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Potential impact of subject-based risk factor control on periodontitis

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Abstract

Aims: To assess the potential impact of the control of subject-based modifiable risk factors on periodontitis.

Background: Cross-sectional and longitudinal data from epidemiological research indicate that risk factors can be identified and, if modified, may improve both periodontal conditions and the outcome of treatment.

Material and Methods: A search was conducted to identify factors involved in the etiology and pathogenesis of periodontal diseases. The factors identified were separated into modifiable and non-modifiable, and control of the subject-based modifiable risk factors were further analyzed.

Results: The analysis was limited to the influence of the control of the remaining modifiable subject-based risk factors. It was observed that most of the subject related risk factors were hitherto not validated in controlled intervention studies. Therefore, the evidence for the efficacy of risk factor control had to be based on results from cohort studies. While the control of most of the modifiable risk factors for periodontitis was not tested, some evidence suggested that smoking cessation may retard the progression of periodontitis.

Conclusions: Although only limited evidence was available, it appeared reasonable to suggest that second to the removal of the bacterial biofilm, smoking cessation was the most important measure in the management of periodontitis.

Keywords: diabetes mellitus; periodontal disease; risk factors; risk management; smoking; smoking cessation

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Cross-sectional and longitudinal data from epidemiological research suggest that risk factors can be identified, and that some of these factors could be controlled to prevent the development and progression of periodontitis as well as to improve the outcome of periodontal treatment.

Current knowledge about the aetiology and pathogenesis of periodontal disease is obtained mainly from the results of epidemiological studies, analysis of tissue histology, clinical trials and animal experiments. Reports from such studies have consistently documented a multifactorial aetiology of periodontal diseases and that the extent and severity of periodontitis increased with age and with inadequate plaque control.

Early detection of the progression of periodontal disease is difficult because it typically relies on comparisons of measurements made with a calibrated probe and non-standardized radiographs over time. Both methods detect periodontal breakdown only after it has occurred. Therefore, emphasis has to be placed on identifying risk factors to assess the likelihood of periodontal disease progression in an earlier stage.

In secondary prevention, the aim is to prevent disease recurrence. To achieve this goal, the periodontitis-susceptible individual is involved in a careful maintenance programme (supportive periodontal therapy, SPT) including repeated instruction in self-performed plaque removal as well as regular professional scaling and root instrumentation. The frequency and treatment measures of oral care providers may be individually adjusted according to the patients' risk profiles.

Terminology

For the purpose of this review, the terminology of the consensus report of the American Academy of Periodontology (AAP) in 1996, Section 1, Periodontal diseases: epidemiology and diagnosis, was adopted. The terms used are defined in Table 1.

Risk factors are part of the causal chain of a particular disease or can lead to the exposure of the host to a disease. The presence of a risk factor implies a direct increase in the probability of a disease occurring, and if a risk factor is absent or removed, a reduction in that probability should occur.

A risk factor may be modified by interventions, thereby reducing the probability that a particular disease will occur. Hence, the control of risk factors can only be addressed in controlled prospective intervention studies.

Table 1. Definitions of terms according to the AAP World Workshop 1996 Consensus report. Section 1 (1996)

Risk factor	An environmental, behavioural or biologic factor confirmed by temporal sequence, which, if present, directly increases the probability of a disease occurring, and, if absent or removed, reduces that probability Risk factors are part of the causal chain
Risk indicator	A probable or putative risk factor, often detected in cross-sectional studies, that has not yet been confirmed by longitudinal studies
Risk predictor	A characteristic that is associated with elevated disease, but may not be part of the causal chain. Predictors are useful for identifying who is at risk but are not useful in identifying likely interventions
Prognostic factor	An environmental, behavioural or biologic factor, which, when present, directly affects the probability of a positive outcome of a therapy rendered for the disease

