Biochemical Evaluation of the Effects of Concentrated Growth Factor Liquid on Osseointegration: A Split-Mouth Design Study

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Purpose: To investigate cytokine levels in peri-implant crevicular fluid and thus evaluate the effects of concentrated growth factor (CGF) on osseointegration. ***Materials and Methods:*** A total of 40 mandibular implants were symmetrically placed in a group of 20 systemically healthy patients enrolled in the study. In each patient, one implant wetted with liquid infiltrated from fibrin matrix was placed in the test side (Group L), and the other implant was placed in the control side without the application of any material (Group C). Peri-implant crevicular fluid was collected at 2, 4, and 12 weeks later. Marginal bone loss was measured with panoramic radiographs taken immediately after implant placement and at 12 weeks. Resonance frequency analysis (RFA) of the implants was performed intraoperatively and at 4 and 12 weeks. ***Results:*** Stability values of the implants in the CGF liquid–treated sites were higher than those of the control group at week 12 ($P = .005$). There was no statistically significant difference between the two groups in terms of marginal bone loss (MBL). Group L showed increased levels of tumor necrosis factor alpha (TNF-α) and receptor activator of nuclear factor kappa-B ligand (RANKL) at 2 and 4 weeks. Also, levels of osteoprotegerin (OPG) were higher in Group L at week 4 compared to Group C ($P = .033$). ***Conclusions:*** The increased TNF-α, RANKL, and OPG levels in this study demonstrate that CGF liquid can be used to accelerate peri-implant bone remodeling in the early phase of osseointegration. *Int J Oral Maxillofac Implants 2023:38:1182–1190. doi: 10.11607/jomi.10066*

Keywords: Concentrated growth factor, peri-implant crevicular fluid, cytokine, osseointegration

After Brånemark introduced the concept of osseointegration, dental implants became popular for the treatment of edentulous patients.[1] Osseointegration is characterized by the structural and functional connection between the implant surface and the bone.[2] A series of biologic events, such as angiogenesis, extracellular matrix formation, and the invasion of bone cells following fibrin polymerization, occur in the early stage of osseointegration.[3,4]

Platelet concentrates have been used widely as regenerative biomaterials in periodontal surgery.[5] Promoting the migration and proliferation of osteogenic cells, platelets accelerate bone regeneration by increasing the formation of blood vessels and inflammatory reactions.[6,7] Experimental studies have revealed that growth factors released from platelets could enhance osteoblastic differentiation on the implant surface, thus improving bone-to-implant contact.[8,9] The platelet concentrate platelet-rich fibrin (PRF) was introduced by Choukroun et al in 2001, and it contains a significant amount of cytokines, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF), and vascular endothelial growth factor (VEGF).[10,11] Concentrated growth factor (CGF) is another platelet derivative that differs from PRF in that it contains many growth factors trapped in a more rigid fibrin structure. It has been reported that CGF, obtained via performing a centrifugation process at variable speeds, accelerates the proliferation and differentiation of bone cells.[12,13] In addition to platelet-derived growth factors, the fibrin network contains blood and tissue cells such as leukocytes, endothelial cells, and fibroblasts, thus fostering tissue remodeling. Because they accelerate soft and hard tissue healing without inciting patient immune system reactions, CGF products are used widely in implant surgery.[12] It has been shown that the application of CGF membranes to implants could enhance osseointegration in the early period.[14] Özveri Koyuncu et al,[15] however, reported that the use of CGF membranes during dental implant surgery had a neutral effect on implant stability. In a study performed by wetting implant

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surfaces with CGF fluid, it was revealed that VEGF was released slowly from the cellular network onto the titanium surface, thus enhancing bone regeneration and healing following angiogenesis.[16]

Bone remodeling is a process in which osteoblasts, osteocytes, and osteoclasts play harmonious roles in bone resorption and formation. The stimulated osteoblasts and osteocytes initiate the remodeling process by producing macrophage colony–stimulating factor and receptor activator of nuclear factor kappa-B ligand (RANKL).[17] The pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α), are released by RANKL and numerous polymorphonuclear leukocytes around the wound. These inflammatory cytokines expressed from B and T lymphocytes are also components of the adaptive immune response.[18] TNF-α and RANKL initiate bone resorption by triggering osteoclastogenesis. As a cytokine of the TNF-α family, RANKL can be induced by TNF-α and stimulate bone resorption. Previous studies have reported that TNF-α initiated bone resorption independently of RANKL.[17,19] Osteoprotegerin (OPG) is a soluble cytokine receptor of the TNF family and is expressed by osteoblasts, fibroblasts, and a number of host cells. OPG binds to RANKL and prevents RANKL-RANK interaction, thus inhibiting osteoclastic activity. The RANKL:OPG ratio is used as an indicator for estimating bone remodeling, osteoclastic activity, and osteogenesis.[20–22]

