Effects of Smoking on Periimplant Health Status and IL-1β, TNF-α, and PGE_2 Levels in Periimplant Crevicular Fluid: A Cross-Sectional Study on Well-Maintained Implant Recall Patients

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Purpose: *The aim of this cross-sectional study was to evaluate the effects of smoking on periimplant health status and inflammatory cytokines interleukin-1β, tumor necrosis factor-α, and prostaglandin E2 levels in periimplant crevicular fluid (PICF) and to determine their correlation with clinical parameters in well-maintained implant recall patients.*

Material and Methods: *A total of 60 dental implants placed in 60 patients (27 patients were smoker and 33 were nonsmoker) were included in the study. Plaque index, gingival index, probing depth, periimplant bone loss, PICF volume, and biochemical cytokine levels in PICF were determined and analyzed statistically. The correlation between PICF cytokine levels and clinical parameters were also analyzed.*

Results: *All clinical parameters with the exception of plaque scores were significantly higher in the smoker group. Significantly increased levels of cytokines were observed in the smoker group. The correlation between the cytokine levels and clinical parameters were more marked in smokers.*

Conclusions: *Although the implants of the smoker patients seem to be clinically healthy, the results demonstrate that the implants are relatively at risk even if in a well-maintained population. (Implant Dent 2013;22:519–524)*

Key Words: dental implant, inflammatory cytokine, smoking, periimplant crevicular fluid

Implant therapy is a growing dental treatment method in partially or totally edentulous patients. Although plaque-induced inflammation and occlusal loading are considered as the most important factors influencing the prognosis of oral implant treatment, smoking is reported as a significant determinant related to the periimplant tissue changes and implant failure.[1,2] Currently, there are an estimated 1.3 billion smokers worldwide,[3] and smoker candidates for dental implant treatment are growing day by day. Thus, certain aspects concerning current dental implant therapy should be considered for smokers in treatment planning, oral surgical procedures, and the maintenance phases of dental implant treatment.

The initiation and early development of an inflammatory reaction in periodontal tissues can be induced by bacterial metabolites such as lipopolysaccharides or by host cells that release several types of cytokines that can activate degradative pathways.[4] Previous studies have indicated that the tissue damage is caused more by the host response rather than from direct bacterial action.[5] Recent studies showed that, in periimplant tissues, inflammatory cytokines have an important role in regulating and amplifying the inflammatory response.[6] The inflammatory cytokines are used as biochemical markers of periodontal and periimplant destruction because of their conspicuously high crevicular concentrations in diseased periodontal and periimplant sites.[5,6] Interleukin(IL)-1β, tumor necrosis factor (TNF)-α, and prostaglandin (PG) E_2 are among the well-known and important inflammatory cytokines in the oral cavity.

In response to a periodontal or periimplant inflammation, IL-1β is

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released from various cells, particularly macrophages, fibroblasts, and osteoblasts to upregulate inflammatory reactions.[7] PGE_2 has been shown to have many proinflammatory effects, such as vasodilatation and enhancement of vascular permeability and activation of osteoclasts at the sites of inflammation, on periimplant tissues.[8] PGE_2 has been associated with osteoclast-mediated bone resorption and is found in elevated concentrations in periodontitis and periimplantitis sites.[9] Another proinflammatory cytokine in the oral cavity is TNF-α. This cytokine stimulates fibroblasts to produce collagenase and enhances apoptosis of matrix-producing cells, limiting the repair capacity of the periodontium.[10]

Smoking is considered a primary behavioral subject-based risk factor for periodontal and periimplant tissue breakdown; but the current understanding of the role of the nature of smoking as a risk factor for periimplant disease, irrespective of level of oral hygiene, is still controversial. Cigarette smoke has a cytotoxic effect on human gingival fibroblasts, which results in a decrease in their capacity for adhesion and proliferation.[11] This could result in impaired maintenance, integrity, and remodeling of oral connective tissue.

In the light of the facts presented, it becomes important to establish the effects of smoking on periimplant tissues even if in patients with healthy periimplant condition and good level of oral hygiene. With this background, the aim of the present cross-sectional study was to evaluate the effects of smoking on periimplant health status and inflammatory cytokines IL-1β, PGE_2, and TNF-α levels in periimplant crevicular fluid (PICF) and to determine their correlation with clinical parameters in well-maintained implant recall patients.

MATERIAL AND METHODS

Patient and Implant Characteristics

In a university-based implant maintenance program, after a periodontal examination, 60 patients who had healthy teeth and implants were asked to participate in the study. Twenty-seven of the patients (12 men and 15 women) were current smokers and 33 of them were nonsmokers (18 men and 15 women). Patients age ranged from 29 to 62 years, with a mean age of 44.9 ± 10.46 years.