Table 2. Modifiable subject-based risk factors for periodontitis

Modifiable risk factors	Method	Investigators (year)	Study
Inadequate oral hygiene	Oral hygiene reinforcement (B)	Bakdash (1994)	PC
		Jenkins et al. (1988)	PC
Microbial pathogens (selection of)			
A. actinomycetemcomitans	Mechanical debridement	Slots et al. (1980)	PC
	Systemic antibiotic therapy	Zambon et al. (1983)	PC
Porphyromonas gingivalis	Mechanical debridement	van Winkelhoff et al. (2002)	PC
Tannerella forsythia	Mechanical debridement	van Winkelhoff et al. (2002)	PC
Tobacco use			
Cigarette	Tobacco cessation (B)	Haber et al. (1993)	CS
Cigar	Tobacco cessation (B)	Krall et al. (1999)	PC
		Albandar et al. (2000)	PC
Pipe	Tobacco cessation (B)	Krall et al. (1999)	PC
		Albandar et al. (2000)	PC
Spit tobacco	Tobacco cessation (B)	Greer & Poulson (1983)	CS
Diabetes mellitus (Types I and II)	Metabolic control with insulin therapy (Type I) or dietary adjustments (Type II) (B)	Emrich et al. (1991)	CS
Alcohol consumption	Alcohol withdrawal (B)	Pitiphat et al. (2003)	PC
Nutrition deficiencies	Nutrition counselling (B)	Nishida et al. (2000a)	CS
		Nishida et al. (2000b)	CS
Stress factors	Stress reduction therapy (B)	Merchant et al. (2003a)	PC
Acquired immune suppression (HIV)	HIV-antiretroviral medication (B)	Barr et al. (1992)	CS
		Lamster et al. (1994)	CS
		McKaig et al. (1998)	CS
Inadequate physical activity	Increased physical activity (B)	Merchant et al. (2003b)	PC
Osteoporosis	Hormone replacement therapy (B)	Reinhardt et al. (1999)	PC

B, behavioural change; CS, cross-sectional studies; PC, prospective cohort studies.

Survey of Modifiable Risk Factors Associated with Periodontitis

For the discussion of plaque-retaining risk factors for gingivitis or for the progression of periodontitis, such as restoration overhangs, subgingival calculus or furcation involvement, the reader is referred to textbooks on periodontal therapy. Therefore, it is recognized that the daily removal of the bacterial biofilm represents the most important risk factor control in periodontal care. Several additional modifiable subject-based risk factors were identified and are presented in Table 2.

Inadequate oral hygiene

While the aim of periodontal therapy is to regain periodontal health, the objective of supportive periodontal therapy is the continued preservation of gingival and periodontal health obtained as a result of periodontal treatment. Proper self-performed mechanical plaque removal and compliance with needs-related recall visits are a critical component of successful prevention and therapy. On the other hand, poor motivation regarding oral health or non-compliance with maintenance protocols negatively influences periodontal stability (Johansson et al. 1984, Wilson et al. 1984, Cortellini et al. 1994, Rieder et al. 2004). Compelling evidence from a variety of animal and clinical studies emphasized the necessity of regular self-performed mechanical plaque removal in conjunction with regular maintenance visits following therapy to be the pre-requisite for effective prevention of periodontal diseases. Further modifiable subject-based risk factors other than control of oral hygiene should be evaluated within the context of this paradigm.

Microbial pathogens

The appearance and growth of dental plaque have been studied for many decades. Over 600 bacterial species have been identified, with more expected in the future (Socransky & Haffajee 2002). A small number of these have been recognized as playing a causal role in the pathogenesis of periodontal disease.

It is acknowledged that the presence of *Actinobacillus actinomycetemcomitans* in younger patients is regarded as a risk factor (risk indicator) for the development of periodontal disease (Genco 1996, Offenbacher & Zambon 1996). However, the presence of *A. actinomycetemcomitans* has not been shown to place adults at a higher risk for the occurrence or the development of periodontal disease. Several other pathogens have been found to have a significant association with the occurrence of periodontal disease. The following odds ratios (ORs) were calculated by van Winkelhoff et al. (2002): *Porphyromonas gingivalis* (OR = 12.3), *Tanerella forsythia* (OR = 10.4), *Peptostreptococcus micros* (OR = 7.7) and *A. actinomycetemcomitans* (OR = 3.1) (van Winkelhoff et al. 2002).

Periodontal effects of microbial pathogen's control

The success of periodontal therapy regarding the reduction of periodontal pathogens below detection levels appears

to differ between species. *P. gingivalis*, *B. forsythia* and *T. denticola* are the most likely species to be affected by mechanical debridement. By contrast, *A. actinomycetemcomitans* does not appear to be effectively reduced to non-detectable levels with these measures (Renvert et al. 1990, Haffajee et al. 1997). Additional supportive therapy with systemic antibiotic treatment proved to be successful for the reduction to non-detectable levels of *A. actinomycetemcomitans* (van Winkelhoff et al. 1989). There are, however, no studies that have documented the effect of the reduction of specific microbial complexes for the prevention of periodontitis.

