ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Research Article *Araştırma Makalesi* DOI: 10.17567/ currresdentsci.1754303

Effects of Tumor Necrosis Factor-Alpha Level in Peri-implanter Sulcular Fluid on Alveolar Bone Loss: A Prospective Study

Peri-implanter Sulkuler Sıvıdaki Tümör Nekroz Faktörü-Alfa Seviyesinin, Alveolar Kemik Kaybına Etkileri: Prospektif Bir Çalışma

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Presented at the 47th International Scientific Congress and 26th Scientific Symposium of the Turkish Periodontology Association, 17-18 November 2017, Istanbul, Türkiye.

Geliş Tarihi/Received	02.10.2023
Revizyon Talebi/Revision Requested	20.10.2023
Son Revizyon/Last Revision	29.11.2023
Kabul Tarihi/Accepted	05.12.2023
Yayın Tarihi/Publication Date	24.07.2025

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Cite this article: Tekin GG, Sarıbaş EE, Yokuş B, Çolak M, Özdemir Kaya E, Talo Yıldırım T, Acun Kaya F, Uysal E. Effects of Tumor Necrosis Factor-Alpha Level in Peri-implanter Sulcular Fluid on Alveolar Bone Loss: A Prospective Study. *Curr Res Dent Sci* 2025;35(3):201-206.

ABSTRACT

Aim: The aim of this study was to investigate the possible relationships between periimplant sulcular fluid tumor necrosis factor alpha (TNF-α) levels and clinical parameters of periodontal disease and the amount of early alveolar bone loss in one-stage and two-stage implant systems.
Method: Standard Plus (SP) one-stage implants were placed in 20 of 40 patients who were missing mandibular 1st molars while Bone Level (BL) two-stage implants were placed in the rest of 20 patients. In order to determine the periodontal status of each individual, Modified Plaque Index (mPI), Modified Gingival Index (mGI), Modified Sulcular Bleeding Index (mSBI), Probing Pocket Depth (PPD) and peri-implanter sulcular fluids (PISF) were recorded before prosthesis loading (month 0), 3rd and 6th months after prosthesis loading. Radiological evaluation was performed with computed tomography (CT) images prior to loading and 6 months after prosthesis loading.
Results: In comparison, PPD values in the SP group are higher than in the BL group (P <.05). TNF-α, PPD values and rate of alveolar bone loss (ABL%) increased significantly between 0th and 6th month in terms of in-group evaluations in the SP group. In BL group, meaningful increases were observed in TNF-α and mSBI values between 0th and 6th months, in PISF volume between first 3 month period and first six month period.
Conclusion: Predictable results were observed to be obtained in two different systems as laboratory clinically and radiologically. TNF-α levels were significantly increased in both groups.
Keywords: Dental implant, tumor necrosis factor alpha, alveolar bone loss

ÖZ

Amaç: Bu çalışmanın amacı, farklı cerrahi prosedürler uygulanan bireylerde tümör nekroz faktör alfa (TNF-α) düzeyini saptamak ve periodontal hastalığın klinik parametreleri ile erken alveoler kemik kaybı miktarı arasındaki olası ilişkileri araştırmaktır.
Yöntem: Alt çene 1. molar dişleri eksik olan 40 hastadan 20'sine Standard Plus (SP) tek aşamalı implantlar, geri kalan 20 hastaya Bone Level (BL) iki aşamalı implantlar yerleştirildi. Her bireyin periodontal durumunu belirlemek için protez yükleme öncesi (0. ay), protez yükleme sonrası 3. ve 6. aylarda Modifiye Plak İndeksi (mPİ), Modifiye Gingival İndeksi (mGİ), Modifiye Sulküler Kanama İndeksi (mSKİ), Sondalama Cep Derinliği (SCD) ölçümleri kaydedildi ve peri-implant sulkus sıvıları (PİSS) alındı. Protez yükleme öncesi ve yüklemeden 6 ay sonra bilgisayarlı tomografi görüntüleri ile radyolojik değerlendirme yapıldı.
Bulgular: SP grubunda SCD değerleri BL grubuna göre daha yüksek bulundu (P <,05). SP grubunda grup içi değerlendirmeler açısından TNF-α, SCD değerleri, alveolar kemik kaybı (AKK) oranı 0. ay ile 6. ay arasında anlamlı olarak arttı. BL grubunda 0-6. aylar arasında TNF-α ve mSKİ değerlerinde, ilk 3 aylık dönem ile ilk altı aylık dönem arasında PİSS hacminde anlamlı artışlar gözlendi.
Sonuç: Laboratuvar klinik ve radyolojik olarak iki farklı sistemde öngörülebilir sonuçlar elde edildiği görüldü. TNF-α düzeyi her iki grupta da anlamlı olarak yükseldi.
Anahtar Kelimeler: Dental implantlar, tümör nekrozis faktör- alfa, tomografi

