RESEARCH PAPER

Evaluation of the Effect of Bone Bioactive Liquid on Osseointegration: A Randomized Controlled Trial Assessing Primary Stability and Bone Turnover Markers

Dr. Shanmuganathan Natarajan [1] Dr. Madhan Kumar Seenivasan [2] Dr. Sowmya Ranjana. A.R[3]
[1] Department of Prosthodontics and Crown & Bridge, Sri Ramachandra Dental College & Hospital, Sri Ramachandra Institute of Higher Education & Research, Iyyappanthangal, Chennai, Tamil Nadu, India.
[2] Department of Prosthodontics and Crown & Bridge, Sri Ramachandra Dental College & Hospital, Sri Ramachandra Institute of Higher Education & Research, Iyyappanthangal, Chennai, Tamil Nadu, India.
E-mail: sowmyaarulalan5696@gmail.com

Abstract:

Background: Osseointegration is critical for the long-term success of dental implants and is influenced by both local bone healing and systemic bone remodeling. Bone Bioactive Liquid (BBL) has been proposed to enhance early bone formation around implants, although its effect on implant stability and biochemical markers of bone turnover remains unclear.
Objective: To evaluate the effect of Bone Bioactive Liquid (BBL) on early osseointegration of dental implants by assessing implant stability and systemic bone turnover markers.
Methods: This prospective, double-blinded randomized controlled clinical trial included 16 patients allocated equally to BBL-treated and untreated groups. Dental implants were placed with or without application of BBL (Theravex Tissue Care Plus). Implant stability was evaluated by resonance frequency analysis and expressed as implant stability quotient (ISQ) on Days 1, 7 and 30. Serum osteocalcin, N-terminal telopeptide (NTX) and bone-specific alkaline phosphatase (BAP) were measured using ELISA. Intergroup comparisons were performed using independent-samples t-tests and associations between ISQ and biochemical markers were assessed using Pearson correlation analysis. Statistical significance was set at $p<0.05$.
Results: Baseline ISQ values were comparable between groups ($p=0.344$). Untreated implants showed significantly higher ISQ values on Days 7 and 30 ($p<0.001$). Osteocalcin and NTX showed no significant intergroup differences at any assessment ($p>0.05$). BAP was significantly higher in the BBL-treated group on Day 30 ($p<0.001$). No significant correlations were observed between ISQ values and the biochemical markers.
Conclusion: BBL application did not improve early mechanical stability of dental implants during the first 30 days after placement. The higher BAP level observed in the BBL-treated group at Day 30 suggests increased osteoblastic activity, although this biochemical response did not translate into greater implant stability during the study period.
Keywords: Dental implants, Osseointegration, Bone bioactive liquid, Implant stability quotient, Bone turnover markers.
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1 | Introduction

Dental implants are widely used in clinical practice for replacing missing teeth to restore oral function and improve patient quality of life, with implant-supported restorations demonstrating superior comfort, chewing efficiency and patient satisfaction compared to removable prostheses. Advances in implant macrodesign, surface engineering and restorative protocols have improved long-term predictability; however, successful outcomes fundamentally depend on stable osseointegration. [1-3] Osseointegration is a dynamic wound-healing process initiated immediately after implant placement, involving clot formation, inflammatory cell recruitment, angiogenesis and subsequent osteogenic differentiation leading to bone formation at the implant interface.

Early healing, particularly within the first week, represents a critical and vulnerable phase where imbalance between bone formation and resorption, persistent inflammation, poor bone quality or systemic factors such as diabetes may compromise integration and increase the risk of implant failure. Implant stability, which transitions from primary mechanical stability to secondary biological stability, is commonly assessed using resonance frequency analysis (RFA) and expressed as implant stability quotient (ISQ), providing a reliable non-invasive measure of osseointegration over time. [4] Recent advances in osteoimmunology emphasize the role of immune modulation in bone healing, where controlled inflammation supports repair, while excessive inflammatory responses promote osteoclastogenesis and bone loss.

Early physicochemical interactions at the implant surface including protein adsorption, fibrin clot formation and cellular adhesion, are influenced by surface characteristics such as hydrophilicity which enhances blood–implant interaction and osteogenic activity. [5] While various surface modifications have been explored, they require permanent alterations to implant design; therefore, liquid-phase adjuncts that modify the immediate biological environment during surgery have gained attention.

