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Apical periodontitis and related risk factors: Cross-sectional study

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ABSTRACT

Objectives: The aim of this cross-sectional study was to investigate an association between the prevalence of root-filled teeth (RFT) or apical periodontitis (AP) and some systemic conditions or smoking habits in an adult Portuguese population.

Methods: Medical histories, including age, gender, presence of cardiovascular disease (CVD), diabetes mellitus (DM), allergies, smoking status, and endodontic treatment data of 421 patients (10,540 teeth) were recorded. The prevalence of root filled teeth and the periapical status were assessed through panoramic radiographies. Periapical status was classified according to the Periapical index and AP was defined as PAI-score $\geq$3. Statistic analysis was performed with PASW Statistics 20.0 using qui-square tests, odds-ratio and confidence intervals (95%).

Results: The overall prevalence of AP and RFT was 2.2% and 4.2%, respectively. RFT increased the possibility of having AP ($p < 0.0001$). Men's group showed a higher percentage of teeth with AP ($p < 0.0001$), less RFT ($p = 0.05$) and more residual roots (2.3%). Smoking increased the probability of having AP ($p = 0.002$) and RFT ($p = 0.045$). A positive correlation was observed between RFT and DM ($p = 0.040$). No statistically significant difference was found between AP and CVD, DM or allergies neither between RTF and CVD or allergies.

Conclusions: The higher prevalence of AP and/or RFT in smoker subjects and in diabetic patients can suggest a relationship between oral and systemic health. More epidemiological studies are required before definitive conclusions can be made.

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Periodontite apical e fatores de risco associados: estudo transversal

Palavras chave:
Periodontite apical
Diabetes mellitus
Fumar
Fatores de risco

RESUMO

Objetivos: O objetivo deste estudo transversal foi investigar a associação entre a prevalência de dentes com tratamento endodôntico (RFT) ou periodontite apical (AP) e algumas condições sistémicas ou hábitos tabágicos numa população adulta portuguesa.

Métodos: Histórias médicas, incluindo idade, género, presença de doenças cardiovasculares (CVD), diabetes mellitus, alergias e hábitos tabágicos, e registos dos tratamentos endodônticos de 421 pacientes (10.540 dentes) foram recolhidos. A prevalência de dentes com tratamento endodôntico e status apical foram avaliados através de radiografias panorâmicas. O status apical foi classificado de acordo com o índice periapical e a AP definida para valores PAI≥3. A análise estatística foi realizada através do PASW Statistics 20.0 utilizando os testes chi-quadrado, valores odds-ratio e intervalos confiança (95%).

Resultados: A prevalência da AP e RFT foi de 2,2% e 4,2%, respectivamente. RFT aumentou a possibilidade de ter AP (p<0,0001). Os homens revelaram uma maior percentagem de dentes com AP (p<0,0001), menos RFT (p=0,05) e mais raízes residuais (2,3%). Fumar aumentou a probabilidade de ter AP (p=0,002) e RFT (p=0,045). Uma relação positiva foi observada entre RFT e DM (p = 0,040). Não se encontraram diferenças estatisticamente significativas entre AP e CVD, DM ou alergias nem entre RTF e CVD ou alergias.

Conclusões: Uma maior percentagem de AP e/ou RFT nos fumadores e nos pacientes com diabetes sugere uma relação entre a saúde oral e sistémica. Mais estudos epidemiológicos são necessários antes de se fazerem conclusões definitivas.

Introduction

Apical periodontitis (AP) is "an acute or chronic inflammatory lesion around the apex of a tooth caused by bacterial infection of the pulp and root canal system".[1] The inflammatory cells cause, among other effects, resorption of the adjacent supporting bone. The diagnosis is primarily based in the observation of a periradicular radiolucency, although it can be supported by patient' symptoms or clinical signs in the acute phases.[1,2] AP is highly prevalent, and the estimated percentage of individuals with AP, in at least one tooth, is 34–70%[3–7], which can rise in older patients.[8–11] Overall, the percentage of teeth with AP has been estimated to range between 1.7% and 6.6%.[5,9,12] However, amongst endodontically treated teeth the percentage is significantly higher.[9,11,13–16]

Root canal treatment is the most frequent therapeutic option for preserving teeth with AP and to restoring perirradicular tissues' health. Therefore, its prevalence can be linked to the presence of severe caries lesions or traumatic injuries that lead to pulp necrosis. The prevalence of individuals with, at least, one root canal treatment is between 41 and 87%.[5,7,17,18] The frequency of root-filled teeth varies between 2.2% and 9.39%.[5,6,9,11,15,19] This broad variation can be due to either different age stratification in the studies or variation within national health care services.