The interactions between cytokines, growth factors, chemokines, and chemical mediators during blood clot formation result in a complex signaling process. High concentrations of cytokines and growth factors promote the migration of macrophages, neutrophils, and lymphocytes into the wound area. It has also been reported that cytokines released from the fibrin matrix may affect signaling pathways.[23] In this study, we hypothesized that the application of CGF liquid to dental implant procedures would contribute to inflammation, proliferation, and the remodeling process throughout healing. Therefore, the aim of this study was to investigate the clinical and biochemical effects of CGF liquid on the osseointegration of dental implants.

MATERIALS AND METHODS

This study was conducted at Hatay Mustafa Kemal University School of Dentistry, Department of Periodontology. The study protocol was approved by the Hatay Mustafa Kemal University Human Ethics Committee (approval no. 2019/119) on condition that Declaration of Helsinki ethical guidelines were observed. The patients who met the inclusion criteria and who volunteered to participate in the study were given detailed information about the study and provided informed consent before the procedure.

Patient Selection

Systemically healthy, nonsmoking individuals meeting the following inclusion criteria were included in the study:

- Above 18 years of age
- Symmetrical edentulous areas in the mandible
- Sufficient bone width and height for correct implant placement, as evaluated via dental volumetric tomography
- Sufficient soft tissue and no abnormal tissue condition (such as frenulum, narrow vestibule, etc) at the implant site

The following patients were excluded from the study:

- Those taking antibiotics, anti-inflammatory agents, corticosteroids, immunosuppressants, anticoagulants, or hormonal contraceptives for any reason within 3 months before the procedure and those taking bisphosphonates at that time or previously
- Individuals receiving soft or hard tissue augmentation procedures and those with any pathology or defect at the implant site
- Individuals with severe periodontal disease and poor oral hygiene
- Patients with severe caries or endodontic lesions in teeth adjacent to the implant site
- Pregnant and lactating women

Randomization and Blinding

Test and control sites were determined by randomly drawing a closed envelope between the drilling procedure and dental implant placement. The clinical and radiologic records of the study were obtained by an experienced periodontist (M.A.) who was unaware of the allocation.

Surgical Procedure

Infiltrative anesthesia was provided with an anesthetic solution containing 1:100,000 epinephrine. A midcrestal incision was made with a no. 15C scalpel, and a full-thickness flap was elevated. The drilling procedure (600 rpm, 25 Ncm) was performed according to the implant diameter and the prosthesis need for the edentulous area. A countersink drill was used for all implants to minimize marginal bone stress. In the presence of a natural tooth adjacent to the implant site, a distance of at least 1.5 mm between the tooth and the implant cavity was maintained, along with at least

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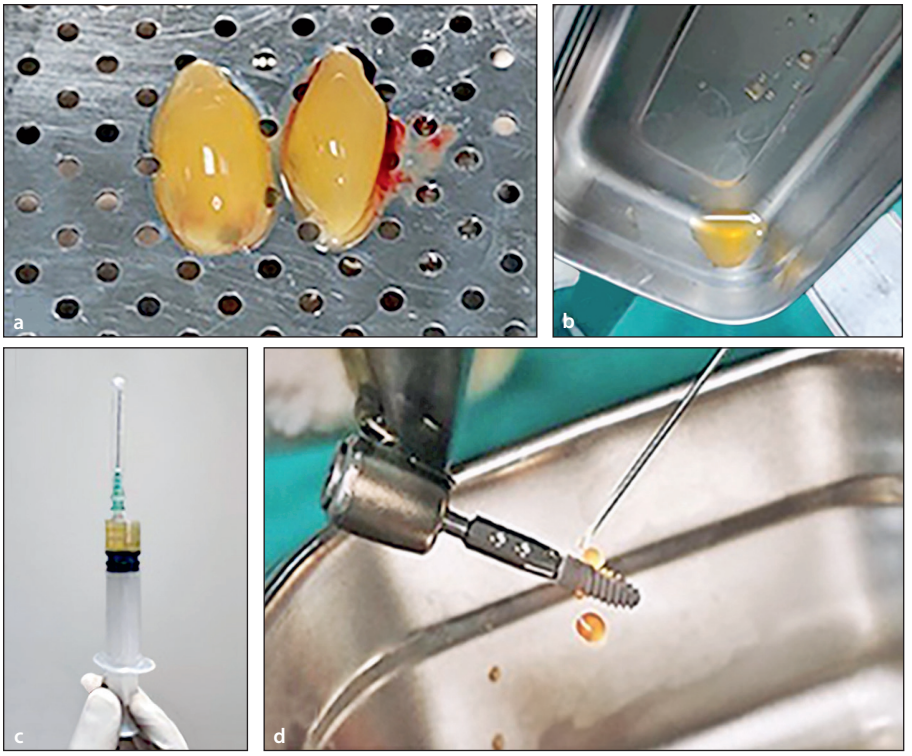

