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Suppression of overt gingival inflammation in tobacco smokers – clinical and mechanistic considerations

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Abstract: Gingivitis is a reversible inflammatory disease of the periodontal tissues. Periodontitis, in addition, involves destruction of the supporting structures of teeth. Diagnoses of gingivitis and periodontitis are predominantly dependent on clinical measurements of key inflammatory indices. Smokers are more susceptible to developing periodontal diseases, yet smoking masks overt signs of inflammation, presenting dental professionals with a clinical conundrum. We review the evidence that tobacco smoke may (i) cause acute periodontal vasoconstriction, (ii) inhibit periodontal angiogenesis in response to inflammatory stimuli, and/or (iii) suppress the production of pro-inflammatory mediators. It is clear that the mechanisms by which cigarette smoking dampens the periodontal inflammatory response are not yet fully understood. Further research into inflammatory suppression is warranted and should point to improved methods of diagnosis, not only in smokers, but also in non-smokers.

Key words: angiogenesis, inflammatory mediators, inflammation, periodontitis, tobacco, vasoconstriction

'… (*tobacco*) smoking counselling should be as much a part of the dentist's (*or dental hygienist's*) job as plaque control …' Riebel J, 2003 (1).

The diagnosis of gingivitis and periodontitis

Gingivitis and periodontitis arise in response to accumulations of oral bacteria in the gingival sulcus and are characterized by tissue changes in the periodontium occurring as part of the

inflammatory process (2). These periodontal diseases are currently diagnosed almost entirely by their clinical presentation (3). Thus, a diagnosis of gingivitis is made on the basis of visual signs of inflammation such as redness, swelling or bleeding on gentle provocation of the gingival sulcus (4). In addition, periodontitis exhibits increased probing depth and clinical attachment and radiographic alveolar bone loss, which reflect the destructive aspects of the disease process (4).

The diagnosis of periodontal disease is most beneficial when the disease can be detected at its earliest phase, when treatment can often be most effective. Bleeding on probing is most commonly used to detect the early stages of gingivitis (5) and increased periodontal probing depth with accompanying clinical attachment loss, the development of periodontitis (6). Both of these clinical signs reflect inflammatory periodontal tissue changes. Bleeding on probing has been correlated with the extent of inflamed gingival connective tissue (7). Once healing within the gingival or periodontal pocket has occurred, visual signs of inflammation and bleeding on probing are also eliminated. As well, 1–2 mm decreases in probing depth can occur after subgingival debridement because of tissue shrinkage and decreased penetration of the probe at pocket depth because of reduced inflammation and resultant reestablishment of the collagen fibrous integrity of the gingival tissues (8). Even larger changes in probing depth can occur by this mechanism in the presence of a long junctional epithelial attachment, as may occur after periodontal flap surgery. Thus the extent and severity of the inflammatory process within the periodontium has a great influence on these common indicators of periodontal disease and our assumptions about the status of periodontitis at a site.

Interpretation of the clinical signs of inflammation of the periodontal tissues can be an important aid in treatment planning. For instance, in early or moderate periodontitis it is often especially important to distinguish between gingival inflammation because of ineffective oral hygiene by the patient and inflammation that is because of inadequate debridement within the pocket by the therapist. In periodontitis patients, assessing bleeding on probing according to the Gingival Index of Loe and Silness (see Table 1) can be distinguished from bleeding on probing 'to pocket depth' as per Ainamo and Bay (see Table 2) (9–11). In the presence of periodontal pockets, inserting a periodontal probe 1 mm or so within the pocket and using a 'gingival sweep' from proximal surface to proximal surface assesses marginal gingivitis (see Fig. 1) and is more likely to reflect daily oral hygiene effectiveness. If there is no bleeding after the gingivitis assessment, but there is bleeding on probing to pocket depth (see Fig. 2), this would indicate the need for repeat debridement either by closed or open