Several epidemiological studies have found an association between chronic dental infection, cardiovascular disease (CVD)[20–25], diabetes mellitus (DM)[26–29] and smoking habits[30,31], most of them relating to periodontal disease.

AP is, in many instances, very similar to periodontal disease regarding the microbial aetiology and the presence of elevated systemic cytokines.[32,33]

Patients with DM, hypertension or coronary heart disease might have decreased tissue resistance to bacterial infection and reduced ability of tissue repair after endodontic treatment. Wang et al.[34] found an increased risk of tooth extraction after nonsurgical endodontic treatment in patients with these diseases. Furthermore, the association of two of those conditions was a significant predictor of extraction or poorer outcome of the endodontic treatment[32,35,36]. However, limited data is available on the long-term prognosis of AP and root-filled teeth, in patients with systemic diseases and smoking habits.

DM, a syndrome characterized by abnormalities in carbohydrate, lipid and protein metabolism, also affects many functions of the immune system. For instance, up-regulation of pro-inflammatory cytokines from monocytes/polymorphonuclear leukocytes and down-regulation of growth factors from macrophages, resulting in dysregulated macrophage phagocytosis.[37] Consequently, there is delay in healing process and commitment of the immune response.[38,39] These events predispose to chronic inflammation, progressive tissue breakdown and diminished tissue repair capability.[40–42] DM has been considered as a possible modulating factor or disease modifier in endodontic infections, in the sense that diabetic individuals, especially when poorly controlled, could be more prone to developing AP.[43,44] The literature on the pathogenesis, progression and healing of endodontic pathology in diabetic patients is still scarce and show controversial results.[29,43,45–47]

Current evidence indicates that smoking is a significant risk factor for the inflammation of the marginal periodontium.[25,48] Cross-sectional and longitudinal studies demonstrated the harmful effects of tobacco smoking on the supporting structures of the teeth.[25,49] Smoking impairs the body's responses to infection, exacerbates bone loss, decreases the blood's oxygen-carrying capacity and causes vascular dysfunction.[50] It can be assumed that smoking can act as a risk factor to the development AP, exerting a negative influence on the apical periodontium of endodontically compromised teeth, allowing the extension of periapical bone destruction and/or interfering with the healing and repair process after root canal treatment.[25]

In the recent years, there has been a high level of interest in research focused on Dentistry, namely Endodontics, related to systemic health. To date, the role of systemic conditions and health-related habits as risk factors for adverse outcome of AP has not been thoroughly explored.

The present study is aimed at exploring an association between endodontic status and systemic conditions, such as, cardiovascular diseases, diabetes mellitus or allergies, and smoking habits as possible risk factors for AP, in an adult Portuguese population.

Methods

The sample included medical histories and endodontic treatment data of all the patients attending the clinic of the Dental Faculty of Oporto University and of the Health Sciences Faculty of Fernando Pessoa University (Oporto) for the first time in 2012. The following were used as inclusion criteria: age (at least 18 years old) and number of teeth (no less than 8 remaining teeth). 421 patients were selected, with a total of 10,540 teeth assessed. The institutional scientific committee of each of the faculties involved formally approved the present study.

Age, gender, aspects of general health (presence of CVD, DM, allergies) and health-related habits (smoking status), were recorded from the medical questionnaire. CVD, DM and allergies were assessed through a dichotomy key (yes/no). Coronary heart disease, stroke, hypertension, atherosclerosis, and myocardial infarction were included in the cardiovascular disease category. Type 1, type 2 and gestational diabetes were included in the DM group. The following criteria were monitored in the allergies' category: pollen season, asthma, atopic dermatitis, Chron's disease, rheumatoide arthritis, allergic rhinitis and allergy medication, such as penicillin.

Smoking status was classified as non-smoker, if the patient answer was never smoker/former smoker for more than 5 years ago, or current smoker.

The periapical status and the prevalence of root-filled teeth (RFT) were assessed using panoramic radiography. The Orthoralix® 9200 DDE (Gendex) was used in all cases. The method of viewing the radiographies was standardized: films were examined in a darkened room using a computer in which the ambient light could be controlled for the best possible contrast. Teeth were categorized as RFT, if they presented any radiopaque material in the pulpal space. Periapical status of each tooth was classified according to the Periapical Index (PAI)[51] and the presence of AP was defined as PAI-score ≥3. In cases of multi-rooted teeth, the worst root score was chosen. Three observers performed the PAI assessment, after training and calibration. The coefficient Cohen's kappa was applied.