Bone Bioactive Liquid (BBL; Theravex Tissue Care Plus), a phosphate-buffered saline solution supplemented with calcium and magnesium ions, has been proposed as an interface-conditioning agent that enhances surface hydration, improves protein adsorption, and promotes osteogenic cell activity. [6] Preclinical studies suggest that BBL may favorably modulate macrophage polarization, reduce pro-inflammatory cytokines, and create a microenvironment conducive to bone regeneration; however, clinical evidence remains limited. [7-9]

In addition to mechanical assessment using ISQ, bone turnover markers such as osteocalcin (bone formation), N-terminal telopeptide (NTX; bone resorption) and bone-specific alkaline phosphatase (BAP; osteoblastic activity) provide insight into the biological processes underlying osseointegration. Osteocalcin, a non-collagenous protein produced by osteoblasts, reflects bone formation and mineralization, whereas NTX indicates degradation of type I collagen and serves as a marker of bone resorption. Bone-specific alkaline phosphatase (BAP) is associated with osteoblastic differentiation and matrix mineralization. Together, these markers provide an integrated assessment of the balance between bone formation and resorption during healing. [10, 11]

Therefore, the present randomized controlled clinical trial was designed to evaluate the effect of BBL on implant osseointegration by assessing implant stability using ISQ values and systemic bone turnover markers, including osteocalcin, NTX and BAP. It was hypothesized that the application of BBL at the time of implant placement would result in significantly improved implant stability and favorable changes in bone turnover markers compared to the control group.

2 | Materials and Methods

Study design and ethical approval

This study was conducted as a prospective, parallel-arm, double-blinded randomized controlled clinical trial. Ethical approval was obtained from the Institutional Ethics Committee of Sri Ramachandra Institute of Higher Education and Research, Chennai (Ref No: CSP-III/25/MAR/19/197, dated 10 March 2026). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki, and participant confidentiality was maintained using coded identifiers.

Sample size estimation

Sample size was calculated using G*Power software (version 3.1) for an independent two-sample t-test with a significance level of 5% and power of 85%. Based on previous data, the effect size was estimated at 0.63, resulting in a minimum requirement of 8 participants per group. Accordingly, a total of 16 participants (8 per group) were included.

Participant recruitment and eligibility

Participants were recruited from the outpatient department of Prosthodontics at Sri Ramachandra Dental College and Hospital. Adult patients requiring implant placement with adequate bone support, good systemic health, and satisfactory oral hygiene were included. Patients with systemic conditions affecting bone healing, uncontrolled metabolic disorders, active periodontal disease, heavy smoking, parafunctional habits or medications influencing bone metabolism were excluded.

Randomization and allocation concealment

Eligible participants were randomly assigned to either the test group (BBL) or control group in a 1:1 ratio using a computer-generated random sequence. Block randomization was used to ensure balanced allocation. Allocation concealment was achieved using sequentially numbered, opaque, sealed envelopes prepared by an independent staff member.

Blinding

A double-blind design was employed. Participants, outcome assessors, laboratory personnel and the statistician were blinded to group allocation. Blood samples and datasets were coded to maintain blinding throughout the study.

Interventions and surgical protocol

All procedures were performed under aseptic conditions using a standardized surgical protocol. Implant placement was carried out under local anesthesia with saline irrigation. Flap or flapless approaches were used based on clinical requirements.

In the test group, Bone Bioactive Liquid (BBL; Theravex Tissue Care Plus, UAE) was applied as an interface-conditioning agent during implant placement. In the control group, implants were

placed without BBL, using only standard saline irrigation. Healing abutments or cover screws were placed as per protocol, and soft tissue closure was achieved with sutures when required. Postoperative care was standardized for all participants.

Follow-up and outcome measures

Participants were followed at predefined intervals (Day 1, Day 7, and Day 30). Clinical evaluation included assessment of healing, discomfort, and complications.The primary outcome was implant stability measured using resonance frequency analysis (RFA) and expressed as implant stability quotient (ISQ). Secondary outcomes included serum levels of osteocalcin, N-terminal telopeptide (NTX) and bone-specific alkaline phosphatase (BAP), measured at baseline and follow-up.

Implant stability assessment

Implant stability was measured using an Osstell device (Osstell AB, Sweden). A compatible SmartPeg was attached, and measurements were recorded in buccolingual and mesiodistal directions. The mean of these readings was taken as the ISQ value. All measurements were performed by a blinded, calibrated examiner using the same device.