Tobacco use

The investigation of the relationship between periodontal disease and the use of tobacco products has received increased attention during the past few years. The prevalence, extent and severity of chronic periodontitis (CP) have been shown to be much higher in smokers than in non-smokers. Also, a dose–response relationship has been demonstrated (Haber et al. 1993, Kaldahl et al. 1996, Tomar & Asma 2000). The reader is referred to recent reviews of this topic (Kinane & Chestnutt 2000, Johnson & Slach 2001, Rivera-Hidalgo 2003, Bergstrom 2004b).

The use of the following tobacco products has been studied to describe their association with periodontal disease: cigarette (Haber et al. 1993, Bergstrom et al. 2000a, Bergstrom 2004b), cigar and pipe smoking (Krall et al. 1999, Albandar et al. 2000, Johnson & Slach 2001) as well as smokeless tobacco, i.e. chewing or spit tobacco and snuff (Greer & Poulson 1983, Poulson et al. 1984, Offenbacher & Weathers, 1985, Robertson et al. 1990).

The biological explanation of the association between tobacco smoking and periodontal disease was based on the potential effects of several substances within tobacco products, such as nicotine, hydrogen cyanide and carbon monoxide.

Smoking seems to be the single most significant modifiable risk factor with a documented effect for periodontitis (Paulander et al. 2004).

Periodontal effects of tobacco cessation

Generally, the periodontal status of former smokers is intermediate between that of never smokers and current smokers, and smoking cessation was shown to be beneficial for the periodontal conditions (Bergstrom et al. 2000b). Recent reports in the literature reveal short-term effects after quitting smoking, as well as the long-term results of smoking cessation on the periodontal status (Bergstrom 2004a). Effects of smoking cessation on the periodontal status or the outcome of periodontal therapy are presented in Table 3.

Despite the lack of data from intervention studies, these findings suggest that smoking cessation may result in a long-term benefit to the periodontal condition.

Diabetes mellitus

Diabetes mellitus has been associated with increased prevalence and severity of periodontal disease (Shlossman et al. 1990, Emrich et al. 1991). The majority of studies demonstrate a more severe periodontal condition in diabetic adults than in adults without diabetes (Papapanou 1996, Verma & Bhat 2004). The type of diabetes does not affect the extent of periodontitis when the duration of diabetes is similar. However, Type I diabetics develop the disease at an earlier age, and, hence, have it for longer periods, and may develop a greater extent and severity of periodontitis (Thorstensson & Hugoson 1993, Oliver & Tervonen 1994). Well-controlled diabetics are more likely to be similar to non-diabetics in their periodontal status (Westfelt et al. 1996).

Periodontal effects of metabolic control of diabetes mellitus

Treatment of Type I diabetes involves dietary adjustment and insulin therapy. Management of Type II diabetes usually consists of dietary controls, exercise, oral hypoglycaemic agents and perhaps insulin.

Effects of metabolic control of diabetes mellitus on the periodontal status were evaluated exclusively on the basis of cross-sectional studies and a few prospective cohort studies. The results are conflicting and no definite conclusion can be drawn (Table 4).

It is important to note that periodontal disease prevalence and severity vary greatly within the diabetes mellitus population, just as it does in the non-diabetic population. The presence of periodontitis in some diabetics may be because of inadequate oral hygiene and smoking rather than the diabetic condition (Haber et al. 1993).

Alcohol consumption

The association of alcohol use and periodontal disease has been investigated. Previous cross-sectional (Larato 1972, Novacek et al. 1995, Sakki et al. 1995, Shizukuishi et al. 1998, Tezal et al. 2001, Yoshida et al. 2001) and case–control studies (Pan et al. 1998) have shown positive associations between alcohol use and periodontal disease. Alcohol consumption impairs neutrophil, macrophage and T-cell functions, increasing the likelihood of connective tissue inflammation and stimulation of alveolar bone resorption.

