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Host-derived biomarkers in gingival crevicular fluid for complementary diagnosis of apical periodontitis

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Abstract

Apical periodontitis (AP) develops as a result of the host's immune inflammatory response to pulpal infection of the dental root canals that leads to the generation of an apical lesion of endodontic origin (ALEO) and potentially to systemic metabolic alterations. Misdiagnosed ALEO is not infrequent due to the lack of diagnostic tools to differentiate apical lesions of different natures. Despite the conservative endodontic treatment shows a high success rate, there are refractory cases that can not be identified early enough during follow up. This evidences the need to develop complementary diagnostic tools, such as oral fluid biomarker analysis. Gingival crevicular fluid (GCF) is a serum transudate that becomes an exudate under inflammatory conditions, carrying molecules from local periodontal tissues and general circulation than can be harvested non-invasively. We aimed to review the available literature analyzing GCF composition in AP patients to evaluate whether GCF has any potential for complementary diagnosis. To the date, only few studies addressing changes of GCF components in AP are available. Most studies support GCF modifications in specific components in AP-affected teeth, suggesting that it might reflect periapical inflammation. GCF has potential for diagnostic tool, treatment follow-up and eventually to assess systemic comprise.

Key words: Gingival crevicular fluid; Periapical periodontitis; Biomarkers; Diagnosis; Prognosis

Core tip: The hallmark of Apical periodontitis (AP) is the development of an apical lesion of endodontic origin and can potentially lead to systemic alterations. Avoiding misdiagnosis and follow up are among the main challenges in its clinical management. The current review addresses the studies evaluating gingival crevicular fluid (GCF) composition in AP patients reported in the literature. Specific components vary in AP-affected teeth, supporting that GCF has potential for complementary diagnosis and treatment follow-up.

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INTRODUCTION

Apical periodontitis (AP) usually results as consequence of pulpal infection caused by bacteria inside the root canal system of the teeth, where they organize in biofilms. End-

odontic bacterial biofilms are conspicuously dominated by Gram-negative anaerobic bacteria[1,2]. The endodontic offenders and their major byproducts, endotoxins, elicit a sustained immune-inflammatory response that attempts to localize the infection and prevent further dissemination at the expense of apical periodontal tissue breakdown, involving periodontal ligament, radicular cementum and alveolar bone[3]. Additionally, increasing evidence links AP with systemic inflammation, elevated risk of cardiovascular diseases (CVD), specially atherogenesis[4], and diabetic metabolic dyscontrol[5].

During the chronic phase of AP, a bone resorptive lesion results evident as an apical radiolucent area in a radiograph. Histologically, apical lesions of endodontic origin (ALEO) consist of granulation tissue (apical granuloma) and can progress to form a radicular cyst, whenever chronic inflammatory process stimulates epithelial rests of Malassez. A radicular cyst is composed of a pathological cavity lined by squamous epithelium and a connective tissue capsule with varying degrees of inflammation. Both, apical granuloma and radicular cyst seem to represent different stages from the same process[3].

Apical lesions usually present clinically as a chronic infection, remaining as asymptomatic AP (AAP). Because the balance among inflammation and bacteria is a dynamic process, AAP may undergo an acute exacerbation and become symptomatic, presenting as symptomatic apical periodontits or acute abscess, or it may evolve from the acute to the chronic stage[6].

Frequently, AP can be managed with conservative endodontic treatment consisting of instrumentation, disinfection and obturation of the root canal from the affected tooth, followed by restoration of the tooth crown[7]. The major aim of the conservative therapy is to significantly reduce bacterial load and to induce consecutive healing of apical tissues. Nevertheless, some epidemiologic studies reveal a prevalence of apical lesions in endodontically-treated teeth as high as 65%[8]. Rehabilitation of these teeth on the other hand, requires long and expensive therapies that involve canal treatment and restoration of the lost crown. Thus, the need for developing complimentary tools for diagnosis and follow up becomes evident. Gingival crevicular fluid (GCF) carries molecules from local periodontal tissues and general circulation and can be harvested non-invasively from the gingival crevice and thus, its composition might reflect AP[9]. Our aim is to review the available literature addressing GCF composition in AP patients in order to identify whether it might have potential as a complimentary diagnostic tool for clinical endodontic practice.

OVERVIEW OF AP PATHOGENESIS

The initiation of the inflammatory response during AP includes the complex interplay of multiple cell types, involving resident and infiltrating cells[10]. Periradicular infiltrates are mainly composed of macrophages, T and B lymphocytes, plasma-cells and polimorphonuclear neutrophils (PMNs)[11-13]. Although macrophages are recognized as one of the major cell types[3], the relative composition of these cellular infiltrates remains controversial and recent data of our work group has revealed a high proportion of mast cells among the inflammatory infiltrates, positioning these cells as the more frequent subpopulation after lymphocytes[14].