Blood sample collection and biomarker analysis

Venous blood samples were collected between 8:00 and 10:00 AM to minimize diurnal variation. Samples were obtained from the antecubital vein under sterile conditions, allowed to clot, centrifuged, and stored at −80°C until analysis. Serum levels of osteocalcin, NTX, and BAP were measured using ELISA kits (Krishgen Biosystems, Mumbai, India). All samples were analyzed in duplicate, and standard curves were generated for each assay. Quality control measures were implemented to ensure reliability.

Data collection and management

Clinical and laboratory data were recorded using standardized case report forms. Data entry was performed using double-entry verification to minimize errors. All data were anonymized and stored securely for analysis.

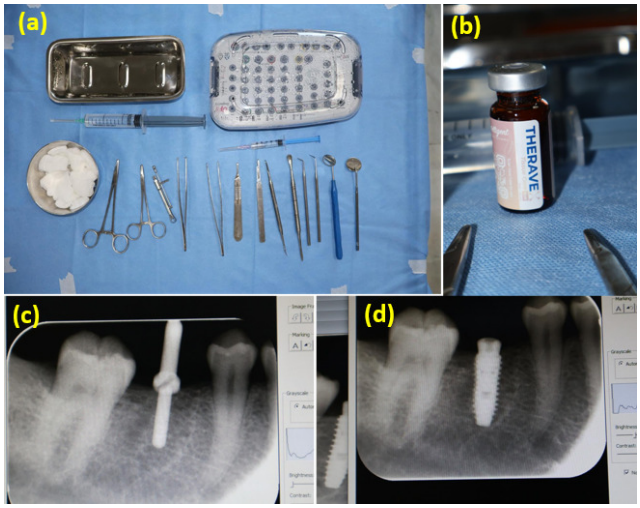
Statistical Analysis

Statistical analysis was performed using SPSS software (version 27, IBM Corp., USA). Continuous variables were expressed as mean ± standard deviation. Intergroup comparisons at each time point (Day 1, Day 7 and Day 30) were performed using independent samples t-tests. Pearson's correlation coefficient was used to assess the relationship between ISQ values and biochemical markers. A p value < 0.05 was considered statistically significant, and $p < 0.01$ was considered highly significant.

3 | Results

Representative clinical and radiographic images demonstrating surgical armamentarium, intraoral site preparation, implant positioning and final implant placement with healing abutment are shown **(Figure 1a–d).** These images illustrate the standardized surgical protocol followed in the study.

Figure 1a: Surgical Armamentarium; b) Intraoral image of edentulous site in 46; c) RVG image with parallel pin placement; d) Implant and healing abutment placed



Intergroup comparison of implant stability showed that Day 1 ISQ values were comparable between untreated and BBL-treated implants, indicating similar baseline primary stability (55.50 ± 0.40 vs 55.24 ± 0.64; $p = 0.344$). By Day 7, untreated implants demonstrated significantly higher ISQ values compared to BBL-treated implants (56.88 ± 0.62 vs 54.98 ± 0.31; $p < 0.001$). This difference became more pronounced by Day 30, with untreated implants showing substantially higher stability (65.38 ± 0.54 vs 58.76 ± 0.35; $p < 0.001$), indicating superior progression of secondary stability in the untreated group **(Table 1).**

	Group	Mean ± SD	t
Day 1	Untreated implant	55.50 ± 0.40	0.979
	BBL treated implant	55.24 ± 0.64	
Day 7	Untreated implant	56.88 ± 0.62	7.782
	BBL treated implant	54.98 ± 0.31	
Day 30	Untreated implant	65.38 ± 0.54	28.987
	BBL treated implant	58.76 ± 0.35	

Table 1: Intergroup comparison of ISQ at days 1, 7 and 30 performed using Independent sample t-test

*p<0.05 is statistically significant

**p<0.01 is statistically highly significant

Site-specific analysis revealed a similar pattern across both jaws. At Day 1, ISQ values were comparable between groups in both upper and lower jaws ($p > 0.05$), confirming absence of baseline imbalance. By Day 7, untreated implants showed significantly higher ISQ values in both upper (56.46 ± 0.58 vs 55.11 ± 0.29; $p = 0.002$) and lower jaws (57.30 ± 0.30 vs 54.76 ± 0.23; $p < 0.001$). This trend persisted at Day 30, with untreated implants maintaining significantly higher stability in both upper (65.64 ± 0.28 vs 58.71 ± 0.29; $p < 0.001$) and lower jaws (65.12 ± 0.65 vs 58.86 ± 0.50; $p < 0.001$), demonstrating consistent intergroup differences irrespective of implant site **(Table 2, Figure 2).**