In a recent prospective cohort study (Pitiphat et al. 2003), the risk ratio for periodontal disease among men reporting regular alcohol intake increased and was dose dependent. These results suggest that alcohol consumption is an independent modifiable risk factor for periodontitis, and reducing alcohol consumption may be beneficial in maintaining periodontal health.

There are no studies on the effect of alcohol withdrawal either on the periodontal status or on the outcome of periodontal therapy.

Nutrition deficiencies

Possible consequences of nutrition deficiencies on oral and periodontal health have been reviewed (Dorsky 2001). Several nutrients have been found to have a negative impact on periodontal health when not sufficiently delivered, such as vitamins, trace metals, antioxidants and proteins (Eklund & Burt 1994, Nishida et al. 2000a, b, Krall et al. 2001, Pitiphat et al. 2002).

There are no studies on the effect of nutrition counselling either on the periodontal status or on the outcome of periodontal therapy.

Stress factors

The negative impact of psychosocial and psychological stress on the human immune system has been recognized. An overall deteriorating influence on a chronic inflammatory disease like periodontitis emerges as plausible (Hildebrand et al. 2000, Merchant et al. 2003a, Firestone 2004). In these studies, the authors examined the association between social support, anger expres-

Table 3. Effects of smoking cessation on the periodontal status or the outcome of periodontal therapy

Investigators (year)	Study	Sample	Results
Bergstrom et al. (1991)	Cross-sectional	210 subjects Dental hygienists 30% current smokers, 32% former smokers and 38% non-smokers	The CEJ–IS distance in bitewing radiographs was significantly greater for current smokers when compared to non-smokers, mean ± SEM 1.71 ± 0.08 mm and 1.45 ± 0.04 mm, respectively. The mean ± SEM for former smokers was 1.55 ± 0.05 mm
Haber et al. (1993)	Cross-sectional	132 IDDM patients and 95 non-diabetic patients Totals of 121 never smokers, 52 former smokers and 54 current smokers	Prevalence of sites with PPD ⩾ 4 mm was higher among current smokers than in never smokers. Effect of smoking was similar to both current smokers and never smokers: no differences between current and former smokers in plaque-positive sites
Jette et al. (1993)	Cross-sectional	1156 adults, age years ⩾ 70	Years of exposure to tobacco products (current smokers versus former smokers) was a statistically significant risk factor for tooth loss and periodontal disease.
Bolin et al. (1993)	Prospective cohort 10-year follow-up	349 subjects	Marginal bone loss in ''always'' smokers: 6%, in ''never'' smokers: 3.9% and ''gave up'' former smokers: 4.4%.
Kaldahl et al. (1996)	Prospective cohort 7-year follow-up	74 subjects 31 heavy smokers (⩾ 20 c/d), 15 light smokers (⩽ 19 c/d), 15 former smokers, 18 never smokers	Heavy smokers and light smokers responded less favourably to therapy than former smokers and never smokers
Krall et al. (1997)	Prospective cohort 6- and 18-year follow-up	584 women and 1231 men 6-year follow-up in 248 women 18-year follow-up in 977 men	Individuals who continued to smoke had 2.4-fold (men) to 3.5-fold risk (women) of tooth loss compared with non-smokers. The rates of tooth loss in men were significantly reduced after they quit smoking cigarettes.
Tomar & Asma (2000)	Cross-sectional	12,329 subjects NHANES III 27.9% current smokers, 23.3% former smokers	Odds ratios: current smokers: 3.97, former smokers: 1.68. Dose–response relationship between c/d and the odds of periodontitis ranging from: OR = 2.79 for ⩽ 9 c/d to OR = 5.88 for ⩾ 31 c/d. Among former smokers, the odds of periodontitis declined with the number of years since quitting, from OR = 3.22 for 0–2 years to OR = 1.15 for ⩾ 11 years.
Bergstrom et al. (2000a)	Cross-sectional	257 dentally aware adults, including 50 current smokers, 61 former smokers and 133 non-smokers	The condition of former smokers was intermediate between current smokers and non-smokers.
Bergstrom et al. (2000b)	Prospective cohort 10-year follow-up	257 dentally aware adults (musicians) in 1982 and 1992. 10-year follow-up of data from Bergstrom et al. (2000a)	The condition of former smokers remained stable, similar to that of non-smokers
Nair et al. (2003)	Prospective cohort	27 subjects after smoking cessation	BoP increased from 16% to 32%, despite improvements in the subjects oral hygiene.
Baljoon et al. (2004)	Prospective cohort	257 dentally aware adults (musicians) in 1982 and 1992	In 1992, the prevalence of vertical bony defects was 42%, 28% and 19% for current smokers, former smokers and non-smokers, respectively.
Paulander et al. (2004)	Prospective cohort 10-year follow-up (1988–1998)	At 10-year follow-up, 1998: 295 individuals for radiographic examination: 53 current smokers 36 former smokers	Relative risks for alveolar bone loss in current smokers: 3.69 (95% CI 2.33–5.85) and in former smokers: 0.70 (95% CI 0.31–1.59)

