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Effects of the association of photobiomodulation and implantation of Biosilicate® scaffolds on the consolidation of critical-sized bone defects

Efeitos da associação da fotobiomodulação e do implante de scaffolds de Biosilicato® na consolidação de defeitos ósseos de tamanho crítico

Efectos de la combinación de fotobiomodulación y la implantación de andamios Biosilicate® en la consolidación de defectos óseos de tamaño crítico

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Abstract
This study aimed to evaluate the effects of photobiomodulation combined with Biosilicate® scaffold implantation on bone callus morphology 15 days after the creation of 8 mm cranial bone defects. Twenty male Wistar rats were allocated into two groups: Control Group – animals underwent bone defect induction but did not receive any treatment; and Biosilicate® + Photobiomodulation Group – animals underwent bone defect induction, received Biosilicate® scaffold implantation, and were treated with laser therapy. The laser irradiation device operated at a wavelength of 830 nm, delivering a fluence of 120 J/cm² per point. Point irradiation was applied to five different regions of the bone defect. Laser therapy was initiated immediately after surgery, with sessions performed every 48 hours, totaling seven applications. Histological analysis revealed that the combined therapy accelerated the regeneration process, as the treated group exhibited increased new bone formation, more granulation tissue, and reduced inflammatory infiltration compared with the control group. These findings suggest that combining photobiomodulation with Biosilicate® scaffolds may enhance bone healing in cases of difficult-to-treat fractures.
Keywords: Laser Therapy; Fractures; Bone; Biocompatible Materials.

Resumo
Este estudo teve o objetivo de avaliar os efeitos da associação da fotobiomodulação com o implante de *scaffold* de Biosilicato® na morfologia do calo ósseo 15 dias após a realização de defeitos ósseos (8mm) em calotas cranianas. Foram utilizados 20 ratos machos *Wistar,* divididos em: Grupo Controle - os animais foram submetidos ao defeito ósseo, mas não receberam nenhum tipo de tratamento; Grupo Biosilicato® e Fotobiomodulação – os animais foram submetidos ao defeito ósseo, receberam o implante de *scaffold* de Biosilicato®, e foram tratados com laser. O aparelho utilizado para a irradiação do laser foi utilizado com comprimento de onda de 830nm, na fluência de 120J/cm^2 por ponto. Foi utilizada a técnica pontual em 5 diferentes regiões do defeito ósseo. O tratamento com laser iniciou-se imediatamente após a cirurgia e as sessões seguiram com intervalo de 48h, totalizando 7 aplicações. A análise histológica demostrou que a interação acelerou o processo de regeneração, pois o grupo tratado apresentou maior neoformação óssea, mais tecido de granulação e menos infiltrado inflamatório quando comparado ao grupo controle. Este estudo sugere que associar as terapias pode contribuir para o tratamento de indivíduos portadores de fraturas de difícil consolidação.
Palavras-chave: Terapia a Laser; Fraturas Ósseas; Materiais Biocompatíveis.

Resumen
Este estudio tuvo como objetivo evaluar los efectos de la fotobiomodulación combinada con la implantación de un andamio de Biosilicato® en la morfología del callo óseo, 15 días después de la creación de defectos óseos de 8 mm en el cráneo. Veinte ratas Wistar macho fueron asignadas a dos grupos: Grupo control – los animales se sometieron a la inducción del defecto óseo, pero no recibieron ningún tratamiento; y Grupo Biosilicato® + Fotobiomodulación – los animales se sometieron a la inducción del defecto óseo, recibieron la implantación del andamio de Biosilicato® y fueron tratados con terapia láser. El dispositivo de irradiación láser operaba a una longitud de onda de 830 nm y una fluencia de 120 J/cm² por punto. La técnica puntual se aplicó en cinco regiones diferentes del defecto óseo. El tratamiento con láser se inició inmediatamente después de la cirugía, con sesiones realizadas cada 48 horas, para un total de siete aplicaciones. El análisis histológico reveló que la terapia combinada aceleró el proceso de regeneración, ya que el grupo tratado presentó una mayor formación de hueso nuevo, más tejido de granulación y una menor infiltración inflamatoria en comparación con el grupo control. Estos hallazgos sugieren que la combinación de estas terapias puede favorecer la consolidación ósea en casos de fracturas de difícil cicatrización.
Palabras clave: Terapia por Láser; Fracturas Óseas; Materiales Biocompatibles.