INTRODUCTION

The aim of modern dentistry is to restore patient's normal contour, function, esthetics, speaking and oral health.[1] There are various treatment methods under the title of fixed and removable prosthetic restorations in the compensation of tooth loss.

Most of the studies among these methods lead to the preference of fixed prostheses due to the problems with removable prostheses Oral implantation which is one of the fixed prosthesis options has turned to a frequently used method.[2]

A dental implant is a prosthetic device made of alloplastic material placed under the mucosa, in the periosteum or in the mandible to support a fixed or removable prosthesis and improve its retention.[3]

Two different surgical procedures are applied for osseointegrated implants as one-stage and two-stage. Both procedures have a pre-loading surgical approach and recovery period, but a second surgical operation is required in the two-stage procedure for the transmucosal abutment.[4] In the meta-analysis of Esposito et al.[5], data on 239 patients were analyzed in 5 randomized clinical studies comparing two surgical procedures. There was no statistically significant difference in terms of prosthesis and implant failures. In partially edentulous patients, the single-stage approach may be preferred as it does not require a single surgical intervention and shortens the treatment time, while the two-stage approach may be preferred in cases where optimal primary stability of the implant cannot be achieved.

Detection of inflammatory mediator levels of GCF in determining periodontal status is a good predictor to characterize inflammatory activity.[6] The similarity of peri-implant sulcus fluid (PISF) components around the implant with GCF components around natural teeth suggests that the components reflecting tissue destruction originate from the alveolar bone, since there is no periodontal ligament in the periimplanter region.[7]

Bacteria and their products, which play an important role in the pathogenesis of periodontal disease, stimulate macrophages, lymphocytes, fibroblasts and endothelial cells, causes cytokines to be the synthesis and secretion of cytokines. Cytokines, which result in the initiation and development of inflammatory activities, are responsible for a lot of pathological events ranging from connective tissue destruction to bone loss.[8]

Tumour necrosis factor alpha (TNF-α) is known as a cytokine that has a very important role in alveolar bone destruction.[9] TNF-α is generated for immune response against bacteria components by monocyte/ macrophages.[10] TNF-α can be considered as the foremost cytokine in immune response. This cytokine works to increase the attachment of polymorphonuclear leukocytes and monocytes to endothelial cells. TNF-α matrix increases connective tissue and bone destruction by stimulating osteoclast formation and activation and inducing stimulation of metalloproteinase (MMP) and Prostoglandin E_2 (PGE_2).[11] TNF-α is a prominent mediator of bone loss associated with peri-implantitis, especially in advanced stages.[12]

Dobresu et al.[13] examined the periimplant sulcus fluid TNF-alpha levels of 20 healthy patients and 34 mucositis and periimplantitis patients, among the cases showing positive and negative developments in the implants applied to 320 patients. It was observed that TNF-alpha level was significantly higher in patients with mucositis and periimplantitis. At the same time, a directly proportional relationship was found between TNF-alpha level and clinical parameters. Similarly, in a meta-analysis of 19 articles by Ghassib et al.[14], TNF-alpha levels were found to be statistically significantly higher in implants with periimplantar mucositis and periodontitis compared to healthy implants. Considering that periimplantar periodontitis is a disease characterised by alveolar bone loss, the effects of high TNF-alpha levels on alveolar bone loss have attracted the attention of researchers. The aim of this study was to evaluate the level of TNF-α, an important cytokine in the pathogenesis of periodontal disease, the rate of alveolar bone loss determined by computed tomography in the peri-implant sulcular fluid of dental implants placed by different surgical procedures and their possible relationships with clinical parameters.

METHODS

This study was carried out on a total of 40 patients, 16 females and 24 males, who were admitted to Dicle University Faculty of Dentistry, Department of Periodontology and had a single missing tooth.

Patients who were missing mandibular 1st molars were included in the study and asked to sign informed consent form. The study was conducted in accordance with the ethical principles set forth by the institutional and/or national research ethics committees and adhered to the guidelines of the 1964 Declaration of Helsinki and its subsequent revisions. Permission were gained from the Dicle Ethical Committee for all applications performed (03.03.2010 - D.Ü.D.F.E.K.2010/04).