The patients who received same dental implant system (Nucleoss T4 implants; Şanlılar Company, İzmir, Turkey) were included. The implants were inserted with a 2-stage technique. The inclusion criteria for the study were agreement to participate, having good oral hygiene confirmed with healthy-colored and healthy-textured gingiva, no visible plaque/tartar or malodor, wearing an implant-supported cement-retained fixed prosthesis (single crown) in function for at least 2 years between 2 natural teeth in maxillary premolar region, absence of any periodontal/periimplant and systemic disease, and absence of medical conditions compromising the participant's immune status or impeding oral hygiene maintenance. To avoid bias arising from dependent variables (several fixtures in 1 individual), "only one root-form dental implant per patient" was accepted as the inclusion criteria for the study. Some of patients had several implant-supported restorations, but only 1 cement-retained implant-supported single crown in maxillary premolar region was included and other restorations were not examined. The individuals wearing screw-retained implant-supported single crowns, implant-supported bridgeworks, or overdenture prosthesis were not included in the study to provide standardization. Subjects were excluded, if they were taking medication that could influence periimplant inflammatory condition, such as 0.12% chlorhexidine rinse, systemic antibiotics, cortisone, or nonsteroidal anti-inflammatory drugs within the past 6 weeks before clinical examination and crevicular fluid sampling. Patients who had undergone any periimplant therapy within the last 6 months were also excluded from the study.

The smoking habits of the participants were evaluated and regular daily cigarette smokers with current consumption more than 10 cigarettes per day were recorded as smokers. Nonsmokers were defined as patients, who irrespective of their previous history of smoking, did not smoke during the healingand the evaluation period. The study protocol had been approved by the local ethical committee, and written informed consent was obtained from all participants.

Clinical Measurements

Before crevicular fluid collection, supragingival plaque was scored using modified plaque index[12] (PI) and removed from each implant. Gingival inflammation was scored using modified gingival index[13] (GI) following crevicular fluid collection. Probing depth (PD) measures were obtained from sampled sites (mesial and distal midpoints in both facial and palatinal aspects of an implant, 4 measurements per implant) of implants using a conventional periodontal probe after PICF sampling. All clinical data were collected by the same investigator who was unaware of the smoking habit of the individuals.

PICF Sampling Procedure

PICF was collected with prefabricated sterile paper strips (PerioPaperr; Proflow, Inc., Amityville, NY) before periimplant probing. For PICF harvesting, the periimplant crevice was carefully dried with air and meticulously kept dry from saliva contamination with a saliva ejector and cotton rolls placed in the vestibulum and sublingual space. Then, the paper strip was inserted into the periimplant sulcus at a site easily accessible until mild resistance was felt without traumatizing the tissues and retrieved after 30 seconds. Samples with visible blood contaminations were discarded. Then, for volume determination, the strip was transferred to the Periotron 8000 device (Oraflow, Inc., Plainview, NY), which had been calibrated using known volumes of phosphate-buffered saline (PBS). The volume of the crevicular fluids was measured in "Periotron units" and then converted into microliters. Immediately after the PICF volumetry, the paper strip was inserted in 1 transport tube with 200 μL PBS. After 15 minutes of shaking at room temperature, the strip was removed, and the eluate was centrifuged (5 minutes, 3000*g*) to remove plaque and cellular elements. Then, the samples were stored at −70°C until processing for IL-1β, TNF-α, and PGE_2 measurements in the laboratory.

All the PICF sampling procedures were performed by the same investigator who was unaware of the smoking status of the participants.

Cytokine Assay

In the laboratory, the samples were processed and analyzed for IL-1β, TNF-α, and PGE_2 according to the standardized protocols issued by the manufacturer of the commercially available enzyme-linked immunosorbent assay kits (DIAsource Immunoassays S.A., Nivelles, Belgium). Cytokines levels were expressed both as the total amounts and total concentrations. The total amounts of cytokines were expressed as picograms per site. Concentrations of cytokines were corrected for PICF volume and were defined as picogram per microliter.

Radiographic Examination

Periimplant marginal bone level changes were calculated from the implant neck to the crestal bone level using standardized periapical radiographs by means of parallel technique. To have a consistent method of data collection, all radiographs were taken by the same investigator. The x-ray unit was operated at 60 kVp, 10 mA, and 0.3 seconds.