Table 2: Intergroup comparison of upper and lower jaw ISQ at days 1, 7 and 30 performed using Independent sample t-test

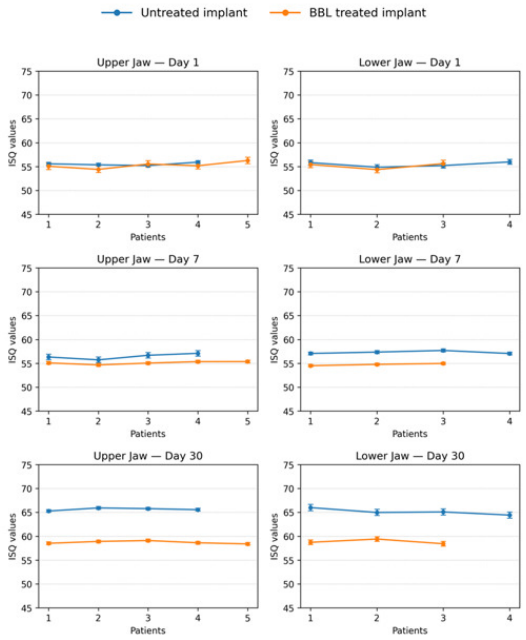
Time	Upper jaw			Lower jaw		
	Untreated implant	BBL treated implant	p value	Untreated implant	BBL treated implant	p value
Day 1	55.52 ± 0.31	55.30 ± 0.68	0.559	55.47 ± 0.52	55.15 ± 0.68	0.498
Day 7	56.46 ± 0.58	55.11 ± 0.29	0.002**	57.30 ± 0.30	54.76 ± 0.23	<0.001**
Day 30	65.64 ± 0.28	58.71 ± 0.29	<0.001**	65.12 ± 0.65	58.86 ± 0.50	<0.001**

*p<0.05 is statistically significant

**p<0.01 is statistically highly significant

Figure 2: Line graph comparing ISQ values between untreated and BBL-treated implants across days and jaw location

Time	Osteocalcin (ng/ml)			NTX (ng/ml)			BAP (ng/ml)		
	Untreated	BBL	p value	Untreated	BBL	p value	Untreated	BBL	p value
Day 1	7.76 ± 0.77	8.15 ± 0.86	0.361	12.01 ± 1.70	13.35 ± 1.68	0.134	8.44 ± 1.47	8.75 ± 2.74	0.788
Day 7	7.33 ± 1.51	6.82 ± 0.78	0.412	11.72 ± 1.70	11.49 ± 1.02	0.75	8.17 ± 2.23	9.62 ± 2.22	0.216
Day 30	7.97 ± 1.42	7.41 ± 0.84	0.356	11.92 ± 1.62	11.79 ± 1.04	0.85	8.76 ± 1.29	12.97 ± 1.98	<0.001**



Intergroup comparison of osteocalcin levels showed no statistically significant differences at any time point. Values were comparable between untreated and BBL-treated implants at Day 1 (7.76 ± 0.77 vs 8.15 ± 0.86; p = 0.361), Day 7 (7.33 ± 1.51 vs 6.82 ± 0.78; p = 0.412), and Day 30 (7.97 ± 1.42 vs 7.41 ± 0.84; p = 0.356). These findings indicate similar osteoblastic activity in both groups throughout the observation period **(Table 3, Figure 3).**

NTX values also did not show significant intergroup differences at any time point. Comparable levels were observed at Day 1 (12.01 ± 1.70 vs 13.35 ± 1.68; p = 0.134), Day 7 (11.72 ± 1.70 vs 11.49 ± 1.02; p = 0.750), and Day 30 (11.92 ± 1.62 vs 11.79 ± 1.04; p = 0.850). This suggests similar bone resorption activity in both groups during healing **(Table 3, Figure 4).**

BAP levels were comparable between groups at Day 1 and Day 7 ($p > 0.05$). However, a statistically significant increase was observed in the BBL-treated group at Day 30 (12.97 ± 1.98 vs 8.76 ± 1.29; $p < 0.001$), indicating enhanced osteoblastic activity at later stages of healing in the BBL group **(Table 3, Figure 5).**

