Evaluation of the Effects of MTA Apexification and Regenerative Endodontic Therapy on Lesion Healing using Fractal Analysis: A Retrospective Study

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DOI 10.23804/ejpd.2024.2178

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Abstract

Aim A comparison between mineral trioxide aggregate (MTA) apexification and regenerative endodontic therapy (RET) in immature permanent teeth is pivotal for optimising treatment outcomes and enhancing clinical decision-making. Understanding the efficacy, limitations and long-term implications of each approach is essential for achieving predictable, successful outcomes when managing immature teeth with necrotic pulps. The aim of this retrospective study was to compare the changes in the periapical bone using fractal dimension (FD) on the periapical radiographs of patients who underwent apexification and RET.

Methods The lesion area was evaluated using fractal analysis on periapical radiographs obtained before and one year after treatment with the ImageJ program. Additionally, periapical status was classified using the periapical index (PAI). The significance level was set at 0.05.

Results In both groups, the FD values increased compared with initial values at one-year follow-up after treatment ($p > 0.05$). There was no statistically significant difference between the groups in terms of the time-dependent changes in FD and PAI ($p = 0.798$, $p = 0.320$).

Conclusions In the present study, we found that the changes in FD and PAI over a one-year observation period were independent of the specific root canal treatment technique used. According to the fractal analysis, neither MTA apexification nor RET with triple-antibiotic paste is superior for immature teeth with pulp necrosis resulting from dental trauma.

KEYWORDS Apexification, fractal analyses, mineral trioxide aggregate, periapical index, regenerative endodontic therapy.

Introduction

Clinicians face various challenges in treating infected pulp caused by caries or trauma in immature permanent teeth [Botero et al., 2017]. Obturation is complex, because the apex is not fully formed, and cleaning and shaping of the root canal system are difficult due to the thin dentinal walls. Apexification is a widely used method for the artificial closure of the apex. Calcium silicate-based materials such as mineral trioxide aggregate (MTA) are used to form the apical plug. Although MTA apexification provides many advantages, root development does not continue and the risk of root fracture does not decrease [Torabinejad and Abu–Tahun, 2010].

The development of the root is crucial for tooth function. Dental pulp cells, including undifferentiated mesenchymal cells, blood vessels and nerves that sustain the dental pulp tissue, are found in the root dentin and root canals. The dental papilla, dental follicle and Hertwig's epithelial root sheath are the primary tissues that contribute to root formation [Li et al., 2017]. In revascularisation, which is another treatment option for necrotic immature teeth, it is thought that apical papilla stem cells, which are assumed to be alive in the apical region, will transform into secondary odontoblasts. Ensuring the continuity of the root tissue is therefore expected to lead to an extension of the root length, closure at the apex and thickening of the dentin walls [Banchs and Trope, 2004]. It has been reported, however, that positive results were not obtained in all revascularisation cases [Al-Habib, 2022; Bukhari et al., 2016; Silujjai and Linsuwanont, 2017]. Fractal analysis (FA) is a robust methodology employed to quantify the complexity and self-similarity of structures across diverse scientific domains, including dentistry. Within dental research, FA has emerged as a valuable tool for assessing structural changes and healing dynamics in periapical lesions following root-canal therapy. Fractal dimension (FD), a pivotal metric derived from FA, offers insights into the geometric intricacies and spatial distribution of bone structures in the periapical region. Various techniques constitute FA, encompassing multifractal analysis, mass methods, box counting and lacunarity analysis, each of which provides distinct perspectives on the fractal characteristics of biological structures [Kato et al., 2020]. These methodologies enable precise quantification of intricate geometric elements (i.e., fractals) within radiographic images, thereby facilitating non-invasive evaluations of bone quality and healing progression. Longitudinal studies have utilised FA to monitor changes in bone density within the periradicular area over time and offered valuable insights into the outcomes of root-canal treatments [Uğur Aydın et al., 2019]. Employing mathematical