1. Introduction

Fractures are defined as a disruption in the continuity of bone, caused by trauma or pathological conditions (Brasileiro Filho, 2006; Rubin et al., 2006). The restoration of bone continuity is a complex reparative process involving multiple biological events, including the participation of various cell types, active gene transcription, and the expression of proteins, transcription factors, and growth factors, which together ensure tissue integrity (Maruyama et al., 2021; Raina et al., 2024; Zhu et al., 2024).

Currently, several strategies are being developed to improve the quality and rate of bone fracture repair (Ehnert & Histing, 2024). Among these, particular attention has been given to the osteogenic properties of low-level laser therapy (LLLT) (Aboelsaad et al., 2009; Santinoni et al., 2017) and bioactive biomaterials (Hench & Polak, 2002; El-Rashidy, 2017; Bai, 2018).

Biomaterials are defined as substances engineered to form specific structures that, alone or as part of a complex system, are used to direct therapeutic or diagnostic procedures by modulating interactions with living systems. Owing to its unique properties, Biosilicate® has become the focus of extensive research, ranging from dental applications to its use in surgical procedures for bone reconstruction (Zanotto, 2004; Crovace et al., 2015; Santos et al., 2024).

Another promising approach to enhancing bone fracture repair is LLLT, for which substantial evidence demonstrates positive effects on bone metabolism and fracture healing (Fávaro-Pípi et al., 2010; Escudero et al., 2019; Bai et al., 2021). Although favorable outcomes have been reported for the combination of Biosilicate® and low-level laser photobiomodulation in stimulating osteoblast proliferation and bone consolidation, their effects on critical-size defects remain unexplored.

The present study aimed to evaluate the effects of combining low-level laser photobiomodulation with Biosilicate® scaffold implantation on bone callus morphology 15 days after the creation of critical-size defects in rat calvariae.

2. Methodology

An experimental, laboratory research of a qualitative nature was carried out (Pereira et al., 2018).

2.1 Experimental Animals

Twenty-three-month-old male Wistar rats were randomly assigned to two groups: Control Group (CG) – animals subjected to the creation of a bone defect without further treatment; and Biosilicate® + Laser Group (GBL) – animals subjected to the bone defect, followed by Biosilicate® scaffold implantation and laser therapy (λ = 830 nm).

2.2 Experimental Model of Critical-Size Bone Defects in Rat Calvariae

Critical-size defects were created using a 2-cm long, 8-mm external diameter trephine drill (WMA, Brazil) operated with a BELTEC micromotor (Brazil) at 13,500 rpm under continuous saline irrigation. Following anesthesia, trichotomy, and asepsis, a midline incision was made in the calvariae region, and an 8-mm diameter bone defect was surgically created. After defect creation, animals in the GBL group received implantation of an 8-mm diameter × 2-mm thick Biosilicate® scaffold, immediately followed by laser irradiation. The scaffold was positioned to fully occupy the circular bone defect. Finally, the incision site was sutured, and local cleaning was performed for all animals.

2.3 Characterization of Biosilicate® Scaffolds

Three-dimensional, highly porous, mechanically competent, bioactive, and biodegradable scaffolds were used in this study, prepared from Biosilicate® (patent WO 2004/074199). This material is a fully crystalline, highly bioactive P2O5–Na2O–CaO–SiO2 vitroceramic (Zanotto, 2004). Scaffolds with a diameter of 3 mm, thickness of 2 mm, approximately 72 ± 6% porosity, and an average pore size of 275 μm were employed. These characteristics are suitable for osteogenesis, as they allow cell migration and vascularization throughout the scaffold (Karageorgiou & Kaplan, 2005; Vitale-Brovarone et al., 2006).