CEJ–IS, cemento-enamel junction–interdental septum; SEM, standard error of the mean; c/d, cigarettes per day.

sion and periodontitis using the State-Trait Anxiety Inventory, the Beck Depression Inventory, the Life Events Scale modified by Savoia, the Self-Report Screening Questionnaire-20 and the Beck Hopelessness Scale. However, the findings of these studies need to be confirmed with further research, as other recent studies reported no association between stress and established periodontitis (Solis et al. 2004).

No scientific studies have been found on the effect of stress reduction therapy on the periodontal status.

Acquired immune suppression (HIV)

A number of studies dealt with the issue of occurrence of periodontal disease in HIV-seropositive subjects and AIDS patients (Barr et al. 1992, Lamster et al. 1994, McKaig et al. 1998).

Periodontal effects of HIV-antiretroviral medication

After controlling for CD4+ counts, HIV-infected persons taking HIV-antiretroviral medication were five times less likely to suffer from periodontitis compared with those not taking such medication (McKaig et al. 1998). The effects of taking HIV-antiretroviral medication on the periodontal status or

Table 4. Effects of metabolic control of diabetes mellitus on the periodontal status

Investigators (year)	Study	Sample	Results
Ervasti et al. (1985)	Cross-sectional	103 subjects 50 adult diabetics and 53 healthy controls	Poorly controlled diabetics had significantly more gingival bleeding than well- or moderately well-controlled diabetics
Tervonen & Knuuttila (1986)	Cross-sectional	The same study group as in Ervasti et al. (1985)	Poorly controlled diabetics showed a higher number of periodontal pockets than well- or moderately well-controlled diabetics
Sastrowijoto et al. (1989)	Cross-sectional	22 Type I (insulin dependent) diabetic adults with normal or poor metabolic control	**Metabolic control seems to have no direct effect on the periodontium (small sample size)**
Sastrowijoto et al. (1990)	Prospective	6 IDDM subjects	**No improvement could be demonstrated for PPD, CAL, BoP and PI (small sample size)**
Seppala et al. (1993)	Prospective cohort 2-year follow-up	Baseline 26 subjects with poorly controlled IDDM (PIDM), 12 subjects with controlled IDDM (CIDM)	PIDM and CIDM had similar PI at both baseline and 1- and 2-years follow-up. PIDM suffered from higher BoP%, more CAL and more alveolar bone loss than CIDM at both baseline and 1- and 2-years follow-up
Tervonen & Oliver (1993)	Retrospective cohort	75 diabetics (Type I or II) well-, moderately and poorly controlled subgroups	Increase in the prevalence, severity and extent of periodontitis with poorer control of diabetes was observed
Karjalainen & Knuuttila (1996)	Cross-sectional	12 newly diagnosed type I diabetic children and adolescents	Gingival bleeding decreased after 2 weeks of insulin treatment and remained at the same level when examined 1 month later while glucose balance was excellent
Bridges et al. (1996)	Cross-sectional	118 diabetic men and 115 age-matched non-diabetic men	**Glycaemic control was not significantly correlated to periodontal status**
Taylor et al. (1998)	Cross-sectional	359 subjects	**Poorer glycaemic control leads to both an increased risk for alveolar bone loss and more severe periodontal disease progression only over non-diabetics**
Christgau et al. (1998)	Prospective cohort	20 well-controlled diabetics (7 IDDM, 13 non-IDDM) 20 healthy control subjects	Metabolically well-controlled diabetics might respond to non-surgical periodontal therapy as well as healthy control patients
Tervonen et al. (2000)	Cross-sectional	35 type I diabetics 10 healthy control subjects	Increased loss of periodontal support in subjects with complicated diabetes mellitus

PPD, periodontal probing depth; CAL, clinical attachment level; BoP, bleeding on probing; PI, plaque index. Bold, no difference.

the outcome of periodontal therapy are presented in Table 5.

