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Dental implants of a Ti-35Nb-7Zr alloy compared to commercially pure titanium implants: *in vitro* and *in vivo* study

Implantes dentários de uma liga de Ti-35Nb-7Zr comparados a implantes de titânio comercialmente puro: estudo *in vitro* e *in vivo*

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ABSTRACT

Objective: This study evaluates the biofunctionality of Ti-35Nb-7Zr alloy dental implants compared to Titaniumfix® (Ti-Cp) implants. **Material and Methods:** Biofunctionality was evaluated through *in vitro* tests using mesenchymal stem cells isolated from rat femur bone marrow, focusing on cell viability, total protein quantification, and alkaline phosphatase activity. *In vivo* tests involved inserting both Ti-Cp and Ti-35Nb-7Zr implants into the tibia of New Zealand albino rabbits for histological and histomorphometric analysis, along with removal torque analysis to assess osseointegration. The analysis of variance ANOVA one factor was performed. In case of statistical differences, Tukey test with a significance level of 5% was used. **Results:** The new alloy exhibited non-cytotoxicity, with cell viability. No significant differences were observed in total protein and alkaline phosphatase tests between the two materials. Histological analysis indicated new bone formation, with no statistical differences in bone area fraction occupancy. Fluorescence analysis demonstrated comparable bone apposition, while removal torque results suggested osseointegration in both implants. **Conclusions:** The Ti-35Nb-7Zr alloy induces osteogenesis and osseointegration as well as Ti-Cp implants, showcasing its potential as an intraosseous biomaterial for use not only in dentistry but also in other fields requiring prosthetic rehabilitation.

KEYWORDS

Beta titanium alloy; Biomaterials; Dental implants; Osseointegration; Osteogenesis.

RESUMO

Objetivo: Este estudo avalia a biofuncionalidade dos implantes dentários de liga Ti-35Nb-7Zr em comparação com os implantes Titaniumfix® (Ti-Cp). **Material e métodos:** A biofuncionalidade foi avaliada por meio de testes *in vitro* usando células-tronco mesenquimais isoladas da medula óssea do fêmur de ratos, com foco na viabilidade celular, quantificação de proteína total e atividade da fosfatase alcalina. Os testes *in vivo* envolveram a inserção de implantes de Ti-Cp e Ti-35Nb-7Zr na tíbia de coelhos albinos da Nova Zelândia para análise histológica e histomorfométrica, juntamente com análise de torque de remoção para avaliar a osseointegração. Foi realizada análise de variância ANOVA de um fator. Em caso de diferenças estatísticas, utilizou-se o teste de Tukey com nível de significância de 5%. **Resultados:** A nova liga não apresentou citotoxicidade, com viabilidade celular. Não foram observadas diferenças significativas nos testes de proteína total e fosfatase alcalina entre os dois materiais. A análise histológica indicou formação óssea nova semelhante, sem diferenças estatísticas na ocupação da fração de área óssea. A análise de fluorescência demonstrou aposição óssea, enquanto os resultados do torque de remoção sugeriram osseointegração assim como os implantes comerciais de Ti-Cp. **Conclusão:** A liga Ti-35Nb-7Zr induz osteogênese e osseointegração, assim como os implantes de Ti-Cp, demonstrando seu potencial como um biomaterial intraósseo para uso não apenas em odontologia, mas também em outros campos que exigem reabilitação protética.

PALAVRAS-CHAVE

Liga de titânio beta; Biomateriais; Implantes dentários; Osseointegração; Osteogênese.

INTRODUCTION

In 2019, according to the Brazilian Institute of Geography and Statistics (IBGE) [1] in the National Health Survey Perception of Health Conditions, Lifestyles, Chronic Diseases and Oral Health (the latest study), around 31.7% of the Brazilian population aged 60 and over have lost all their teeth. In the population aged 18 or over, 33.0% used some kind of dental prosthesis. With the increase in life expectancy, which according to a 2022 survey shows that the life expectancy of the Brazilian population will increase to 75.5 years, one can imagine how much this impacts on the quality of life of these people.

It is already known that dental implants bring better results in the rehabilitation of masticatory function, phonation, comfort and aesthetics, improving the quality of life of those who use them.

Titanium (Ti) and its alloys have a unique range of characteristics resulting from their exceptional mechanical and chemical properties, non-toxicity and compatibility with human tissue for use as dental implants. The growing recognition of titanium alloys in the field of tissue engineering has inspired the development of next-generation biomaterials.

Titanium, as a transition element, exists in two crystal structures: α (compact hexagonal) and β (body-centered cubic). The allotropic properties of titanium are strongly influenced by the solute elements, with those that increase the transformation temperature being labeled as α stabilizers and those that suppress it as β stabilizers.