Table 1. **The Gingival Index of Loe and Silness (9)**

Gingival Index	
0	No inflammation (normal gingiva)
1	Mild inflammation (minor colour change, small change in texture, no bleeding on palpation/probing)
2	Moderate inflammation (redness, oedema, glazing, bleeding on palpation/probing)
3	Severe inflammation (marked redness, oedema, ulceration, tendency to spontaneous bleeding)

Table 2. **The Gingival Bleeding Index of Ainamo and Bay (10)**

Gingival Bleeding Index	
Negative	Absence of bleeding on probing after 10 s
Positive	Appearance of bleeding on probing after 10 s

approaches and/or systemic or local antibiotic use. In addition, there is some uncertainty whether sites of periodontitis, once established, actually continue to progress for prolonged periods in terms of attachment loss even in the presence of signs of inflammation (12) or whether the rate of attachment loss may just vary widely and be very slow at times (13). In other words, even in the presence of clinical signs of periodontitis, not all periodontitis sites seem to exhibit continued attachment loss over prolonged periods according to current measurement techniques. At treated periodontitis sites, however, it is clear that maintaining a status of no bleeding on probing to pocket depth is a reliable indicator of no continuing attachment loss (14). In contrast, sites exhibiting persistent bleeding on probing over many years during maintenance therapy, do exhibit progressive attachment loss (15).

Therefore, in contemporary practice, clinical signs of inflammation and their interpretation play a pivotal role in the diagnosis and treatment planning for gingivitis and periodontitis.

The effects of tobacco smoke on diagnostic measures of gingivitis and periodontitis

Cigarette smoking is a well-established risk factor for periodontitis (1, 16–21). However, despite the strong association of cigarette smoking with the destructive aspects of periodontitis, cigarette smokers tend to have increased fibrosis and reduced clinical signs of inflammation of the periodontium – a clinical conundrum for dental health professionals (17–24). In periodontal patients, bleeding on gentle probing is significantly reduced in a dose-response manner in cigarette smokers when compared with non-smokers despite similar levels of plaque (18, 19, 23, 24). Once cigarette smokers quit smoking, bleeding on probing not previously apparent can be found within weeks,

