Association between cigarette smoking and the prevalence of post-endodontic periapical pathology: a systematic review

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The objective of this systematic review was to evaluate the impact of cigarette smoking on the course of periapical healing in patients undergoing endodontic therapy. Materials and methods The systematic review of the literature was developed following the recommendations of the Cochrane Collaboration and following the PRISMA Declaration. Searches of MEDLINE (PubMed), Web of Science and Scopus were searched from inception to September 2020. To ensure saturation of the literature, references of relevant articles identified through the search, conferences, thesis databases were scanned , OpenGrey, Google Scholar, and ClinicalTrials.gov, among others. Authors were contacted by email in case of missing information. There was no language limitation. Results In the selection of studies, we initially identified 206 references with the search strategy. After removing 14 duplicates, we examined 192 titles / abstracts. Finally, six studies met the inclusion criteria for the qualitative synthesis. Conclusion The best current available evidence detailed in this systematic review suggests that smoking has no association with the prevalence of post-endodontic periapical pathology in cross-sectional studies. Considering that there are no longitudinal studies to support this result, more studies are needed to rule out the association of smoking and post-endodontic periapical pathology with larger sample studies that adjust to all possible covariates.

Introduction

Around 16 million people in the world experience serious health problems related to the habit of smoking. Smoking habit causes approximately 7 million global deaths annually, and it is expected that by 2030 tobacco consumption will cause a mortality of 10 million people per year. [1,2] Smokers are more likely to develop cerebrovascular diseases, chronic obstructive pulmonary disease (COPD), bronchitis, pneumonia, tachycardia, arterial hypertension and type 2 diabetes mellitus, as well as neurological degenerations such as depression and cognitive impairment. [3]

Cigarette Smoking-Associated Alterations are directly linked to the release of chemical component during tobacco combustion, including nicotine, carbon monoxide, nitrosamine, oxidation radicals and hydrogen cyanide among others. [4,5] Smoking is known to have deleterious effects on the immune response. Such effects are reflected by impaired immune reactions such as phagocytosis, neutrophil diapedesis and chemotaxis, in addition to generating high systematic concentrations of free radical and pro-inflammatory cytokines. [6,7] Likewise, cigarette smoking has deleterious effects on local and systemic blood flow, since it causes vascular dysfunction given the modification of the osmotic pressure. Moreover, some Chemical compounds of cigarettes such as nicotine induce vasoconstriction, thus restricting the tissular supply of nutrients and preventing cell proliferation and tissue repair, consequently leading to a progressive tissue break down.[8-10] Notably, both the immune and vascular systems are key components of all tissue remodelling and healing processes.[9]

Endodontic disease manifest at both the pulpal and periapical levels .Pulp and periapical reactions to noxious stimuli are characterized by an initial neurogenic inflammatory response, since the nervous system governs the vascular system by the release of potent vasoactive neuropeptides which act directly on the endothelial and smooth muscle cells, thus affecting the vascular permeability, and exerting pro-inflammatory and immune reactions at the site of the injury.[11] Such inflammatory responses depend on the course, the nature and magnitude of the causal agent and the ability of the tissue to respond and recover from the noxious stimuli, which allows differentiating into an acute or chronic inflammatory response.[12]

A recent systematic review and meta-analysis described cigarette smoking as a critical etiologic factor, influencing the course of pulpal and periapical pathology in terms of susceptibility, progression and prevalence with moderate certainty of evidence.[13] However, much is still not known about the biological aspects of the impact of smoking cigarettes habit on the evolution of the endodontic pathology, and the post-endodontic healing capacity of periapical tissues. In view of the foregoing, this systematic review aimed to assess the impact of smoking cigarettes on the periapical healing course in patients undergoing endodontic therapy.

Method and materials

The systematic review of the literature was developed following the recommendations of the Cochrane Collaboration and following the PRISMA Statement.[14] The focused question of this systematic review was: what is the impact of smoking cigarettes on the periapical healing course in patients undergoing endodontic therapy.? The null hypothesis (H0) is that there is no association between tobacco smoking and an impaired post- endodontic periapical healing capacity in humans.