In order to characterize the oral health status of the subjects, additional clinical data such as the number of missing teeth as well as residual roots were also recorded.

Statistical analysis was performed with PASW Statistics 20.0 (version 20, SPSS®). A descriptive statistical study of the selected variables was performed. Data were analyzed by estimating frequencies in percentages. The association and the level of significance between two variables were evaluated using the qui-square test. The odds-ratio and the respective confidence intervals (95%) were obtained by association measures in 2 × 2-cross tabs. For statistic analysis tooth was adopted as sampling unit.

Results

The sample included a total of 421 patients' records. From these 43% were male and 57% female, with a mean age of 41 ± 16 years old (range 18–82 years). Of the 10,540 examined teeth, 2.2% had AP and 4.2% had RFT. The prevalence of AP was greater in root-filled teeth (Fig. 1 and Table 1) and in the men's group ($p < 0.05$) (Table 2). The probability of having AP in men was almost two times higher than in women (Table 2).

A significant association was observed between smoking status, AP and RFT (Table 3). RFT were more prevalent in DM and CVD groups ($p < 0.05$) (Table 3). No significant association was found between AP and CVD, DM or allergies groups, neither between RFT and allergies (Table 3).

Regarding the number of absent teeth, there was no significant association between the different systemic diseases, habits or gender ($p > 0.05$) (Table 1). Similarly, no significant association was found between the number of residual roots in the different groups ($p > 0.05$) (Table 1).

Discussion

The total prevalence of AP (2.2%) recorded in this study is in agreement with other European countries.[60,9,11] Similar values of RFT (4.2%) were also found in other epidemiological studies, with prevalence's ranging between 1.3% and 4.8%.[9,11,15,19,52,53] By contrast, others authors have reported values ranging

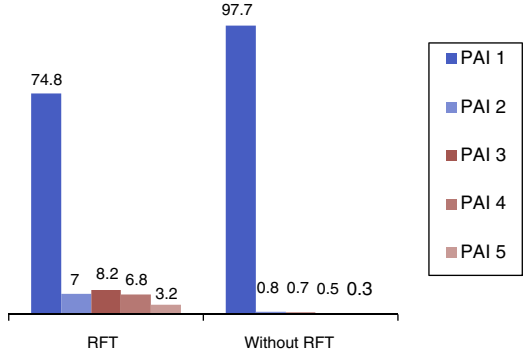

Fig. 1 – Periapical status (PAI) in teeth with RFT and without RFT. Values present as %.

Table 1 – Prevalence of apical periodontitis (AP) and root-filled tooth (RFT), residual roots (RR) and missing teeth (MM).

Study' population	AP	RFT	RR	MT	AP*RFT
	2.2	4.2	1.73	87.86	18.2

Gender	Male				Female			
	AP	RFT	RR	MT	AP	RFT	RR	MT
	2.82	3.9	2.28	84.45	1.7	4.7	1.31	90.4
Smoking status	Smoking				Non-Smoking			
	AP	RFT	RR	MT	AP	RFT	RR	MT
	3	4.9	3.18	83.74	1.87	3.93	1.46	89.86
Diabetes mellitus	DM				Non-DM			
	AP	RFT	RR	MT	AP	RFT	RR	MT
	2.4	6	0.98	100	2.38	4.27	1.96	86.6
CVD	CVD				Non-CVD			
	AP	RFT	RR	MT	AP	RFT	RR	MT
	2.4	3.5	1.35	95.01	2.4	4.65	2.06	85.37
Allergies	Allergies				Non-allergies			
	AP	RFT	RR	MT	AP	RFT	RR	MT
	1.6	5.5	1.2	88.9	2.5	4.26	2.02	87.1

Values are presented as number (%).

between 34% and 87%. Differences in health care services and socioeconomically related factors[34] may account for this discrepancy (1.3% till 34%)[7,9,11,15,19,34,52,54–56] The present results point out that AP is less prevalent in women than in men. Women might be more health conscious and seek dental care more often.[9,57] In fact, in the present study women showed less residual roots and more RFT, although not statistically significant.

