# Effects of Intraoperative Photobiomodulation on Osteogenic Differentiation of Human Jaw Bone Explants Harvested During Cyst Surgery: A Paired Ex Vivo Translational Experimental Study

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*Article*

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## Abstract

**Background:** Surgical removal of jaw cysts results in bone defects that may compromise regeneration. Photobiomodulation (PBM) has been proposed as a minimally invasive adjunct capable of influencing osteogenic activity, but translational evidence using freshly harvested human jawbone tissue remains limited. **Objective:** To evaluate the effects of intraoperative PBM on osteogenic differentiation and cellular viability in human jaw bone explants obtained during cystectomy. **Materials and Methods:** This paired translational ex vivo experimental study enrolled 40 patients undergoing surgical treatment for medium to large cystic lesions of the maxilla or mandible. From each patient, paired bone explants were harvested intraoperatively, with one explant exposed to diode PBM and the other serving as a control. Explants were cultured under standardized conditions and assessed using morphometric analysis, immunofluorescence staining for alkaline phosphatase (ALPL) and osteocalcin (OCN), confocal microscopy, and quantitative live/dead viability assays. Viable osteogenic cultures suitable for paired analysis were obtained in 34 patients and constituted the final analytic cohort. **Results:** PBM-treated explants showed higher numbers of osteoblast-like cellular structures and greater osteogenic surface area occupancy than paired controls. Immunofluorescence demonstrated increased ALPL and OCN expression in laser-treated samples. Quantitative viability analysis showed comparable cell survival between groups, with no evidence of laser-induced cytotoxicity. Inter-individual variability in osteogenic response was observed. **Conclusions:** In this exploratory paired ex vivo model, intraoperative PBM was associated with enhanced osteogenic activity in human jaw bone explants. These findings are limited to surrogate cellular outcomes and require confirmation through studies incorporating quantitative mineralization and clinical healing parameters.

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**Keywords:** jaw cysts; PBM therapy; low-level light therapy; bone regeneration; osteogenic differentiation; alkaline phosphatase; osteocalcin; confocal microscopy; ex vivo study; paired experimental study

## 1. Introduction

Bone regeneration represents a critical aspect of contemporary oral and maxillofacial surgery, particularly following the surgical management of cystic jaw lesions [1–3]. Although these lesions are generally benign, their surgical removal results in bone defects, which may compromise local structural integrity and delay functional rehabilitation. Consequently, there is interest in therapeutic strategies to enhance bone healing while minimizing surgical morbidity [4,5].

Autologous bone remains the gold standard for skeletal regeneration due to its osteogenic, osteoinductive, and osteoconductive properties [6]. However, the biological behavior of bone tissue following surgical trauma is influenced by multiple factors, including local vascularization, cellular viability, and the defect microenvironment [7,8]. In this context, the use of bone explants harvested intraoperatively offers a unique opportunity to investigate osteogenic potential under clinically relevant conditions, closely reflecting the biological reality encountered in maxillofacial surgery [9,10].

Mesenchymal stem cells derived from bone tissue play a central role in bone regeneration through their capacity to proliferate and differentiate into osteoblasts [11–13]. The modulation of osteoblastic activity represents a key target in regenerative strategies, aiming to accelerate matrix synthesis and mineralization [14,15]. Experimental models based on human bone explants allow direct assessment of cellular viability, differentiation markers, and functional activity, providing valuable translational insights [13,14].

PBM has emerged as a promising adjuvant therapy in regenerative medicine [16,17]. Low-level laser therapy has been shown to influence mitochondrial activity, cellular metabolism, and gene expression, thereby promoting cell proliferation and differentiation [18,19]. In bone tissue, PBM has been associated with increased osteoblastic activity, enhanced expression of osteogenic markers, and improved mineralization [20,21]. Despite encouraging results, the biological effects of laser therapy remain dependent on irradiation parameters and the biological context in which it is applied [22].

Within the field of oral and maxillofacial surgery, the potential role of PBM as an adjunct to the surgical treatment of jaw cysts remains insufficiently explored, particularly in experimental models using human bone tissue [9,10]. Investigating the response of bone explants obtained during cyst surgery may contribute to the development of minimally invasive, biologically optimized therapeutic protocols [23].

The present study evaluates the effects of PBM on human bone explants harvested during surgical treatment of jaw cysts, with a focus on osteogenic differentiation, cellular viability, and functional activity. By integrating surgical practice with experimental laboratory analysis, this research aims to provide a translational framework for optimizing bone regeneration in maxillofacial surgery [24,25].

