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Investigation of the IL-1 β Genotype and its Levels on Patients Treated with Osteointegrated Dental Implants

Osteointegre Dental İmplant Tedavisi Gören Hastalarda IL-1 β Genotipi ve Seviyelerinin İncelenmesi

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ABSTRACT

Objective: In our study, we aimed to investigate the relationship between the Interleukin-1β (IL-1β) +3953 gene polymorphism, the levels of this interleukin and smoking in osteointegrated dental implant losses.

Materials and Methods: 56 patients with implants and 238 healthy control subjects were included in this study. PCR and RFLP methods was used to determine the IL-1β +3953 gene polymorphisms. Serum IL-1β levels were measured using ELISA.

Results: The IL-1β +3953 CC, TT and CT genotype frequencies for the controls and study cases were 61.2%, 10.1% ,43.6%, and 48.2%, 8.9% and 42.9%, respectively. IL-1β +3953 T allele carriers increased more in the patient group (51.8%) compared to the control group (38.8%). These cases also had an increased plaque index, bleeding index, pocket deepness and serum IL-1β levels, but none of them were statistically significant (p>0.05). Implant losses were more frequent in C allele carriers than in T allele carriers, but this was not statistically significant (p>0.05) Three of the five patients that experienced implant loss and smoked, lost the implant earlier and had a higher average plaque and bleeding index.

Conclusion: Based on our results, we can suggest that being an IL-1β positive genotype and a smoker can have an effect on implant losses. The study group should be enlarged to comment with statistically significant results.

Keywords: IL-1β +3953, Implant, Interleukin, polymorphism

ÖZ

Amaç: Çalışmamızda osteointegre dental implant kayıplarında interlökin-1β (IL-1β) +3953 gen polimorfizminin serum interlökin düzeyleri ve sigara içimiyle ilişkisini araştırmayı amaçladık.

Yöntemler: İmplant yapılan 56 olgu ve 238 sağlıklı kontrol öalışmaya dahil edilmiştir. IL-1β +3953 polimorfizmi, polimeraz zincirleme reaksiyonu ve restriksiyon fragmanı uzunluk polimorfizmi yöntemleri kullanılarak tayin edilmiştir. Serum örneklerinde IL-1β seviyesi ELISA yöntemi ile saptanmıştır.

Bulgular: IL-1β +3953 polimorfizmi; CC, TT ve CT genotip frekansları kontrol ve hasta grubu için sırasıyla 61.2%, 10.1% , 43.6%, ve 48.2%, 8.9% ve 42.9% olarak bulunmuştur. IL-1β +3953 T alleli taşıyanların hastalarda (51.8%) kontrol grubuna (38.8%) göre daha yüksek bulunmuştur ve bu kişilerde plak indeksi, kanama indeksi, cep derinliği ve serum IL-1β düzeylerinin arttığı, sigara içme ve implant kaybı oranının yükseldiği fakat istatistiksel anlamlılığa ulaşmadığı tespit edilmiştir (p>0,05). İmplant kaybında, C alleli taşıyanlarda T alleli taşıyanlara göre daha anlamlı bulunmasına rağmen istatistiksel olarak anlamlı olmadığı görülmüştür (p>0,05). İmplant kaybı olan beş hastanın üçünde IL-1β pozitif olduğu, hepsinin sigara kullandığı, implantların erken dönemde kaybedildiği, plak ve kanama indekslerinin ortalama değerlerden yüksek olduğu ve cep derinliklerinin normal sınırlar arasında olduğu görülmüştür.

Sonuç: Sonuç olarak implant kaybında IL-1β pozitif genotipe sahip olma ve sigara içiminin önemli bir etken olduğu izlenimi edinilmiş ancak olgu sayısının arttırılmasıyla istatistiksel anlamlılığa ulaşılabileceği sonucuna ulaşılmıştır.

Anahtar Kelimeler: IL-1β +3953, implant, interlökin, polimorfizm

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INTRODUCTION

Examples of biological complications in dental implants can be summarized as; fistula formation, inflammatory reactions around the implant sulcus, periimplant mucositis and periimplantitis (1). Dental implant success rates range between 95% and 99% , but there can be implant losses later due to biological and technical complications (2-5). It was found that there were two main reasons for implant losses (6, 7): 1. The biofilm layer over the implant surface might cause enflamatory reactions and bone losses occur; 2. Biomechanical burden and genetic factors.