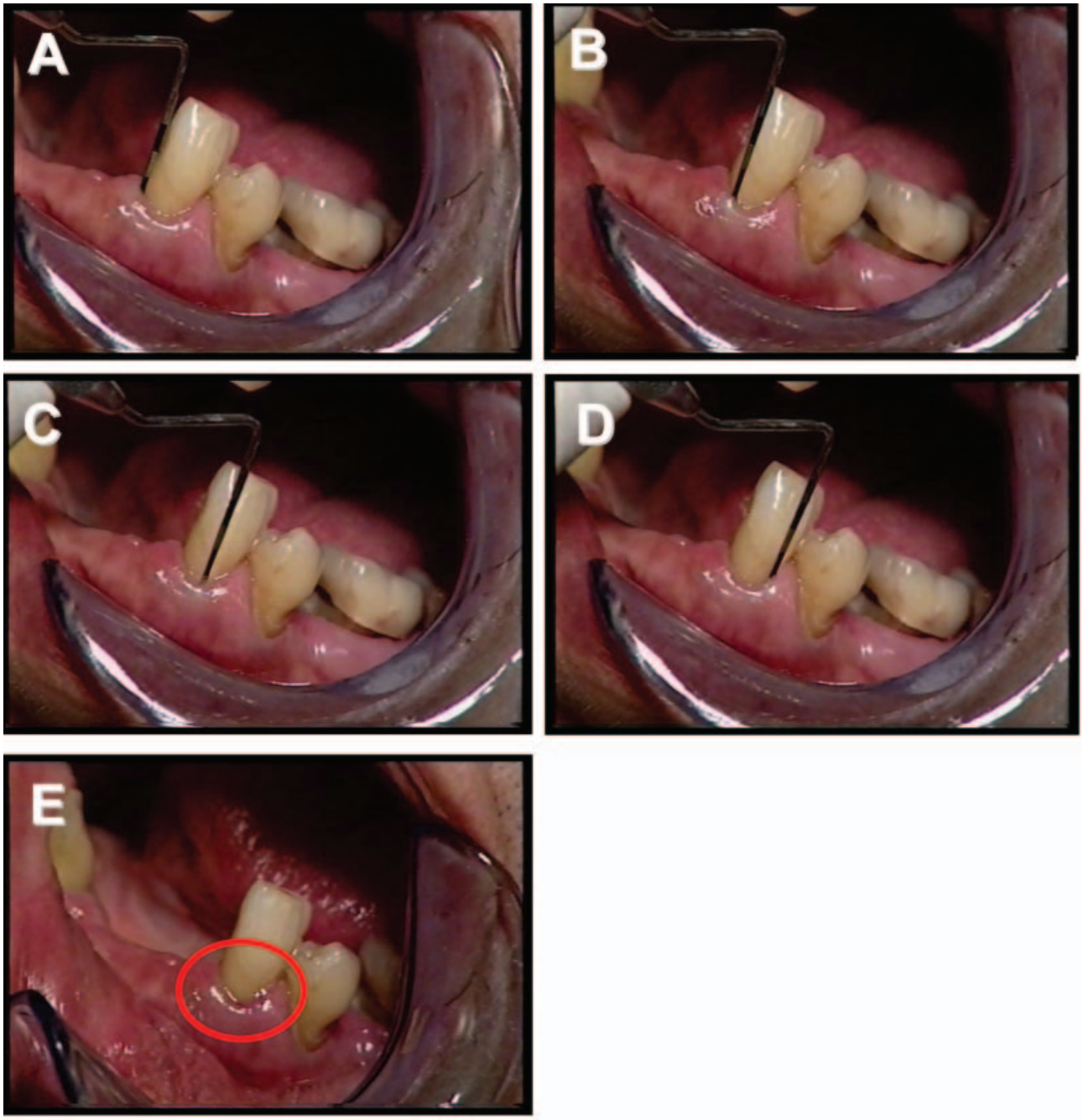

Fig 1. Assessment of marginal gingivitis by a 'gingival sweep' from proximal surface to proximal surface. No/minimal bleeding was noted following the gingival sweep, as shown in Box E.

even in the presence of improved plaque control (20, 25). This apparently suppressed inflammatory response is also reflected in significantly reduced gingival crevicular fluid volumes and flow rates in smokers (21, 25). Probing depths are also altered in smokers in a somewhat paradoxical manner (see Fig. 3). The extent of probe penetration into the tissues at the base of the pocket is less in smokers than in non-smokers (22). This results in probing depths in smokers exhibiting a better correlation to the true or histological attachment level and could result in increased probing depths after smokers quit smoking.

It is thus apparent that cigarette smoking masks the clinical signs of gingivitis and periodontitis and complicates the usual approach to the diagnosis of these diseases. On the one hand, the destructive aspects of periodontitis are greater and the response to treatment of periodontitis is poorer in cigarette smokers (16–18, 26, 27). On the other hand, cigarette smoking