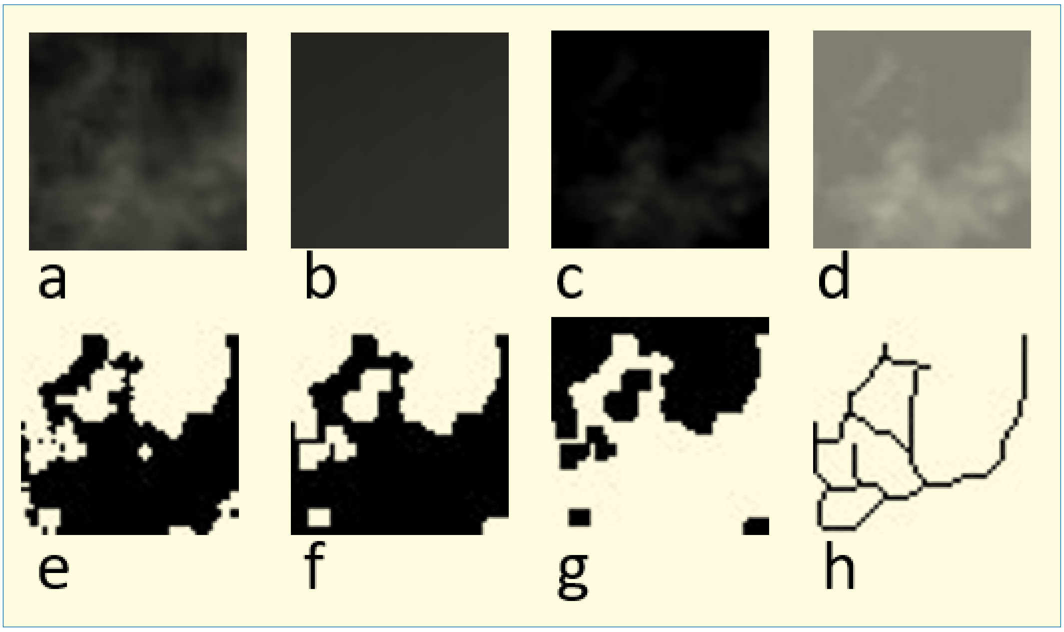

FIG. 1
a. Region of interest; **b**. Process with Gaussion blurr filters; **c.** Blurred image substracted from original image; **d.** Add of 128 gray value; **e.** Thresold; **f.** Dilate process after erode option; **g.** Invert; **h.** Skletonization.

morphology image-processing techniques alongside FD calculations allows for a detailed analysis of bone trabecular patterns during radiographic examinations; for example, the box-counting algorithm has been effectively applied to quantify trabecular patterns at the bone-marrow interface, thereby enhancing assessments of bone quality and structural integrity [White and Rudolph, 1999].

The FD obtained as a result of FA is related to mineral and density changes in trabecular structures [Uğur Aydın et al., 2019]. Studies on accuracy have demonstrated that FD values perform satisfactorily when contrasted with the bone-mineral-density screening test using periapical and panoramic radiographies [Ince Yusufoglu et al., 2021; Kavitha et al., 2015]; for this reason, FD has been successfully used to detect changes in the periapical bone after endodontic treatment [Chen et al., 2005]. Higher FD values indicate greater complexity, whereas lower FD values denote lower trabeculation [Kurşun–Çakmak and Bayrak, 2018]. In this study, FA was performed on periapical images to evaluate bone quality after two different endodontic treatments. The periapical index (PAI) is widely used to evaluate the healing of periapical tissues in endodontics [Ørstavik et al., 1986].

The PAI is a scoring system that uses a scale of 1–5 that ranges from healthy to severe periodontitis with accentuated characteristics to assess apical periodontitis via radiographs. The PAI is a subjective assessment tool, however, which imposes a limitation in its use. In the literature, only one study has evaluated the outcomes of revascularisation using FA [i.e., Aricioglu et al., 2022].

The aim of this study was to compare the 12-month healing between apexification and revascularisation on necrotic immature incisors using FA. The primary outcome of this study was to evaluate the outcome of revascularisation compared to the apexification using FA, and the secondary outcome was to assess healing using PAI.

Materials and Methods

Study design

This study was designed to be a retrospective clinical trial. Based on a previous study, a power calculation was performed and sample size was determined (G*Power 3.1 software; Heinrich Heine University, Dusseldorf, Germany) [Uğur Aydın et al., 2019].