Fig 1 Preparation of CGF. *(a)* Placement of CGF matrices on the perforated plate. *(b)* Obtaining the CGF liquid. *(c)* Drawing the liquid into the syringe. *(d)* Wetting the implant surface with the liquid until there is no dry area.

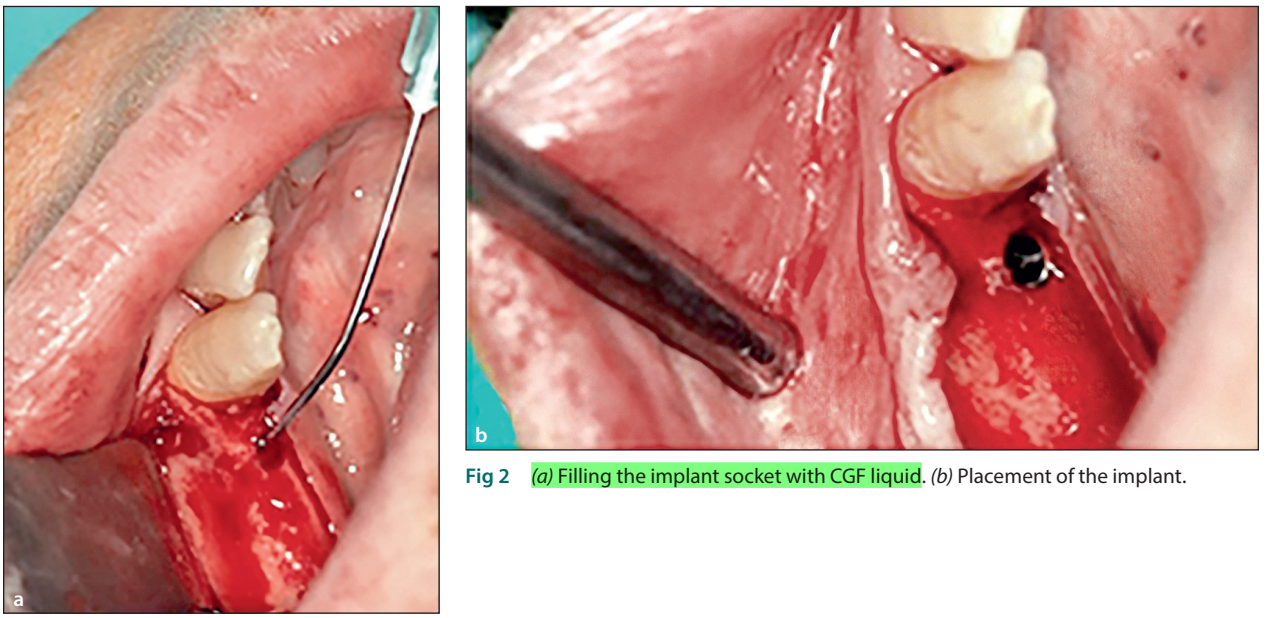

Fig 2 *(a)* Filling the implant socket with CGF liquid. *(b)* Placement of the implant.