The measurements were performed using image-analyzing software (Image J, version 1.33u; Wayne Rasband, National Institutes of Health, Bethesda, MD). Radiographs were digitally calibrated using the known implant thread pitch as a reference. Periimplant bone level was determined by measuring the distance between the implant shoulder and the first crestal bone-to-implant contact on mesial and distal aspects of implants. Mesial and distal values were averaged to obtain a single bone level value per implant. Bone level at the time of implant placement was compared with that at the time of last follow-up visit.

Statistical Analysis

SPSS 11.5 software for Windows (SPSS, Chicago, IL) was used for statistical analysis, and the level of significance was set at $P < 0.05$. The participants were divided into 2 groups according to their smoking habits as smokers (S) group (n = 27) and nonsmokers (NS) group (n = 33). The independent samples *t* test (Student's *t* test) was used for comparison of the clinical data, PICF volume, biochemical cytokine levels in PICF, and periimplant bone loss over time between smoker and nonsmoker patients. The relationships among PICF cytokine levels and the clinical parameters were analyzed by Pearson correlation test.

RESULTS

All the recalled patients met the inclusion criteria and were included in the study. All implants were diagnosed as clinically successful and implant-supported restorations had been in function for a mean of 39.05 ± 4.93 months (range, 33–48 months).

Smoker participants were, on average, 3.25 years older and had their implants in function for 0.92 months longer compared with the nonsmoker controls. The differences regarding age and loading period were not statistically significant ($P = 0.234$ for patient age, $P = 0.478$ for duration of implant function). The demographic characteristics, clinical parameters, and biochemical cytokine levels of the patients are shown in Table 1.

Clinical Parameters

Statistically, all clinical parameters with the exception of plaque scores in the S group were significantly higher than in the NS group (Table 1). Although PI in the S group was higher than in the NS group, the difference did not reach statistical significance ($P = 0.377$). Smokers do have significantly more marginal bone loss than nonsmokers ($P = 0.001$).

Biochemical Cytokine Levels

Cytokine levels were expressed both as the total amount and concentration (Table 1). When the total amounts of cytokines were compared, significantly increased levels of IL-1β, TNF-α, and PGE_2 were observed in the S group ($P = 0.001$, $P = 0.047$, and $P = 0.001$, respectively). When the data were expressed as concentration, IL-1β and PGE_2 levels in the S group were significantly higher than in the NS group ($P = 0.005$ and $P = 0.017$, respectively). Although TNF-α concentration in the S group was higher than in the NS group,

Table 1. Comparisons Between S and NS Groups Regarding Demographic Characteristics, Clinical Parameters, and PICF Constituents

Data	S Group (n = 27) Mean ± SD	NS Group (n = 33) Mean ± SD	*P*
Demographic characteristics			
Male/female	12/15	18/15	
Age (y)	46.36 ± 11.35	43.11 ± 9.15	0.234
TIF (mo)	39.56 ± 5.81	38.64 ± 4.13	0.478
Clinical parameters			
GI	1.00 ± 0.67	0.64 ± 0.63	0.039*
PI	0.59 ± 0.64	0.45 ± 0.50	0.377
PD (mm)	1.56 ± 0.69	1.18 ± 0.39	0.011*
PICF volume (μL)	0.33 ± 0.06	0.22 ± 0.06	0.001*
Bone loss	1.12 ± 0.35	0.77 ± 0.28	0.001*
Cytokine levels (total)			
IL-1β (pg/site)	21.12 ± 5.21	15.97 ± 3.49	0.001*
TNF-α (pg/site)	2.73 ± 1.85	1.76 ± 1.64	0.047*
PGE_2 (pg/site)	7.13 ± 0.17	6.61 ± 0.59	0.001*
Cytokine levels (concentration)			
IL-1β (pg/μL)	67.54 ± 6.53	62.47 ± 6.88	0.005*
TNF-α (pg/μL)	8.51 ± 4.57	7.03 ± 4.01	0.186
PGE_2 (pg/μL)	32.78 ± 5.44	29.92 ± 3.52	0.017*

Note that all clinical parameters with the exception of plaque scores in the S group were significantly higher than in the NS group. In terms of biochemical aspect, significantly increased levels of inflammatory cytokines were observed in the S group compared with NS group.
*Statistically significant.
TIF indicates time of implant function (mo).

