated in both class II and III furcations, in humans, the histologic evidence for complete periodontal regeneration is limited to class II furcations. There are several explanations for the discrepancies observed in the healing outcomes between animals and humans. First of all, in most studies, the defects in animals were surgically created and either immediately treated (i.e., without a plaque accumulation phase intended to mimic a chronic inflammatory process) or plaque infected by placement of foreign materials or ligatures. Secondly, inherent differences are present between the used animals models and human defects regarding anatomy and innate healing capacity thus making the extrapolation of the findings from animal “experiments” to the human situation difficult. Furthermore, anatomic factors, such as location of the defects (i.e., buccal or lingual) and of the furcation entrance (apical or coronally to the mesial and distal bone level), root trunk length, and local developmental abnormalities such as enamel pearls and root concavities, presence or absence of attached gingiva and of gingival recessions may

substantially affect the wound healing and subsequently, the histological and clinical outcomes [21, 123].

An excellent example illustrating the enormous differences between animal models and the clinical situation encountered in humans are the outcomes reported in class III animal and human furcation defects. While a substantial number of studies have provided evidence for regeneration in animal class III furcations following treatment with OFD and different biomaterials or combinations thereof [81–88, 90, 91, 94, 95, 98, 100, 103, 104, 107–109, 111], the findings from the very limited number of human studies (i.e., two studies) have failed to demonstrate periodontal regeneration [67, 68]. The observation that in one animal study [93] periodontal regeneration of class III furcations was also observed following treatment with OFD alone provides additional support for the impressive innate healing potential in animals. Therefore, caution should be taken when extrapolating the results obtained in animal class II and class III furcations into the real clinical scenario in humans. Conversely, the question may be asked whether the results obtained in animal models utilizing class II furcation defects can be extrapolated to humans.

The present analysis has also clearly pointed to the paucity of human histologic evidence in furcations. There may be several aspects related to the limited number of human histological studies performed in humans. First of all, teeth that show complete defect fill as detected clinically and radiographically cannot be removed for obvious ethical reasons. It should thus be kept in mind that the inconsistent findings of periodontal regeneration may be due to the histological evaluation of teeth presenting very advanced destruction of

**Table 22** Histological results of treated human type II and III furcation defects (6 studies)

No.	Authors Year	No. of patients No. of furcations	Defect type Defect localization Defect nature Defect size (mm)	Healing time Biomaterials	Healing type	Histological results
1	Gottlow et al. [67]	10 12 teeth—5 examined histologically—of which 3 teeth with furcations	Class II/III Mandible and maxilla, n.r.	3 months GTR (ePTFE)	Regeneration	Formation of new connective tissue attachment. Predictable restitution of the attachment apparatus was accomplished.
2	Mellonig et al. [68]	4 4	Class III Mandible, n.r.	6 months rhPDGF + $\beta$ -TCP + mm. (collagen membrane)	Regeneration Long junctional epithelium	3 root surfaces demonstrated periodontal regeneration, other 3 showed new attachment, and one surface revealed junctional epithelium. The other teeth presented a furcation mostly occupied by an open space, with plaque colonization. One Class III furcation showed partial closure to a Class II, the others remained class III.
3	Harris et al. [113]	1 3	Class II, Maxillary and mandible height, n.r.	6 months Graft (DFDBA + PHA + tetracycline) + rm polylactic acid	Regeneration Long junctional epithelium	One tooth presented new bone, cementum and connective tissue attachment coronal to the notch. The other 2 defects showed new connective tissue attachment inserting into new cementum in the notch area. PHA and non-vital bone graft particles were also present. Some signs of ankylosis were also recognizable.
4	Stoller et al. [51]	1 1	Class II Mandible Height: 3 mm Depth: 3 mm	25 months GTR (polylactic acid rm)	Regeneration	Two furcations changed postoperatively into class I, and one in class II furcation.
5	Nevins et al. [122]	5 (histologic evaluation for 4 defects)	Class II location, n.r. Height $\geq$ 2 mm Depth $\geq$ 4 mm	9 months Root conditioning (tetracycline) + DFDBA combined with rhPDGF-BB (0.5 or 1.0 or 5.0 mg/mL)	Regeneration	Periodontal regeneration was observed on the root surfaces. In the areas presenting clinical attachment gain (2 mm vertical, 3 mm horizontal), new cementum and bone were observed.
6	Cameo et al. [24]	4 4	Class II Mandible and maxilla Height: 5.75 mm Depth: 4.75 mm	9 months tetracycline root conditioning + rhPDGF-BB (0.5/1.0 mg/mL) + DFDBA	Regeneration	Regeneration of bone (lamellar and woven), cementum (cellular), PDL (horizontal and tangential fibers) coronal to the reference notch and coronal to the original alveolar crest.