Translational evidence in this context refers to the demonstration of osteogenic cellular responses in freshly harvested human jawbone tissue under clinically relevant conditions. Unlike conventional in vitro studies using immortalized cell lines, explant-based models preserve native cell–matrix interactions and may better approximate early regenerative processes.

## 2. Materials and Methods—Paired Translational Ex Vivo Experimental Study

### *2.1. Study Design*

This study was designed as a paired, translational ex vivo experimental study evaluating the effects of intraoperative PBM on osteogenic behavior in human jaw bone explants. A within-subject

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paired design was used, whereby laser-treated and untreated explants were obtained from the same patient to minimize inter-individual variability.

The primary outcomes were osteogenic differentiation, osteoblast-like cellular organization, and cellular viability, assessed under standardized in vitro conditions.

This study was designed as an exploratory translational ex vivo investigation with planned paired inferential comparisons. No a priori power calculation was performed due to the absence of preliminary human data regarding the variability of osteogenic outcomes in jaw bone explants following intraoperative PBM. The sample size of 40 patients was determined based on feasibility considerations, expected explant viability rates reported in primary human bone culture studies, and the aim to obtain at least 30 paired evaluable samples. The final evaluable cohort of 34 paired samples was considered adequate for exploratory inferential analysis.

### *2.2. Study Population and Ethical Approval*

Bone explants were harvested from 40 consecutive patients undergoing surgical treatment for cystic lesions exceeding 10 mm in greatest radiological dimension, classified as medium (10–20 mm) or large (>20 mm) of the maxilla or mandible at the Department of Oral and Maxillofacial Surgery, Emergency County Clinical Hospital of Târgu Mureș, Romania, between January and December 2023. Eligibility criteria included patients presenting cystic lesions of sufficient size to permit safe harvesting of adjacent bone tissue through the standard surgical approach [26]. Exclusion criteria included a history of radiotherapy or chemotherapy in the head and neck region, osteonecrosis or osteoradionecrosis, active cystic infection or suppuration, and systemic diseases or treatments known to impair bone metabolism significantly [27]. The study protocol was approved by the Institutional Ethics Committee (approval no. 13555/21.06.2022) and conducted in accordance with the Declaration of Helsinki.

Bone harvesting did not require additional surgical maneuvers beyond routine clinical procedures. All specimens were anonymized before laboratory processing. Due to the intrinsic variability of primary explant cultures, the final analytic cohort consisted of samples demonstrating successful cell outgrowth and osteogenic differentiation. This approach reflects an exploratory biological model rather than a population-based clinical cohort.

### *2.3. Bone Explant Harvesting Procedure*

Bone explants were collected intraoperatively during cystectomy procedures. Following surgical exposure of the cystic cavity via a standard vestibular approach, small cortical bone fragments were obtained from the surgical access area, without removing perilesional bone tissue or modifying the standard surgical protocol.

Only cystic lesions of medium to large dimensions were included, as smaller lesions do not allow reliable or reproducible explant harvesting. Immediately after collection, bone fragments were placed under sterile conditions in transport medium and prepared for experimental processing (Figure 1).

Cortical thickness and bone density were not quantitatively measured, and explants were harvested from clinically accessible cortical bone adjacent to cystic cavities. Although efforts were made to select morphologically comparable fragments within each pair, intrinsic variability in bone microarchitecture may have influenced osteogenic potential.

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**Figure 1.** Handling of a tissue-like specimen in a liquid medium under controlled laboratory conditions. The sample was transferred using sterile forceps into a test tube and prepared for subsequent analyses. All procedures were performed under standard aseptic conditions.

*2.4. Experimental Groups and PBM Protocol*

PBM was applied immediately after surgical harvesting of bone explants within the operating room environment, before transport to the laboratory. Although irradiation was performed on explanted tissue, the procedure was conducted intraoperatively, during the surgical session, and therefore reflects an intraoperative adjunct rather than a delayed laboratory intervention.

For each patient, two morphologically comparable bone explants were harvested and assigned as follows:

- Control explant: no laser exposure
- Laser-treated explant: subjected to intraoperative PBM

Laser irradiation was performed using a diode dental laser (Litemedics Prime, Litemedics, Romania) (Figure 2) with the following parameters:

- Wavelength: 980 nm
- Output power: 1 W
- Emission mode: pulsed.
- Pulse frequency: 20 kHz
- Duty cycle: 50%
- Average power: 0.5 W
- Peak power: 1 W
- Operating mode: biostimulation
- Fiber diameter: 320 μm
- Irradiation distance: 50 mm (non-contact)
- Exposure time: 40 seconds

Direct temperature monitoring was not performed; however, non-contact irradiation, pulsed mode, and limited exposure time were selected to minimize thermal accumulation.