Sample inclusion and exclusion criteria

Patients who were referred to Istanbul University Faculty of Dentistry, Department of Pedodontics and were treated by the same paediatric dentist (G.K.) were included in the study. Ethical approval was obtained from the local ethics board (2019/53, Istanbul University Faculty of Dentistry Ethics Committee, Istanbul), in compliance with the Helsinki Declaration. The inclusion criteria were as follows: no systemic or periodontal disease; traumatised immature anterior permanent teeth; symptomatic or diagnosed with apical periodontitis with sinus tract; no response to heat, cold and electrical pulp testing; no external or internal resorption or root fracture; no more than one root or root canal; sufficient root-canal filling and coronal restoration for teeth treated by apexification; and patients who had follow-up radiographs one year after their therapy. The exclusion criteria were: the presence of systemic or periodontal disease; teeth without a history of dental trauma; responsive to heat, cold or electrical pulp testing; the presence of external or internal resorption or root fracture; more than one root or root canal; inadequate root-canal filling or coronal restoration in teeth treated by apexification; and a lack of follow-up radiographs one year after therapy. Table 1 shows the cases included in this study.

No technique-choice protocol was used for the allocation of apexification or revascularisation. Apexification group: A calcium hydroxide dressing was used between sessions. After the apical plug was created at the apical area using MTA (MTA Angelus® white, Lodrina, Brazil), the root canal was immediately obturated with gutta-percha, then the coronal restoration was completed with resin composite. Regenerative endodontic therapy (RET) group: 5 mL of 0.5% NaOCl saline and 0.2% chlorhexidine were used for irrigation, then 3Mix-MP paste containing metronidazole, ciprofloxacin and minocycline were placed in the root canals. In the second appointment, intracanal bleeding was induced through over-instrumentation,

Group	Sex	Age (years)	FD		PAI	
			T0	T1	T0	T1
Apexification	M	7.51	1.256	1.424	4	2
Apexification	F	9.19	1.294	1.333	4	2
Apexification	F	9.99	1.356	1.401	4	2
Apexification	M	10.08	1.236	1.444	4	3
Apexification	M	12.69	1.425	1.411	2	2
Apexification	M	11.41	1.477	1.364	2	2
Apexification	M	12.00	1.331	1.294	4	2
Apexification	F	12.23	1.472	1.457	3	2
Apexification	F	8.17	1.274	1.333	2	1
Apexification	M	6.54	1.416	1.401	4	1
Apexification	M	9.08	1.268	1.322	4	2
Apexification	M	7.34	1.353	1.349	4	3
Apexification	M	8.31	1.426	1.409	4	3
Apexification	M	7.89	1.483	1.396	4	2
Apexification	F	8.18	1.424	1.328	4	1
Apexification	M	9.28	1.443	1.334	3	2
RET	M	9.26	1.368	1.311	2	3
RET	M	17.48	1.332	1.349	3	1
RET	F	7.90	1.380	1.393	2	1
RET	M	10.99	1.303	1.360	2	1
RET	M	8.74	1.352	1.372	3	1
RET	M	8.65	1.420	1.356	3	3
RET	M	10.50	1.345	1.315	4	1
RET	M	10.24	1.283	1.339	4	3
RET	M	8.69	1.492	1.400	3	1
RET	F	7.51	1.464	1.420	4	4
RET	F	9.19	1.259	1.305	2	1
RET	F	9.99	1.346	1.325	3	1
RET	F	10.08	1.260	1.456	3	2
RET	M	12.69	1.333	1.211	2	1
RET	M	11.41	1.334	1.344	2	1
RET	M	12.00	1.311	1.399	4	3
RET	M	12.23	1.283	1.369	3	1
RET	F	8.17	1.268	1.316	2	1

RET: Regenerative endodontic therapy. FD: Fractal dimension. PAI: Periapical index. T0: Before treatment. T1: After treatment.

TABLE 1. The distribution of the 34 teeth according to the main variables analysed.

then MTA (MTA Angelus® white, Lodrina, Brazil) was placed on the blood clot, and treatment was completed with resin composite restoration. All patients were treated by one paediatric dentist (G.K.). Standardised digital periapical radiographs were

	Apexification group	RET group	
Fractal dimension	Mean±SD	Mean±SD	1p
T0	1.371±0.09	1.341±0.07	0.256
T1	1.375±0.05	1.352±0.05	0.209
2p	0.859	0.527	

1Student's t-test 2Paired-samples t-test

TABLE 3 Time-dependent changes in the FD value of groups.