When an alloy has a higher fraction of β stabilizers, resulting in a stabilized β phase after annealing, it is recognized as a metastable β-Ti alloy. In these alloys, the evolution of the microstructure through thermomechanical treatments significantly influences the customization of implants with low Young's modulus and high strength [2-4].

According to Andrade et al. [5] and Ahmed et al. [6], the mechanical performance of implants plays a crucial role in their clinical longevity. This highlights the relevance of using low-modulus materials such as beta titanium alloys to improve load distribution and minimize stress shielding. Young's modulus, a mechanical property that quantifies material stiffness, is defined as the ratio of stress to strain. In implantology, materials with a modulus of elasticity closer to that of bone tissue are preferred, as they enhance load transfer and reduce the risk of bone resorption due to stress shielding.The Ti-35Nb-7Zr alloy exhibits a Young's modulus of approximately 35 GPa, which is comparable to that of cortical bone (around 30 GPa), and significantly lower than that of conventional implant materials such as Ti-cp, (~110 GPa) Ti-6Al-4V (~110 GPa) and stainless steel (~185 GPa). This biomechanical compatibility makes Ti-35Nb-7Zr a promising alternative for improving the long-term success of orthopedic and dental implants [7].

The aim of this study was to evaluate the osteogenesis and osseointegration of Ti-35Nb-7Zr alloy implants through *in vitro* and *in vivo* tests comparing them with Ti-cp (Ti-Cp, commercially pure titanium) implants by Titaniumfix®, a partner in this project.

MATERIAL & METHODS

The alloy production

The Ti-35Nb-7Zr alloy is produced by arc furnace fusion with a non-consumable tungsten electrode under an argon atmosphere (99% purity) in a water-cooled copper crucible. High purity Ti, Nb and Zr plates are used. The plates are produced in Lorena Engineering School at University of São Paulo, and were cut into strips of size appropriate to the size of the crucible by means of a guillotine and then pickled in acid solution suitable for each metal. The clean material is weighed in proportions suitable to obtain ingots of approximately 65 g. The ingots are vacuum encapsulated in quartz tubes and then subjected to solubilization at 1000 °C for 2 hours cooled in water (1000 °C/2h WQ) and recrystallized at 700 °C for 30 minutes water cooled (700 °C/30 min WQ).

The thermal treatment consists of the solubilization of the alloys in the β field in order to guarantee better homogeneity and eliminate the possible influences of the initial structure (crude fusion). After the solubilization, the ingots were passed through the process of cold-rolling Swaging up to the diameter of 6 mm (reduction in area 84%) in FENN 3F equipment, with a power of 30 CV and a speed of 1,700 rpm.

Obtaining and characterization of samples

For *in vitro* study, both samples exhibited polished flat surfaces (discs) measuring 4mm long by 4mm wide by 1.5mm thick. For *in vivo* study, screw shaped implants of both Ti-Cp and Ti-35Nb-7Zr were 10 mm x 3.75 mm in size, matching commercial dimensions.

Biological evaluation

In vitro tests

For cell isolation and proliferation, bone marrow cells from rat femurs were cultured for 10 days in L-glutamine (α-MEM, Gibco, Invitrogen, USA) with 10% of fetal bovine serum (Gibco, Invitrogen), 7 ml beta-glycerophosphate (Sigma-Aldrich, USA), 5 μg/ml ascorbic acid (Sigma-Aldrich, USA) and 50 μg/ml gentamicin (Gibco, Invitrogen, USA)) to promote osteoblastic differentiation, and kept at a temperature of 37 °C in a humid oven atmosphere containing 5% of CO_2 (Sanyo). The culture medium was changed every three days, and the culture progression was evaluated by microscopy. Five samples from each group were used and all the assays were performed in triplicate, which were representative of three distinct primary cultures. All tests were developed in accordance with ISO-10993-5 [8] and they were performed in LEIC (Interdisciplinary Laboratory in Cell Studies at São Paulo State University, Brazil).

Cell interaction was evaluated by FE-SEM (Field Emission Scanning Electron Microscopy) (Zeiss - EVO MA10, São Paulo, Brazil), after 7 days of culture (n=2 for each experimental group).For the *in vitro* evaluation the samples were placed at the bottom of well plates, and the cells were directly seeded onto their surface, For cell viability, the cells were cultured on the samples at a concentration of 2 x 10^4 viable cells/disc for 07 days and MTT (3-[4,-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide; thiazolyl blue) (Sigma Aldrich, St Louis, USA) test was performed. Data of the cell viability was expressed in absorbance was measured at 570 nm using a microplate spectrophotometer (ELISA reader – EL808IU Biotek Instruments. USA). and data were expressed as percentage compared to the control group. The protein total quantification was determined using the same lysate of ALP, by Lowry test. To determine ALP, the method was used through the releasing of thymolphthalein monophosphate, after 7 days, with a commercial Kit (Labtest Diagnóstica, Belo Horizonte, BR) in accordance with the manufacturer's recommendations. Absorbance was measured at 590 nm in a UV 1203 spectrophotometer. The results were expressed as ALP μmol thymolphthalein/min/ml. All tests were performed as previously described by Andrade et al. [9].