Elicitation of the immune inflammatory response against bacteria from the infected root canal is known to play a pivotal role in AP, involving phagocytosis, activation of humoral and cellular responses and production of inflammatory mediators, including cytokines, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α[15], reactive oxygen species (ROS) and matrix metalloproteinases (MMPs)[16], among others. As consequence, the breakdown of the extracellular matrix from the periodontal tissues leads to the development and progression of an ALEO[17]. The host might respond to bacteria and cytokine dumping from apical lesions through systemic inflammation, as for other chronic inflammatory processes, such as chronic periodontitis. Systemic inflammation in turn, has been increasingly associated with elevated risk of systemic conditions, such as CVD[4].

GCF

Endodontic diagnosis and treatment is challenging from a clinical point of view. Difficulties include differential diagnosis of apical lesions, such as apical granuloma, radicular cyst (true and pocket cysts), apical scars and other non inflammatory lesions, whereas conservative treatment outcome is difficult to predict in the short term based upon clinical and radiographic criteria, requiring long follow up periods[18,19]. Thus, the need for the developing of new methods for diagnosis and follow up, such as the analysis of oral fluid biomarkers, becomes evident and might contribute to optimize the associated human and economic costs. Additionally, it might result in improvements of the treatment modalities and prevention of possible systemic consequences derived from chronic apical foci.

Classic studies addressing the pathogenesis of AP have been performed within the frame of the available sampling methods, including apical exudates *via* root canals[20] and the analysis of ALEO. Nevertheless, they are limited by the lack of proper healthy controls and/or the impediment to carry out longitudinal treatment follow-up, respectively. GCF sampling on the other hand is harvested non-invasively, is site-specific and thus, permits longitudinal follow up and adequate healthy controls for the affected teeth[17].

Under physiologic conditions GCF is proposed to represent a transudate from serum, whereas under inflammatory conditions it becomes an exudate that carries molecules from both, interstitial periodontal tissues and general circulation[21], that might reflect local periodontal and systemic inflammation[22]. GCF analysis has widely been used in periodontics and can provide adjunctive

Table 1 Summary of the studies analyzing gingival crevicular fluid composition in apical periodontitis

Ref.	Study groups	Parameters	*n*	Results ($P < 0.05$)
Dezerega *et al*[16]	AAP and healthy controls	Oxidative balance	AAP, $n = 10$ controls, $n = 13$	Statistically non significant.
	AAP pre and post endodontic intervention	Oxidative balance	$n = 16$	Increase in total antioxidant status after the intervention
Garrido Flores *et al*[47]	AAP and healthy controls	Total protein concentration and TNF-α levels	$n = 14$	Higher TNF-α levels in AAP
Shin *et al*[11]	AP and healthy controls	MMP-8 and substance P levels	$n = 35$	Higher levels of MMP-8 and substance P in AP. *P* value not reported
	AP pre and post endodontic intervention	MMP-8 y substance P levels	$n = 35$	Decrease in MMP-8 and substance P after the intervention
Burgener *et al*[46]	AP and healthy controls	Total protein concentration and IL-1β y DSP levels	$n = 40$	Higher total protein concentration in AP
Belmar *et al*[17]	AAP and healthy controls	MMP-9 and MMP-2 activity	$n = 20$	Higher pro-MMP-9 activity in AAP. Active MMP-2 bands detected only in AAP

AAP: Asymptomatic apical periodontitis; TNF: Tumor necrosis factor; AP: Apical periodontitis; MMP: Matrix metalloproteinase; IL: Interleukin; DSP: Dentin sialoprotein.

information for health care professionals along side with traditional oral clinical examination, including disease presence, severity, healing phase and treatment outcome[23-28]. Furthermore, it has been suggested that the analysis of local changes in oral fluids have a potential to build up a diagnostic bridge from mouth to systemic conditions[29]. In this context, the remaining question would be whether GCF might also reflect the local and systemic changes associated with AP.

ANALYSIS OF GCF COMPOSITION IN AP

The studies addressing the changes in GCF composition are shown in Table 1. The first report using GCF analysis in AP was an analytic study from Belmar *et al*[17], evaluating the activity of MMP-2 and -9 in teeth with AL and healthy contralateral controls in AAP individuals. MMPs enclose a family of genetically distinct, but structurally related zinc-dependent proteolytic enzymes that can synergistically degrade almost all extracellular matrix and basement membrane components, and regulate several cellular processes, including inflammation. MMPs are classified based on their primary structures and substrate specificities into different groups, where collagenases (MMP-1, -8 and -13) and gelatinases (MMP-9 and -2) are regarded to play a pivotal role in the breakdown of the periodontal tissues[30]. The authors found higher activity levels in AAP for both enzymes, as well as unidentified gelatinolytic bands of 48-56 kDa, suggestive of MMP-13. Although statistically significant differences were found only for the MMP-9 proform, active MMP-2 was exclusively identified in GCF from AAP teeth. In line with these results, MMP-2 and MMP-9 have been identified in experimentally-induced AP in animal models, human apical granulomas and radicular cysts, as well as exudates from apical abscesses[31-33]. Gelatinolytic MMP activity in ALEO in humans was confirmed in a recent study reporting higher activity of MMP-2 and MMP-9 in comparison to healthy periodontal ligament controls[16].