PAI 1	Normal periapical structure
PAI 2	Minor changes in the bone structure, not pathognomonic of apical periodontitis
PAI 3	Structural bone changes with mineral loss, characteristic of apical periodontitis
PAI 4	Well-defined apical radiolucency, characteristic of apical periodontitis.
PAI 5	Severe periodontitis with exacerbation and bone expansion

TABLE 2 Stages of PAI [Ørstavik et al., 1986].

obtained via a parallelling holder (Endo-Bite anterior, KerrHawe, Bioggio, Switzerland) using the same intraoral X-ray device (Kodak 2100 230V; Carestream Health Inc., Rochester, New York, USA).

An analysis was performed at the following intervals: before (T0) and one year after endodontic treatment (T1). The five stages of root development are listed according to Cvek's classification: less than half the root length (I); half the root length (II); two-thirds the root length (III); a wide-open apical foramen and nearly complete root length (IV); and a closed apical foramen and finished root development (V). The first four stages of Cvek describe teeth with open apices and a lack of apical constriction development but major morphologic changes, whereas Cvek Stage V describes mature, completely developed teeth [Cvek et al.; 1992].

Fractal analysis

At T0 and T1, the FD of the apical lesions was measured, and the degree-of-healing was compared by analysing changes in the FD. FA was performed using the White and Rudolph approach [White and Rudolph, 1999]. A maxillofacial radiologist with 10 years of experience (S.B.) performed FA. When 20 of the photos were reanalysed one month later to test intraobserver reliability, it was determined that the correlation coefficient for intraobserver reliability was 0.896.

The images were analysed using the ImageJ Version 1.3 software (National Institutes of Health, Bethesda, Maryland, USA). Each region of interest (ROI) (30 × 30 pixels) was chosen at a distance of 1 mm from the root apex (Fig. 1a). At T0 and T1, the same site and scale was chosen for the ROIs. The high and medium-bright portions in the image, which were caused by superficial soft tissue and the varying thickness of the overlaying bone, were blurred in the ROI by applying the 'Gaussian Blur (sigma = 35 pixels)' filter (Fig. 1b). The original image was subtracted from the blurred image (Fig. 1c), adding 128 grey tones for every pixel (Fig. 1d). The image was then changed to a two-colour image by selecting the 'threshold' option (i.e., black and white) (Fig. 1e). After using the 'erode' option to reduce the image's noise, 'dilate' was used to enlarge the already-existing sections (Fig. 1f). The trabecular bone's outline was then visualised by using the 'invert' option to convert white to black and black to white (Fig. 1g). The trabecular structure was finally highlighted as skeletal using the 'skeletonisation' option (Fig. 1h). The box counting method was used to divide the dimensions into squares of 2, 3, 4, 6, 8, 12, 16, 32 and 64 pixels to obtain the FD. High FD indicates that the ROI has a complex structure, and low FD indicates decreased trabecular terminal points [Uğur Aydın et al., 2019].

PAI evaluation

In addition, periapical status was evaluated using the PAI by assigning scores of 1-5 prior to root canal treatment and

	Apexification group	RET group	
PAI	Mean±SD (median)	Mean±SD (median)	1p
T0	3.50±0.82 (4)	2.83±0.79 (3)	0.019*
T1	2.0±0.63 (2)	1.67±1.03 (1)	0.104
2p	0.001*	0.001*	

[1]Mann-Whitney U test [2]Wilcoxon's signed-rank test *p<0.05

TABLE 4 Time-dependent changes in the PAI score of groups.