Biological evaluation tests *in vivo*

For this study were used seven New Zealand albino rabbits weighing about 3.0 kg at 5 months of age, in each rabbit two implant was implanted in each tibia, divided according to the material of manufacture: commercial implants of Ti-Cp by Titanium fix®® and Ti-35Nb-7Zr implants. This research was approved by the Research Ethics Committee of the School of Dentistry of São José dos Campos/UNESP protocol nº 007/2016 and was carried out in accordance with the Ethical Principles for Animal Experimentation, adopted by the National Council of Control of Animal Experimentation (CONCEA).

Surgery procedures, medications and postoperative were performed as described in our previous study [10]. The surgery site for implant installation was performed with the drill sequence standardized by the company Titaniumfix®, at 1200 rpm (revolutions per minute), for the use of implants with a diameter of 3.75 mm by 10.0 mm in length. The two implants, TiCp and alloy, were manually installed, with the aid of surgical assemblers, in the right and left tibia of each animal until reaching primary stability, where there was an initial mechanical adaptation between the bone and the implant. During this procedure, irrigation was maintained with 0.9% sodium chloride, avoiding the heating resulting from the friction of the drill with the bone, which may cause tissue necrosis.

After implant placement, muscle tissue was sutured with absorbable wire (Monoglyde Poliglecarpone 25), the skin was sutured with silk thread (Ethicon/Johnson & Johnson) and again alcohol antisepsis was performed. The animals received antibiotic therapy with benzylpenicillin, benzylpenicillin procaine, benzylpenicillin potassium and dihydrostreptomycin base sulfate in a 6,000,000 IU (Pentabiotico - Fort Dodge) intramuscularly at a dose of 1.35 ml/kg in the immediate postoperative period. After surgery,

the rabbits were placed in individual cages with food and water *ad libitum* and monitored until the 6-week euthanasia period.

Application of fluorescent markers

During the research, bone markers of apatite union were administered subcutaneously, to verify the process of bone neoformation. A sequence of two different color markers, tetracycline (Oxytetracycline Hydrochloride 50 ml - Terramycin) and alizarin (Labsynth Products for Laboratories Ltda.) were used. The applications were performed in the periods of 7 and 14 days for tetracycline, 21 and 28 days for alizarin.

The obtained slides were observed under a fluorescence microscope (Zeiss Axiophot 2 (Carl Zeiss, Oberköchen, Alemanha),with 10x eyepiece and 20x objective, under a fixed focus, coupled with an Axiocam MRC 5 (Zeiss) camera) to analyze bone formation times, according to alizarin and tetracycline markers deposition, and to quantify the neoformed tissue by measuring the distance between the different markers in the bone tissue. This distance was divided by the time interval between the periods of administration of the bone marker, to obtain the mineral apposition rate.

Removal torque test

After the euthanasia period of the animals, 14 implants of 7 tibiae were surgically exposed, the tissues covering the implants were carefully removed and the left tibias were immobilized in a vise. The reverse torque test was performed using a digital torque gauge (Mark-10 Corporation, USA), whose torque wrench was kept on the long axis of the implant. Counterclockwise rotation was applied and the maximum torque values (N.cm) required to fracture the bone at implant-bone interface were measured.

Histological and histomorphometric analysis

Initially the 7 right tibias were immediately fixed with 10% formalin, and they were submitted to histological processing using the methylmethacrylate and cut into the Labcut (Extec) in Bone Tissue Laboratory at the São Paulo State University, technique as described previously in Vasconcellos et al. [10].

For the histomorphometric analysis, sections of each implant were evaluated for the fraction of bone area occupied between the threads (BAFO). Two fields per section were photographed representing the mesial and distal interface of the implant. The images were obtained from a light microscope (Zeiss Axiophot 2, Carl Zeiss, Oberköchen, Germany), with 200x original magnification, under a fixed focus, coupled with an Axiocam MRC 5 (Axioplan 2, Carls Zeiss, Germany) camera that allows Images directly in computer.

The images were analyzed by a blind investigator for both groups. Firstly, the total area of a thread of the implant was calculated and then the percentage of area occupied by the newly formed bone tissue in the same thread was calculated. The areas were calculated using Image J software (Java version 1.6.0_20 / 64-bit). The data evaluated and the rate of bone neoformation calculated in percentage (%).