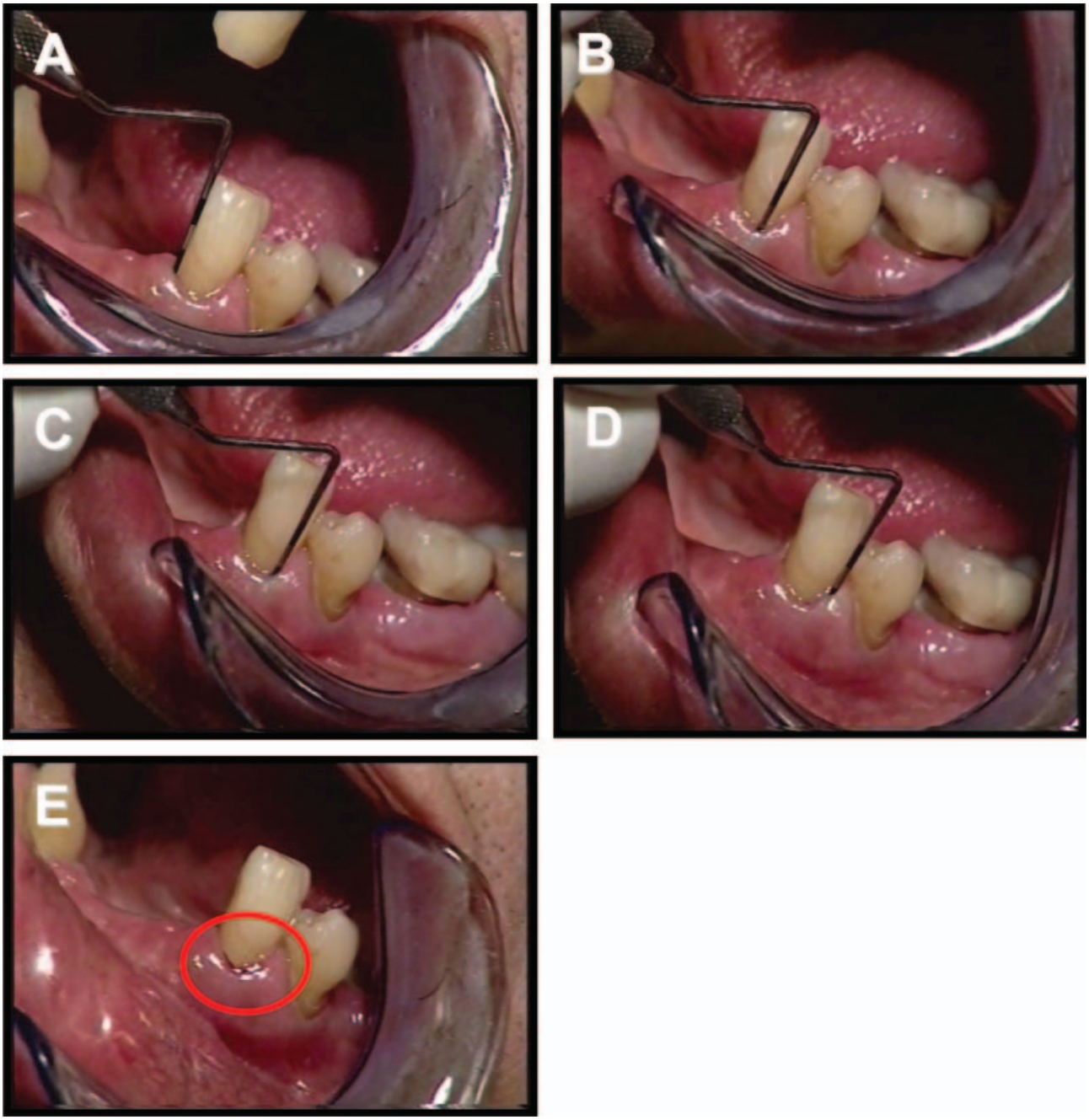

Fig 2. Assessment of bleeding on probing to pocket depth. Bleeding was apparent after probing to pocket depth, as shown in Box E. Probing was performed at the same site, and in the same patient, as shown in Fig. 1.

can drastically alter the typical presentation of gingivitis and periodontitis by masking the signs of inflammation. Thus, the diagnosis of these diseases is made more difficult yet the disease effects are worse!

While there is mounting evidence to show several profound effects of tobacco smoke on multiple facets of the human inflammatory and immune system, this review will now focus solely on the literature documenting potential mechanisms of a reduced bleeding response in the periodontal tissues of smokers.

Tobacco smoke and vasoconstriction of the periodontal microvasculature

Traditionally, the reduced bleeding response in smokers has been attributed to gingival vasoconstriction induced by the