The inclusion criteria were observational studies published in peer reviewed articles (within journals classified as Q1 to Q4), defining the association between smoking cigarette habit, with the periapical healing course in patients undergoing conventional endodontic therapy (clinical and radiographic repair criteria). Studies that did not define the evaluation method, in vitro or animal studies, studies that did not associate directly “smoking cigarette with post-endodontic periapical healing,” narrative reviews, case reports, and expert opinions were excluded.

Information sources

The literature search was conducted following the recommendations by the Cochrane Collaboration. Medical subject headings (MeSH), Emtree language, Descriptors in health sciences (DeCS), and text words related to a complete search strategy were used. MEDLINE (PubMed), Web of Science, and Scopus were searched from inception to September 2020 (appendix 1). To ensure literature saturation, references from relevant articles identified through the search, conferences, thesis databases, OpenGrey, Google Scholar, and ClinicalTrials.gov were scanned, among others. The authors were contacted by email in case of missing information. There was no language limitation.

Appendix 1 Search strategy translated for each database

BASE DE DATOS	ESTRATEGIA DE BUSQUEDA	FINDINGS
PubMed	(Smokers OR no smokers AND smoking OR tobacco)	178089
	(Endodontics OR endodontic risk factors AND periodontitis OR pulpal disease AND apical periodontitis AND periodical condition AND root canal therapy OR periodical periodontitis OR root canal treatment) NOT implants	29545
	#1 AND #2	174
Scopus	(smokers OR no AND smokers AND smoking OR tobacco)	188435
	(endodontics OR endodontic AND risk AND factors AND periodontitis OR pulpal AND disease AND apical AND periodontitis AND periodical AND condition AND root AND canal AND therapy OR periodical AND periodontitis OR root AND canal AND treatment) AND NOT implants	6
	#1 AND #2	1
ISI web	(TS=(Smokers OR no smokers AND smoking OR tobacco))	8696
	(TS=(Endodontics OR endodontic risk factors AND periodontitis OR pulpal disease AND apical periodontitis AND periodical condition AND root canal therapy OR periodical periodontitis OR root canal treatment) NOT TS= (implants))	197735
	#1 AND #2	29

Data collection

Each reference was reviewed by title and abstract, which were analyzed based on the PECOS format for observational studies: Population: Human permanent teeth, Exposition: Cigarette smoking, Comparison: No smoking, Outcome: Post endodontic periapical healing and Study design: observational studies.

Full-texts of relevant studies were scanned, pre-specified inclusion and exclusion criteria were applied, and the data were extracted. Disagreements were resolved by consensus and where disagreement could not be solved, a third reviewer resolved any conflict. Relevant data were collected in duplicate by using a standardized data extraction sheet that contained the following information: author names, year of publication, title, study design, geographic location, objectives, inclusion and exclusion criteria, number of patients included, losses to follow- up, timing, definition of outcomes, outcomes and association measures, and funding source.