Interleukin 1 (*IL-1*), prostoglandin E2 (Pg E2) and matrix metalloproteinases (MMP) are usually connected with both the seriousness and activity of the periodontal disease (8). Previously, people carrying at least one T allele have been described as *IL-1* genotype-positive (8-10). Thus, we used this term in our study as suggested. It has previously been demonstrated that there is a 2.7 times higher risk of dental losses in *IL-1* genotype positive patients compared to *IL-1*genotype negative ones (11). In a retrospective study it was shown that *IL-1* positive genotype patients had a significantly higher risk of bleeding (12).

There are two main theories for the bone-implant relationship. One is the initially accepted theory of fibro-osseos integration - it is known that there is an organised collagen mesh between the bone and implant surfaces. This fibro-osseos sttructure is just like periodontal membrane, but it was thought that as they were arranged parallel to the implant surface, they were weakening the bone-implant relationship (13). The second theory is known as the 'osteo-integration' theory, and was first defined by Branemark et al. (14) as a direct relationship between the bone tissue and the implant (14).

Interleukin-1 (*IL-1*) is a type of cytokine that is secreted from macrophages/monocytes and mainly activates T helper cells. Recently, more preimplant infections were detected in patients with increments of *IL-1* compared to healthy patients and it was demonstrated that in those people with periodontal infections and increased cytokines, there were 2.7 times more dental losses than in other patients (15). It was found that proinflamatory cytokine *IL-1β* was significantly higher in the perimplantitis area than in healthy areas (16, 17). *IL-1* is now thought to be major mediator in chronic inflamatory cases such as periodontitis (18). In the scope of all of those studies it was also realised that specific gene polymorphisms of the *IL-1* gene region might be related to periodontitis risk (19, 20).

The aim of our study was to investigate the relationship between the *IL-1*β 3953 polymorphism and complications in osteointegrated dental implants, to determine the differential complications between smoking and non-smoking patients and to identify the success of dental implants in relation to periodontal diseases.

MATERIALS AND METHODS

Study Subjects

Our study was approved by the İstanbul University Medical Ethics Committee (03/10/2006 and 041895). All subjects provided written informed consent before they participated in the study. All participants signed an informed consent before enrollment and Institutional Ethical committee approval was obtained for the study. The patient group (26 males and 30 females) was chosen from those attending the Faculty of Dentistry, in the Department of Oral Medicine and Oral Surgery. The control group contained 238 healthy participants (88 males and 150 females). The inclusion criteria for the patient group of the study were: optimal oral hygiene alongside no history of partial or total loss of teeth, bruxism, previous chemotherapy or radiotherapy, alcohol or drug addiction.

All surgical procedures were carried out under local anesthesia. The implants were engrafted using the standard protocol Zimmer Dental Tapered Screw-Vent / Swiss Plus dental implant system. In total, 126 implants were used over 56 patients. EDTA-tubes were used for DNA analysis. Before the operation and on 8th week following the operation, serum specimens were taken and maintained at -20 °C to determine *IL-1β* levels. All measurements and determinations were performed in the Department of Molecular Medicine, Istanbul University.

Polymorphism Analysis and ELISA

The method previously described by Sun et al. (21) was used. The primers used for the polymerase chain reaction (PCR) for the *IL-1β* +3953 localization were: forward 5′-GTT GTC ATC AGA CTT TGA CC-3′, and reverse, 5′-TTC AGT TCA TAT GGA CCA GA-3′ from (MBI Fermentas, Vilnius, Lithuania). The gene fragments were amplified using a 25 µL reaction mixture containing approximately 100 ng of template DNA, 0.5 µL of each primer, all four deoxyribonucleoside 5′ triphosphates (each at 0.2 mM), 1.5 mM MgCl2 and 1.0 U of *Taq* polymerase in a 1x reaction buffer (MBI Fermentas, Vilnius, Lithuania). The PCR reaction was carried out with an initial melting stage of 5 minutes at 94˚C; followed by 35 cycles of 1 minute at 94˚C, 1 minute at 55˚C, 1 minute at 72˚C, and a final elongation step of 7 minutes at 72˚C.

The restriction endonuclease Taq I was used to determine the *IL-1β* +3953 polymorphism. The Taq I digestion generated fragments of 135 bp and 114 bp for the C allele, and for the T allele, a single fragment of 249 bp. PCR and restriction products were electrophoresed in in 2% (w/v) agarose gels and stained with ethidium bromide (Figure 1).