	Healed (n=26)	Unhealed (n=8)	
FD	Mean±SD	Mean±SD	1p
T0	1.354±0.08	1.358±0.08	0.910
T1	1.358±0.05	1.378±0.05	0.347
2p	0.795	0.547	
FD change	0.004±0.08	0.021±0.09	0.624

[1]Student's t-test [2]Paired-samples t-test

TABLE 5 Changes in FD values between baseline and postoperative radiographs for healed and unhealed cases and the difference in FD change between healed and unhealed cases.

one year post-treatment (Table 2) [Ørstavik et al., 1986]; and the root with the highest PAI score was included for each tooth. According to the PAI scores, the patients were categorised as 'healed' (PAI < 3) or 'unhealed' (PAI ≥ 3) after one year, similar to previous studies [Tosun et al., 2022; Zandi et al., 2019]. PAI scoring was performed by two calibrated independent observers (i.e., one maxillofacial radiologist [S.B.] and one endodontist [Z.U.A.]) for each group, and consensus was reached in cases where there was a discrepancy between the scoring of the two observers. The correlation coefficients for interobserver and intraobserver reliability were calculated (0.854 and 0.802, respectively).

Statistical analysis

For statistical analysis, the IBM® SPSS® Statistics 22 software (SPSS Inc., Chicago, IL) was used. FD and PAI were compared using Student's *t*-test and the Mann–Whitney U test. To compare initial and one-year outcomes, the paired samples *t*-test and Wilcoxon's signed-rank test were used for FD and PAI, respectively. The level for significance was established at 0.05.

Results

A total of 30 patients who were 7–12 years of age were enrolled in this study; the mean age of study sample was 9.69 ± 2.27 years. MTA apexification was performed in 16 teeth, and revascularisation treatment was performed in 18 teeth. Age and sex distribution within and between the groups were statistically similar ($p = 0.999$). It was observed that the cases included in the study were Class III teeth according to the classification made by Cvek et al. [Cvek et al.; 1992]. The mean follow-up period of the patients included in our study was 14.6 ± 3.4 months for the apexification group and 12.6 ± 2.8 months for the RET group. Following endodontic treatment, the FD values did not differ significantly from baseline in either apexification group (from 1.371 ± 0.09 to 1.375 ± 0.05) or RET group (from 1.341 ± 0.07 to 1.352 ± 0.05) (Table 3; $p > 0.05$). There was no significant difference between the two groups for the time-dependent change in FD (0.004 ± 0.09 and 0.011 ± 0.08 for the apexification group and the RET group, respectively). When comparing within or between groups, there was no significant difference between males (apexification group; 0.003 ± 0.10, RET group; −0.003 ± 0.07) and females (apexification group; 0.006 ± 0.06, RET group; 0.040 ± 0.08) in terms of the time-dependent increase in FD ($p > 0.05$). According to the PAI, the success rate was 81.25% and 72.2% for the apexification group and the RET group, respectively. No significant difference was found in the PAI score changes among the two groups after one year ($p > 0.05$). Both groups showed a significant improvement in PAI ($p < 0.05$; Table 4). There was no statistically significant difference in FD between the healed and unhealed groups (Table 5).

Discussion

Increased visibility of the trabecular pattern following demineralisation, which shows the structure of trabeculae may lead to an increase in FD despite a bone-density loss. Instead, when massive trabecular struts are joined to one another, FD may occasionally decrease as a result of a drop in trabeculae density [Aktuna Belgin and Serindere, 2020]. To accurately assess FD changes, additional results such as improvements in clinical and radiographic conditions should therefore be considered. In the current study, periapical conditions were assessed using the PAI to ascertain whether the change in FD values following root-canal therapy was brought on by the newly created trabecular pattern or decalcification.

To assess periapical status, Orstavik et al. graded the size of periapical lesions on conventional radiographs from 1–5

[Ørstavik et al., 1986]; the periapical lesions can alternatively be classified as 'healed' and 'unhealed' [Tosun et al., 2022]. In this study, the teeth were determined to be 'healed' or 'unhealed' depending on their periapical images. The one-year success rates were 81.25% and 72.2% for MTA apexification and RET, respectively. Several clinical studies have reported a favourable outcome of MTA apexification and RET ranging between 76.5–100% [i.e., Alobaid et al., 2014; Annamalai and Mungara, 2010; Holden et al., 2008; Jeeruphan et al., 2012; Mente et al., 2013; Moore et al., 2011; Pace et al., 2014; Sarris et al., 2008; Simon et al., 2007; Witherspoon et al., 2008] and 78–100% [i.e., Alobaid et al., 2014; Cehreli et al., 2011; Chen et al., 2012; Chueh et al., 2009; Jeeruphan et al., 2012; Jung et al., 2008; Kahler et al., 2014; Petrino et al., 2010; Saoud et al., 2014; Shah et al., 2008], respectively. Our results for MTA apexification were in line with those in the literature, but the RET success rate was lower.