Criteria of patients to be included in the study: Individuals who had optimum oral hygiene, were missing mandibular 1st molars, had suitable bone volume for implant placement, had no surgical risk systematically, had no systematical disease, were not addicted to alcohol, cigarette and medicine and had a tooth extracted at least 6 months ago in the area where the implant would be placed were included in the study.

Choice of Materials

40 ITI® solid screw implants with SLA surface were used in the study. 20 of them were determined as Standard Plus (SP) (ITI® Dental Implant System, Institute Straumann, Waldenburg, Switzerland) and the rest 20 as Bone Level (BL) (ITI® Dental Implant System, Institute Straumann, Waldenburg, Switzerland).

Surgical Operations

Operation sites were sterilized with antiseptic solution with 10% of povidon iodine. Following local anesthesia, full thickness mucoperiosteal flap was elevated by making sulcular incision along with midline crestal incision.

The diameter and length of the implant were determined by examining the CT cross sections of the region in which implant would be placed. 20 single-stage (SP) and 20 two-stage (BL) implants, with diameters between 4.1-4.8 mm and lengths between 10-12 mm, were applied to the patients. In SP implants, after the element that provides form to gingiva was placed, flaps were closed with 3.0 silk sutures. On the other hand, In BL implants after closure screws were placed, flaps were closed with sutures.

Area of surgery and oral hygiene check were made in patients' 1st and 2nd month periodic controls. At the 3rd month healing caps were placed. Gingiva on implant was removed by making window shaped incision under local anesthesia.

Clinical Indexes Used

Patients' clinical index measurements (Modified Plaque Index (mPI),[15] Modified Gingival Index (mGI),[16] Modified Sulcular Bleeding Index (mSBI),[15] Probing Pocket Depth (PPD),[17] were recorded at the 0th month prior to loading, at the 3rd and 6th months following loading and gingival crevicular fluids were taken. Clinical measurements were made using Williams periodontal probe.

Radiological Evaluations

CT images were examined prior to prosthesis loading and at the 6th month after prosthesis loading. In order to determine rate of alveolar bone loss (ABL), implant length (IL) was taken as the distance between implant neck and apex. Bone level was expressed as average of the distances between implant apex and buccal, lingual, mesial and distal surfaces respectively.

Peri-implant Sulcular Fluid Sampling

PISF samples were obtained using standardised special paper strips produced for Periotron according to the method of Rudin et al.[18] A previously calibrated Periotron 8000® (Pro-Flow Inc., Amityville, Newyork, USA) device was used for volume quantification of the obtained PISF samples. All PISF sampling was performed before recording other clinical parameters except mPI so as not to affect PISF volume and flow rate. After isolating the sampling area with sterile cotton rolls, the teeth were air-dried and PISF samples were taken from the buccal, lingual, mesial and distal regions of the implant using paper strips. The paper strips were placed in sterile eppendorf tubes containing 600ml phosphate buffer solution, the tubes were wrapped with paraffin and stored at -20°C until the day of analysis.

Laboratory Procedures

TNF-α levels were measured by IMMULITE® 1000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA) using the immuno-chemiluminescence principle after centrifugation at 600 rpm for 6 min and vortexing. The assay sensitivity of TNF-α is 4 pg/mL and the assay range is between 4 and 500 pg/mL.

Statistical Analysis

The data were analysed for compliance with the assumption of normal distribution using the Kolmogorov-Smirnow test and for homogeneity using the Levene test. Repeated measures ANOVA test was used for intra-group comparisons. When there was statistical significance, Bonferroni multiple comparison tests were used to determine between which periods the difference was between. The relationship between the variables was evaluated by Sperman Rank Correlation analysis. The differences between the two groups were analysed by independent student t-test.

RESULTS

A total of 40 patients, 16 women and 24 men, were included in the study. The average age of the SP placement group was 30,750 ± 8,583 years and the BL placement group was 37,000±11,814 years.

The mean values and standard deviations of the clinical parameters for the SP and BL groups are given in Table 1. In the SP group, PPD values increased significantly between the 0th and 6th months (*P* =.009). In BL group, significant increases were observed in mSBI values between the 0th and 6th months (*P* =.024) and in PISF volume between the first 3 months and the first 6 months (*P* =.031, *P* <.001). The evaluation of clinical parameters between SP and BL Groups in terms of time-dependent change is given in Table 2. When the 6th month values were compared according to the clinical parameters, it was observed that the difference between the mean PPD values of the SP group and the BL group was significant. (t=2.518, *P* <.05).