Risk of bias

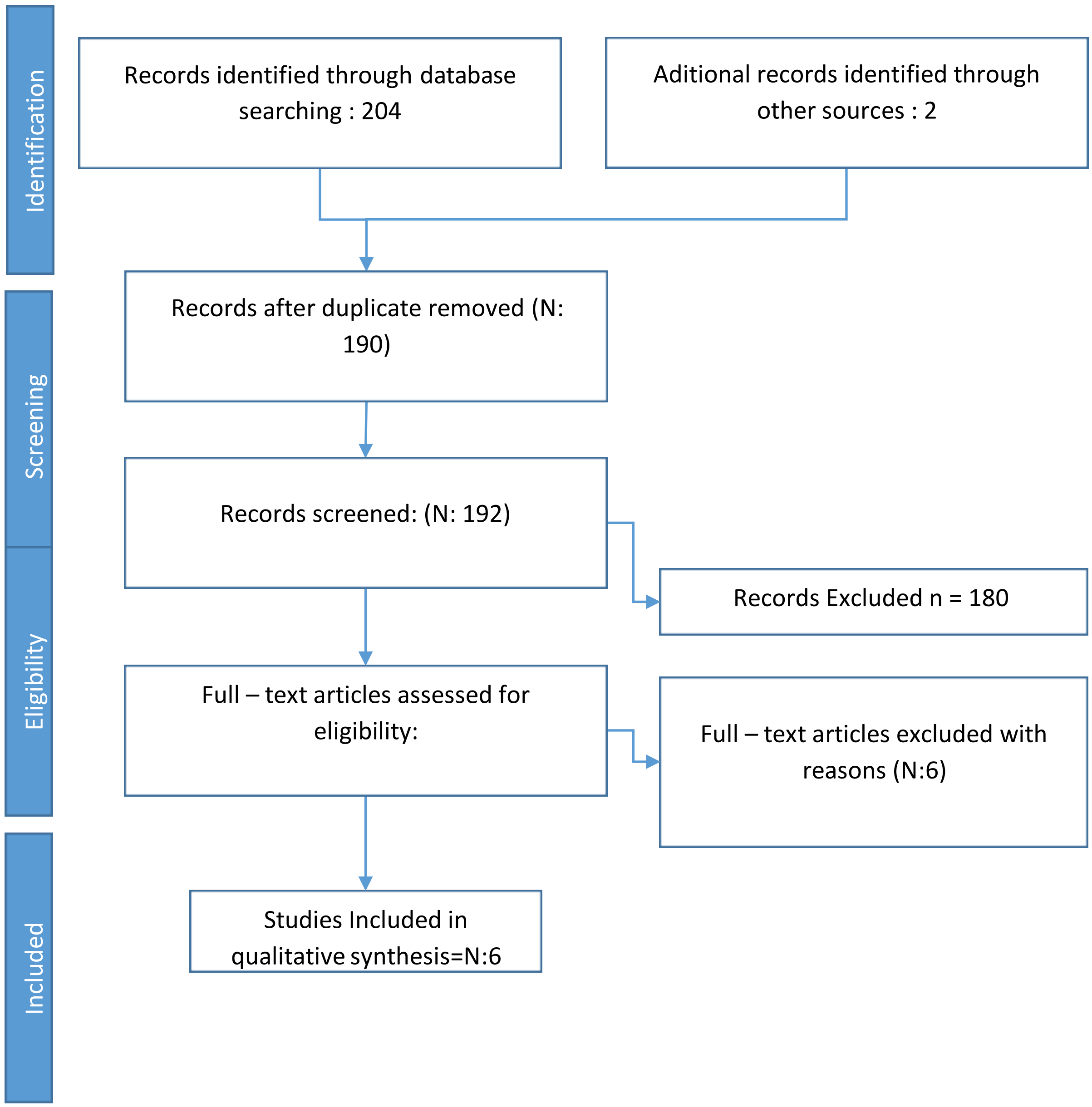
The assessment of the risk of bias was performed independently by two evaluators by using the Newcastle-Ottawa Scale for cross-sectional, cohort, and case-control studies.[15]

RESULTS

Study selection

We initially identified 206 references with the search strategy. After the removal of 14 duplicates, we screened 192 titles/abstracts. Finally, six studies met the inclusion criteria for qualitative synthesis. (Figure 1)

Figure 1 Flow diagram of the literature research



Characteristics of included studies

A total of six studies published between 2004 and 2020 were included in the systematic review (Table 1): All the studies compared the post endodontic prevalence of apical periodontitis in smokers vs non-smokers patients. The studies were conducted in Croatia, Saudi Arabia, Spain, Poland. All the studies of them were cross-sectional study, with a follow-up period of at least 12 months. The average group of participants in the articles included individuals between the ages of 20 and 65, but another study included an age range from 18 years. The language of publication for all studies was english.

Table 1 CONT. Characteristics of studies assessing the post endodontic prevalence of apical periodontitis in smokers vs non-smokers patients.