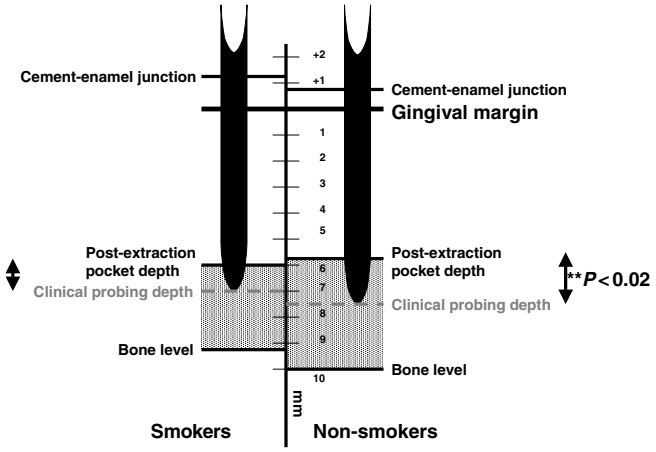

Fig 3. Diagrammatic representation of the mean clinical and post-extraction measurements* at sites with probing depths >4 mm in smokers and non-smokers**. *All measurements are related to the datum at the gingival margin; scale (mm). **249 sites were measured. Adapted, with permission, from Biddle AJ, *et al*. Comparison of the validity of periodontal probing measurements in smokers and non-smokers (*J Clin Periodontol* 2001: **28**: 806–812, published by Blackwell Publishing).

actions of nicotine-stimulated adrenaline and noradrenaline on α_1-adrenergic receptors (18, 28, 29). There is some evidence to support this theory in animal models (30, 31). However, does the available evidence support this hypothesis in humans?

Systemic nicotine administration is known to cause increased blood pressure, increased heart rate, increased respiratory rate and decreased skin temperature in humans (32). Furthermore, tobacco smoke can lead to localized vasoconstriction in certain tissues (28, 32). However, in other tissues tobacco smoking may actually cause vasodilatation (32–35).

Meekin *et al*. (36) have used laser Doppler flowmetry to measure relative periodontal blood flow before, during and after smoking. Only healthy gingival sites were assessed in order to avoid the complication of periodontal disease. Heavy smokers, light smokers, and non-smokers (who sham smoked only) were defined by serum cotinine measurements. The authors found no significant temporal differences in relative gingival blood flow in, or between, any of the three smoking groups, even during peak systemic nicotine concentrations. In contrast, a vasoactive effect of smoking in forehead skin was apparent in some smokers. Previously, Baab and Öberg (36) had used laser Doppler flowmetry in 12 smokers, and also concluded that that smoking does not impair gingival blood flow in humans.

In a more recent study, Mavropoulos *et al*. used laser Doppler flowmetry to continuously measure acute alterations to gingival blood flow before, during and for 10 min after smoking (35). Using subjects with histories of only limited cigarette consumption (0–5 cigarettes per day, mean age 25 years), a modest hyperaemic response was noted, composed of increased blood pressure and a small, but significant, vasoconstrictive effect. The authors suggest that repeated vasoconstriction promote gingival vascular dysfunction and periodontitis. However, Mavropoulos *et al*. also point out that the gingival vasoconstriction that did occur was much less than typically occurs in peripheral skin (the thumb) in the same subjects, and was overcome by arterial perfusion pressure (35).

While it is difficult to compare the studies of Meekin *et al*. (36), Baab and Oberg (33) and Mavropoulos *et al*. (35) because of significant variations in study design, including the smoking habits, and other characteristics, of the study populations, the methods employed to analyse the data, and the lack of a non-smoking control group in the latter two studies, the weight of the evidence suggests that gingival vasoconstriction in response to tobacco smoke is, at most, limited in comparison with other areas of the body in humans.

Tobacco smoke and angiogenesis in periodontal tissues

The Laser Doppler flowmetry experiments discussed above were designed to monitor acute responses. These studies, therefore, do not rule out the possibility of chronic alterations to the gingival vasculature, such as changes in the size and number of newly formed blood vessels. As there is no convincing evidence of acute, tobacco-induced vasoconstriction in the periodontal microvasculature of humans, then a valid alternative hypothesis would be that tobacco smoke components, or metabolites, restrict the periodontal angiogenic responsiveness to plaque bacteria.

Hanioka *et al*., have recently demonstrated that smokers exhibit a lower gingival oxygen sufficiency in healthy gingival sites compared with non-smokers, coupled with a reduced ability to adapt this function in inflamed sites, i.e. the oxygen saturation of haemoglobin in the gingiva did not differ between healthy and inflamed gingiva in smokers (37). This suggests that smoking leads to a functionally impaired gingival microcirculation (37).