To reveal tissue cells at the interface with the implant, the slides were stained with toluidine blue and histological analysis were performed by optical microscopy (Zeiss Axiophot 2, Carl Zeiss, Oberköchen, Germany) for observation of bone tissue, osteoid tissue and also cell nuclei such as osteoblasts, osteoclasts, bone marrow cells allowing the observation of bone remodeling that occurs in the process of osseointegration of implants and cell identification.

Statistical analysis of the results

Data are represented by mean and standard deviation graphs. Data were analyzed using GraphPad Prism 5.0 software. The analysis of variance ANOVA one factor was performed. In case of statistical differences, Tukey test with a significance level of 5% was used.

RESULTS AND DISCUSSION

Ti-35Nb-7Zr alloy implants

Before the implants were placed in the rabbit tibias, their surface topography was characterized by means of scanning electron microscopy (SEM) (Inspect S50 -FEI - Montreal, QC, Canada0 as seen in Figure 1. It is observed the regularity of the shape of the screw threads on both the alloy and the Ti-Cp.

EDS analysis

An Energy dispersive spectroscopy (EDS) analysis was carried out in random areas and points of the alloy implants, demonstrating as showing in

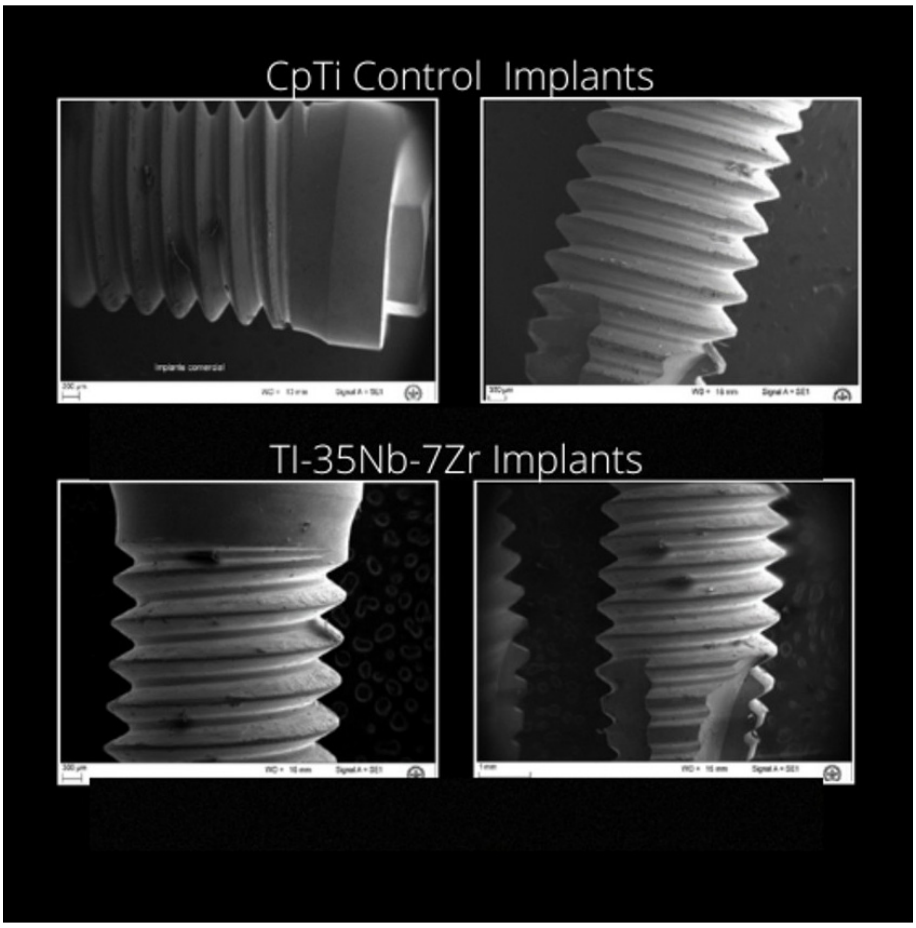

Figure 1 - Micrography of Titaniumfix® Ti-Cp commercial implants and Ti-35Nb-7Zr implants.

Figure 2, the quantification and composition of the alloy

In vitro tests

The cell viability results, Figure 3, showed that Ti-Cp and the Ti-35Nb-7Zr alloy exhibited the same behavior, as there was no statistically significant difference in cell viability between them ($p>0.05$), demonstrating good *in vitro* biocompatibility, in accordance with results reported in the literature [10,11].

The quantification of total protein and alkaline phosphatase activity is important because it indicates the presence of adsorbed proteins responsible for the differentiation and proliferation of osteoblastic cells, leading to bone matrix formation [11]. In this study, no significant difference was observed between Ti-Cp and the alloy ($p>0.05$).

In vivo tests

The animals did not present any physical trauma, increasing their weight in 1 to 1,500 kg, until the end of the experiment, indicating maintenance of good health systemic. After the established period of 42 days, animals were euthanized and during the collection of the material, the implants presented good stability to the bone tissue, with no signs of inflammation or infection.