#Art	Title of Article	first author	journal	year	sample (#)	Sample characteristics (Smoker and/or non-smoker)	Periapical diagnosis	Indice periapical (PAI)	CRITERIOS DE REPARACION
1	Tobacco smoking an d dental periapical condition.	Bergstro¨m J, Babcan J,	European Journal of Oral Sciences	2004	247	81 current smokers, 63 former smokers, 103 non- smokers	periapical disease by x-ray	NO	RX
2	High prevalence of apical periodontit is amongst smokers in a sample of Spanish adults.	Segura-Egea, J J	Int Endod J	2008	180	109 SMOKERS AND 71 NON-SMOKERS	periapical disease by x-ray	SI	RX
3	THE INFLUENCE OF TOBACCO SMOKING ON DENTAL PERIAPICAL CONDITION IN A SAMPLE OF AN ADULT POPULATION OF THE ŁÓDŹ REGION, POLAND	KATARZYNA SOPIŃSKA, ELŻBIETA BOŁTACZ-RZEPKOWSKA	Int J Occup Med Environ Health.	2020	703	317 NON-SMOKERS, 386 SMOKERS	periapical disease by x-ray	NO	RX
4	Tobacco Smoking and Dental Periapical Condition in a Sample of Saudi Arabian Sub-Population	Laila A. Bahammam	JKAU: Med. Sci	2012	98	20 SMOKERS AND 78 NON-SMOKERS	periapical disease by x-ray	NO	RX
5	Influence of tobacco smoking on dental periapical condition in a sample of Croatian adults	Romana Perši´c Bukmir	Wien Klin Wochenschr.	2016	259	151 NON-SMOKERS, 108 SMOKERS	periapical disease by x-ray	SI	RX
6	Relationship between Smoking and Endodontic Variables in Hypertensive Patients	Segura-Egea, J J	JOE	2011	100	50 SMOKERS, 50 NON-SMOKERS	periapical disease by x-ray	yes	RX

Table 1 CONT. Characteristics of studies assessing the post endodontic prevalence of apical periodontitis in smokers vs non-smokers patients.

OBJETIVO	RELACION ENDODONCIA CON AP - TABAQUISMO	Analisis Estadístico	Nivel de Confianza	CONCLUSION
The objective of this study was to investigate whether smoking could be associated with the prevalence or severity of periapic lesions.	The prevalence of periapic lesions among individuals with enddodontic treatment was 69% in current smokers, 74% in ex-smokers and 85% in non-smokers	anova no paRAMETRIC (Kruskal-Wallis).	p: 0,128	It is concluded that these observations do not support the assumption that smoking is associated with apical periodontitis.
The goal is to study the prevalence of apical periodontitis in smoking and non-smoking patients.	Among smoking patients with clogged teeth, 36 (71%) had PA that affected at least one treated tooth. Among non-smokers with root-sealed teeth, 12 (55%) had PA that affected at least one treated tooth (P x 0.19).	KAPPA DE COHEN	p<0.05	In this study population, smoking was significantly associated with a higher frequency of duct treatment and with a higher prevalence of apical periodontitis.
The objective of the study was to assess the influence of smoking on the prevalence of PA in the population of the region of Ododo, Poland	No significant difference was found in the percentage of teeth treated endodontically with AP (37.6% vs 35.8%)	Chi2 test	p<0.06	Smokers are a group facing an increased risk of PA and therefore there is a need for early detection and treatment of cavities and their complications in this group of patients
Based on the assumption that smoking could influence apical periodontitis, the objective of this exploratory study was to investigate the possible association of smoking with the prevalence of periapical lesions.	The frequency of PA patients with endodontics in smokers and non-smokers was 5.73% and 5.12%, respectively. The frequency of patients with PA without PSTN was 0.95% in smokers and 1.46% in non-smokers.	T statistical test	p<0.05	These observations do not favor the assumption that smoking is associated with apical periodontitis. However, the research was cross-cutting by design and the conclusion should be considered temporary until confirmed by long-term observations.
The objective of this study was to investigate the difference in the periapical state of the teeth treated endodoonically and untreated in current smokers and never smokers.	Smoking patients with endodoontically treated teeth, 67 (72.0%) they had PA. Among the never smokers with endodoontically treated teeth, 93 (78.8%) they had PA	chi-square test	P=0.328	This study strongly supports the hypothesis that smoking influences the periapical state of the teeth, but not on teeth treated with endodontics. However, since this study was cross- cutting by design, conclusions should be considered temporary until confirmed by long-term observations.
The objective of this study was to investigate the relationship between smoking and the prevalence of apical periodontitis and duct treatment in hypertensive patients.	Among smoking patients with RCT, 20 (70%) had PA that affected at least 1 treated tooth. Among non-smokers with RCT, 9 (90%) had PA that affected at least 1 treated tooth.	chi-square test	P> 0,05	The prevalence of apical periodontitis and root canal treatment was significantly higher in hypertensive smoking patients compared to non-smokers.

