Stress and Inflammation as a Detrimental Combination for Peri-implant Bone Loss

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ABSTRACT

The causes of peri-implant bone loss continue to be controversial. To determine the impact of biomechanical stress and inflammation, we investigated a total of 80 interforaminal implants *in situ* for more than 10 years. Two stress groups, with 14 patients each, were established: a low-stress situation with single-standing implants, and an increased-stress situation with splinted implants. To categorize inflammation, we introduced a Composite Inflammation Score using 4 inflammatory parameters. Peri-implant bone loss was calculated from digital panoramic radiographs. To differentiate between the effects of stress and inflammation, we compared bone loss in both stress groups at equivalent levels of inflammation. With greater Composite Inflammation Score values, a clear discrepancy between single-standing and splinted implants was evident ($p = 0.117/0.000$, regression analysis; $p = 0.135/0.000$, analysis of variance; $p = 0.002$, t tests). While stress and inflammation alone may not necessarily be detrimental factors, the presence of stress heightens peri-implant bone loss significantly as inflammation increases.

KEY WORDS: peri-implant bone loss, biomechanical stress, inflammation, single-standing implants, splinted implants.

Stress and Inflammation as a Detrimental Combination for Peri-implant Bone Loss

INTRODUCTION

The key success criterion in oral implantology is the maintenance of osseointegration, which has been defined as the direct anchorage of implants in the living bone without interposing soft tissue (Brånemark *et al.*, 1983). Uncontrolled ongoing bone loss will thus decrease osseointegration and jeopardize the integrity of the implant. Peri-implantitis and biomechanical stress are the main factors implicated in bone loss around successfully integrated implants (Esposito *et al.*, 1998).

Bone loss caused by plaque-induced inflammation has been documented in both animal (Hickey *et al.*, 1991) and human studies (Mombelli *et al.*, 1987). As for biomechanical factors, bone loss has been observed in animal models with dynamic loading (Hoshaw *et al.*, 1994; Isidor, 1997; Miyata *et al.*, 2000; Duyck *et al.*, 2001). Static loading, however, appears to increase bone density (Gotfredsen *et al.*, 2001). In the clinical setting, bone loss has been related to increased stress resulting from the superstructure design (Quirynen *et al.*, 1992), as well as to occlusal factors (Lindquist *et al.*, 1988, 1997). In the presence of peri-implantitis, dynamic loading (Miyata *et al.*, 1998) may, again, be more detrimental than static loading (Gotfredsen *et al.*, 2002). Since clinical data on stress and inflammation are scarce, further insight into the impact of each factor alone, as well as into both factors combined, would be valuable.

In the study presented here, stress is categorized by 2 different attachment mechanisms, and inflammation is categorized by means of a newly developed Composite Inflammation Score. It was hypothesized that, at equivalent inflammation levels, bone loss is greater for increased stress levels.

MATERIALS & METHODS

Patients and Implant Characteristics

The study group consisted of 28 edentulous patients with interforaminal implants (ITI solid screw; Straumann, Basel, Switzerland) *in situ* for, on average, over 10 yrs (range, 7.5 to 13.5 yrs). Informed patient consent and approval from the university's ethical commission were duly obtained (Ref. no. 2780).

Starting from a cohort of 14 patients with 36 single-standing implants with non-rigid telescopic attachments (Heckmann *et al.*, 2004b), a corresponding number of 14 patients with 44 implants splinted over bar attachments was chosen. The criterion for the selection of those for the splinted-implant group was the best possible match with the single-standing-implant group for co-factors of bone loss and inflammation. Almost identical values were obtained in terms of gender, smoking habits, bite force, mean age, and time implants had been *in situ*. The unique construction design of the non-rigid telescopic attachment and the long *in situ* time of the implants, coupled with the patients' elevated ages, account for the sample size. The implants were comprised of one-

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Table 1. Details on Stress Groups and Composite Inflammation Score