1-mm-thick bone plates on the buccal and lingual aspects of the implant. Two CGF matrices obtained from centrifuged blood were placed on a perforated cover in a Surgident PRF Box (Fig 1a). Thus, a liquid leaking from the fibrin network was allowed to flow into the box (Fig 1b). For Group L, the liquid was collected with a syringe and applied over the implant surface until it was completely wet (Figs 1c and 1d). In addition, the implant site was filled with CGF liquid (Fig 2a). Then, the implant (T6, NucleOSS) was placed at bone level at a speed of 40 rpm with an insertion torque of 25 Ncm (Fig 2b), and a healing abutment was fitted on top of the implant. Implant placement without the CGF liquid was performed for Group C. Implant stability was determined using resonance frequency analysis (RFA) after placement. The flaps were sutured around the healing abutments with 5-0 silk sutures. The patients were prescribed an appropriate analgesic and mouth rinse to use when needed.

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The sutures were removed 10 days after surgery. All surgeries were performed by a dentist with at least 5 years of experience (O.F.A.).

Preparation of the CGF Liquid

Before starting surgery, about 9 mL of blood for each of two non-anticoagulant tubes was drawn from the cubital vein of the patient's forearm, and then the blood samples were centrifuged. CGF was obtained using an automatically adjusted centrifuge device (Medifuge CGF, Silfradent), fired at alternating and controlled speeds (2 minutes at 2,700 rpm, 4 minutes at 2,400 rpm, 4 minutes at 2,700 rpm, and 3 minutes at 3,000 rpm). Centrifugation resulted in three layers in the tube: a red blood cell layer at the bottom, a platelet-poor serum layer at the top, and a fibrin gel layer containing growth factors and platelets in the middle. The serum in the upper layer was removed with a sterile syringe, and the fibrin layer was removed from the tube using a clamp. The red blood cells in the lower layer were removed from the fibrin structure with scissors. The fibrin matrices were placed into a Surgident box for obtaining the liquid.

Clinical Measurements and RFA

Four surfaces (mesial, distal, buccal, and lingual) of each healing abutment were evaluated for plaque index (PI),[24] gingival index (GI),[24] pocket depth (PD), and gingival bleeding index (GBI).[25] All clinical measurements were repeated 2, 4, and 12 weeks after the procedure. RFA was performed intraoperatively and postoperatively at weeks 4 and 12 with a Penguin RFA implant stability monitor to determine the implant stability quotient (ISQ).

Measurement of Marginal Bone Loss

To assess the marginal bone loss (MBL) around implants, the technique recommended by Haas et al[26] was modified and used in the present study. The calibrated digital panoramic radiographs were taken with Planmeca technology immediately after implantation and 12 weeks later (Fig 3). The implant platform at the level of the alveolar crest was considered the threshold for measuring the change in marginal bone level. The threads not surrounded by bone in the mesial and distal parts of the implant were determined for measuring MBL. An average value for total bone loss was obtained.[27] When mean MBL around the implant exceeded 1 mm,[28] the patient was excluded from the study. All radiologic measurements were performed by two blinded examiners (M.A.), and the measurements were evaluated to assess agreement between the examiners.

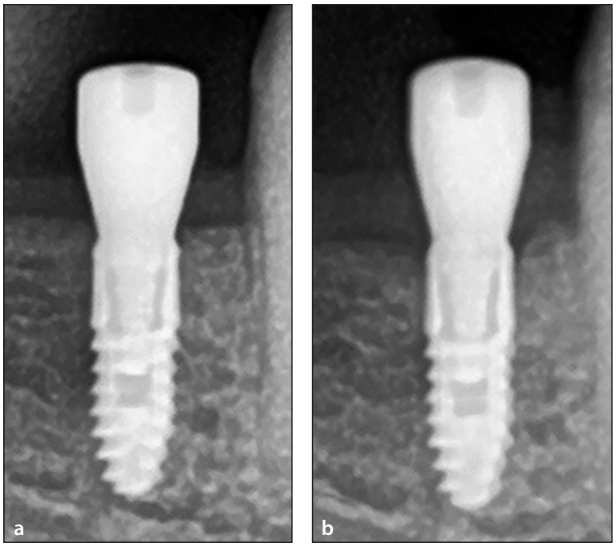

Fig 3 Sections from panoramic views of an implant in the study group. *(a)* Immediately after implantation. *(b)* The area 12 weeks after implantation. Note the change in the marginal bone level around the implant at the end of the 12th week.