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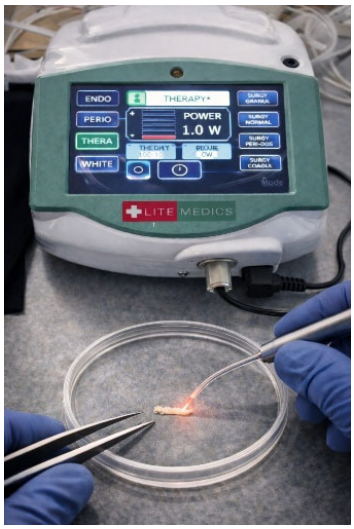


**Figure 2.** Experimental setup for dental laser application under controlled laboratory conditions. A Lite Medics laser unit was operated in therapy mode at an output power of 1.0 W, delivering focused laser energy to a tissue-like sample positioned in a sterile Petri dish and stabilized with precision forceps, illustrating laser–tissue interaction in a simulated clinical environment.

The laser fiber was positioned perpendicular to the explant surface to ensure uniform irradiation while avoiding direct contact and thermal tissue effects. Based on the output power (1 W), exposure time (40 s), and estimated irradiation area at a distance of 50 mm, the calculated energy delivered per explant was approximately 40 J, corresponding to an estimated energy density of approximately 80 J/cm², within the reported biostimulatory range for bone tissue. These parameters fall within ranges recommended by the World Association for Photobiomodulation Therapy (WALT) guidelines for osteogenic stimulation [16].

The selected parameters were chosen to promote cellular PBM while minimizing the risk of thermal alteration.

The selected wavelength (980 nm) and irradiation parameters were based on previously reported PBM studies demonstrating enhanced osteogenic activity in human or mammalian bone tissue within the near-infrared spectrum. Near-infrared wavelengths (800–1000 nm) are known to achieve deeper penetration and effective mitochondrial photostimulation. The selected power output and exposure time were chosen to deliver energy within the biostimulatory window reported for osteogenic differentiation while avoiding thermal effects.

The estimated irradiation spot diameter at 50 mm distance was approximately 8 mm, corresponding to an irradiated area of approximately 0.5 cm². Based on a total delivered energy of 40 J, the calculated energy density was approximately 80 J/cm².

### *2.5. Transport and Laboratory Processing*

Bone explants were transported to the laboratory within a maximum interval of three hours following harvesting. All subsequent experimental procedures were carried out at the Department of Immunology, Center for Advanced Medical and Pharmaceutical Research (CCAMF), George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mureș.

Upon arrival, explants were processed under sterile conditions according to a standardized protocol applied uniformly to all samples.

### *2.6. Explant Culture and Cell Isolation*

Bone fragments were rinsed with Dulbecco's phosphate-buffered saline (DPBS) to remove blood residues and transferred to culture flasks containing Dulbecco's Modified Eagle Medium (DMEM) supplemented with fetal bovine serum and antibiotics.

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Explants were cultured using the explant technique, allowing spontaneous migration of cells from the bone fragments. Cultures were maintained at 37°C, in a 5% $CO_2$ humidified atmosphere, with periodic medium replacement. Cellular outgrowth from the explants was monitored microscopically.

Once sufficient cell confluence was achieved, bone fragments were removed, and adherent cells were detached using enzymatic dissociation and prepared for further expansion or differentiation assays.

For each culture, five randomly selected non-overlapping microscopic fields were acquired at identical magnification. Imaging locations were standardized by scanning the central culture region. Mean values per explant were used for analysis.

### *2.7. Osteogenic Differentiation Protocol*

Cells derived from explant cultures were induced toward osteogenic differentiation using a standard osteogenic induction medium containing β-glycerophosphate, L-ascorbic acid, and dexamethasone.

Cultures were maintained under controlled conditions with regular medium changes until the appropriate stages of osteogenic differentiation were reached, allowing assessment of early and late osteoblastic markers.

### *2.8. Immunofluorescence Staining and Confocal Microscopy*

Osteogenic differentiation was evaluated by immunofluorescence staining for alkaline phosphatase (ALPL) and osteocalcin (OCN), established markers of osteoblastic differentiation and matrix maturation.

Cells were fixed, permeabilized, and incubated with primary antibodies against ALPL and OCN, followed by fluorochrome-conjugated secondary antibodies. Nuclear counterstaining was performed using 4′,6-diamidino-2-phenylindole (DAPI).