Fluorescent labels were detected for all samples as seen in Figure 4, with tetracycline (brown labels) and alizarin (red labels). The evidence of bone labeling shows that continuous osteoblastic activity was present in regions close to the implant surface, demonstrating bone formation and remodeling over the 4 weeks in which the markers were applied. Note the presence of the Havers System (SH) where calcification occurs in concentric lamellae and intermittent calcifications. According to Bottino et al. [12,13], the observation of sustained bone activity levels near the implant over several weeks supports the high kinetics of modeling/remodeling that are responsible for leading to the biomechanical fixation of the implant due to the process of maturation.

The technique to evaluate the bone apposition was to identify the lines or labels of the staining

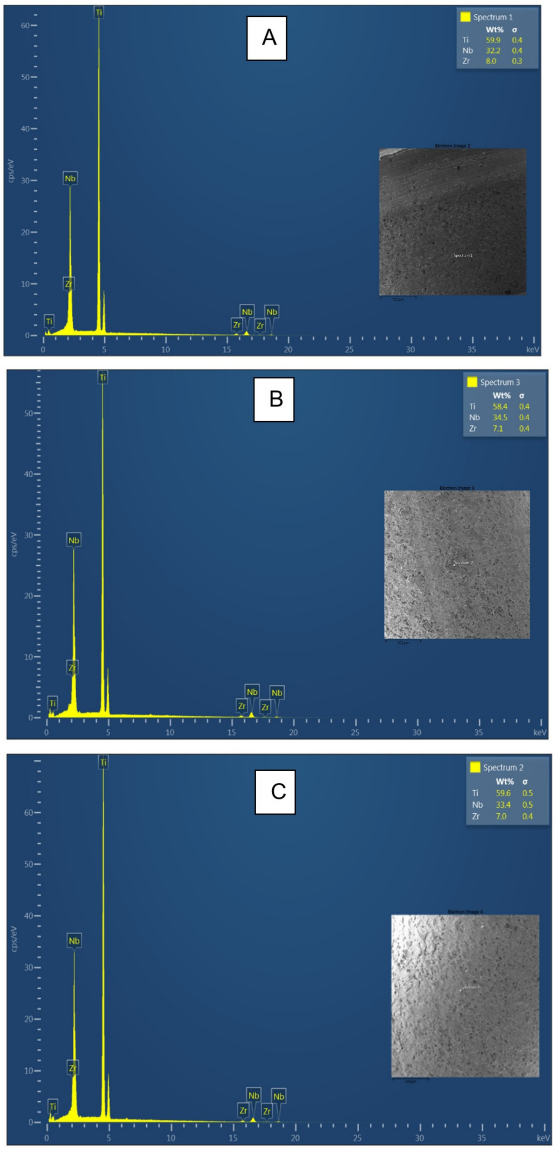

Figure 2 - (A), (B) and (C) show the chemical composition of the elements of the Ti-35Nb-7Zr implants through EDS analysis.

in the histological slides and to measure the distance between them. The relationship between the interval of administration of the fluorescent markers and the distance measured on the slide made it possible to calculate the rate of bone formation in the unit of distance (μm) per unit of time (day) [14,15].

Considering the bone apposition calculated in this study, it can be observed in Figure 5, that bone neoformation was greater in the first 7 days in both implants, when osteogenesis is more active and where a greater bone apposition was observed. This apposition was decreasing in the periods of 14 and 21 days when the kinetics of remodeling is smaller also in both implants. However, there was no statistical difference in bone apposition of the implants (Ti-Cp and alloy) independently of period ($p > 0.05$).

To evaluate histomorphometrically the osseointegration of the implants studied, the slides obtained in the histological preparation were analyzed according to the bone area fraction occupied (BAFO), expressed as percentage of bone occupied in the mesial and distal flanks of each thread. Subsequently, the percentages were calculated for each implant.

In the histomorphometric analysis, the two implants (Ti and Ti-35Nb-7Zr) presented a very similar fraction of occupied bone area (BAFO) in according with studies found in the literature for Ti-Nb-Zr and Ti-Nb-Zr-Ta systems, and there was no statistically significant difference between them ($P > 0.05$) (Figure 6).