Table 2. Correlations Between IL-1β, TNF-α, and PGE_2 Levels in PICF and Clinical Parameters in S and NS Groups (Pearson Correlation Coefficients)

Groups	GI	PI	PD	PICF	Bone Loss
Cytokine level (Total)					
IL-1β					
S	0.677**	0.702**	0.539**	0.537**	0.608**
NS	0.335*	0.501**	0.351*	0.387*	0.354*
TNF-α					
S	0.652**	0.625**	0.908**	0.731**	0.635**
NS	0.548**	0.419*	0.355*	0.694**	0.373*
PGE_2					
S	0.567**	0.747**	0.674**	0.646**	0.809**
NS	0.474**	0.396*	0.426*	0.566**	0.415*
Cytokine level (concentration)					
IL-1β					
S	0.646**	0.525**	0.589**	0.520**	0.491**
NS	0.528**	0.364*	0.389*	0.429*	0.397*
TNF-α					
S	0.593**	0.504**	0.947**	0.757**	0.645**
NS	0.553**	0.439**	0.873**	0.364*	0.326*
PGE_2					
S	0.536**	0.576**	0.839**	0.507**	0.693**
NS	0.388*	0.359*	0.688**	0.475**	0.361*

Significant positive correlations between clinical parameters and biochemical cytokine levels were found in all patients. Note that the correlation between the cytokine levels and clinical parameters were more marked in smokers.
*$P < 0.05$.
**$P < 0.01$.

the difference did not reach statistical significance ($P = 0.186$).

Correlation of Biochemical Cytokines With Clinical Parameters

Significant positive correlations between clinical parameters and biochemical cytokine levels were found in the S and NS patients (Table 2). Although all the correlations were significant at $P < 0.001$ level in smokers, most of the correlations were at $P < 0.005$ level in nonsmokers.

DISCUSSION

Although the findings of many previous studies[14–18] described smoking as a risk factor for implant failures, there are some articles[19–21] that report no significant difference between smokers and nonsmokers regarding the success rate of dental implants. Therefore, the consideration of patient's smoking status in implant treatment planning seems to be controversial.

Smoking primarily has a systemic influence by altering the host response and by directly damaging periodontal and periimplant cells.[22] Local influence of smoking on microcirculation is also critical in periodontal and periimplant health. Because of the sensitive structure of periimplant tissues compared with periodontal tissues, the mentioned effects of smoking may make patients more susceptible to periimplant tissue breakdown. Therefore, identification of the effects of smoking in patients who had good oral hygiene and healthy implants also seem to be crucial. Thus, we performed a cross-sectional study focusing on interactions between implant prognosis and smoking in well-maintained implant recall patients with healthy implants and teeth to provide early quantitative facts including the likelihood of smoking-associated risks for implant prognosis. Our clinic's standard recall frequency includes first, third, sixth, and 12th months for the first year postloading and then annual recalls to evaluate the clinical and radiographic status of periimplant tissue and implant-supported prosthesis. Another goal of recall is to give an oral hygiene motivation to the patients. A retrospective study by Anner et al[23] reported that smoking and attendance in a regular supportive periodontal program were statistically associated with implant survival. Current standards of care for the assessment of attachment loss around implants include radiographic and clinical examination. Neither of these methods have high sensitivity to detect the sites at risk.[24] The production of biochemical cytokines by periimplant tissue may be an early response to local inflammation of tissue.

In this study, the extent of plaque accumulation presented similar pattern for S and NS participants. Therefore, the changes in the inflammatory cytokine levels and clinical parameters could be attributed to the effects of smoking rather than plaque accumulation. This suggests that tobacco itself can directly produce periimplant breakdown, regardless of bacterial plaque levels. Sham et al[25] reported that an enhanced risk for inflammatory periimplant complications might be expected in smokers because of tobacco smoking-associated vasoconstrictive effects at the end-arterial gingival vessels. Cigarette smoke contains more than 4000 toxins including nicotine, carbon monoxide, nitrosamines, benzenes, aldehydes, and hydrogen cyanide. Because tobacco's toxic effects are multiple including reduced blood flow, chemotactic activity of leukocytes, or collagen synthesis, pathogenic mechanisms of smoking on periimplant disease are quite complex.[17] Hypotheses associated with the detrimental effect of smoking are summarized as the direct cutaneous vasoconstrictive action of nicotine; the increased levels of fibrinogen, hemoglobin, and blood viscosity; excessive levels of carboxyhemoglobin in blood; compromised polymorphonuclear leukocyte and macrophage function; and increased platelet adhesiveness.[26] Sørensen et al[27] reported that collagen metabolism was effected by smoking-induced alterations in vitamin C turnover and by a change in inflammatory cell response. Yamano et al[28] reported that nicotine might inhibit bone-matrix–related gene expression required for wound healing and, thereby, diminish implant osseointegration at a late stage. Periimplant tissues and oral tissues are exposed to increased heat during smoking. Heat and toxic by-products of cigarette

smoking have also been considered as risk factors for impaired healing and, thus, may affect the success and complications of implant treatment.[22] In our study, the increased sign of biochemical activity in PICF might be in response to toxic products of smoking and hot smoke that occurred during smoking.