The higher prevalence of AP in RFT confirms previous observations linking AP to endodontic treated teeth.[9,27,49,56,58–61] Paradoxically, in some studies, the prevalence of AP may appear very low and not so closely associated to root filled teeth due to a lower number of remaining teeth, suggesting that those affected by AP may have been extracted, resulting in an unknown proportion of root canal treated teeth being lost to follow-up.[1,58]

Other considerations, as the quality of root canal treatment, not considered in this study, may also significantly influence the perirradicular status of endodontic treated teeth.[62]

Despite some limitations of conventional radiography for detection of periapical bone lesions, panoramic radiographs are still used in epidemiological studies.[6,7,9,19,63] Moreover, cost-effectiveness of high-resolution Cone Beam Computed Tomography (CBCT) images, in clinical routine and research, should be weighed.[64] Additionally, the PAI index has been widely used in endodontic literature allowing for comparison with previous studies.[6,7,11,19,35,63,65] The reproducibility of the PAI index between the observers has been found.

Present data revealed a statistically significant association between smoking habits and the prevalence of AP and RFT, in agreement with others studies.[35,36,66,67] Besides, Krall et al.[50] reported a significant dose dependent relationship between the number of cigarettes smoked and the risk of having RFT. In the present study, we couldn't identify the number of cigarettes smoked being only considered current/former smokers and non-smokers subjects.

Smoking interferes with the wound healing process by affecting the fibroblasts growth, the microvasculature and the immune's system normal functioning[48,68] Nicotine has

Table 2 – Apical periodontitis (AP) and root-filled tooth (RFT) according to gender.

	OR	CI	p^*
AP*RFT	14.81	11.07–19.82	**<0.0001**
AP*Gender	1.68	1.29–2.17	**<0.0001**
RFT*Gender	0.82	0.676–1.00	**0.05**

Values are presented as odds-ratio (OR) and confidence intervals (CI 95%). Testing of group differences by *qui-square test. At bold (P) are the relationships between the variables that are significant.

Table 3 – Apical periodontitis (AP) and root-filled tooth (RFT) in smoking, diabetes mellitus (DM), cardiovascular disease (CVD) or allergies' groups.

	OR	CI	p^*
Smoking			
Smoking*AP	1.63	1.19–2.24	**0.002**
Smoking*RFT	1.27	1.01–1.61	**0.045**
DM			
DM*AP	1.03	0.60–1.75	0.92
DM*RFT	1.44	1.02–2.04	**0.040**
CVD			
CVD*AP	0.98	0.70–1.37	0.91
CVD*RFT	0.75	0.58–0.98	**0.035**
Allergies			
Allergies*AP	0.64	0.40–1.03	0.067
Alllergies*RFT	1.31	0.99–1.73	0.054

Values are presented as odds-ratio (OR) and confidence intervals (CI 95%). Testing of group differences by *qui-square test. At bold (P) are the relationships between the variables that are significant.

been linked to thicker *Streptococcus mutans* biofilms, suggesting that smoking can increase the development of caries.[69] Socio-economical factors, prevalence of dental caries, regularity of dental care or even association with other systemic conditions[35] were not taken into consideration, in the present study. Root canal treatment is only one of the possible options for the treatment of teeth with AP, and we didn't considerer other therapeutics[70–72]. However, there was no association with number of absent teeth or prevalence of residual roots with the smoking status.

In the present study a range of cardiac pathologies, like coronary heart disease, stroke, hypertension, atherosclerosis and myocardial infarction were included in the CVD group. This was due to the non-specific records of the medical cardiac conditions. Hypertension leads to shortened life expectancy and, if persistent, is an important risk factor for coronary heart disease, stroke or heart failure.[73] No statistically significant association was found between AP and CVD ($p < 0.05$). Segura-Egea[35] found a significant association between hypertension and AP, but only within smokers. There must be considered some confounding factors in the interpretation of these results. Aleksejuniene et al.'s observations[65] suggest that dentists, in some countries, are more radical and prefer to extract teeth with AP in patients displaying cardiovascular problems. Moreover, these individuals may be generally more health concerned and seek dental care more often.

Marotta et al.[29] found that AP was significantly more prevalent in teeth of diabetic individuals than in non-diabetic controls. Nevertheless, this only occurred in untreated teeth. Another study showed that worse periapical status correlates with poorer glycemic control levels in diabetic patients.[74] On the other hand, Wolle et al.[46] showed that the extension of the periapical lesion in type 2 diabetes was similar to that seen in control, non diabetic, animals. Since diabetes is the third most prevalent condition in medically compromised patients seeking dental treatment[75], dentists should be aware of the possible relationship between endodontic infections and DM. In the Segura-Egea et al.'s review[32] DM was associated with a higher prevalence of AP, greater size of osteolityc lesions, greater likelihood of asymptomatic infections and worse prognosis of RFT. Our study failed to associate a higher prevalence of AP in diabetic patients ($p = 0.918$). Similar to what succeeded with the CVD group, that included a range of cardiac pathologies we were unable to distinguish between type 1, 2 or gestational diabetes.