Determination of Serum *IL-1β* Levels was performed using commercial ELISA (Enzyme Linked Immunosorbent Assay) assay kits (Biosource, Nivelles, Belgium).

Statistical Analysis

The student's t test and Anova were used to determine the effects of genotypes and alleles on the activities. The Serum *IL-1β* levels of the patient and control groups were compared using the Wilcoxon test. Pearson analyses were used to examine the

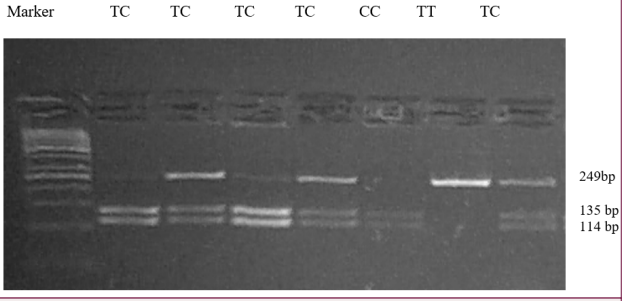

Figure 1. Gel electrophoresis after restriction of the IL-1β+3953 gene region
Taq I digestion generated the following fragments for the C allele, fragments of 135 bp and 114 bp; T allele, a single fragment of 249 bp and were electrophoresed in in 2% (w/v) agarose gels and stained with ethidium bromide

Table 1. The study parameters in patient and control groups

	Control (n=238)	Patient (n=56)
(Female/Male)	150/ 88	30 / 26
Age (years)	43.70+15.06	46.46+12.00
Plaque index		40.82± 17.39
Bleeding index		32.68± 18.69
Pocket Deepness (mm)		1.81± 0.45
IL-1β I level (pg/mL)*	0.415±0.71	0.780±0.9340
IL-1β II level (pg/mL)**		0.837±1.4483

All values of the table were given as mean±standart deviation (x±SD)
*IL-1β I level: IL-1β levels immediately before the operation
**IL-1β II level: IL-1β levels 8 weeks after the operation

Table 2. IL-1β+3953 genotype and allele frequencies in groups

	Control	Patient	p
IL-1β+3953 Genotype			
CC	145 (61.2%)	27 (48.2%)	
TT	24(10.1%)	5 (8.9%)	
TC	68 (43.6%)	24 (42.9%)	0.11
C+	213 (89.9%)	51 (91.1%)	0.78
T+	92 (38.8%)	29 (51.8%)	0.07

differences in genotype distribution between the patients and the control subjects. The Chi-Square, Fisher Kruskal Wallis and Mann-Whitney tests were used to differentiate the genotype and allele frequencies between the groups.

Table 3. The results of IL-1β positive and negative patients

	IL-1β(-) (n:27)	IL-1β(+) (n:29)
Gender (Female/Male)	14/13	16/13
Smoking(%)/ non-smoking(%)	12 (37.5)/15 (62.5)	20 (62.5)/9 (37.5)
Implant loss(%)/ No implant loss (%)	2 (40.0)/25 (49.0)	3 (60.0)/26 (51.0)
Age (year)	44.11±13.80	48.66±9.78
Plaque Index	39.58±15.67	41.98±19.06
Bleeding Index	30.00±15.42	35.17±21.27
Pocket Deepness (mm)	1.73±0.37	1.89±0.51
IL1 level (pg/mL)	0.65±0.72	0.77±1.06

Values of the table were given as mean±standart deviation (x±SD)

RESULTS

There was no significant difference in the ages or interleukin levels between the groups (p>0.05) (Table 1). There was no significant difference between the groups in terms of genotype or allele distribution (p:0.119 X2:4.25). The *IL-1β* +3953 T allele carriers increased almost significantly in the patient group compared to the control group (p:0.076; X2:3.14; Odds ratio (OR) : 1.69 %95 CI:0.94-3.04). (Table 2).

The *IL-1β* Positive cases had an increased plaque index, bleeding index, pocket deepness and serum *IL-1β* levels, but none of these values were statistically significant (p>0.05) (Table 3).

Implant losses were more frequent in C allele carriers than in T allele carriers, but this was not statistically significant (p>0.05) (Table 4).