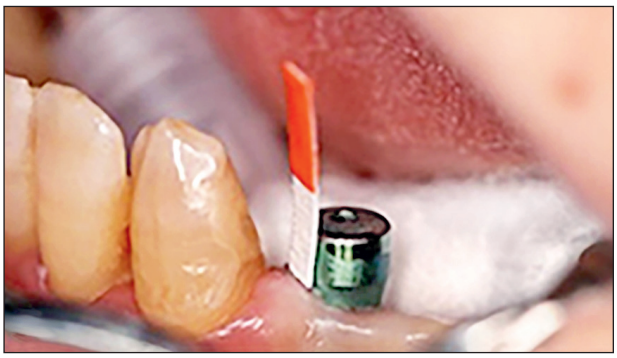

Fig 4 Obtaining peri-implant crevicular fluid with a PerioPaper (Oraflow).

Determination of Peri-implant Bone Density

CBCTs of each patient were obtained with PaX-i3D (Vatech) for assessing the implant locations before surgery. Bone density was calculated in a rectangular area with a perimeter of 20 to 25 mm (area: 30 or 40 mm^2) in subsequent sagittal slices at the implant location using a software program (Ez3D2009, version 1.0, Vatech). Thus, the average pixel values obtained were stated as gray values (GVs).

Collection of Peri-implant Crevicular Fluid

First, the implant site was isolated from saliva and dried with air. An absorbent filter paper strip (PerioPaper, Oraflow) was placed 1 mm into the pocket in the mesial and distal surfaces of the healing abutment and was left there for 30 seconds to allow absorption of a sufficient amount of peri-implant crevicular fluid (Fig 4).

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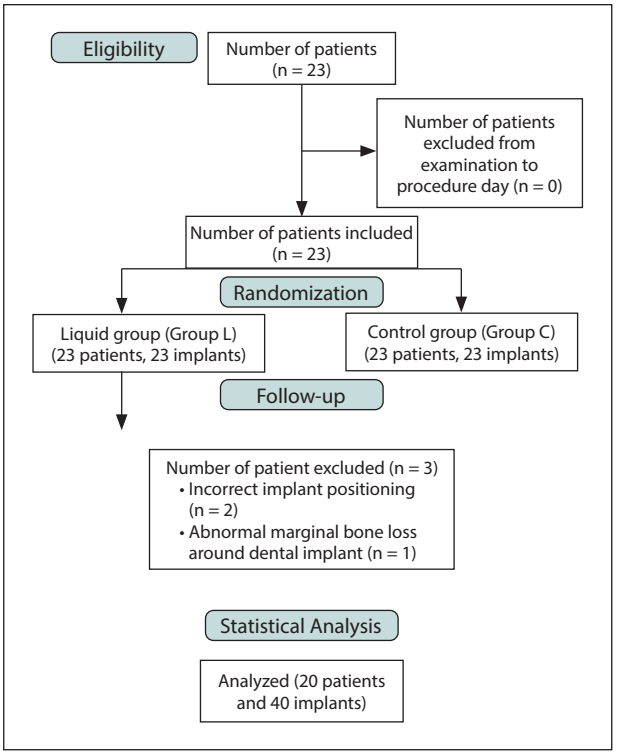

Fig 5 Flowchart of the study.

The volume of the fluid was measured with a calibrated electronic device (Periotron 8010, Oraflow). Paper strips contaminated with blood or plaque were excluded from the study. The paper strips were transferred into an Eppendorf tube covered with paraffin wax and stored at –80°C until analysis.

Biochemical Analysis

Initially, fresh phosphate-buffered saline ([PBS] pH: 7.00, 137 mM sodium chloride, 10 mM disodium phosphate, and 2.7 mM potassium chloride, PBS of 300 µL) was added to each Eppendorf tube, left at 25°C for 30 minutes, and then centrifuged at 12,000 × g at 4°C for 15 minutes. Following centrifugation, the strips in the Eppendorf tube were removed, and the supernatant obtained was used for enzyme-linked immunoassay (ELISA). TNF-α (Boster Biological Technology), soluble RANKL (Elabscience), and OPG (Boster Biological Technology) levels were measured by ELISA at 450 nm wavelength using commercial kits and the Thermo Fisher Scientific Multiskan GO ELISA reader. All analyses were performed in accordance with manufacturer instructions.

Statistical Analysis

The data were analyzed at 95% confidence using IBM SPSS 21 software. Continuous variables were expressed as mean, standard deviation, median, minimum, and maximum. Categorical variables were expressed as frequencies and percentages. The normality of the distribution of the data was analyzed using Shapiro-Wilk test, and Mann-Whitney *U* and Student *t* tests were used to compare independent groups. Wilcoxon signed rank test and Friedman test were used to compare dependent variables. *P* was .05 for all analyses.