Risk of bias assessment

A bias analysis of the included studies was performed using the Newcastle-Ottawa Quality Measurement Scale .[15] This scale evaluates aspects related to the selection, comparability and exposure of the subjects included in both the case and the groups of analytical observational studies. In the case of cross-sectional studies, the adaptation made by Herzog et al. [16] where the maximum score is 10 points, and studies are considered to be at low risk of bias when they score seven or more points.

The six studies assessed using the Newcastle-Ottawa Quality Measurement Scale were cross-sectional studies at a general level, 66.6% of the evaluated studies were classified as having a high risk of bias, because they obtained less than seven points out of 10 possible in the global rating (Table 1).

From the evaluation by categories, it can be seen that all the studies included in this review presented a high risk of bias, since the 6 studies obtained less than four points out of five possible. In contrast, in the comparability category, most of the included studies were evaluated as having a low risk of bias, because they obtained two points out of two possible; the Bahammam study did not obtain any points in this category. And finally, for the Outcome / Exposure category, all studies were rated as low risk of bias, because they obtained two or more points out of three possible for this category (Table 1).

Table 1. Evaluation according to the Newcastle - Ottawa Quality Assessment Scale

EVALUATION ACCORDING TO THE NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE				
STUDY	**SELECTION**	**COMPARABILITY**	**OUTCOME**	**CONCLUSION**
		CROSS-SECTIONAL STUDIES		
Bergström et al., 2004	★	★★	★★★	HIGH RISK
Segura-Egea et al., 2008	★	★★	★★★	HIGH RISK
Segura-Egea et al., 2011	★	★★	★★★	HIGH RISK
Bahammam, 2012	★★	-	★★	HIGH RISK
Peršić Bukmir et al., 2016	★★	★★	★★★	LOW RISK
Sopińska and Bołtacz-Rzepkowska, 2020	★★★	★★	★★★	LOW RISK

Discussion

The aim of this systematic review was to assess the prevalence of post endodontic chronic apical periodontitis in non-smokers vs smokers' patients.

Patients who had not smoked more than 200 cigarettes in their entire life were included in the non-smoke group. Smoking patients were classified as smokers (15 or more cigarettes a day), and patients with a mild smoker (1 to 5 cigarettes a day) The age of the average patients was 20 to 84 years between men and women. [13,17,18,19]

Recent systematic reviews have evaluated the prevalence of periapical lesions of endodontic origin in endodontically untreated teeth in non-smokers and smoker patients. Such studies have concluded that smoker patients are more likely to present apical periodontitis than non-smokers. [13,17,18,19]

Bergstrom et al; (2004); suggested that smoking may elicit greater destruction of periodontal bone when an existing pathology occurs and could delay the repair process, thus provoking a worse immune response, since nicotine diffuses through blood vessels and prevents it way osteoclastic proliferation, [20] French D et al; (2019) suggested that smoking could degrade connective tissue and compromise bone repair caused by locall ischemia generated by tobacco compsumption, [21] Pretropoulus et al; (2004) found that smoking bloks the formation of Intelerleucine 1-Alpha and interleukin 8 by macrophages important cells in the bone healing process. [22] Futhermore, Smoking could have an impact on periradicular tissues by reducing local oxygen levels. Segura-Ega et al; (2015) posits that the role of cigarettes in this process has become relevant since it could compromise the endodontic result compared to non-smoking patients due to its effects on bone metabolism, facilitating the degeneration of the apical bone. [17]