A Patients and Implants			B Type of Bar Attachment	
Patients	Telescopic att.	Bar att.	Description	Number
Total number	14	14		
Gender (m/f)	7/7	7/7	Round or oval	8
Smokers/Non-smokers	2/12	1/13	on 4 implants	
Mean age, range in yrs	75.5, 64.5-84.5	74.6, 61.9-83.9	without extensions	
Opposite jaw status			Round or oval	4
Fixed restoration or natural teeth	1	1	on 2 implants	
Removable partial denture	1	2		
Complete denture	12	11	U-shaped	1
			on 2 implants	
Patient recruitment			Round or oval	1
Dental school	14	3	on 3 implants	
Private practice 1/2/3	0/0/0	3/5/3	with extensions	
Implants				
Total number	36	44		
Type (one-part/two-part)	0/36	24/20		
Length in mm (10/12)	0/36	7/37		
Diameter in mm (3.3/4.1)	6/30	0/44		
Number per patient (2/3/4)	9/2/3	5/2/7		
Mean <i>in situ</i> time, range in yrs	10.0, 8.3-12.9	10.0, 7.5-13.5		
C Inflammatory parameters				
Parameter	Sites*	Description/Reference	Score Values	
Modified Plaque Index	m d	Degree of plaque accumulation (Mombelli <i>et al.</i> , 1987)	0: no plaque 1: plaque detected by probe 2: plaque visible to naked eye 3: abundant plaque	
Sulcus Fluid Flow Rate	mean of m ₁ , m ₂ (m) d ₁ , d ₂ (d)	Severity of peri-implant mucosal exudation, Periotron values transformed into score values (cf. Spörlein and Tetsch, 1986)	0: 01-13 1: 14-26 2: 27-39 3: ≥ 40	
Modified Bleeding Index	m d	Degree of peri-implant mucositis (Mombelli <i>et al.</i> , 1987)	0: no bleeding 1: isolated blood spots 2: confluent blood line 3: heavy bleeding	
Keratinized Mucosa	mean of v, l (m) v, l (d)	Width of peri-implant keratinized tissue visualized by Schiller [K] Solution transformed into score values (cf. Cox and Zarb, 1987)	0: ≥ 2 mm 1: 1 mm 2: 0 mm	
Composite Inflammation Score	m d	Sum of score values of single parameters Modif. Plaque Index, Sulcus Fluid Flow Rate, Modif. Bleeding Index and Keratinized Mucosa		

* m = mesial, d = distal, v = vestibular, l = lingual.

and two-part types, with the same endosteal design and supra-alveolar implant-abutment connection. Similar healing and loading protocols were applied; thus, implant geometry above bone level was the sole difference (Table 1; cf. Fig. 1).

Comparison of Stress: Single-standing and Splinted Implants

The study began with 2 different biomechanical conditions. In the single-standing group, non-rigid telescopic copings transferred minor stresses to the implants, due to certain construction peculiarities (Heckmann *et al.*, 2001, 2004b). Splinted bar attachments, for example, are expected to induce greater stress, since they cannot be screwed into place without misfit (Jäger and Wirz, 1994; Smedberg *et al.*, 1996; Heckmann *et al.*, 2004a), and counteract the functional deformation of the mandible (Hobkirk and Schwab, 1991).

Classification of Inflammation: Composite Inflammation Score

To standardize the inflammation, we introduced a Composite Inflammation Score. The score values of 4 clinical inflammatory parameters were added: Modified Plaque Index, Sulcus Fluid Flow Rate, Modified Bleeding Index, and the width of the Keratinized Mucosa.

The Modified Plaque Index represents the cause of inflammation, both Sulcus Fluid Flow Rate and Modified Bleeding Index the degree of inflammation, while Keratinized Mucosa is a modulating factor.

To allow for comparability with the radiographic analysis, we referred all measurements taken to the mesial and distal aspects, resulting in 160 sites. The modified Plaque Index and modified Bleeding Index scores were applied as measured. Sulcus Fluid Flow Rate was assessed twice and the mean value calculated.

Since Keratinized Mucosa was not to be measured mesially and distally, vestibular and lingual values were averaged. Both Sulcus Fluid Flow Rate and Keratinized Mucosa values were transformed into scores (Table 1). All measurements were carried out by two

calibrated examiners.