2.4 Low-Level Laser Application

A portable DMC therapeutic laser (λ = 830 nm, fluence 120 J/cm²) was used. Laser therapy began immediately after surgery and was administered in seven sessions at 48-hour intervals. The laser was applied using a point-contact technique at five locations: the central region, superior edge, inferior edge, left edge, and right edge of the bone defect.

2.5 Euthanasia

Animals were euthanized 24 hours after the last treatment session (postoperative day 15) via anesthetic overdose. Calvariae were surgically resected for subsequent analyses.

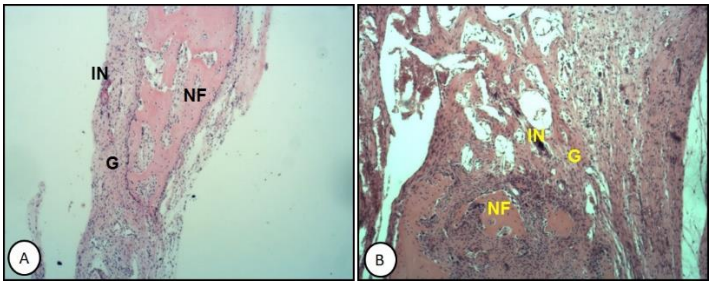
2.6 Histological Analysis

Following euthanasia, calvariae were dissected, fixed in 10% formalin for 24 hours, and decalcified in EDTA (ethylenediaminetetraacetic acid) solution for approximately 30 days. Semi-serial 5 μm sections were prepared and stained with hematoxylin and eosin (H&E). A qualitative analysis was performed to describe morphological features of the defects according to the following criteria: presence of inflammatory process, granulation tissue, new bone formation, and tissue necrosis. The study was approved by CEUA/UFSCar (No. 083/2012).

3. Results

Figures 1 and 2 illustrate the morphological findings obtained from the qualitative descriptive analysis.

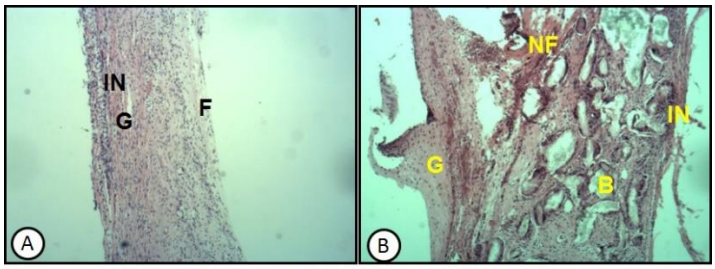
Figure 1 - Histological section of the defect edge. **A)** Control Group; **B)** Biosilicate® + Laser Group. **NF**: new bone formation; **G**: granulation tissue; **IN**: inflammatory infiltrate. Staining: hematoxylin and eosin (H&E). Magnification: 400×.



Source: Authors.

The CG showed moderate inflammatory infiltrate, intense granulation tissue presence, and slight new bone deposition with moderate fibrosis at the defect edges, suggesting the early phase of bone repair (Figure 1A). The GBL group showed moderate inflammatory infiltrate, intense granulation tissue, and moderate fibrosis at the lesion edges. However, this group exhibited greater new bone formation compared to the control group (Figure 1B).

Figure 2 - Histological section of the defect center. **A)** Control group; **B)** Biosilicate® + Laser Group. **NF**: New bone formation; **G**: granulation tissue; **IN**: inflammatory infiltrate; **F**: Fibrosis; **B:** Biosilicate®. Staining: hematoxylin and eosin (H&E). Magnification: 400×.



Source: Authors.