Image acquisition was performed using a Leica TCS SP8 confocal microscope (Leica Microsystems, Germany). Identical acquisition parameters, including magnification, laser power, detector gain, and field of view, were applied to all samples to allow reliable qualitative and morphometric comparisons between laser-treated and control cultures.

Morphometric analysis was performed using ImageJ/Fiji software (National Institutes of Health, USA). Osteoblast-like structures were identified through manual and threshold-assisted segmentation based on fluorescence intensity and morphological criteria, including cell size, shape, and marker positivity. Identical segmentation thresholds and analysis parameters were applied uniformly across paired control and laser-treated samples to ensure consistency.

Image analysis was performed by two investigators blinded to group allocation. Predefined morphological criteria were applied, and inter-observer agreement was assessed. To minimize observer bias, all morphometric analyses were performed using identical threshold parameters. Additionally, measurements were repeated independently by two investigators blinded to group allocation, and mean values were used for analysis. Inter-observer variability was assessed and showed high agreement (intraclass correlation coefficient >0.90).

Variations in cumulative area values relative to cell counts reflect differences in individual cell size and clustering patterns, as segmentation measured contiguous fluorescent regions rather than individual cells.

### *2.9. Cell Viability Assessment*

Cell viability was assessed using a live/dead fluorescence assay based on Calcein AM and Ethidium Homodimer III. Viable cells were identified by green cytoplasmic fluorescence, whereas non-viable cells exhibited red nuclear staining.

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Stained cultures were imaged immediately using confocal microscopy, and cell viability was quantified by calculating the percentage of live cells relative to total cells in three standardized, non-overlapping fields per explant. Mean viability values were then compared between paired laser-treated and control samples.

### *2.10. Experimental Yield and Data Analysis*

Viable osteogenic differentiation and cell populations were obtained in 34 out of 40 patients (85% yield). These cases constituted the final experimental cohort included in the comparative analysis. The remaining explants (n = 6) failed to generate sufficient cellular outgrowth or osteogenic differentiation and were excluded based on predefined quality criteria.

Inferential statistical analysis was performed using GraphPad Prism software (version 9.0, GraphPad Software, San Diego, CA, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Differences between paired groups (Control vs. Laser-treated) were analyzed using the paired Student's t-test for normally distributed data or the Wilcoxon signed-rank test for non-parametric data. Results are expressed as mean ± standard deviation (SD) or median with interquartile range (IQR). A p-value < 0.05 was considered statistically significant.

## 3. Results

### *3.1. Study Cohort and Experimental Yield*

Bone explants were harvested from 40 patients undergoing surgical treatment for cystic lesions of the maxilla or mandible and processed according to the standardized experimental protocol. Analysis of excluded samples revealed no systematic clustering by anatomical localization, patient age, or cyst type. Due to the biological variability of primary human bone explant cultures, measurable osteogenic differentiation and viable cell populations were observed in 34 of 40 patients (85% yield). These 34 cases constituted the final experimental cohort included in the paired comparative analysis between laser-treated and non-treated explants. The remaining samples (n = 6) did not yield sufficient cellular viability or osteogenic differentiation for reliable morphometric evaluation and were therefore excluded. A flow diagram summarizing patient inclusion is presented in Figure 3.

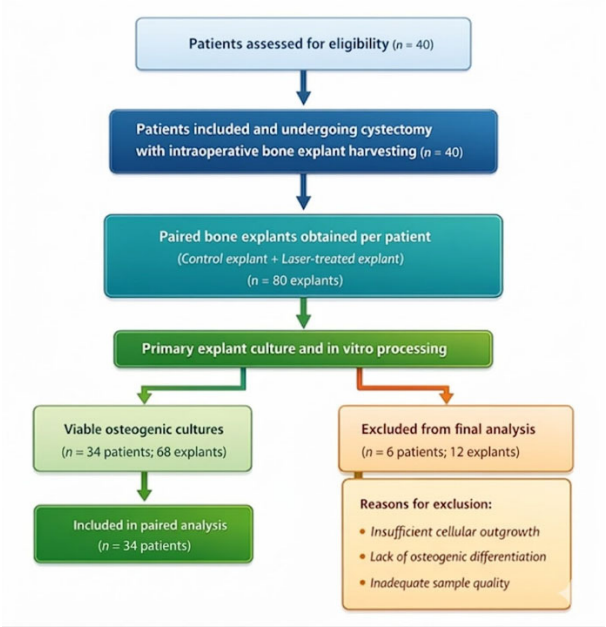


**Figure 3.** Flow diagram of patient inclusion, explant processing, and paired statistical analysis.

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**Table 1.** Comparison of included and excluded samples.