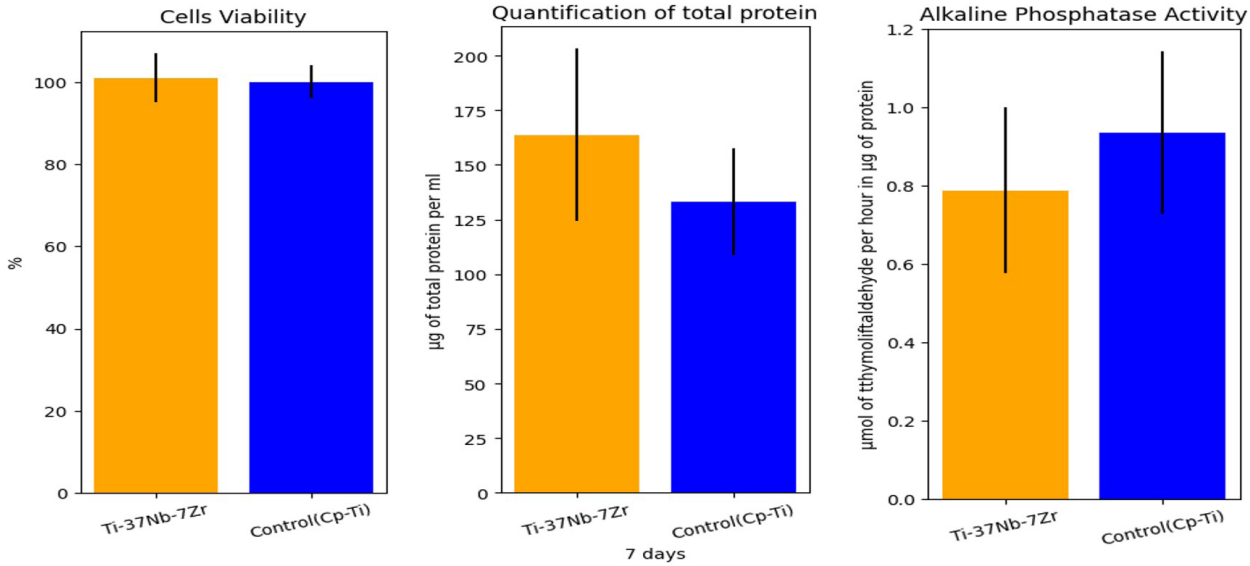

Figure 3 - *In vitro* tests analysis of cell viability, quantification of total protein and alkaline phosphatase activity.