The power analysis of the study was performed on the levels of cytokine measured at three different times. In this analysis, the partial eta squared was calculated as 0.258, and the effect size was calculated as 0.589. Considering the smallest of the correlations between each time measurement, it was determined at the level of 0.453. Because Mauchly sphericity test could not provide sphericity, the epsilon value was determined as 0.656, taking into account the Greenhouse-Geisser epsilon value. With all these arguments and with 95% power, the number of patients required to be taken at each measurement time was found to be 13. However, because nonparametric test analysis would be performed, it was accepted that the minimum number of individuals to be included in the study should be 15, with an increase of 15%. Considering that there may be data missing for this study, 20 individuals were included in each study group for a stronger analysis.

RESULTS

A group of 23 individuals was included in this study. However, three patients were excluded from the study due to MBL > 1 mm around the implant (n = 1) and incorrect implant positioning (n = 2). Thus, 40 implants in 20 patients were evaluated for the statistical analysis (Fig 5). Among the participants were 9 men and 11 women. The mean age of the participants was 54.25 ± 14.13 years (range: 25–79 years).

In the comparison of the PI, GI, PD, and GBI scores relating to the implants, no significant differences were found between Group L and Group C ($P > .05$; Table 1).

The characteristics of the placed implants and the bone density in the implant locations are shown in Tables 2 and 3, respectively. The distribution of the implants in terms of diameter and length was similar across groups ($P = .939$ and $P = .562$, respectively). Also, the bone density in the implant locations did not show any difference between the groups ($P = .841$). The mean ISQ value obtained intraoperatively was 74.90 ± 5.23 for Group L. The ISQ value at week 12 was increased to 79.80 ± 1.76. It was found that the resonance frequency value at postoperative week 12 was significantly higher than the intraoperative and week 4 values ($P = .001$). Similarly, the resonance frequency of the implants in Group C significantly increased at week 12 ($P = .005$). The ISQ value at week 12 in Group L was

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Table 1 Intragroup Comparison of Clinical Parameters

Parameters	Time (weeks)	Group L	Group C	P^{β}
PI	2	0.90 ± 0.79	0.95 ± 0.69	.665
	4	1.00 ± 0.56	1.20 ± 0.89	.305
	12	0.70 ± 0.66	1.05 ± 0.76	.083
	P^{α}	.250	.641	
GI	2	0.80 ± 0.83	0.85 ± 0.59	.782
	4	0.65 ± 0.67	0.95 ± 0.69	.132
	12	0.65 ± 0.59	0.50 ± 0.51	.257
	P^{α}	.695	.054	
PD (mm)	2	2.55 ± 1.15	2.45 ± 1.36	.480
	4	2.00 ± 0.56	2.05 ± 0.51	.739
	12	1.80 ± 0.62	1.65 ± 0.59	.180
	P^{α}	.030	.016*	
GBI (%)	2	0.35 ± 0.49	0.45 ± 0.51	.157
	4	0.35 ± 0.49	0.50 ± 0.51	.083
	12	0.15 ± 0.37	0.20 ± 0.41	.564
	P^{α}	.102	.063	

P^{α} = Friedman test; P^{β} = Mann-Whitney *U* test; **P* values < .05 are statistically significant.

Table 2 Comparison of Implant Characteristics

Implant properties		Group L n (%)	Group C n (%)	*P*
Diameter (mm)	3.5	10 (27.8)	9 (25)	.939
	4.1	10 (22.8)	11 (25)	
Length (mm)	8	1 (50)	–	.562
	10	19 (24.4)	20 (25.6)	

n, number of implants, Chi-square test, significance level; *P* values < 0.05 are statistically significant.

Table 3 Peri-implant Bone Density

	Group L	Group C	*P*
Gray value	801.90 ± 33.07	802.38 ± 30.10	.841
Min – max	565.30 – 1075.30	611.30 – 1,078.60	

Mann-Whitney *U* test, *P* values < .05 are statistically significant.

Table 4 Intra- and Intergroup Comparison of Resonance Frequency Values (ISQ)

	Group L		Group C		
Interval	mean ± SD	min – max	mean ± SD	min – max	P^{β}
Baseline	74.90 ± 5.23	63.00 – 82.00	75.80 ± 3.48	66.00 – 81.00	.685
Week 4	75.60 ± 3.71	66.00 – 80.00	76.00 ± 2.22	72.00 – 79.00	.788
Week 12	79.80 ± 1.76	77.00 – 84.00	78.50 ± 2.30	73.00 – 81.00	.005*
P^{α}	.001*		.005*		

P^{α}, Friedman test; P^{β}, Mann-Whitney *U* test; **P* values < .05 are statistically significant.