| Variable | Included Samples (n = 34) | Excluded Samples (n = 6) |
|---|---|---|
| Mean age (years) | 41.8 ± 11.6 | 43.2 ± 10.9 |
| Gender (M/F) | 23 / 11 | 4 / 2 |
| Maxilla (n) | 17 | 3 |
| Mandible (n) | 17 | 3 |
| Large cysts (>20 mm) | 19 | 3 |
| Medium cysts (10–20 mm) | 15 | 3 |

No relevant differences were observed between included and excluded samples regarding age, gender, anatomical localization, or cyst size, suggesting that sample exclusion was primarily related to biological variability in explant viability.

The final analytic cohort included 34 patients (23 males, 11 females) with a mean age of 41.8 ± 11.6 years. Explants were evenly distributed between the maxilla (n = 17) and mandible (n = 17). Table 2 illustrates the summary of paired quantitative outcomes.

**Table 2.** Summary of paired quantitative outcomes in control and PBM-treated explants (n = 34).

| Outcome | Control (mean ± SD) | PBM-treated (mean ± SD) | Paired difference (mean ± SD) | p-value |
|---|---|---|---|---|
| Osteoblast-like structures (count) | 1685 ± 782 | 3148 ± 1186 | 1463 ± 611 | <0.001 |
| Osteoblastic area occupancy (%) | 14.2 ± 7.1 | 23.6 ± 9.4 | 9.4 ± 4.3 | <0.001 |
| Cell viability (%) | 91.8 ± 4.6 | 92.5 ± 4.2 | 0.7 ± 1.9 | 0.18 |

Data are presented as mean ± standard deviation. Comparisons were performed using a paired Student's t-test. PBM: photobiomodulation.

### *3.2. Osteoblast-like Cellular Structures: Quantitative Paired Analysis*

Quantitative morphometric analysis revealed statistically significant differences between PBM-treated and control explants regarding the number of osteoblast-like cellular structures. In the paired analysis of 34 patients, PBM-treated explants demonstrated higher cellular counts than controls (3148 ± 1186 vs. 1685 ± 782; mean paired difference 1463 ± 611; $p < 0.001$). The increase was observed across the majority of paired samples despite inter-individual variability. PBM-treated cultures generally exhibited a greater density of smaller and more uniformly distributed osteoblast-like structures, whereas control cultures displayed fewer and more clustered cellular aggregates. Individual paired values are presented in Supplementary Table S1, and a graphical representation is shown in Figure 4.

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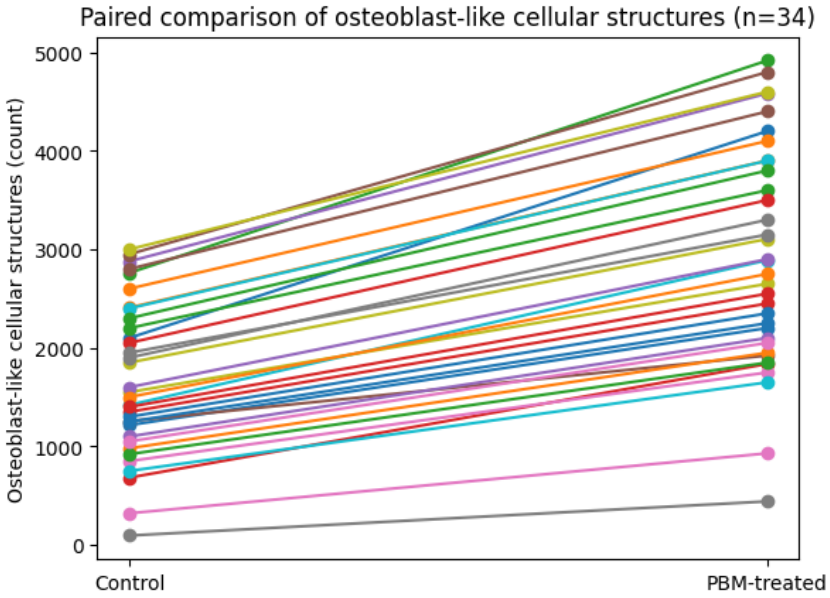


**Figure 4.** Paired comparison of osteoblast-like cellular structure counts in control and photobiomodulation (PBM)-treated bone explants (n = 34). Each point represents an individual paired sample, and connecting lines indicate patient-matched observations. PBM-treated explants demonstrated significantly higher cellular counts compared with controls (paired Student's t-test, $p < 0.001$). Horizontal clustering of values illustrates inter-individual variability.