*rhPDGF-BB*, recombinant human platelet-derived growth factor BB; *DFDBA*, demineralized freeze-dried bone allograft; *PHA*, porous hydroxyapatite; *n.r.*, not reported; *PDL*, periodontal ligament; *rm*, resorbable membrane

**Table 23** Histomorphometrical results (height in mm, area in mm<sup>2</sup>, volume, or area in %) of treated human degree II and III furcations

No.	Study	No. of defects Degree III	NB mm	Defect height mm	NC mm	Collagen fibers on tooth surface mm	Junctional epithelium mm
1	Gottlow et al. [67]	3 teeth Patient I: 1 tooth, class II Patient II: 2 teeth, class III	I: n.r. II: 7; 7	I: n.r. II: n.r.; n.r.	I: n.r. II: 2.8 mm; n.r.	I: n.r. II: 2.8 mm; n.r.	I: n.r. II: n.r.; n.r.
2	Mellong et al. [68]	1/III mandible 1/III mandible 1/III mandible 1/III mandible	n.r. n.r. n.r. n.r.	DM, MD: 0.00 mm; 0.97 mm DM: 2.04 mm DM, MD: 0.56; 0.00 mm DM, MD: 0.00 mm; 1.35 mm	2.14 mm; 2.45 mm DM: 5.49 mm DM, MD: 0.00 mm; 0.00 mm DM, MD: 0.00 mm; 1.35 mm	DM, MD: 0.00 mm; 0.97 mm DM: 2.04 mm DM, MD: 0.00 mm; 0.00 mm DM, MD: 0.00 mm; 1.35 mm	DM, MD: 1.19 mm; 1.57 mm DM: 0.50 mm DM, MD: 3.47 mm; 2.35 mm DM, MD: 0.83 mm; 0.4 mm
3	Harris et al. [113]	3	n.r.	n.r.	n.r.	n.r.	n.r.
4	Stoller et al. [51]	1	3 mm	n.r.	n.r.	n.r.	n.r.
5	Nevins et al. [122]	4	≥2 mm	n.r.	n.r.	n.r.	n.r.
6	Camelo et al. [24]	4	5.75 mm	n.r.	n.r.	n.r.	n.r.

NC, new cementum; NB, new bone; MD, mesial surface of distal root; DM, distal surface of mesial root; n.r., not reported; no., number

periodontal supporting apparatus which in turn may have limited their regenerative potential [124]. Secondly, despite the fact that human histological evidence of periodontal regeneration provides strong proof of principle even if inconsistency is observed in the outcome in cases involving molars, the removal of a block biopsy is extremely challenging due to obvious anatomical considerations (i.e., multi-rooted teeth) and may lead to extensive hard and soft tissue defects.

## Conclusions

Within their limits, the present data suggest that:

- (a) While human histologic evidence has demonstrated periodontal regeneration in class II furcations, the evidence in class III furcations is extremely weak to nonexistent.
- (b) Caution should be taken when extrapolating histologic outcomes derived from class II furcation defects in animals to the clinical situation in humans.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** For this type of study (e.g., systematic review and meta-analysis), formal consent is not required.

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