Additionally, MMP-8 has also been immunolocalized to human periapical granuloma and inflamed pulp, and its levels decreased with statistical significance after intracanal calcium hydroxide medication[34]. MMP-13 on the other hand was suggested to associate with the proliferation of epithelial tissue and the development of a radicular cyst from a preexisting granuloma[3,34,35]. In line with these findings, a study performed in experimentally-induced apical lesions proposed that MMP-13 along with MMP-8 act sequentially in the development and progression of ALEO, respectively[36].

Numerous works support that MMP-2, -9, -8 and -13 play an important role in both, the initiation and progress of inflammatory bone resorption and soft tissue breakdown during pathological processes, including periodontitis. Among them, MMP-8 and MMP-9 are by far the predominant MMPs in GCF, and their major source are regarded to be PMNs, monocytes and macrophages[16,22,24,37-41]. MMP-8 and MMP-9 are substantially involved in the progression of chronic periodontitis[37,39,42] and might represent the most promising biomarkers for periodontal inflammation and disease severity[43]. Additionally, increments of MMPs-8 and -9 associated with an altered lipid profile and have been proposed to represent early markers of atherosclerosis in individuals with marginal periodontal diseases[44,45].

Another study from Burgener *et al*[46] analyzed the total protein concentration, and the levels of IL-1β and dentin sialoprotein (DSP) in subjects with AP and healthy contralateral control teeth and found significantly elevated total protein concentration in the former. The studies of Belmar *et al*[17] and Burgener *et al*[46] applied a similar methodology, in which they included a healthy contralateral control tooth and excluded the presence of marginal periodontal diseases. Nevertheless, the studies differed in the normalization methods for result expression. While the former expressed absolute values in a standard time of 30 s GCF collection, the later normalized IL-1β and DSP levels by the total protein content. In this regard, a wide range of studies performed in chronic periodontitis demonstrate that total protein content in GCF represents

a variable itself, increasing along with periodontal inflammation. This might be explained primarily by albumin extravasation from serum. Consequently, the best proposed method of standardization for the specific protein determinations in GCF is through a fixed time of sample collection[22,42]. This difference might explain the lack of differences found for IL-1β and DSP.

In addition, TNF-α was reported to be higher in GCF from AAP when compared to healthy contralateral teeth[47]. In contrast to the previous study, the authors did not find statistically significant differences in total protein concentration between both groups. In line with the reported changes in GCF, TNF-α was higher in ALEO in comparison with healthy periradicular tissues[48]. IL-1 and TNF-α, on the other hand, were identified in apical exudates of teeth with ALEO and particularly, IL-1 levels were statistically higher in larger lesions and tended to associate with the presence of clinical symptoms, but it was not statistically significant[15].

Recently, an oxidant imbalance in favor to a pro-oxidant status was reported by our group in GCF from AAP *vs* healthy contralateral teeth. A week after the completion of the endodontic treatment, the oxidative status reached similar levels to those observed for healthy controls. The authors also measured the oxidant status and the activity of MMP-2 and MMP-9 in ALEO and a pro-oxidant status was also found when compared with healthy periodontal ligaments, in direct correlation with the size of the apical lesion[16]. Large evidence links ROS with tissue damage in inflammatory diseases. ROS can activate pro-inflammatory signaling pathways and induce bone resorption[49,50]. In support of these results, ROS production by blood PMNs was higher in individuals with ALEO compared to healthy controls, and their levels decreased after the extraction of the affected teeth[13]. These data suggest that an oxidative imbalance might play a central role in local and systemic mechanisms involved in the pathogenesis of ALEO and that these changes might be reflected in GCF from the affected teeth.

In summary, GCF represents a simple, non invasive and useful tool in monitoring periodontal inflammation and treatment response. Up to now, only few studies have analyzed the changes in GCF components that might be involved in the pathogenesis of AP individuals. Despite this fact, all of them report identifiable differences in at least one of its specific components, either when compared to healthy controls or in prospective follow up approaches. These studies suggest that GCF might reflect periapical inflammation, although the results among the different studies are not completely consistent. Future studies are needed to further clarify whether GCF reflects local or systemic inflammation in AAP in order to establish a new diagnostic tool for traditional clinical endodontics to aid in complimentary diagnosis, treatment follow-up and to assess potential systemic comprise.

CONCLUSION

GCF composition can be modified in the presence of AP, supporting its usefulness for potential diagnostic tool, treatment follow-up and eventually to assess systemic comprise.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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