The score values for each inflammatory parameter were divided into 3 classes, representing 3 biologically homogeneous groups (I, II, III). Composite Inflammation Score values were grouped with score values ≤ 1 (I), 2-3 (II), and ≥ 4 (III). For the individual parameters Modified Plaque Index, Sulcus Fluid Flow Rate, Modified Bleeding Index, and Keratinized Mucosa, the groups' score values were 0 (I), 1 (II), and ≥ 2 (III).

Radiographic Analysis

We took digital panoramic radiographs to measure the bone loss mesially and distally. Since one- and two-part implants differ in their configuration above bone level, the standard parameter Distance Implant Bone (Weber *et al.*, 1992) could not be applied without bias. Instead, a modified procedure, independent of supraosseous landmarks, was introduced (Fig. 1).

Each implant was calibrated based on the distance between the uppermost and the lowermost visible thread crests, with 1.25 mm between 2 adjacent crests (Sidexis®, Sirona, Bensheim, Germany). The reference points were the apex and the coronal bone-to-implant contact projected to the midline of the implant. Bone loss was calculated as the length of the corresponding rough surface minus the distance between the reference points. The entire analysis was carried out by one single researcher. Single-standing and splinted implants were evaluated alternately, with 3 measurements averaged for each site.

Statistical Analysis

Bone loss may be influenced by both stress and inflammation and was therefore taken as a dependent variable. Independent variables were the factor variable stress (value 0 for lower stress in single-standing, value 1 for increased stress in splinted implants) and the concomitant variable inflammation. To analyze differences between both stress groups, we used 3 different methods: regression analysis, analysis of variance, and two-sample *t* tests.

We carried out regression analysis to demonstrate the correlation between bone loss and inflammation. Since data had been gathered from records comprising both bone loss and inflammatory parameters, it was necessary to test in advance whether Composite Inflammation Score, Modified Plaque Index, Sulcus Fluid Flow Rate, Modified Bleeding Index, and Keratinized Mucosa were equally distributed across both stress groups, by the Mann-Whitney-test. As a result, regression analysis was applicable only to the Modified Plaque Index ($p = 0.395$) and the Modified Bleeding Index ($p = 0.870$) in the strict sense. The regression lines for Sulcus Fluid Flow Rate ($p = 0.000$), Keratinized Mucosa ($p = 0.000$), and Composite Inflammation Score ($p = 0.001$) were to be extrapolated. Since the regression lines for the factor variable values 0 (single-standing) and 1 (splinted) differed in slope, analysis of covariance was not applicable. Instead, linear regression analysis was used for each stress group and inflammatory parameter separately.

Due to the limited applicability of the regression analysis, an additional method, based on the 3 biologically homogeneous groups, was used. The analysis of covariance served to evaluate the general variability of

Figure 1. Radiographic analysis of bone loss for one- and two-part implants. A calibration factor was determined based on the known distance between the uppermost and the lowermost thread crests (distance between 2 adjacent crests: 1.25 mm) and the length measured on the radiograph. The reference points were the apex and the coronal bone-to-implant contact projected to the midline of the implant. The distance between these points was subtracted from the length of the rough surface.

Table 2. Regression Analysis for the Relationship between Bone Loss and Inflammation (Inflammatory parameters as independent variables; P values refer to the null hypothesis of slope zero.)

Inflammatory Parameter	Type of Implant	Slope	95% Confidence Int.		P value
			Lower	Upper	
Composite Inflammation Score	single-standing	0.089	0.023	0.201	0.117
	splinted	0.565	0.432	0.697	0.000
Modified Plaque Index	single-standing	0.119	0.091	0.330	0.263
	splinted	0.605	0.185	1.025	0.005
Sulcus Fluid Flow Rate	single-standing	0.336	0.073	0.600	0.013
	splinted	1.315	0.963	1.667	0.000
Modified Bleeding Index	single-standing	0.384	0.080	0.688	0.014
	splinted	0.649	0.086	1.212	0.024
Keratinized Mucosa	single-standing	0.382	0.677	0.087	0.012
	splinted	0.994	0.646	1.342	0.000