The control group exhibited moderate inflammatory infiltrate, prominent granulation tissue, absence of new bone formation, and moderate fibrosis at the defect center, indicating the early phase of repair (Figure 2A). The treated group presented moderate inflammatory infiltrate, moderate granulation tissue, and moderate fibrosis at the lesion center. Notably, this group displayed greater new bone formation compared with the control group (Figure 2B).

Morphological findings from the qualitative descriptive analysis are summarized in Table 1.

Table 1 - Morphological findings from qualitative descriptive analysis.

Morphological Finding	Control Group (Edge)	Treated Group (Edge)	Control Group (Center)	Treated Group (Center)
Bone formation	Low	Moderate	Absent	Moderate
Granulation	Intense	Intense	Intense	Moderate
Inflammation	Moderate	Moderate	Moderate	Moderate
Fibrosis	Moderate	Moderate	Moderate	Moderate
Necrosis	Absent	Absent	Absent	Absent

Source: Authors.

4. Discussion

A critical-size defect refers to a bone lesion that cannot heal spontaneously and requires intervention to achieve consolidation. Autologous grafts remain the "gold standard" for lesions exceeding the critical size due to their osteogenic, osteoconductive, and osteoinductive properties (Souza, 2010; Greer et al., 2020). However, grafts have several limitations, including risk of rejection, strong antigenic responses, potential transmission of infectious agents, and the requirement for donor-recipient tissue compatibility. To overcome these limitations, synthetic biomaterials are increasingly employed, often reducing or eliminating the need for biological grafts (Souza, 2010).

Among the synthetic biomaterials studied, Biosilicate® has received considerable attention, with applications ranging from dentistry to surgical bone reconstruction (Fernandes et al., 2012; Fernandes et al., 2019). Another promising strategy for enhancing bone repair is low-level laser therapy, which has been shown to accelerate and improve the quality of bone healing. Therefore, it was hypothesized that the combination of Biosilicate® scaffolds and low-level laser therapy could synergistically enhance bone regeneration in critical-size defects.

In the present study, animals treated with the combination of photobiomodulation and Biosilicate® showed qualitatively greater new bone tissue compared to the control group, suggesting that this interaction may be beneficial in the bone repair process by potentially accelerating tissue regeneration.

These findings are consistent with several studies reporting positive effects of combined treatments. Magri et al. (2021), in a systematic review, evaluated studies investigating the interaction between bioceramics and photobiomodulation in bone regeneration. Additionally, Bossini et al. (2011) demonstrated, through morphometric analysis, that tibial defects in osteopenic rats filled with Biosilicate® and irradiated with 120 J/cm² laser exhibited larger areas of new bone compared with other groups

Similarly, Fangel et al. (2011) analyzed the effects of combining LLLT at 60 and 120 J/cm² with Biosilicate® in tibial defects of osteopenic rats and found that 120 J/cm² laser with Biosilicate® improved the biomechanical properties of the bone callus. Arruda et al. (2011) also reported that laser irradiation in the presence of the biomaterial (vitroceramic derived from the Bioglass® composition: 45% SiO_2, 24.5% Na_2O, 24.5% CaO, 6% P_2O_5) enhanced the quality of newly formed bone tissue and its integration with the material.

Conversely, some studies have reported negative or neutral effects of combining biomaterials and laser therapy in bone repair. Oliveira et al. (2010) investigated the effects of LLLT at 60 and 120 J/cm² and Biosilicate® grains (~180–212 μm) on tibial defects in healthy rats. Morphological and morphometric analyses revealed that the laser-only groups exhibited statistically higher new bone formation compared with the control and Biosilicate® groups. Interestingly, groups receiving both the biomaterial and laser, at both fluences, showed statistically lower new bone formation, even compared with controls.