In our study, we detected significantly higher GI and PD scores in the periimplant sulcus of the smoker patients compared with nonsmokers. Similarly, Ataoglu et al[29] reported significantly increased peri-implant disease parameters in smokers. The increased PICF volume is a useful marker of inflammation of peri-implant tissue.[29] In our study, PICF volume measurements as well as cytokine levels showed a statistically significant increase in smoker participants compared with non-smoker individuals. Ataoglu et al[29] reported lower PICF neutrophil elastase activity and IL-1β levels and higher TNF-α levels in smokers. Their study population contained patients with healthy periimplant condition and patients with periimplant disease parameters. In this study, PICF cytokine levels were expressed both as total amount and as concentration. Previous studies claimed that data presentation by use of total activity rather than concentration was more sensitive in the reflection of the existing clinical periodontal status.[29,30] In this study, correlations were more marked in smokers compared with nonsmokers even in well-maintained population with healthy implants in both total amount and concentration level. Biochemical changes occurring as a part of the host inflammatory response may be considered as the early signs of tissue breakdown around dental implants. This investigation corroborates that smoking evokes an inflammatory process within the periimplant crevice in patients who have good oral hygiene without any sign of periimplant mucositis or periimplantitis.

Crestal bone response is believed to be critical for the long-term clinical success of dental implants. Studies showed a significant increase in periimplant marginal bone loss in smokers compared with nonsmokers.[24,31–33] de Souza et al[34] reported that causative mechanism of the connection between smoking and periimplant bone loss was vasoconstriction of the periimplant tissue. In the previous studies, patients were pooled irrespective of their periodontal/periimplant health or oral hygiene status and all types of patients (healthy, with periimplant mucositis, and periimplantitis) were included. The current study differed from previous studies with a special emphasis on the patient population that included only patients with healthy periodontal/periimplant condition and good oral hygiene. The values generally accepted as success criterion for bone loss is less than 1.5 mm for the first year postloading and less than 0.2 mm of additional loss for each following year.[35] The aforementioned success criterion is 27 years old and do not reflect the complete reality today. Recently, a new health scale for dental implants was established.[36] This current scale approved 4 clinical categories that contain conditions of implant success, survival, and failure. Although mean crestal bone loss was within the limits of the guideline for "clinical success (scale 1)" of dental implants in smokers, the results showed that periimplant bone loss was significantly greater in smokers compared with nonsmokers during the average 3-year follow-up period even though in a well-maintained population. Similarly, Vandeweghe and De Bruyn[37] reported that smoker patients had significantly more periimplant bone loss (mean = 1.56 mm) than nonsmokers (mean = 1.32 mm) in a mean follow-up of 12 months. Levin et al[33] reported that current smokers demonstrated higher periimplant bone loss than former smokers and both (current and former smokers) demonstrated higher bone loss than nonsmokers in a mean follow-up of 6 years. In the aforementioned study, the authors used panoramic radiograph to measure bone loss and reported that mean marginal bone loss for all implants was 0.14 mm during the first year and 0.07 mm/y during 1 to 5 years. Nitzan et al[38] evaluated the radiographic evidence of success of dental implants among smokers and nonsmokers and reported that smokers had more marginal bone loss (0.153 mm) than nonsmokers (0.047 mm). The reported values were smaller than our results. This might be because of the difference of the tools used to measure bone level. The higher marginal bone loss could be partially explained by the findings of Oates et al,[24] which demonstrated elevated pyridinoline levels in PICF of smokers. In the current study, periimplant bone loss was more close to the limit of "satisfactory survival (scale 2)" in smoker participants according to the health scale of Misch et al[36] Thus, additional predisposing factors such as plaque accumulation and poor oral hygiene must be well controlled to prevent the fast growing pattern of inflammatory process around implants. Further studies, focusing on the question whether the bone resorption will exceed the limits of the guideline for clinical success of dental implants in smokers during the long-term follow-up in well-maintained population, are necessary.

CONCLUSION

Although the periimplant tissues of the smokers in this study seem to be healthy, the clinical and biochemical parameters demonstrate that the implants are relatively at risk in intermediate-term follow-up. Even if in a well-maintained population, a regular and strict recall of smokers undergoing implant treatment is necessary. Semiannual recalls rather than annual recalls after the first year of postloading is recommended for oral hygiene motivation and early detection of possible clinical and radiographic signs of periimplant diseases.

DISCLOSURE

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

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