In this study, treatment with MTA apexification and RET were compared in terms of FD in anterior teeth with an open apex and apical periodontitis following dental trauma. There was no significant difference in MTA apexification one year after treatment compared with baseline; and no significant difference was observed in the RET group one year after treatment compared with baseline. In healed cases, while there was no significant difference between the mean FD values of one year post-operative images and baseline images; previous studies have reported that the mean FD value increased with recovery and increased trabeculation after endodontic treatment [i.e., Ince Yusufoglu et al., 2021; Tosun et al., 2022; Uğur Aydın et al., 2019]. Another study revealed a reduction in FD following successful treatment; the study authors' explanation suggested a transition from dense reactive to normal-density bone following successful treatment [Yu et al., 2009]. In our results, there was no significant difference between the FD value on the one-year post-operative radiographs and the FD value on the initial radiograph in unhealed cases. The PAI is considered to be an important measure in the follow-up of patients with periapical pathology [Kirkevang et al., 2015]; we therefore evaluated the FD value changes after endodontic treatment by categorising them as PAI scores (i.e., healed or unhealed). No significant relation between FD change in healed and unhealed subjects was detected, which is in accordance with previous research [Tosun et al., 2022]. FA did not play a major role in determining the outcome of the tooth for the quantitative assessment of changes in periapical trabecular bone following MTA apexification and RET. FA is considered to be effective because radiographic settings such as kilovolt peak, milliampere, or X-ray beam angle have little effect on FD values [Huang et al., 2013; Jolley et al., 2006; Shrout et al., 1997]. Although it has been suggested that ROI size, shape and location may alter FD [Baksi and Fidler, 2011]; this was not confirmed by a follow-up study [i.e., Amer et al., 2012]. For comparability, the baseline and follow-up radiographs were taken using the same periapical radiography method and exposure setting. Consistent with previous studies, there was no significant difference between male and female patients in terms of changes in FD values [Ince Yusufoglu et al., 2021; Shrout et al., 1997; Tosun et al., 2022]. This implies that FD calculation should offer useful information on the condition of trabecular bone in all patients, regardless of their sex. Quantitative change in bone trabeculation in the periapical region that was affected by pulp necrosis following dental trauma was evaluated using FA in children treated with MTA apexification or RET. Time-dependent changes in FD was independent of those two endodontic treatment techniques.

The low sample size and only one-year follow-up are limitations to this research. Randomised controlled clinical studies with larger sample sizes and longer follow-up periods are therefore required to evaluate trabecular changes in periapical tissues following both the treatment options evaluated in this study and the treatment options that use other materials and techniques in teeth with open apexes. Due to the retrospective nature of this study, the FD values we obtained could not be supported by clinical and histologic findings. As such, future studies to investigate the relationship between FD change and clinical and/or histologic findings after MTA apexification and RET are needed.

Conclusion

Neither MTA apexification nor RET with triple antibiotic paste is superior according to fractal analysis in immature teeth with pulp necrosis as a result of dental trauma. This is the first study to use FA to compare results of MTA apexification and regenerative endodontic treatment after dental trauma in children.

Declarations

Ethical Approval
Ethical approval was obtained from the local ethics board (2019/53, Istanbul University Faculty of Dentistry Ethics Committee, Istanbul). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Competing interests
The authors declare that they have no conflict of interest.

Authors' contributions
Y.K. made study concept and design, drafting of manuscript, and critical revision. G. K. made acquisting of data. Z. U. A. made study concept and design, acquisting of data, analysis, interpretation of data, and drafting of manuscript, S. B. made acquisting of data, analysis, interpretation of data, drafting of manuscript, and critical revision. G. A. made critical revision.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data avaliability statement
The anonymised statistical data is available from the corresponding author (Y.K.) upon reasonable request.

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