Figure 2. Mean values of bone loss for single-standing (black) and splinted (grey) implants in biologically homogeneous groups I, II, and III with number of sites (n) and standard deviation (SD). P values for comparisons within groups are shown in the diagrams. P values for comparisons between biologically homogeneous groups for single-standing and splinted implants, respectively, are depicted below the diagrams. (A) Unlike single-standing implants, splinted implants showed a distinct increase in bone loss toward greater Composite Inflammation Scores. Hence, the greatest differences were found in the third group. (B-E) Illustration of the dependency of bone loss on Modified Plaque Index (B), Sulcus Fluid Flow Rate (C), Modified Bleeding Index (D), and Keratinized Mucosa (E). As with Composite Inflammation Score, there is a general trend toward higher score values for splinted implants.

the splinted implants, a notable increase was seen. A comparison within the Composite Inflammation Score groups I to III revealed higher bone loss in group I for the single-standing implants and in group II as well as group III for the splinted implants (Fig. 2A).

With regard to the 4 underlying parameters, only moderate differences in bone loss were found for the single-standing implants, while a clear increase from groups I to III was found for the splinted implants. This was most evident for Sulcus Fluid Flow Rate and Keratinized Mucosa. When comparing both stress groups within each biologically homogeneous group in terms of Modified Plaque Index, Sulcus Fluid Flow Rate, Modified Bleeding Index, and Keratinized Mucosa, we observed the greatest differences in group III, particularly for Sulcus Fluid Flow Rate and Keratinized Mucosa, and only minor differences in groups I and II (Figs. 2B-2E).

DISCUSSION

This study was designed to differentiate between the impact of inflammation and stress on bone loss in two different implant-stress

bone loss within both stress groups for each inflammatory parameter. Two-sample *t* tests were used for pairwise comparisons of the biologically homogeneous groups and the stress groups.

RESULTS

Regression Analysis

Unlike the single-standing implants, significant positive associations in the splinted-implant group were observed between bone loss and the inflammatory parameters (Table 2): Composite Inflammation Score (slope = 0.565; *p* = 0.000), Modified Plaque Index (slope = 0.605; *p* = 0.005), Sulcus Fluid Flow Rate (slope = 1.315; *p* = 0.000), Modified Bleeding Index (slope = 0.649; *p* = 0.024), and Keratinized Mucosa (slope = 0.994; *p* = 0.000).

Analysis of Variance and *t* Tests

The analysis of variance revealed fewer differences in the single-standing than in the splinted groups: Composite Inflammation Score (*p* = 0.135 vs. 0.000), Modified Plaque Index (*p* = 0.407 vs. 0.020), Sulcus Fluid Flow Rate (*p* = 0.015 vs. 0.000), Modified Bleeding Index (*p* = 0.025 vs. 0.079), and Keratinized Mucosa (*p* = 0.039 vs. 0.000).

The *t* tests showed a slight increase in bone loss throughout the biologically homogeneous groups of Composite Inflammation Scores in the single-standing implants, while in

groups. The only inflammatory parameters to be included were those that clearly reflected inflammation-induced bone loss, not bone loss caused by biomechanical factors.

With regard to the Composite Inflammation Score, all statistical tests revealed an increasing discrepancy in bone loss between single-standing and splinted implants as score values increased. One explanation for bone loss may therefore be seen in the different biomechanical conditions, since possible co-factors were controlled. Thus, increased stress in splinted implants might enhance the susceptibility to inflammatory bone loss, or *vice versa*. If one considers single-standing implants as being at high, and splinted implants at low, Composite Inflammation Score levels, stress and inflammation alone do not necessarily provoke bone loss.

Since the Composite Inflammation Score was established on the basis of 4 different inflammatory parameters, its strong point lies in the combination of them. Similarly, the individual parameters revealed a tendency toward greater bone loss in the splinted implants. These parameters underline the fact that higher plaque formation, bleeding, exudation of sulcus fluid, and lack of keratinized mucosa may be associated with more bone loss around splinted implants. Site-specific inflammation is more likely to occur around splinted bar constructions, in addition to the assumed stress situation. The differences in bone loss found, however, cannot be explained by a niche effect, since sites of equivalent inflammation were compared in

all cases. The reason for the negative correlation between Keratinized Mucosa and bone loss in the single-standing implants remains unclear. However, the missing positive correlation is concurrent with relevant literature, suggesting that keratinized mucosa might be dispensable around implants which are easily accessible to oral hygiene (Wennström *et al.*, 1994).