*3.3. Morphometric Analysis of Osteoblastic Area Occupancy*

Morphometric analysis demonstrated a significantly greater percentage of surface area occupied by osteoblast-like structures in PBM-treated explants compared with controls (23.6 ± 9.4% vs. 14.2 ± 7.1%; mean paired difference 9.4 ± 4.3%; $p < 0.001$). PBM-treated samples showed more homogeneous cellular distribution and increased confluence, whereas control cultures exhibited discontinuous areas of cellular growth. These findings are illustrated in Figure 5, and individual values are reported in Supplementary Table S2.

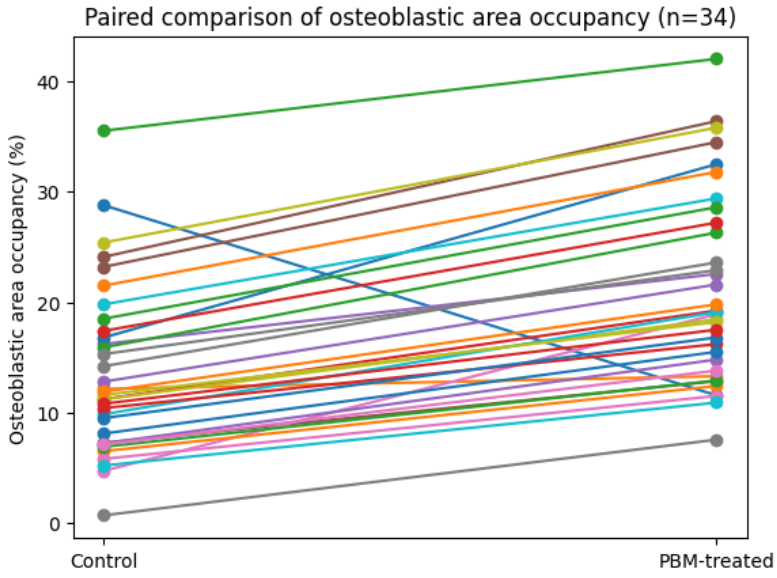


**Figure 5.** Paired comparison of osteoblastic area occupancy (%) between control and photobiomodulation (PBM)-treated human jaw bone explants (n = 34). Each point represents an individual paired sample, and connecting lines indicate patient-matched observations. PBM-treated explants demonstrated greater osteoblastic

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surface occupancy compared with controls in the majority of samples, with inter-individual variability preserved.

### *3.4. Immunofluorescence Assessment of Osteogenic Marker Expression*

Immunofluorescence staining confirmed expression of alkaline phosphatase (ALPL) and osteocalcin (OCN) in both groups. PBM-treated cultures exhibited qualitatively stronger and more widespread fluorescence signals compared with paired controls. Confocal microscopy revealed increased numbers of ALPL-positive cells at early differentiation stages and enhanced OCN expression in more mature osteoblast-like cells. These findings are consistent with increased osteogenic differentiation following PBM exposure.

### *3.5. Cell Viability Analysis*

Live/dead fluorescence assays demonstrated high cellular viability in both groups. Quantitative analysis showed comparable viability between PBM-treated and control cultures (92.5 ± 4.2% vs. 91.8 ± 4.6%; $p = 0.18$). No increase in non-viable cells was observed following PBM exposure, indicating the absence of cytotoxic effects under the applied irradiation parameters.

### *3.6. Summary of Experimental Findings*

Overall, PBM-treated explants demonstrated:

- Higher osteoblast-like cellular counts ($p < 0.001$)
- Increased osteoblastic surface occupancy ($p < 0.001$)
- Enhanced osteogenic marker expression (qualitative)
- Comparable cellular viability ($p = 0.18$)

These findings indicate a consistent association between intraoperative PBM and increased osteogenic activity in human jawbone explants.

Individual paired morphometric values are provided in Supplementary Tables S1 and S2.

## 4. Discussion

Bone regeneration following surgical management of cystic lesions of the maxilla and mandible remains an important clinical challenge, particularly in cases involving medium to large defects where spontaneous healing may be delayed or incomplete [28–30]. Although cystic lesions are typically benign, the residual bone defects may compromise structural stability and delay functional rehabilitation. Consequently, interest has grown in adjunctive strategies capable of enhancing osteogenesis while maintaining a minimally invasive surgical approach [31–33]. PBM has emerged as a potential candidate due to its reported effects on cellular metabolism, proliferation, and differentiation [18,19].