Furthermore, Tim et al. (2014) and Pinto et al. (2013) evaluated LLLT at 120 J/cm² and Biosilicate® scaffolds, used independently or in combination, in tibial defects at different experimental time points. Tim et al. reported that the combination of Biosilicate® scaffold and laser did not significantly differ from controls, whereas Pinto et al. (2013) suggested that Biosilicate® accelerated bone repair, but laser therapy did not enhance its bioactive properties.

Data from the present study suggest that the combination of Biosilicate® and photobiomodulation in critical-size bone defects accelerates bone regeneration, enhancing new bone formation. The underlying mechanisms remain unclear. Oliveira et al. (2010) proposed that the combination could induce excessive local stimulation, which may be detrimental. However, in their studies, defects were smaller (2 mm and 3 mm) compared with the 8 mm defects in the present study, suggesting that in critical-size defects, the stimulus is distributed over a larger area, potentially improving outcomes.

In the studies by Bossini et al. (2011) and Fangel et al. (2011), although the defects were not critical-sized, osteopenic animals positively influenced outcomes. Other studies report that laser therapy stimulates bone metabolism in osteopenic rats (Rennó et al., 2007; Diniz et al., 2009) and that Biosilicate® promotes osteoblast differentiation during bone repair in osteopenic rats (Bossini et al., 2011).

In summary, the present study demonstrates that combining these treatments may represent a viable strategy for bone tissue regeneration. However, comparisons between studies are complicated by differences in experimental models, dosimetric parameters, and treatment durations. A significant gap persists in the literature regarding the efficacy of combining therapeutic lasers with bioactive materials in bone repair, highlighting the need for further research.

5. Conclusion

Based on the results of this study, the combination of low-level laser photobiomodulation and Biosilicate® scaffold implantation enhanced bone regeneration, as the treated group exhibited increased new bone formation, more prominent granulation tissue, and reduced inflammatory infiltrate compared with the control group. Therefore, these findings suggest that combining these therapies may provide a safe and effective strategy for managing fractures that are difficult to consolidate.

References

Aboelsaad, N. S., Soory, M., Gadalla, L. M., Ragab, L. I., Dunne, S., Zalata, K. R., & Louca, C. (2009). Effect of soft laser and bioactive glass on bone regeneration in the treatment of bone defects (an experimental study). *Lasers in Medical Science, 24*(4), 527–533. https://doi.org/10.1007/s10103-008-0599-3

Arruda, E. R. B., Rodrigues, N. C., Taci, C., & Parizotto, N. A. (2011). Biocompatibilidade e bioatividade do biovidro genérico 45S5 cristalizado sob condições controladas. *Revista CITINO: Ciência, Tecnologia, Inovação e Oportunidade, 1*(1), 19–25.

Bai, J., et al. (2021). Low level laser therapy promotes bone regeneration by coupling angiogenesis and osteogenesis. *Stem Cell Research & Therapy, 12*, 432. https://doi.org/10.1186/s13287-021-02493-5

Bossini, P. S., Fangel, R., Habenschus, R. M., Rennó, A. C., Benze, B., Zuanon, J. A., Neto, C. B., & Parizotto, N. A. (2009). Low level laser therapy (670 nm) on viability of random skin flap in rats. *Lasers in Medical Science, 24*(2), 209–213. https://doi.org/10.1007/s10103-007-0516-y

Bossini, P. S., Rennó, A. C., Ribeiro, D. A., Fangel, R., Peitl, O., Zanotto, E. D., & Parizotto, N. A. (2011). Biosilicate® and low-level laser therapy improve bone repair in osteoporotic rats. *Journal of Tissue Engineering and Regenerative Medicine*, 5(3), 229–237. https://doi.org/10.1002/term.299
Brasileiro Filho, G. (2006). *Bogliolo patologia* (7ª ed.). Rio de Janeiro: Guanabara Koogan.