While the numbers of subjects are extremely limited (three smokers), Mirbod *et al*. observed that the periodontal vasculature was composed of smaller numbers of large vessels, but larger numbers of small vessels, compared with non-smokers (38). However, mean vascular densities did not differ between

smokers and non-smokers. In a similar study, Sonmez *et al.* examined the vascular surface density and microvessel numbers in periodontal tissues obtained from smokers and non-smokers with chronic periodontitis (39). In the total tissue area, these authors noted no differences in either the vascular surface density or microvessel numbers between study groups. Stratification of smokers by daily cigarette consumption did not alter the findings.

It should be remembered that in diseased periodontal tissues the total area that can be defined as inflamed (i.e. an infiltration of inflammatory leucocytes is present) is small compared with the total tissue area (40). When inflamed and non-inflamed regions of the periodontium are considered separately, there is evidence to suggest that tobacco smoking does indeed suppress the angiogenic responsiveness of the periodontal tissues. In non-smokers, a significantly larger number of capillaries and post-capillary venules (defined as small Von Willebrand factor-positive endothelial cells) were observed in areas of inflammation, when compared with either inflamed areas in smokers or compared with non-inflamed areas in the non-smokers (40). Conversely, the number of vessels did not differ between inflamed and non-inflamed areas of smoker's tissues. Capillaries and post-capillary venules are those vessels associated with vascular permeability and cell migration. Therefore, the inflammatory response in smokers with periodontitis may not be accompanied by an equivalent increase in vascularity (40).

Tobacco and suppression of pro-inflammatory mediators

There are other potential mechanisms that could lead to reduced overt inflammation in the periodontal tissues of tobacco smokers. One obvious mechanism would be the local suppression of the production, or action, of key inflammatory mediators.

In vitro, nicotine has been shown to suppress the production of the inflammatory mediators interleukin-1 (IL-1) and IL-8 in activated macrophages (41). Furthermore, Ryder *et al.* have analysed the influence of tobacco smoke on gene expression in a specific leucocyte population that represents a major source of inflammatory mediators – monocytes (42). Tobacco smoke induced a significant increase in mRNA expression levels in multiple genes, including those encoding the pro-inflammatory stimuli IL-1α, cyclooxygenase-2 (COX-2) and phospholipase-A_2. Among the genes whose activity was decreased was the suppressive regulator of inflammation IFN-γ.

Although conflicting reports are available, suppression of the production of major inflammatory mediators in the periodontium does not seem to occur *in vivo*, reflecting the results of Ryder *et al.* (42). The concentrations of several pro-inflammatory cytokines (tumour necrosis factor-α, IL-6 and IL-8) may actually be increased in the gingival crevicular fluid of smokers compared with non-smokers with periodontitis (43, 44). Overall, then, it would appear that tobacco smoke-induced inflammatory masking does not occur through the suppression of the production of inflammatory mediators.

Conclusions

Cigarette smoking is not only a risk factor for the development of periodontitis that also reduces the response to conventional treatments of periodontitis, but – by masking the inflammatory response – smoking also makes clinical decision-making about the diagnosis and treatment planning for this disease much more difficult. It is also apparent that while smoking may suppress gingival angiogenesis, the mechanisms by which cigarette smoking dampens periodontal inflammation are not yet fully understood.

The finding that the inhibition of gingival inflammation, as measured by bleeding on probing, is reversible (20, 25) has important implications in clinical practice. Oral health professionals should advise patients who are planning to quit of the possibility of inflammatory recovery in the periodontal tissues, and, therefore, increased gingival bleeding. This would prevent anxiety over these gingival changes, which could compromise cessation attempts by patients (20).

Dental hygienists and dentists can, and should, play a leading role in reducing the burden of tobacco use in their communities by advocating, advising and facilitating smoking cessation among their patients (45). Further research into inflammatory suppression is warranted and should point to improved methods of diagnosis not only in smokers but also in non-smokers.

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