At date no systematic review and meta-analysis has evaluated the prevalence of periapical lesions in smokers and non-smokers after endodontic therapy. Results from the present investigation show that the prevalence of apical periodontitis in smokers compared to non-smokers is similar as there are no statistically significant differences between both groups, which generates the hypothesis that once the factor etiological and infection by endodontic therapy the periapical tissue is able to repair when starting a bone repair process even under the influence of cigarettes. [17,20,21]

The healing process of choric the apical periodontitis depends on the activity of osteoblasts, the bone- forming cells. [23] Osteoblasts originate as mesenchymal stem cells in the bone marrow under the influence of bone morphogenic proteins (BMPs), these stem cells they are induced to differentiate and give rise to spindle-shaped osteoprogenitor cells. Growth factors such as transforming growth factor β (TGFβ), fibroblast-derived growth factor (FGF), BMPs, platelet-derived growth factor (PDGF), and colony stimulating factor (CSF) can induce and / or increase the proliferation of osteoprogenitor cells [23,24] .Osteoprogenitor cells accumulate in sites of bone formation by different mechanisms such as local proliferation, chemotactic attraction of osteoprogenitor cells from adjacent sites, or by both processes [23,24] .BMPs induce the final differentiation of osteoprogenitor cells into metabolically active cuboidal osteoblasts that coat the bone surface and begin the process of bone apposition [23,24] . Osteoblasts secrete collagen and BMP, as well as various growth factors to initially form osteoid tissue which will eventually mineralize and form mature bone. When the osteoid apposition is complete, the osteoblasts differentiate into flat lining cells that cover the new bone. [23,24.]

The initially formed bone will eventually be resorbed and replaced by new bone formations in cycles through a process known as remodelling. Therefore, it can be deduced that the bone healing process in the apical lesion involves repeated cycles of apposition and remodelling. Fig1 [23,24.]

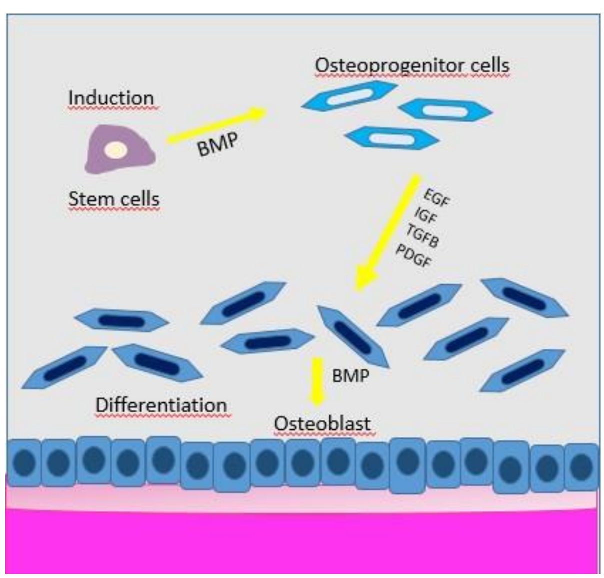


Fig 1. Apposition of new bone. Osteoprogenitor give rise to the formation of new osteoblasts and subsequent new bone.

Osteoprogenitor cells originate as bone marrow mesenchymal stem cells induced by BMPs to differentiate into osteoprogenitor cells. Certain growth factors, including epidermal growth factor (EGF), insulin-like growth factor (IGF), TGFβ, and PDGF, are chemotactic and proliferating factors for osteoprogenitor cells. Consequently, spindle-shaped osteoprogenitor cells accumulate alongside the future site of bone apposition. BMPs cause the eventual differentiation of osteoprogenitor cells into metabolically active cuboidal osteoblasts that coat the bone surface and produce osteoid (shown in pink) which will then mineralize into bone (shown in purple.) [23,24.]