Fouad[43] found a poorer treatment outcome of teeth with pre-operative AP, for diabetic as compared with non-diabetic patients, suggesting that some bacterial species may be more prevalent in necrotic pulps of diabetic than in non-diabetic patients.

Our results, although without association between AP and DM, show that RFT were more prevalent in the DM' group according to previous data published.[76] These patients may be more prone to develop caries[77] as wells as severe caries lesions[78] with a direct negative effect on dental pulp integrity, specially in non-controlled patients.[79]

Several risk factors have already been identified[80] that can affect the severity, prognosis and the outcome of the endodontic treatment of teeth with AP. Allergies, an immune response to foreign substances, might also be considered an AP' modifier, through the present results. An interesting and borderline link was found between AP and allergies, however not statistically significant ($p = 0.067$). More studies are required to confirm this association.

In the present investigation the tooth was the unit of study. Many authors refer the same methodology. Furthermore, Lopez-Lopez[76] showed similar results when considering the tooth or the individual respecting some systemic conditions

Results of cross-sectional studies should be interpreted with caution, preventing the accurate assessment of which of the endodontically treated teeth recorded as having AP, actually represent a treatment failure or a lesion in a healing process. Other uncontrolled variables, namely the presence of AP pre-operatively and the time elapsed since the respective treatment can introduce bias in the results. Additional studies that provide long-term observations and randomized clinical trials are needed to clarify the prevalence of AP and related risk factors.

Conclusion

The influence of related risk factors over the prognosis of apical periodontitis is a valid tool for the clinician' treatment decision. The data in the present study suggest an association between some systemic diseases, as CVD, DM, allergies and smoking status with RTF and AP, which must be further explored.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Erikson HM. Epidemiology of apical periodontitis. In: Orstavik D, Pitt Ford TR, editors. Essential endodontology: prevention and treatment for apical periodontitis. Oxford: Blackwell Science d.; 1998. p. 179–91.
2. Caplan D. Epidmiologic issues in studies of association between apical periodontitis and systemic health. Endodontic Topics. 2004;8:15–35.
3. Odesjo B, Hellden L, Salonen L, Langeland K. Prevalence of previous endodontic treatment, technical standard and occurrence of periapical lesions in a randomly selected adult, general population. Endod Dent Traumatol. 1990;6: 265–72.