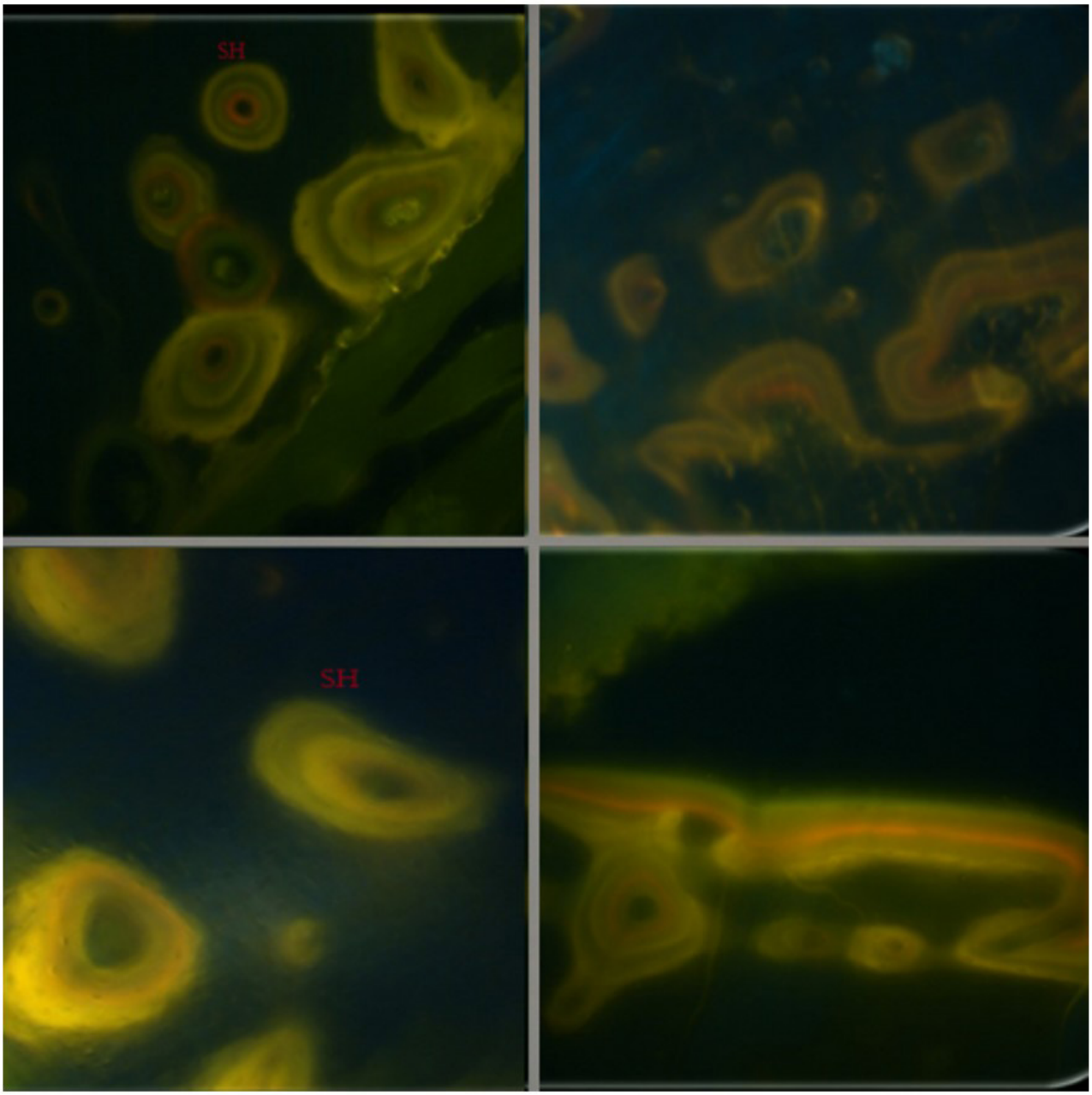

Figure 4 - Fluorescence photomicrography 200x showing the labeling of fluorescent dyes (brow lines: tetracycline and red lines: alizarin).

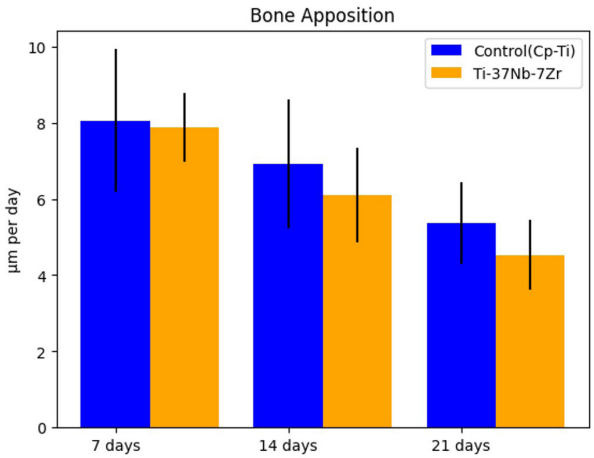

Figure 5 - Bone apposition.

In the histological analysis, we identified bone neoformation in both types of implants. Compact bone is observed with numerous Havers systems, formed by concentric bony lamellae arranged around a central canal. The lamellae with gaps of osteocytes, also arranged in concentric rings, were intercommunicated by canaliculi. In both implants, in the inferior and superior regions of the cortical bone, signs of new bone formation were observed, suggesting osseointegration in longer periods [13,14]. We also observed the delimitation of the area of neoformed bone tissue and the preexisting bone cortex (Figure 7).

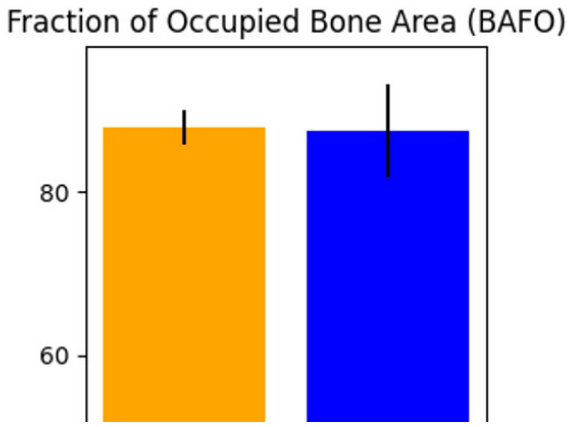

Figure 6 - Fraction of occupied bone area (BAFO) in control and Ti-35Nb-7Zr implants.

Torque removal analysis

Removal torque forces have been used as a safe biomechanical measure of anchorage or osseointegration where the forces required to remove the implants can be interpreted as an increase in the strength of osseointegration [16]. The results, as showed in Figure 8, did not present a significant statistical difference between the implants of the alloy and implants of Ti-Cp ($p > 0.05$). These results indicate that in addition to histological and histomorphometric analysis, the biomechanical analysis of implants to torque removal also demonstrates that there was similar osseointegration between Ti-Cp and Ti-35nb-7Zr implants.