Table 5 Marginal Bone Loss Around Dental Implants

	Group L	Group C	*P*
Mean ± SD	0.12 ± 0.04	0.17 ± 0.06	1.000
Min – max	0 – 0.65	0 – 0.90	
Median	0	0	

Independent Sample *t* test and Mann-Whitney *U* test; *P* values < .05 are statistically significant.

statistically significantly higher than that of Group C ($P = .005$; Table 4).

The MBL around the 80 implants in the test and control groups was evaluated by two blinded examiners specialized in their fields (M.A.). In the study in which 160 sites (80 mesial and 80 distal surfaces) were included for the statistical analysis, the correlation between the examiners was 84% (r = 0.840, $P = .000$). The MBL around dental implants in Group L and Group C are shown in Table 3. Accordingly, the difference in the reduction in marginal bone levels during the study period was not statistically significant between groups ($P = 1.000$; Table 5).

The mean TNF-α and RANKL levels measured in the peri-implant crevicular fluid of Group L were significantly higher at weeks 2 and 4 when compared to Group C ($P < .05$). The OPG levels were significantly higher in Group L than in Group C at week 4 ($P = .033$); however, this difference was not significant at other time points ($P > .05$). On the other hand, neither Group L nor Group C showed any significant difference between the RANKL:OPG ratio at any time point ($P > .05$). The reduction in TNF-α levels and the RANKL:OPG ratio were statistically significant in Group L over time ($P < .05$). The levels of RANKL at weeks 2, 4, and 12 were 4.56 ± 4.26 pg/dl, 6.13 ± 6.89 pg/dl, and 2.17 ± 2.64 pg/dl in Group L, respectively. A significant reduction in peri-implant crevicular fluid RANKL levels was observed in Group L ($P = .024$). The levels of all cytokines did not present a statistically significant change for Group C ($P > .05$; Table 6).

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Table 6 Comparison of Cytokine Levels

Biomarkers (pg/mL)	Time (weeks)	Group L	Group C	*P*
TNF-α	2	1.69 ± 1.80	0.46 ± 0.24	.001*
	4	0.96 ± 0.94	0.39 ± 0.26	.011*
	12	0.64 ± 0.71	0.42 ± 0.24	.334
	P	.001*	.675	
RANKL	2	4.56 ± 4.26	2.03 ± 1.66	.001*
	4	6.13 ± 6.89	2.65 ± 1.74	.006*
	12	2.17 ± 2.64	1.37 ± 0.87	.455
	P	.024*	.086	
OPG	2	5.62 ± 6.01	3.57 ± 2.86	.053
	4	7.67 ± 6.48	4.62 ± 4.53	.033*
	12	6.80 ± 4.76	4.51 ± 3.83	.126
	P	.165	.819	
RANKL:OPG	2	1.38 ± 1.46	0.66 ± 0.62	.060
	4	0.97 ± 0.94	0.68 ± 0.44	.580
	12	0.42 ± 0.49	0.44 ± 0.33	.501
	P	.001*	0.308	

Wilcoxon signed rank test; **P* values < .05 are statistically significant.

DISCUSSION

Microbial dental plaque results in inflammatory reactions in periodontal soft and hard tissues because it harbors a large number of pathogenic microorganisms.[29] Various studies have reported that TNF-α, RANKL, and the RANKL:OPG ratio increased while OPG decreased in the gingival crevicular fluid, particularly in cases with dental plaque–induced periodontitis.[30,31] In this study, microbial dental plaque around the dental implants was evaluated, and no difference could be found between the groups in terms of mean plaque scores. There were also no differences in GI, PD, or GBI scores. Therefore, primary outcomes of this study, including implant stability, MBL, and cytokine levels, are discussed irrespective of the presence of dental plaque and the gingival condition.

Fibrin formation and various proteins in the blood clot are of great importance in the integration of titanium surfaces with bone. Several studies have shown that the fibrin network formed within the first 4 hours after the development of a wound facilitates the adhesion of inflammatory cells and cells involved in tissue repair to the implant surface, thus accelerating the osseointegration process.[32,33] Angiogenesis and clot stabilization occurring in the first 3 to 4 days lead to the formation of immature bone between the existing bone and the implant on fourteenth day.[34] Primary stability is important for implants during the first week after implantation and reaches its lowest level within 2 weeks.