The causes of peri-implant bone loss have been investigated in various studies, most of which were based on animal models (Hoshaw *et al.*, 1994; Miyata *et al.*, 2000; Duyck *et al.*, 2001; Hürzeler *et al.*, 1998). Regardless of their usefulness for particular scientific questions, animal studies often do not produce long-term data (Gotfredsen *et al.*, 2001) and are not easily applicable to the situation in humans, *i.e.*, occlusal overload is difficult to monitor, or intra-oral force devices may not match the real-life situation (Carr *et al.*, 1996).

For this reason, clinical studies would be of considerable value, which, for ethical reasons, excludes invasive methods. Moreover, one has to seek valid assumptions to determine stress. In the few studies on this subject, long cantilevers (Lindquist *et al.*, 1988) and parafunctions (Lindquist *et al.*, 1988; Quirynen *et al.*, 1992) were reported to be associated with bone loss. The multifactorial etiology of poor oral hygiene and extensive loading in combination (Lindquist *et al.*, 1988) is also concurrent with the study presented. But, in a long-term follow-up of the same patients, smoking was underlined as being even more critical. The authors also suggested that signs of parafunction might not truly reflect the loading situation (Lindquist *et al.*, 1997).

Taking this as a basis, the approach applied in the study distinguishes between the effects of stress and those of inflammation on bone loss. Stress was categorized by 2 different attachment mechanisms (single-standing, splinted), and the inflammatory situation was standardized based on a Composite Inflammation Score. Clinical and radiographic parameters were recorded in patients whose implants had been *in situ* for more than 10 yrs.

Slight differences in implant geometry were not considered to affect the results. Though the number of implants *per* patient could not be exactly matched for all single-standing and splinted implants, the basic character of the attachment systems, with their implications for biomechanical stress, remained unchanged.

No attempt was made to measure the stress situation in splinted implants over time, since this would not produce information of great value to this study. This approach would have required the removal of the bars, with the risk of refixation (Jäger and Wirz, 1994). Furthermore, the obvious limitations of *in vivo* tests (Lindquist *et al.*, 1997; Gotfredsen *et al.*, 2001) must be pointed out. Nevertheless, there is considerable evidence of increased stress in splinted implants from *in vitro* tests (Jäger and Wirz, 1994; Heckmann *et al.*, 2001) and combined *in vitro* and *in vivo* studies (Hobkirk and Schwab, 1991; Smedberg *et al.*, 1996; Heckmann *et al.*, 2004a).

While one- and two-part implants were used in this study, the microgap between implant and abutment was located above bone level in both groups and should therefore not notably have contributed to the total degree of inflammation (Broggini *et al.*, 2003).

Although the reliability of the clinical parameters presented

has been controversial (Verhoeven *et al.*, 2000), these parameters nevertheless appear to be appropriate for monitoring the peri-implant soft-tissue conditions (Mombelli and Lang, 1994). The Composite Inflammation Score is therefore intended as a plausible combination of well-established inflammatory parameters. An evaluation of the Composite Inflammation Score on the basis of longitudinal data would be valuable. With the design at hand, however, only cross-sectional ten-year data were available.

Due to the impracticality of taking peri-apical radiographs in elderly patients with severely atrophied mandibles, we used digital panoramic radiographs (De Smet *et al.*, 2002) to calculate peri-implant bone loss. The radiographic analysis rests upon the assumption that the implants were placed as recommended, with the coronal border of the rough surface and the adjacent bone at the same level (Weber *et al.*, 1992).

Ultimately, the hypothesis of this study was supported in relation to moderate and increased levels of inflammation: In splinted implants, a proportional relationship between inflammation and bone loss appears to exist. In single-standing implants, however, almost no correlation was found. The increasing discrepancy between the two implant groups can therefore be ascribed to the splinted attachment type. Thus, on the basis of the assumed stress situations, neither stress nor inflammation alone would induce notable bone loss, whereas stress coupled with inflammation constitutes a detrimental combination.

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