There are no controlled intervention studies documenting the effect of anti-retroviral medication on the periodontal condition.

Inadequate physical activity

Increased physical activity improves insulin sensitivity and glucose metabolism and may therefore impede the onset of periodontal disease (Merchant et al. 2003b).

Periodontal effects of increased physical activity

In one prospective cohort study, lower levels of physical activity were associated with a higher prevalence of periodontitis in men (Table 6) (Merchant et al. 2003b).

However, no evidence was found documenting that improved physical activity could influence the periodontal condition.

Osteoporosis

Factors that are increasingly investigated in recent studies include osteoporosis, mainly in relation with hormone substitute therapy in post-menopausal osteoporotic women (Payne et al. 1999).

Periodontal effects of hormone replacement therapy

One prospective cohort study suggested that oestrogen supplementation may be associated with reduced gingival inflammation and reduced frequency of clinical attachment loss in osteoporotic women in early menopause (Reinhardt et al. 1999). The effect of hormone replacement therapy in post-menopausal women regarding the influence on the periodontal status or the outcome of periodontal therapy has not yet been determined (Table 7).

Discussion

Evidence supporting a multifactorial aetiology for periodontal disease continues to accumulate. The procedure of drawing conclusions related to the cause(s) of periodontal disease is a particularly complicated issue in epidemiological research. Determining the contribution of each risk factor to the progression of the disease when multiple risk factors are present is complex.

It is important, therefore, that for studying the impact of more than one factor on the progression of periodontal disease, multifactorial methodology should be used. With this approach, individual contributions of the various risk factors can be determined. For example, in an attempt to estimate the effects of smoking and diabetes mellitus on the periodontium, it was suggested that smoking had a greater impact on disease progression compared with systemic predispositions, such as diabetes mellitus (Haber et al. 1993), or genetic disorders, such as IL-1 polymorphism associated, with tobacco smoking (Meisel et al. 2004). However, additional studies of this type will be needed to support these hypotheses.

Table 5. Effects of taking HIV-antiretroviral medication on the periodontal status or the outcome of periodontal therapy

Investigators (year)	Study	Sample	Results
McKaig et al. (1998)	Cross-sectional	326 HIV-infected adults. Part of the sample was receiving HIV-antiretroviral therapy	Risk ratio for HIV-associated periodontal disease: 5
Ceballos-Salobrena et al. (2000)	Cross-sectional	154 AIDS patients receiving highly active antiretroviral therapy (HAART) including HIV-protease inhibitors	Prevalence of HIV/periodontitis-gingivitis: 0.6%. Prevalence of all oral lesions, particularly oral candidiasis, herpes simplex labiali, Kaposi's sarcoma and periodontal disease, decreased more than 30% after the institution of highly active antiretroviral treatment (HAART)
Pinheiro et al. (2004)	Cross-sectional	161 HIV-seropositive Brazilians taking antiretroviral therapy (70.8%)	Prevalence of periodontal disease: 4.4%

Table 6. Effects of increased physical activity on the periodontal status

Investigators (year)	Study	Sample	Results
Merchant et al. (2003b)	Prospective cohort 10 years	39,461 male subjects	Men with a high physical activity had a 13% lower risk of periodontitis (RR = 0.87) compared with inactive men. In a subsample of men with radiographs ($n = 137$), the physically active had less average bone loss ($\beta = -0.29$, p-value = 0.03) after multivariate adjustment compared with those who were inactive

RR, relative risk.

Table 7. Effects of hormone replacement therapy on the periodontal status

Investigators (year)	Study	Sample	Results
Reinhardt et al. (1999)	Prospective cohort, 2-year follow-up	75 post-menopausal women	E2-deficient subjects had more BoP%: 43.8% *versus* 24.4% ($p < 0.04$)

E2, serum oestradiol; BoP, bleeding on probing.

Conclusion

Next to plaque removal, smoking cessation was the single modifiable subject-based risk factor, identified in the present review, that showed an improvement of the periodontal status. It is suggested, therefore, that smoking cessation be incorporated as an integral part of preventive measures for periodontitis.

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