Table 1. Mean values and standard deviations of clinic parameters for SP and BL groups

Clinic parameters	n	0 Month	3 Month	6 Month
SP mPI	20	0.275± 0.370	0.138 ± 0.249	0.138±0.262
BL mPI	20	0.138±0.221	0.113±0.236	0.075±0.142
SP mGI	20	0.150±0.307	0.187±0.279	0.175±0.363
BL mGI	20	0.113±0.339	0.125±0.308	0.075±0.230
SP mSBI	20	0.287±0.284	0.625±0.825	0.450±0.402
BL mSBI	20	0.187±0.291	0.421±0.481	0.562±0.584
SP PPD	20	2.213±0.603	2.487±0.971	2.913±0.840
BL PPD	20	1.937±0.715	1.913±0.563	2.150±1.061
SP PISF	20	41.600±31.316	50.485±25.640	48.850±24.841
BL PISF	20	29.325±12.173	50.038±26.723	57.725±16.849

**mPI, modified plaque index; mGI, modified gingival index; mSBI, modified sulcular bleeding index; PPD, probing pocket depth; PISF, periimplanter sulcular fluid.*

Table 2. Time-dependent change in clinic parameters between groups and SP-BL groups

Clinical Parameters	0. Month	3. Month	6. Month
mPI	t=1,423; *P* .=165	t=0.325; *P* .=747	t=0.935; *P* .=357
mGI	t=0.366; *P* .=716	t=0.671; *P* .=506	t=1.038; *P* .=.306
mSBI	t=1.099; *P* .=278	t=0.995; *P* .=326	t=-0.709; *P* .=482
PPD	t=1.314; *P* .=197	**t=2.289; *P* .=028***	**t=2.518; *P* .=16***
PISF	t=1.634; *P* .=115	t=0.054; *P* .=957	t=-1.322; *P* .=194

**P .<05, mPI, modified plaque index; mGI, modified gingival index; mSBI, modified sulcular bleeding index; PPD, probing pocket depth; PISF, periimplanter sulcular fluid.*

Time-dependent change in TNF-α level between groups were compared and there was not any significant difference observed (*P* >.05). Time-dependent change in TNF-α level of SP and BL groups were given in Table 3. TNF-α level change of both groups at 0-3rd months and 3-6th months were not significant. However in both groups change in TNF-α level in 0-6th months was significant (SP group TNF-α level 3.857, *P* <.05, BL group TNF-α level 5.137, *P* <.05).

Mean values and standard deviations of ABL% amount in SP and BL groups were given in Table 4. Radiographic data belonging to groups and evaluation of the data regarding time dependent change were given in Table 4. When the values in terms of ABL% amounts were compared, at 0th and 6th month there was not any statistically significant difference between the two groups. In SP group change of ABL% amount at 0-6th months was significant (ABL% -2.110, *P* <.05). Whereas in BL group ABL% change in 0-6th was not statistically significant (ABL% 1.120, *P* >.05).

Table 3. Time-dependent change in TNF-α level of SP and BL groups

TNF-α	0-3 Month	3-6 Month	0-6 Month
SP	-1.136 (*P*=1.000)	-2.721 (*P*=.101)	**3.85 (*P*=.005*)**
BL	2.725 (*P*=.129)	2.411 (*P*=.187)	**5.137 (*P*=.001*)**

** P .<05; TNF-α, tumor necrosis factor alpha*

Table 4. Mean values and standard deviations of ABL% amount in SP and BL groups.

ABL%	SP	BL
0 Month	4.116±6.113	3.695±4.341
6 Month	6.226±6.669	4.315±4.815l
0-6 Month Difference	**-2.110 (0.006*)**	-1.120 (0.366)

**P* <.05; ABL%, rate of alveolar bone loss.

Positive correlation analysis results of ABL% with clinical parameters and TNF-α level in SP and BL groups were examined; SP and BL Group 0th month: There was not a positive correlation between ABL% and clinic parameters and TNF-α level. SP Group 6th month: Positive correlation of ABL% with mPI (r=0.550, *P* =.016) was found. BL Group 6th Month: Positive correlation was not observed between ABL% and clinical parameters and TNF-α level.