Bacteria emerging from the infected root canal provide a continues stimulus for the activation of immune cells such as T lymphocytes and macrophages, thus activating and maintaining osteoclastic signals Figure 2. The apical lesion represents a successful attempt by the host to prevent highly pathogenic bacteria present in the infected root canal to spread to the adjacent bone [23,24] . When these bacteria have been eliminated by endodontic therapy and the canal has been properly sealed, this stimulus ceases. Then the osteoclastic activity, initiated by IL-1β and TNFβ, will decrease and the surrounding osteogenic potential will take over. [23,24]

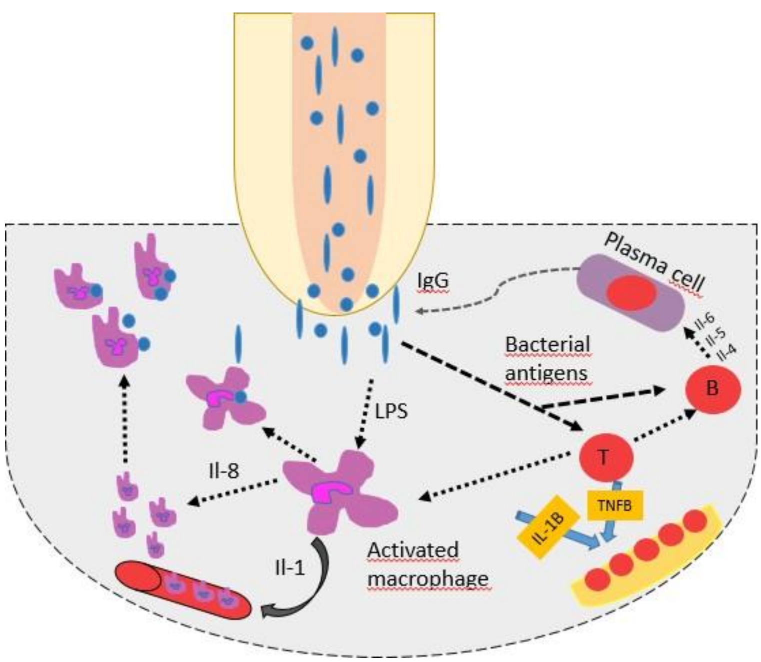


Fig 2. Host response at the apical lesion. The main goal of the host response is to eliminate the bacteria their respective sub products emerging from the infected root canal. To meet this goal, specific IgGs are required. These IgGs can be produced locally by activating B lymphocytes, which then become plasma cells that secrete IgG. This process requires the prior local activation of antigen-specific T lymphocytes. Activated lymphocytes produce a number of cytokines necessary for the activation of B lymphocytes and the maturation of plasma cells. Interferon gamma is another cytokine derived from T lymphocytes that activates local macrophages and causes them to produce IL-1, which in turn induces the expression of binding molecules on local endothelial cells. PMNs adhere to the local endothelium, making them available for recruitment by chemotaxis at the site where bacteria emerge. Two cytokines produced by locally activated lymphocytes and macrophages, TNFβ and IL-1β, are the primary signals that induce local osteoclastic bone resorption. Such bone resorption can be seen as a destructive side effect of the local activity of the host response. [24]

Gradual apposition of new bone, followed by its remodelling and subsequent cycles of apposition, will eventually result in the healing of the bone defect, initially elicited by the dynamic encounter between bacteria and the immune system [23,24]

However, to date, few studies evaluate the periapical repair process in smoking patients.

Conclusions

The best current available evidence detailed in this systematic review suggests that smoking has no
association with the prevalence of post-endodontic periapical pathology in cross-sectional studies. Whereas there are no longitudinal studies to support this result. Further studies are needed to rule out the association of smoking and post-endodontic periapical pathology with studies with a larger sample that fit all possible covariates.

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