Table 3: Intergroup comparison of osteocalcin, NTX, BAP at days 1, 7 and 30 performed using Independent sample t-test

*p<0.05 is statistically significant

**p<0.01 is statistically highly significant

Figure 3: Bar graph of Osteocalcin at day 1, 7 and 30 for untreated vs BBL treated implant

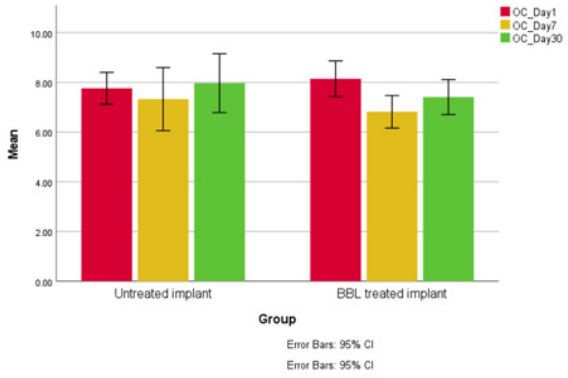


Figure 4: Bar graph of NTX at day 1, 7 and 30 for untreated vs BBL treated implant

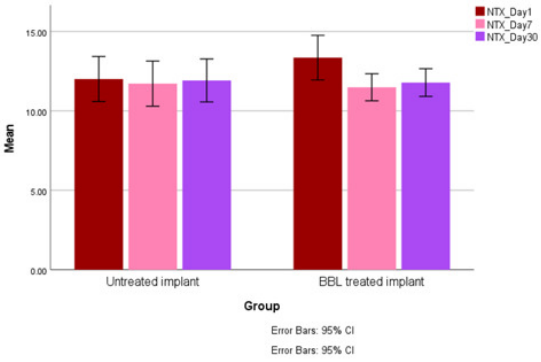
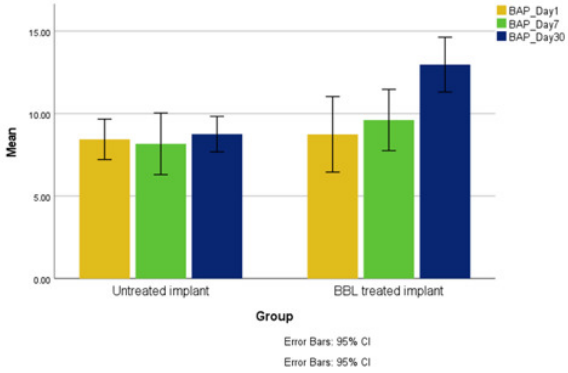


Figure 5: Bar graph of BAP at day 1, 7 and 30 for untreated vs BBL treated implant



Correlation analysis showed no statistically significant associations between ISQ values and bone turnover markers at any time point in either group. Although a relatively strong positive

correlation was observed between ISQ and NTX at Day 1 in the untreated group (r = 0.8094), it was not statistically significant (p = 0.0895). All other correlations were weak to moderate and non-significant, indicating that implant stability was not directly explained by variations in these biochemical markers **(Table 4).**

Table 4: Correlation of ISQ with osteocalcin, NTX and BAP at Days 1, 7 and 30 using Pearson correlation

Untreated implant			
Time	**Variables**	**Pearson correlation coefficient**	**p value**
Day 1	ISQ vs osteocalcin	-0.1554	1.000
	ISQ vs NTX	0.8094	0.0895
	ISQ vs BAP	0.5999	0.6955
Day 7	ISQ vs osteocalcin	-0.5440	0.9801
	ISQ vs NTX	0.1662	1.000
	ISQ vs BAP	-0.5112	1.000
Day 30	ISQ vs osteocalcin	-0.0412	1.000
	ISQ vs NTX	-0.6799	0.3815
	ISQ vs BAP	0.4109	1.000
BBL-treated implant			
Time	**Variables**	**Pearson correlation coefficient**	**p value**
Day 1	ISQ vs osteocalcin	-0.0203	1.000
	ISQ vs NTX	-0.2716	1.000
	ISQ vs BAP	0.5017	1.000
Day 7	ISQ vs osteocalcin	-0.1116	1.000
	ISQ vs NTX	-0.3113	1.000
	ISQ vs BAP	-0.5715	0.8334
Day 30	ISQ vs osteocalcin	-0.0804	1.000
	ISQ vs NTX	-0.1420	1.000
	ISQ vs BAP	0.0813	1.000