DISCUSSION

According to Branemark and Schroeder's original research reports, there are two implant systems as one stage, and two stage.[19] In this study, dental implants were placed in one-stage and two-stage and early results were compared clinically, radiologically and biochemically. This study showed that PPD values in the SP group were higher than those in the BL group. In terms of intragroup evaluations, TNF-α, PPD values, and ABL ratio increased significantly between the 0th and 6th months in the SP group. In the BL group, significant increases were observed in TNF-α and mSBI values between the 0th and 6th months and in PISF volume between the first 3 months and the first 6 months.

In a randomised split-mount clinical study, Nemli et al.[20] radiologically evaluated single-stage and two-stage implants at 6 months and 12 months in patients with posterior single tooth deficiency. Regardless of time, PPD results were found to be lower in single-stage implants than in two-stage implants. There may be several reasons for this different result. This study included 20 patients and used a split-mounth design. Our study was performed on 40 patients with a single missing tooth. The difference between the study design and the implants used may have affected the study results. Heydenrijk et al.[21] compared the two systems in 60 edentulous patients followed up for 5 years. While there were significant differences in PPD value between the groups in the early period, they showed that there was no significant difference in PPD value between the two groups at the end of 5 years. Similarly, in our study, the difference in PPD value between the two groups was significant in the early period, but the 5-year follow-up and the fact that the study was conducted in edentulous mouths may have affected the study result. In a study by Chehroudi et al.[22] on rats, more connective tissue width and less epithelial growth towards the apical region were found in two-stage implant systems compared to single-stage implant systems. This connective tissue region was shown to prevent apical migration of the overlying epithelial attachment. In the present study, the higher PPD value in the SP group compared to the BL group may be explained by the greater connective tissue width in two-stage implants. Since there was no significant increase in other clinical parameters in the SP group, we think that this result is not pathological. It is very important to monitor early bone loss in the first year. The use of a periodontal probe for clinical follow-up of minor bone changes may be easier than radiographic follow-up. Early bone loss can be seen especially in the facial region. Facial bone destruction cannot be detected with conventional peri-apical and panoramic radiographs.[23]

There was no statistically significant difference between the SP group and the BL group in terms of the respective ABL results. As for the intra-group analysis, a significant increase in %ABL was observed only in the SP group between 0 and 6 months (P <.05). The higher PPD value in the SP group can be explained by the significant increase in ABL in this group. In previous studies, it has been shown that the increase in PPD is parallel to the peri-implant bone loss because soft tissue is attached to the implant material only by weak epithelial attachment on the implant surface.[24,25] In the early postoperative period, 1 mm bone loss around the implant is considered normal due to healing and remodelling. In the late period, an annual loss of 0.1 mm is considered normal due to bone remodelling with the effect of occlusal forces following implant prosthesis construction.[26] However, small amounts of physiologically defined marginal bone loss occur immediately after implantation in one-stage implants and after the implant is opened to the oral environment in two-stage implants.[27] Gheisari et al.[28] placed a total of 310 implants in 140 patients, 170 single-stage and 140 two-stage implants. When they evaluated radiographs taken after implant surgery and 6 months after loading, they found no significant difference in the amount of marginal bone loss between the two systems. In a split-mounth study conducted by Astrand et al.[29] to compare two-stage and one-stage systems, no significant difference was detected in the retention rate and the amount of marginal bone loss in the two surgical systems according to the results of the 1-year observation period after loading. Siadat et al.[30] placed 17 of a total of 34 implants in 11 patients in a single-stage and 17 in a two-stage random manner. Radiography images taken at 6th and 12th months after loading were examined and no significant difference was found in terms of crestal bone loss. Menini et al.[31] reported that marginal bone loss in 19 single-stage and 19 two-stage short implants was similar in both systems in their radiological evaluations at 6 and 12 months. Similarly, in our study, no significant difference was found in the ABL rate between the two groups. Although these studies evaluated later results compared to our study, there was no difference in terms of ABL between the two systems. Venza et al.[32] evaluated 180 single-stage and 186 two-stage implants with radiographic images taken at the 1st year, 2nd year and 3rd year. Bone loss was significantly higher in the one-stage system than in the two-stage system. Unlike this study, the reason for the higher ABL rate in the one-stage system in our study may be related to the dental implant surgical procedure, number of implants, gingival phenotype, the neck of the implant, and the shape of the implant.