It was also found that plaque index, bleeding index and pocket deepness increased in the case of implant loss, but this was also not significant (p>0.05).

The *IL-1* levels were not significantly different in the patient or control groups (p:0.858) (Table 5).

In the patient group it was determined that the *IL-1* levels (p:0.037) and plaque indices (p:0.028) were significantly higher in females than in males (Table 6).

DISCUSSION

Pietruski et al. (22) found that *IL-1* levels significantly increased one day after operation, but concluded that this was due to tissue damage as a result of implantation. We chose to take serum specimens on the same day of the operation and then 8 weeks after the operation to compare the *IL-1* levels to eleminate the

Table 4. Implant lossed due to IL-1β+3953 genotypes

	No Implant Loss (n=51)	Implant Loss (n=5)
IL-1β GENOTYPE		
CC	25 (49%)	2 (40%)
TT	4 (7.8%)	1 (20%)
TC	22 (43.1%)	2 (40%)
ALLELE		
C+	47 (92.2%)	4 (80%)
C-	4 (7.8%)	1 (20%)
T+	26 (51. 0%)	3 (60%)
T-	25(49.0%)	2 (40%)

Table 5. IL-1 Levels in different genotypes and alleles of control and patient groups

	IL-1 levels (pg/mL)	
IL genotypes	**Control Group**	**Patient Group**
CC	0.43±0.73	0.65±0.72
TT	0.51±1.12	0.780±0.82
TC	0.32±0.44	0.775±1.12
C+	0.51±1.12	0.714±0.92
C-	0.37±0.57	0.780±.82
T+	0.39 ±0.73	0.77±1.06
T-	0.438±0 .73	0.65±0.72

All values of the table were given as mean±standart deviation (x±SD)

Table 6. Gender differences of parameters in patient group

	Female (n:30)	Male (n:26)
IL1 β level (pg/mL)	0.97±1.09	0.45±0.55
IL1 β II level (pg/mL)	0.68±1.19	1.00±1.70
Plaque Index	45.43±21.58	35.48±8.31
Bleedig Index	3.76±22.33	30.28±13.36
Pocket Deepness (mm)	1.88±0.51	1.74±0.37

All values of the table were given as mean+standart deviation (x±SD)
*IL-1β I level: IL-1β levels immediately before the operation
**IL-1β II level: IL-1β levels 8 weeks after the operation

post operation inflammation process, but we could not find any statistical difference between those results.

There was an incremental change in frequency of implant losses in C allele carriers, but not a statistically significant one (p>0.05). The CT genotype was more frequent in the control group (albeit non-significantly) and this result correlates with the results of Sakellari et al. (23).

Rogers et al. (24) determined no relationship between *IL-1* genotypes and implant loss. In another study, it was found that *IL-1* gene polymorphism increased the periimplant infection frequency (25). In our study, we were able to conclude that bleeding index, plaque index and pocket deepness increased and as a result of all those parameter changes, the risk of periodontitis and periimplant also increased.

In a previous study, it was found that the risk of dental loss was 2.7 times higher in *IL-1* positive cases than in *IL-1* negative cases (26). In one study, it was previously found that periodontal diseases were more frequent in *IL-1* positive people, and in the same study it was also demonstrated that the coincidence of *IL-1* positivity and smoking significantly increased the risk of implant loss (27-29). We also found that 11 of the 24 smoking patients were successfully cured by the implants even though they were *IL-1* positive; 3 of the 5 patients with implant losses were *IL-1* positive, but this was not a significant enough number to assess the relationship of *IL-1* positivity and smoking in total.

When we compared the bleeding index, plaque index and pocket deepness of the patients with (n=5) and without (n=51) implant losses, all of those parameters increased in the former group, but the number of implant losses was not enough for statistical significance. When we compared the gender differences of the parameters in the patient group,the *IL-1* levels 8 weeks after the operation (p:0.037) and plaque indices (p:0.028) were found to be significantly different.

Finally, supported by the previous studies, *IL-1* positive patients were found to have an increased incidence of perimplantitis and periodontitis; a risk assesment can be carried out before implant surgery to have more successful results.

Ethics Committee Approval: Ethics committee approval was received for this study from the Medical Ethics Committee of Istanbul University (Decision Date: 03/10/2006; Decision Number: 041895).

Informed Consent: Written informed consent was obtained from the subjects who participated in this study.

Peer-review: Externally peer-reviewed.

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