*p<0.05 is statistically significant
**p<0.01 is statistically highly significant

4 | Discussion

This randomized controlled clinical trial evaluated the effect of Bone Bioactive Liquid (BBL) on early osseointegration using implant stability quotient (ISQ) and systemic bone turnover markers. Osseointegration is a dynamic process in which primary mechanical stability is gradually replaced by biological stability through bone remodeling (Brånemark et al., 1977; Albrektsson et al., 1981). [12, 13] The present findings indicate that BBL did not improve early implant stability within the first 30 days.

Baseline ISQ values were comparable between groups, indicating similar primary stability and effective randomization. ISQ measurements at placement primarily reflect mechanical factors rather than biological integration (Meredith et al., 1996). [14] However, untreated implants demonstrated significantly higher ISQ values at Day 7 and Day 30, suggesting a greater gain in secondary stability. These findings contrast with preclinical observations where BBL improved bone-to-implant contact at later stages (Ferrés-Amat et al., 2021). [7] The discrepancy may be explained by differences in observation periods, as bone maturation continues beyond the early healing phase.

Early implant healing involves clot formation, inflammatory cell recruitment, angiogenesis, and osteogenic differentiation (Davies et al., 2003; Berglundh et al., 2003). [15, 16] A temporary reduction in stability during early remodeling, commonly referred to as the stability dip, is well documented (Raghavendra et al., 2005). [17] Although BBL is proposed to enhance surface hydrophilicity and improve early biological interactions, the present study did not demonstrate improved ISQ values. This may be due to already optimized implant surface characteristics, as moderately roughened surfaces are known to enhance osseointegration (Wennerberg et al., 2009). [18] In addition, the chairside application of BBL may provide insufficient exposure time to significantly modify surface properties compared to preclinical protocols.

Osteocalcin and NTX did not differ significantly between groups, indicating comparable systemic bone formation and resorption activity. Systemic bone turnover markers are known to reflect global skeletal remodeling rather than localized peri-implant changes (Delmas et al., 2000; Shetty et al., 2016). [19, 20] In contrast, BAP was significantly higher in the BBL group at Day 30, suggesting increased osteoblastic activity during later healing (Seibel MJ, 2005). [10] However, this biochemical change did not correspond with improved mechanical stability, supporting the concept that metabolic activity may precede structural maturation (Einhorn et al., 1998). [21]

The pattern of implant stability was consistent in both the maxilla and mandible, indicating that the observed differences were not influenced by anatomical variation in bone density. This aligns with previous findings that although bone quality varies between jaws, stability trends can remain consistent when standardized protocols are followed (Jaffin et al., 1991). [22]

The findings indicate that BBL does not provide a measurable advantage in early implant stability.

Untreated implants achieved ISQ values within the range considered favorable for early loading (Sennerby et al., 2008) whereas BBL-treated implants showed comparatively lower values. [23] Although BBL may influence biological activity, its clinical benefit in enhancing early mechanical stability appears limited under the present conditions. Similar variability in outcomes has been reported with other adjunctive therapies such as platelet concentrates, where clinical benefits remain inconsistent despite promising biological effects (Miron et al., 2017). [24]

The strengths of this study include its randomized controlled design, double blinding, standardized surgical protocol, and use of both mechanical and biochemical outcome measures. Serial ISQ measurements enabled evaluation of early healing dynamics and standardized blood collection reduced pre-analytical variability. However, the study had limitations. The sample size was small, and follow-up was limited to 30 days, restricting assessment of long-term outcomes. Systemic biomarkers were used instead of local peri-implant markers, which may have limited sensitivity for detecting localized changes. Radiographic and histomorphometric assessments were not performed, and factors such as insertion torque and bone density were not included as covariates.

5 | Conclusion

Application of Bone Bioactive Liquid at implant placement did not improve implant stability during the first 30 days of healing. Untreated implants demonstrated significantly higher ISQ values at Day 7 and Day 30. Osteocalcin and NTX levels were comparable between groups, while bone-specific alkaline phosphatase was significantly higher in the BBL-treated group at Day 30, indicating increased osteoblastic activity. However, this biochemical change was not associated with improved mechanical stability within the study period.

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