4. Saunders WP, Saunders EM. Prevalence of periradicular periodontitis associated with crowned teeth in an adult Scottish subpopulation. Br Dent J. 1998;185:137–40.
5. Lopez-Lopez J, Jane-Salas E, Estrugo-Devesa A, Castellanos-Cosano L, Martin-Gonzalez J, Velasco-Ortega E, et al. Frequency and distribution of root-filled teeth and apical periodontitis in an adult population of Barcelona, Spain. Int Dent J. 2012;62:40–6.
6. Loftus JJ, Keating AP, McCartan BE. Periapical status and quality of endodontic treatment in an adult Irish population. Int Endod J. 2005;38:81–6.
7. Tsuneishi M, Yamamoto T, Yamanaka R, Tamaki N, Sakamoto T, Tsuji K, et al. Radiographic evaluation of periapical status and prevalence of endodontic treatment in an adult Japanese population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100:631–5.
8. Eriksen HM, Bjertness E. Prevalence of apical periodontitis and results of endodontic treatment in middle-aged adults in Norway. Endod Dent Traumatol. 1991;7:1–4.
9. Rocha JL, Braga AC, Carvalho MFIP-V. Prevalence of apical periodontitis and endodontic treatment in an adult Portuguese population. Arch Oral Res. 2012;8:219–27.
10. Figdor D. Apical periodontitis: a very prevalent problem. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94:651–2.
11. Jimenez-Pinzon A, Segura-Egea JJ, Poyato-Ferrera M, Velasco-Ortega E, Rios-Santos JV. Prevalence of apical periodontitis and frequency of root-filled teeth in an adult Spanish population. Int Endod J. 2004;37:167–73.
12. De Moor RJ, Hommez GM, De Boever JG, Delme KI, Martens GE. Periapical health related to the quality of root canal treatment in a Belgian population. Int Endod J. 2000;33:113–20.
13. Skudutyte-Rysstad R, Eriksen HM. Endodontic status amongst 35-year-old Oslo citizens and changes over a 30-year period. Int Endod J. 2006;39:637–42.
14. Boucher Y, Matossian L, Rilliard F, Machtou P. Radiographic evaluation of the prevalence and technical quality of root canal treatment in a French subpopulation. Int Endod J. 2002;35:229–38.
15. Weiger R, Hitzler S, Hermle G, Lost C. Periapical status, quality of root canal fillings and estimated endodontic treatment needs in an urban German population. Endod Dent Traumatol. 1997;13:69–74.
16. Buckley M, Spangberg LS. The prevalence and technical quality of endodontic treatment in an American subpopulation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995;79:92–100.
17. Chueh LH, Chen SC, Lee CM, Hsu YY, Pai SF, Kuo ML, et al. Technical quality of root canal treatment in Taiwan. Int Endod J. 2003;36:416–22.
18. Georgopoulou MK, Spanaki-Voreadi AP, Pantazis N, Kontakiotis EG. Frequency and distribution of root filled teeth and apical periodontitis in a Greek population. Int Endod J. 2005;38:105–11.
19. Gencoglu N, Pekiner FN, Gumru B, Helvacioglu D. Periapical status and quality of root fillings and coronal restorations in an adult Turkish subpopulation. Eur J Dermatol. 2010;4: 17–22.
20. Janket SJ, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95:559–69.
21. Grau AJ, Becher H, Ziegler CM, Lichy C, Buggle F, Kaiser C, et al. Periodontal disease as a risk factor for ischemic stroke. Stroke. 2004;35:496–501.
22. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodontol. 1996;67 10 Suppl:1123–37.
23. Golebiewska M, Taraszkiewicz-Sulik K, Kuklinska A, Musial WJ. Periodontal condition in patients with cardiovascular diseases. Adv Med Sci. 2006;51 Suppl. 1:69–72.
24. Khader YS, Albashaireh ZS, Alomari MA. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. J Periodontol. 2004;75:1046–53.
25. Cotti E, Dessi C, Piras A, Mercuro G. Can a chronic dental infection be considered a cause of cardiovascular disease? A review of the literature. Int J Cardiol. 2011;148:4–10.
26. Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. J Periodontol. 2006;77:1289–303.
27. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. Nat Rev Endocrinol. 2011;7:738–48.
28. Katagiri S, Nitta H, Nagasawa T, Izumi Y, Kanazawa M, Matsuo A, et al. Effect of glycemic control on periodontitis in type 2 diabetic patients with periodontal disease. J Diabetes Investig. 2013;4:320–5.
29. Marotta PS, Fontes TV, Armada L, Lima KC, Rocas IN, Siqueira JF Jr. Type 2 diabetes mellitus and the prevalence of apical periodontitis and endodontic treatment in an adult Brazilian population. J Endod. 2012;38:297–300.
30. Walter C, Friedmann A. Evidence supports the impact of smoking cessation protocols in periodontal therapy. J Evid Based Dent Pract. 2013;13:142–4.
31. Chambrone L, Preshaw PM, Rosa EF, Heasman PA, Romito GA, Pannuti CM, et al. Effects of smoking cessation on the outcomes of non-surgical periodontal therapy: a systematic review and individual patient data meta-analysis. J Clin Periodontol. 2013;40:607–15.
32. Segura-Egea JJ, Castellanos-Cosano L, Machuca G, Lopez-Lopez J, Martin-Gonzalez J, Velasco-Ortega E, et al. Diabetes mellitus, periapical inflammation and endodontic treatment outcome. Med Oral Patol Oral Cir Bucal. 2012;17:e356–61.
33. Martin-Gonzalez J, Carmona-Fernandez A, Perez-Perez A, Sanchez-Jimenez F, Sanchez-Margalet V, Segura-Egea JJ. Expression and immunohistochemical localization of leptin in human periapical granulomas. Med Oral Patol Oral Cir Bucal. 2015;20:e334–9.
34. Wang CH, Chueh LH, Chen SC, Feng YC, Hsiao CK, Chiang CP. Impact of diabetes mellitus, hypertension, and coronary artery disease on tooth extraction after nonsurgical endodontic treatment. J Endod. 2011;37:1–5.
35. Segura-Egea JJ, Castellanos-Cosano L, Velasco-Ortega E, Rios-Santos JV, Llamas-Carreras JM, Machuca G, et al. Relationship between smoking and endodontic variables in hypertensive patients. J Endod. 2011;37:764–7.
36. Lopez-Lopez J, Jane-Salas E, Martin-Gonzalez J, Castellanos-Cosano L, Llamas-Carreras JM, Velasco-Ortega E, et al. Tobacco smoking and radiographic periapical status: a retrospective case–control study. J Endod. 2012;38: 584–8.
37. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabet Med. 1997;14:29–34.
38. Vernillo AT. Diabetes mellitus: relevance to dental treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;91:263–70.
39. Graves DT, Liu R, Oates TW. Diabetes-enhanced inflammation and apoptosis: impact on periodontal pathosis. Periodontol 2000. 2007;45:128–37.
40. Manfredi M, McCullough MJ, Vescovi P, Al-Kaarawi ZM, Porter SR. Update on diabetes mellitus and related oral diseases. Oral Dis. 2004;10:187–200.
41. Kidambi S, Patel SB. Diabetes mellitus: considerations for dentistry. J Am Dent Assoc. 2008;139 Suppl.:8S–18S.

42. Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. J Am Dent Assoc. 2008;139 Suppl.:19S–24S.
43. Fouad AF. Diabetes mellitus as a modulating factor of endodontic infections. J Dent Educ. 2003;67:459–67.
44. Siqueira JF Jr. Treatment of Endodontic Infections. London: Quintessence Publishing; 2011.
45. Segura-Egea JJ, Jimenez-Pinzon A, Rios-Santos JV, Velasco-Ortega E, Cisneros-Cabello R, Poyato-Ferrera M. High prevalence of apical periodontitis amongst type 2 diabetic patients. Int Endod J. 2005;38:564–9.
46. Wolle CF, Zollmann LA, Bairros PO, Etges A, Leite CE, Morrone FB, et al. Outcome of periapical lesions in a rat model of type 2 diabetes: refractoriness to systemic antioxidant therapy. J Endod. 2013;39:643–7.
47. Ferreira MM, Carrilho E, Carrilho F. Diabetes mellitus and its influence on the success of endodontic treatment: a retrospective clinical study. Acta Med Port. 2014;27:15–22.
48. Duncan HF, Pitt Ford TR. The potential association between smoking and endodontic disease. Int Endod J. 2006;39:843–54.
49. Bergstrom J, Babcan J, Eliasson S. Tobacco smoking and dental periapical condition. Eur J Oral Sci. 2004;112:115–20.
50. Krall EA, Abreu Sosa C, Garcia C, Nunn ME, Caplan DJ, Garcia RI. Cigarette smoking increases the risk of root canal treatment. J Dent Res. 2006;85:313–7.
51. Orstavik D, Kerekes K, Eriksen HM. The periapical index: a scoring system for radiographic assessment of apical periodontitis. Endod Dent Traumatol. 1986;2:20–34.
52. De Cleen MJ, Schuurs AH, Wesselink PR, Wu MK. Periapical status and prevalence of endodontic treatment in an adult Dutch population. Int Endod J. 1993;26:112–9.
[53]. Diogo P, Palma P, Caramelo F, Marques dos Santos J. Estudo da prevalência de periodontite apical numa população adulta portuguesa. Rev Port Estomatol Med Dent Cir Maxilofac. 2014;55:36–42.
54. Dugas NN, Lawrence HP, Teplitsky PE, Pharoah MJ, Friedman S. Periapical health and treatment quality assessment of root-filled teeth in two Canadian populations. Int Endod J. 2003;36:181–92.
55. Kirkevang LL, Orstavik D, Horsted-Bindslev P, Wenzel A. Periapical status and quality of root fillings and coronal restorations in a Danish population. Int Endod J. 2000;33:509–15.
56. Segura-Egea JJ, Jimenez-Pinzon A, Poyato-Ferrera M, Velasco-Ortega E, Rios-Santos JV. Periapical status and quality of root fillings and coronal restorations in an adult Spanish population. Int Endod J. 2004;37:525–30.
57. Frisk F, Hakeberg M. Socio-economic risk indicators for apical periodontitis. Acta Odontol Scand. 2006;64:123–8.
58. Marques MD, Moreira B, Eriksen HM. Prevalence of apical periodontitis and results of endodontic treatment in an adult, Portuguese population. Int Endod J. 1998;31:161–5.
59. Holmlund A, Holm G, Lind L. Severity of periodontal disease and number of remaining teeth are related to the prevalence of myocardial infarction and hypertension in a study based on 4,254 subjects. J Periodontol. 2006;77:1173–8.
60. Engstrom S, Gahnberg L, Hogberg H, Svardsudd K. Association between high blood pressure and deep periodontal pockets: a nested case-referent study. Ups J Med Sci. 2007;112:95–103.
61. Kirkevang LL, Vaeth M, Horsted-Bindslev P, Wenzel A. Longitudinal study of periapical and endodontic status in a Danish population. Int Endod J. 2006;39:100–7.