The present paired ex vivo translational study evaluated the influence of intraoperative PBM on osteogenic behavior in human jaw bone explants harvested during cystectomy procedures. By employing a within-subject paired design, PBM-treated explants were directly compared with non-treated controls obtained from the same patient, thereby minimizing inter-individual biological variability [34,35]. The results demonstrated a consistent trend toward enhanced osteogenic activity in explants exposed to PBM, including increased numbers of osteoblast-like cellular structures, greater osteoblastic surface area occupancy, and enhanced expression of osteogenic markers.

These findings are consistent with previous experimental studies reporting that low-level laser irradiation can stimulate osteoblastic proliferation and differentiation through mitochondrial activation, increased adenosine triphosphate synthesis, and modulation of intracellular signaling pathways involved in bone metabolism [18–22,25]. Most prior investigations, however, have relied on animal models or immortalized cell lines [36,37]. The present study extends these observations to freshly harvested human jaw bone explants, a model that preserves native cell–matrix interactions

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and more closely reflects the clinical biological environment encountered during oral and maxillofacial surgery [34,36].

Although bone explants preserve native cell–matrix interactions, they do not fully reproduce the complex in vivo environment that governs post-cystectomy healing. In clinical settings, bone regeneration is influenced by mechanical stability, vascular ingrowth, inflammatory signaling, and interaction with the cystic cavity and surrounding periosteum. The explant-based model isolates early cellular osteogenic responses under controlled conditions, thereby allowing evaluation of PBM effects on resident bone-derived progenitor populations. However, the absence of vascularization, immune modulation, and biomechanical loading limits direct extrapolation to defect ossification in vivo. Consequently, the present findings should be interpreted as reflecting modulation of early osteogenic potential rather than definitive acceleration of clinical bone healing.

In addition to increased cellular counts, morphometric analysis demonstrated a higher percentage of surface area occupied by osteoblast-like cellular structures in PBM-treated explants. Effective bone regeneration depends not only on the presence of osteogenic cells but also on their spatial distribution and coordinated matrix deposition [38,39]. The more uniform cellular organization observed following PBM may reflect a more proliferative and metabolically active osteogenic phenotype [40,41]. While this observation does not directly indicate enhanced mineralization, it suggests a biological environment potentially favorable for subsequent bone formation.

Immunofluorescence analysis confirmed the expression of alkaline phosphatase and osteocalcin in explant-derived cultures, validating successful osteogenic differentiation under the applied experimental conditions [42,43]. Laser-treated samples generally exhibited more intense and widespread marker expression, suggesting enhanced differentiation and matrix maturation. Importantly, live/dead assays demonstrated preserved cellular viability in both experimental groups, with no evidence of laser-induced cytotoxicity. These findings support the biological safety of the applied PBM parameters and are consistent with previous reports indicating that near-infrared PBM can stimulate cellular activity without inducing thermal damage when appropriate parameters are used [18–22,43,44].

Despite the overall trend toward enhanced osteogenic activity, inter-individual variability was observed. A small proportion of samples demonstrated limited osteogenic response, which may reflect differences in patient age, local bone quality, vascularization, or proximity to cystic pathology [47,48]. Such variability is expected in primary human tissue models and highlights the biological heterogeneity of bone regeneration. Although exploratory, these findings highlight the need for individualized PBM protocols. The paired design used in this study partially mitigates this limitation by focusing on relative differences within the same patient rather than absolute values across individuals [35,47].

The experimental yield also warrants consideration. Viable osteogenic cultures suitable for paired analysis were obtained in 34 of 40 patients, reflecting the intrinsic variability of primary bone explant cultures. This variability may indicate biological heterogeneity in osteogenic responsiveness among individuals. From a clinical perspective, this observation raises the possibility that PBM effects may not be uniform across all patients, but rather more pronounced in biologically responsive bone conditions. Factors such as local bone quality, vascularization, and patient-specific regenerative capacity may influence responsiveness to PBM. Therefore, PBM should currently be considered a potentially beneficial adjunct whose effectiveness may vary, and future studies should aim to identify predictors of biological response.

In clinical practice, cystic jaw defects may heal spontaneously or be managed using autogenous bone grafts, xenografts, alloplastic substitutes, platelet-rich fibrin, or staged approaches such as marsupialization. Within this therapeutic spectrum, PBM is not intended to replace established regenerative strategies but rather to function as a minimally invasive adjunct. In defects where spontaneous healing is predictable, PBM may offer incremental biological stimulation without additional morbidity. In larger defects typically managed with grafting materials, PBM could

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potentially be used as an adjunct to enhance osteogenic activity around graft particles or host bone interfaces. Compared with biologic adjuncts such as platelet-rich fibrin, PBM presents a non-material, device-based intervention with minimal additional surgical burden. However, these conceptual roles remain hypothetical and require validation through controlled clinical studies comparing PBM with existing regenerative adjuncts.