The osseointegration process, also known as *secondary stability*, starts in the second week and peaks in the eighth week.[35] Han et al[36] emphasized that implant stability should not be measured before the third week. RFA is frequently used to determine the stability of an implant. An implant stability value in the range of 0 to 100 is obtained via RFA.[37] ISQ values between 40 and 80 have been considered ideal for clinically stable implants.[38] Primary stability values were obtained for all implants included in this study. There was no difference between Groups L and C in terms of insertion torque. However, a higher stability value was observed at week 12 in Group L compared to Group C.

Pirpir et al[14] reported that the application of CGF products improved implant stability. In the present study, ISQ values increased in both groups at the end of 12 weeks. This increase in secondary stability for Group C is expected as result of the natural process of osseointegration. Studies have stated that bone density has an impact on implant stability.[39,40] However, the bone densities (GVs) obtained from the CBCT images in this study did not show any difference between the groups. The increase in the ISQ values of Group L at week 12 may be related to the growth factor effect, as in the aforementioned study. On the one hand, other factors, such as the surgical technique, implant length, and implant diameter, may influence the primary stability of the implant.[41,42] In a study by Bischof et al,[43] however, it was reported that implant characteristics such as length and diameter have no effect on primary stability. In this study, the dental implants placed in Groups L and C shared a similar distribution of implant characteristics.

Marginal bone stability around dental implants has been considered one of the main criteria for long-term implant success and esthetics.[44] A number of factors, including smoking, periodontal disease or poor oral hygiene, insufficient crestal bone width, surgery with or without flaps, implant malpositioning, excessive heating of the bone, the absence of platform switching, excessive pressure and compression of the cortical bone, and soft tissue factors have been associated with the loss of marginal bone in the early period.[45–47] Because of this, patients with abnormal bone loss around the implant (> 1 mm, circumferential, bone dehiscence, etc) were excluded from the study to prevent them from affecting the study results. Several imaging techniques may be used to assess MBL around dental implants. Although the use of periapical radiographs has been noted most often,[48,49] panoramic radiographs may also be used to measure MBL.[50,51] In addition, Ivanauskaite et al[52] concluded that panoramic radiographs were superior to bitewing radiographs for assessing marginal bone changes in mandible. In this study performed

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in mandible, the measurements on panoramic radiographs taken immediately after the surgery and during week 12 of the healing process showed no difference between the groups in terms of MBL.

Implant osseointegration is a bone remodeling process in which a series of inflammatory events occur. The inflammatory events are directed by various cytokines such as IL-1, IL-6, and TNF-α. TNF-α in the tissue induces the expression of RANKL from osteoblasts.[53] High levels of TNF-α and RANKL and low OPG levels initiate osteoclastic bone resorption. In addition, a high RANKL:OPG ratio is associated with loss of bone mass.[21] The factors that induce the release of RANKL also regulate OPG expression from osteoblasts.[54] Animal studies have shown that the physiologic expression of TNF-α by inflammatory cells such as neutrophils and monocytes without any pathologic process supports bone regeneration and could be the first step of the remodeling process.[55] It has also been reported that growth factors in various platelet concentrates induce neutrophil-, macrophage-, and lymphocyte-related inflammatory reactions in the healing area.[23] Within the first month of the early healing period in the present study, higher levels of peri-implant crevicular fluid TNF-α, RANKL, and OPG were observed for implants treated with CGF liquid compared to implants in the control group. While the OPG levels were highest at week 4 in Group L, the RANKL:OPG ratio remained consistent in Group C throughout the course of the study. These findings may indicate an active remodeling process in the early phase of implant osseointegration in Group L. In addition, it has been suggested that the high growth factor concentration in the CGF liquid when it is applied into the socket could contribute to implant stability by increasing the bone density between the implant and the adjacent bone.[56]

CONCLUSIONS

The limitations of this study include the lack of a surgical guide during implant placement and the lack of measurements in the second month after surgery. Within the limitations of this study, it was observed that CGF liquid showed positive effects on the healing of peri-implant tissues by fostering biochemical events in a controlled manner. In this study, CGF liquid was applied to the surface of the implant and the socket for a minute or two. We conjecture that long-term application of CGF liquid to implant surfaces in a sterile tube could further accelerate implant osseointegration. Further studies are needed.

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