Dental plaque, calculus accumulation and ongoing inflammation are considered as an increased risk for the formation of peri-implantitis.[33] In addition, it has been reported that plaque formation, bleeding, sulcus fluid exudation and the absence of keratinized mucosa may be associated with bone loss in the peri-implant region.[34] In our study, we think that the relationship between ABL% and mPI in the SP group is compatible with the information.

PISF volume did not show any difference among groups during the study period. It showed a significant increase only in the group of BL between 0-3 and 0-6 months. From the point of laboratory results, a significant difference in TNF-α level was not detected between the groups. In SP and BL groups, at the level of TNF-α increase was observed significantly between 0 and 6 months. A relationship between TNF-α level and clinical parameters and ABL% was not found. Ghassib et al.[35] found that TNF-α is a cytokine whose amount increases when inflammation increases in their meta-analysis of 19 articles. In our study, TNF-α level did not differ significantly between the two groups, but it showed a significant increase between the 0th and 6th months in both groups.

This may be related to the significant increase in month PPD value, ABL% and mSBI value in the BL group. This result is consistent with studies showing the relationship of TNF-α with periodontal diseases.[36,37]

Machtei et al.[38] found a positive correlation between TNF-α and ABL in all 3 groups in their study comparing natural teeth with one-stage and two-stage implants functioning for 1-6 years. In addition, TNF-α level was found to be higher in the one-stage system than in the two-stage system. In our study, no correlation was found between TNF-α and ABL. In addition, no significant difference was observed between the two implant systems in terms of TNF-α level in our study. The reason for these differences may be explained by the early results of our findings.

CONCLUSION

In our study, no significant differences were found between one-stage and two-stage implant systems in terms of clinical and radiological findings except PPD. In conclusion, we believe that both surgical procedures are treatment options that can be applied to patients with the right indication. After a successful implant treatment, routine examination, patient education, maintenance and re-evaluation stages are very important to prevent peri-implant diseases and to intervene early in these diseases. Although TNF-α levels showed a significant increase in both groups, there was no difference between the groups during the study period. We believe that long-term follow-up studies in larger populations are needed to better understand the

diagnostic value of ABL and TNF-α, which are modified periodontal clinical parameters used within the study limits, in determining implant health.

Ethics Committee Information: Our study was conducted with the permission received from Dicle University Ethics Committee (Date: 03.03.2010, No: D.Ü.D.F.E.K.2010/04).
Informed Consent: All participants signed an informed consent form.
Peer-review: Externally peer-reviewed
Author Contributions: Concept – G.G.T., E.E.S., F.A.K.; Design G.G.T., E.E.S.; Supervision – G.G.T., E.E.S.; Resources – GGT, EES, TTY, FAK; Materials – G.G.T., E.E.S., B.Y.; Data Collection and/or Processing – G.G.T., T.T.Y., M.Ç., E.Ö.K., B.Y.; Analysis and/or Interpretation – G.G.T., E.E.S., E.U.; Literature Search – G.G.T.; Writing – G.G.T., E.E.S.; Critical Review – G.G.T., E.E.S.
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: It was supported by Dicle University Scientific Research Projects Coordination Office with project number 11-DH-69.
Etik Komite Onayı: Çalışmamız Dicle Üniversitesi Etik Kurulu'ndan (Tarih: 03.03.2025, No: D.Ü.D.F.E.K.2010/04) alınan izinle yürütülmüştür.
Hasta Onamı: Tüm katılımcılar bilgilendirilmiş onam formunu imzalamıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Fikir –G.G.T., E.E.S., F.A.K.; Tasarım – G.G.T., E.E.S.; Denetim – G.G.T., E.E.S.; Kaynaklar – G.G.T., E.E.S., T.T.Y., F.A.K.; Malzemeler – G.G.T., E.E.S., B.Y.; Veri Toplama ve/veya İşleme – G.G.T., T.T.Y., M.Ç., E.Ö.K., B.Y.; Analiz ve/veya Yorumlama – G.G.T., E.E.S., E.U.; Literatür Taraması – G.G.T.; Yazım – G.G.T., E.E.S.; Eleştirel İnceleme – G.G.T., E.E.S.
Çıkar Çatışması: Yazarların beyan edecekleri çıkar çatışması bulunmamaktadır.
Finansal Destek: Dicle Üniversitesi Bilimsel Araştırma Projeleri Koordinasyon Ofisi tarafından 11-DH-69 proje numarasıyla desteklenmiştir.
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