From a translational perspective, intraoperative application of PBM may represent a feasible adjunct. However, the present ex vivo findings reflect cellular responses and should not be interpreted as evidence of improved clinical healing. The technique can be integrated into standard surgical workflows, does not require additional surgical sites, and adds minimal operative time [40,45,46]. The observed cellular effects suggest a potential biological role in modulating early regenerative processes. However, direct extrapolation to clinical bone healing outcomes should be interpreted cautiously, as the present study was conducted in an ex vivo experimental setting and did not include radiological or clinical follow-up [44–46].

The selected PBM parameters were chosen within commonly reported biostimulatory ranges; however, photobiomodulation effects are known to depend on wavelength, energy density, and exposure conditions. Although the present protocol used a 980 nm diode laser, similar biological responses have been reported across near-infrared wavelengths, suggesting that the observed effects may reflect a broader PBM phenomenon rather than device-specific characteristics. From a practical standpoint, intraoperative application required approximately 40 seconds and did not alter the surgical workflow or require additional surgical sites. The learning curve is minimal for clinicians familiar with diode laser devices, although variability in fiber positioning and distance may influence delivered energy. Cost considerations are also relevant; however, diode lasers are already widely used in oral surgery practices, and PBM application would not require additional consumables. Nevertheless, formal cost-effectiveness analyses comparing PBM with other adjunctive approaches are needed.

Several methodological considerations should be acknowledged. First, the study focused on early cellular and morphometric indicators of osteogenic differentiation rather than long-term mineralization or biomechanical outcomes. Second, cortical thickness and local bone density were not quantitatively assessed, which may have influenced explant viability and osteogenic potential [47,48]. Third, temperature monitoring during laser irradiation was not performed; however, non-contact irradiation, pulsed emission mode, and short exposure time were selected to minimize thermal effects [18,21,22]. Future studies incorporating thermal monitoring and standardized bone characterization would further strengthen the interpretation of results.

The primary limitation is that the analytic cohort was defined by successful explant viability and osteogenic differentiation, introducing potential post-enrollment selection bias.

The present study relies on surrogate biological endpoints, including osteoblast-like cell counts, surface occupancy, and osteogenic marker expression, which reflect early cellular events rather than clinically measurable outcomes.

While enhanced osteogenic marker expression suggests increased differentiation potential, these findings do not directly translate into clinically relevant outcomes such as radiographic bone fill, reduced healing time, or improved implant feasibility. The ex vivo design precludes assessment of vascularization, mechanical stability, and remodeling processes that determine functional bone regeneration. Accordingly, the results should be considered hypothesis-generating and supportive of biological plausibility rather than evidence of clinical efficacy.

Another limitation relates to morphometric analysis, which included partially manual segmentation of osteoblast-like cellular structures. To reduce observer bias, identical segmentation parameters were applied across samples, and analyses were performed in a blinded manner. Nevertheless, automated quantitative approaches may improve reproducibility in future investigations [38–41]. Additionally, variations in cumulative area measurements relative to cell counts reflect differences in cellular clustering patterns rather than inconsistencies in segmentation.

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Within these limitations, the consistency of findings across quantitative, morphometric, and immunofluorescence endpoints supports a biologically relevant effect of PBM on osteogenic activity in human jaw bone explants. These results contribute to the growing body of evidence suggesting that PBM may influence early regenerative processes in bone tissue [18–22,25]. Future studies correlating these cellular findings with in vivo healing dynamics, radiological bone fill, and clinical outcomes are necessary to determine the clinical applicability of intraoperative PBM in cystic lesion management [44–49].

## 5. Conclusions

This paired translational ex vivo experimental study demonstrated that intraoperative laser photobiomodulation was associated with increased osteogenic differentiation, improved cellular organization, and enhanced expression of osteogenic markers in human jaw bone explants harvested during cystectomy. Laser-treated samples exhibited higher numbers of osteoblast-like cellular structures and greater osteogenic surface occupancy compared with paired controls, without evidence of cytotoxicity.

These findings are limited to surrogate cellular outcomes derived from an exploratory ex vivo model and should be interpreted as hypothesis-generating. Prospective clinical studies evaluating radiographic bone fill, healing time, and functional rehabilitation outcomes are required to determine the clinical effectiveness of intraoperative photobiomodulation in cystic defect management.

**Supplementary Materials:** The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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