62. Moreno JO, Alves FR, Goncalves LS, Martinez AM, Rocas IN, Siqueira JF Jr. Periradicular status and quality of root canal fillings and coronal restorations in an urban Colombian population. J Endod. 2013;39:600–4.
63. Kamberi B, Hoxha V, Stavileci M, Dragusha E, Kuci A, Kqiku L. Prevalence of apical periodontitis and endodontic treatment in a Kosovar adult population. BMC Oral Health. 2011;11:32.
64. Estrela C, Bueno MR, Leles CR, Azevedo B, Azevedo JR. Accuracy of cone beam computed tomography and panoramic and periapical radiography for detection of apical periodontitis. J Endod. 2008;34:273–9.
65. Aleksejuniene J, Eriksen HM, Sidaravicius B, Haapasalo M. Apical periodontitis and related factors in an adult Lithuanian population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90:95–101.
66. Segura-Egea JJ, Jimenez-Pinzon A, Rios-Santos JV, Velasco-Ortega E, Cisneros-Cabello R, Poyato-Ferrera MM. High prevalence of apical periodontitis amongst smokers in a sample of Spanish adults. Int Endod J. 2008;41:310–6.
67. Kirkevang LL, Wenzel A. Risk indicators for apical periodontitis. Community Dent Oral Epidemiol. 2003;31:59–67.
68. Mani A, Tejnani A, Pawar B, Marawar P. The relationship between periodontitis and systemic diseases – hype or hope? JCDR. 2013;7:758–63.
69. Huang R, Li M, Gregory RL. Effect of nicotine on growth and metabolism of *Streptococcus mutans*. Eur J Oral Sci. 2012;120:319–25.
70. Hanioka T, Ojima M, Tanaka K, Matsuo K, Sato F, Tanaka H. Causal assessment of smoking and tooth loss: a systematic review of observational studies. BMC Public Health. 2011;11:221.
71. Toure B, Faye B, Kane AW, Lo CM, Niang B, Boucher Y. Analysis of reasons for extraction of endodontically treated teeth: a prospective study. J Endod. 2011;37:1512–5.
72. Johnson GK, Guthmiller JM. The impact of cigarette smoking on periodontal disease and treatment. Periodontol 2000. 2007;44:178–94.
73. Carretero OA, Oparil S. Essential hypertension. Part I: Definition and etiology. Circulation. 2000;101:329–35.
74. Sanchez-Dominguez B, Lopez-Lopez J, Jane-Salas E, Castellanos-Cosano L, Velasco-Ortega E, Segura-Egea JJ. Glycated hemoglobin levels and prevalence of apical periodontitis in type 2 diabetic patients. J Endod. 2015;41:601–6.
75. Dhanuthai K, Sappayatosok K, Bijaphala P, Kulvitit S, Sereerat T. Prevalence of medically compromised conditions in dental patients. Med Oral Patol Oral Cir Bucal. 2009;14:E287–91.
76. Lopez-Lopez J, Jane-Salas E, Estrugo-Devesa A, Velasco-Ortega E, Martin-Gonzalez J, Segura-Egea JJ. Periapical and endodontic status of type 2 diabetic patients in Catalonia, Spain: a cross-sectional study. J Endod. 2011;37:598–601.
77. Hegde MN, Tahiliani D, Shetty S, Devadiga D. Salivary alkaline phosphatase and calcium in caries-active type II diabetes mellitus patients: an in vivo study. Contemp Clin Dent. 2014;5:440–4.
78. Moore PA, Weyant RJ, Etzel KR, Guggenheimer J, Mongelluzzo MB, Myers DE, et al. Type 1 diabetes mellitus and oral health: assessment of coronal and root caries. Community Dent Oral Epidemiol. 2001;29:183–94.
79. Lima SM, Grisi DC, Kogawa EM, Franco OL, Peixoto VC, Goncalves-Junior JF, et al. Diabetes mellitus and inflammatory pulpal and periapical disease: a review. Int Endod J. 2013;46:700–9.
80. Siqueira JF Jr. Systemic implications of endodontic Infections. In: Treatment of endodontic infections. London: Quintessence Publishing; 2011.