Crovace, M. C., et al. (2015). Biosilicate® – A multipurpose, highly bioactive glass-ceramic: In vitro, in vivo and clinical trials. *Journal of Non-Crystalline Solids, 432*, 90–110. https://doi.org/10.1016/j.jnoncrysol.2015.04.018

Ehnert, S., & Histing, T. (2024). Advances in fracture healing research. *Bioengineering, 11*(1), 67. https://doi.org/10.3390/bioengineering11010067

El-Rashidy, A. A., Roether, J. A., Harhaus, L., Kneser, U., & Boccaccini, A. R. (2017). Regenerating bone with bioactive glass scaffolds: A review of in vivo studies in bone defect models. *Acta Biomaterialia, 62*, 1–28. https://doi.org/10.1016/j.actbio.2017.08.030

Escudero, J. S. B., et al. (2019). Photobiomodulation therapy (PBMT) in bone repair: A systematic review. *Injury, 50*(11), 1853–1867. https://doi.org/10.1016/j.injury.2019.09.031

Fangel, R., Bossini, P. S., Rennó, A. C., Ribeiro, D. A., Wang, C. C., Toma, R. L., Nonaka, K. O., Driusso, P., Parizotto, N. A., & Oishi, J. (2011). Low-level laser therapy, at 60 J/cm² associated with a Biosilicate® increase in bone deposition and indentation biomechanical properties of callus in osteopenic rats. *Journal of Biomedical Optics*, 16(7), 078001. https://doi.org/10.1117/1.3598847

Fávaro-Pípi, E., et al. (2010). Comparative study of the effects of low-intensity pulsed ultrasound and low-level laser therapy on bone defects in tibias of rats. *Lasers in Medical Science, 25*(5), 727–732. https://doi.org/10.1007/s10103-010-0771-3

Fernandes, K. R., et al. (2012). Comparação dos efeitos do laser de baixa potência e do ultrassom de baixa intensidade associado ao Biosilicato® no processo de reparo ósseo em tíbias de ratos. *Revista Brasileira de Ortopedia, 47*(1), 9–14. https://doi.org/10.1590/S0102-36162012000100014

Fernandes, M. C. S., & Morelli, M. R. (2019). Desenvolvimento de arcabouços de óxido de titânio e Biosilicato® para regeneração óssea. *Cerâmica, 65*(381), 1–8. https://doi.org/10.1590/0366-69132019653813001

Greer, N., Yoon, P., Majeski, B., & Wilt, T. J. (2020). *Orthobiologics in foot and ankle arthrodesis sites: A systematic review* (VA Evidence-based Synthesis Program Reports). Department of Veterans Affairs (US). https://pubmed.ncbi.nlm.nih.gov/32574000/

Hench, L. L., & Polak, J. M. (2002). Third-generation biomedical materials. *Science, 295*(5557), 1014–1017. https://doi.org/10.1126/science.1067404

Karageorgiou, V., & Kaplan, D. (2005). Porosity of 3D biomaterial scaffolds and osteogenesis: Review. *Biomaterials, 26*(27), 5474–5491. https://doi.org/10.1016/j.biomaterials.2005.02.002

Magri, A. M. P., Parisi, J. R., de Andrade, A. L. M., & Rennó, A. C. M. (2021). Bone substitutes and photobiomodulation in bone regeneration: A systematic review in animal experimental studies. *Journal of Biomedical Materials Research Part A, 109*(9), 1765–1775. https://doi.org/10.1002/jbm.a.37192

Maruyama, M., Rhee, C., Utsunomiya, T., Zhang, N., Ueno, M., Yao, Z., & Goodman, S. B. (2021). Insights into the cellular and molecular mechanisms that govern fracture healing. *International Journal of Molecular Sciences, 22*(2), 943. https://doi.org/10.3390/ijms22020943

Oliveira, P., Ribeiro, D. A., Pipi, E. F., Driusso, P., Parizotto, N. A., & Rennó, A. C. (2010). Low level laser therapy does not modulate the outcomes of a highly bioactive glass-ceramic (Biosilicate) on bone consolidation in rats. *Journal of Materials Science: Materials in Medicine, 21*(4), 1379–1384. https://doi.org/10.1007/s10856-009-3955-3

Pereira, A. S. et al. (2018). *Metodologia da pesquisa científica*. [free ebook]. Santa Maria: Editora da UFSM.

Pinto, K. N., Tim, C. R., Crovace, M. C., Matsumoto, M. A., Parizotto, N. A., Zanotto, E. D., Peitl, O., & Rennó, A. C. (2013). Effects of biosilicate scaffolds and low-level laser therapy on the process of bone healing. *Photomedicine and Laser Surgery, 31*(6), 252–260. https://doi.org/10.1089/pho.2012.3435

Raina, D. B., Isaksson, H., Lidgren, L., & Tägil, M. (2024). Delivery of growth factors to enhance bone repair. *Frontiers in Bioengineering and Biotechnology, 12*, 1344769. https://doi.org/10.3389/fbioe.2024.1344769

Rennó, A. C. M., McDonnell, P. A., Parizotto, N. A., & Laakso, E.-L. (2007). The effects of laser irradiation on osteoblast and osteosarcoma cell proliferation and differentiation in vitro. *Photomedicine and Laser Surgery, 25*(4), 275–280. https://doi.org/10.1089/pho.2006.2042

Rubin, E., Gorstein, F., Rubin, R., Schwarting, R., & Strayer, D. (2006). *Rubins patologia: Bases clinicopatológicas da medicina* (4ª ed.). Rio de Janeiro: Guanabara Koogan.

Santinoni, C. D., Oliveira, H. F., Batista, V. E., Lemos, C. A., & Verri, F. R. (2017). Influence of low-level laser therapy on the healing of human bone maxillofacial defects: A systematic review. *Journal of Photochemistry and Photobiology B: Biology, 169*, 83–89. https://doi.org/10.1016/j.jphotobiol.2017.03.004

Santos, A. O. dos, Silva, A. C. de O., Silva, L. M. de O., et al. (2024). Eficácia de diferentes tratamentos de consultório para hipersensibilidade dentinária: Um estudo clínico randomizado. *Brazilian Dental Journal, 35*(6), 531–537. https://doi.org/10.1590/0103-6440202304189

Souza, C. F. S. (2010). *Estudo histomorfométrico da reparação óssea em ratos após o uso de biomaterial de origem sintética* [Dissertação de mestrado, Universidade Federal da Paraíba].

Tim, C. R., Pinto, K. N. Z., Rossi, B. R. O., Fernandes, K., Matsumoto, M. A., Parizotto, N. A., & Rennó, A. C. M. (2014). Low-level laser therapy enhances the expression of osteogenic factors during bone repair in rats. *Lasers in Medical Science, 29*(1), 147–156. https://doi.org/10.1007/s10103-013-1302-9

Vitale-Brovarone, C., Verné, E., Robiglio, L., Appendino, P., Bassi, F., Martinasso, G., Muzio, G., & Canuto, R. (2007). Development of glass-ceramic scaffolds for bone tissue engineering: Characterization, proliferation of human osteoblasts and nodule formation. *Acta Biomaterialia, 3*(2), 199–208. https://doi.org/10.1016/j.actbio.2006.09.002

Zanotto, E. D., Ravagnani, C., Peitl Filho, O., Panzeri, H., & Guimarães Lara, E. H. (2004). *Process and compositions for preparing particulate, bioactive or resorbable biosilicates for use in the treatment of oral ailments* (Patente internacional WO 2004/074199 A1). WIPO – World Intellectual Property Organization.

Zhu, S., Chen, W., Masson, A., & Li, Y.-P. (2024). Cell signaling and transcriptional regulation of osteoblast lineage commitment, differentiation, bone formation, and homeostasis. *Cell Discovery, 10*, 71. https://doi.org/10.1038/s41421-024-00689-6