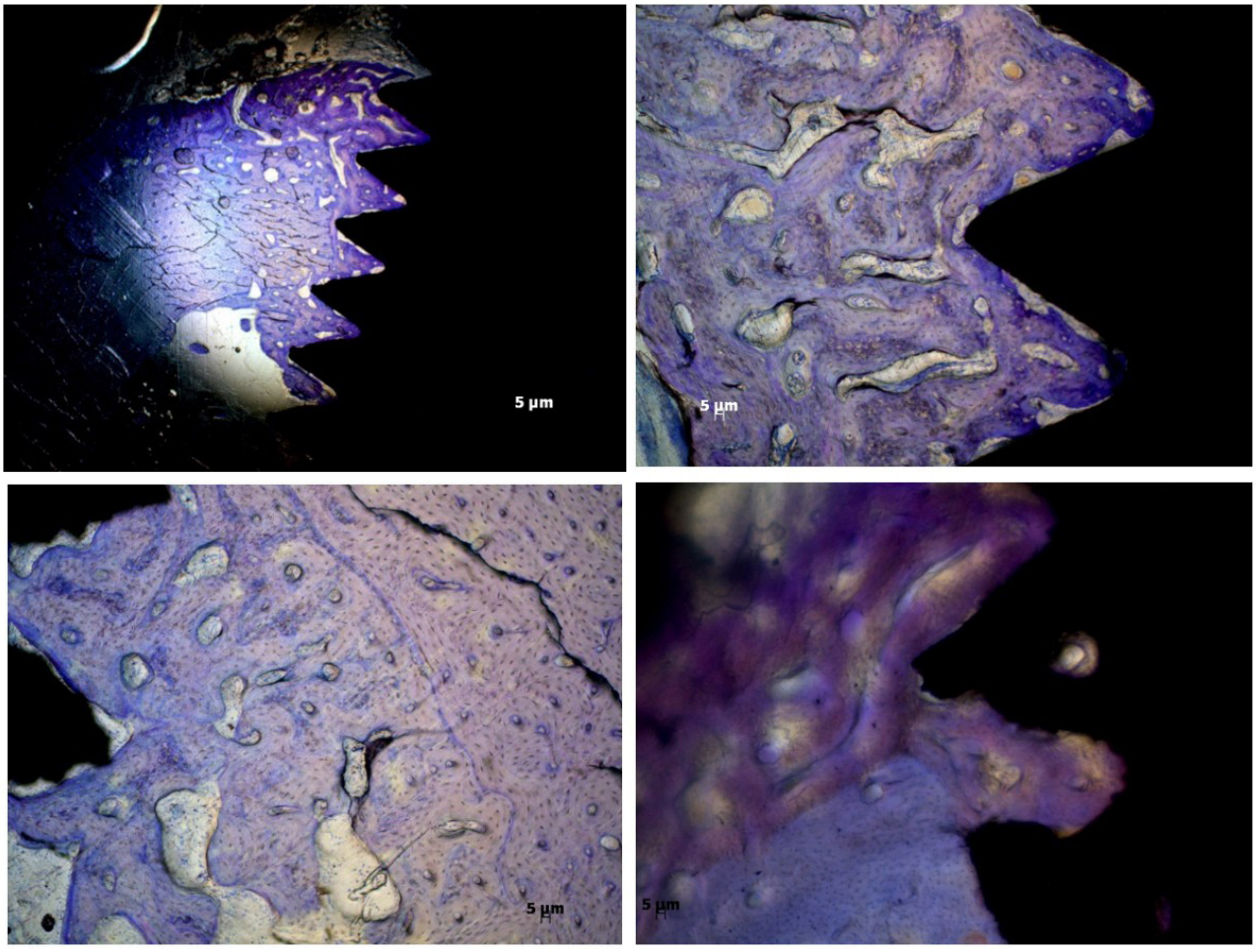

Figure 7 - Neoformation bone on Ti-35Nb-7Zr implant.

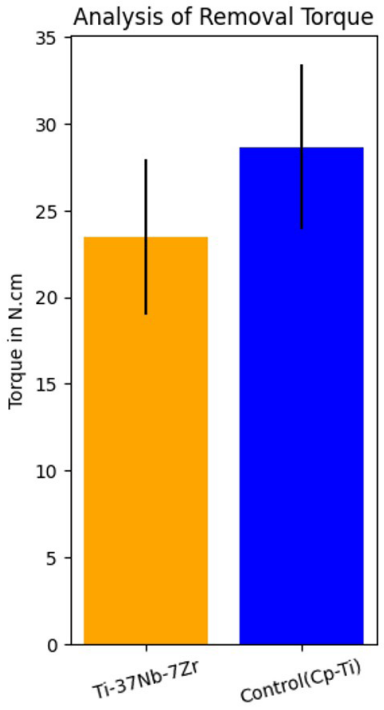

Figure 8 - Analysis of removal torque.

CONCLUSION

Regarding *in vitro* tests, it is possible to conclude that Ti-35Nb-7Zr presents biocompatibility inducing osteogenesis.

The results obtained *in vivo* evaluations, through the fraction of occupied bone area (BAFO), confirm osteointegration of both the TI-35Nb-7ZR alloy and Ti-Cp, since they presented a similar percentage value of newly formed bone. Fluorescence analysis, after administration of the tetracycline and alizarin markers, shows that bone apposition on Ti-35Nb-7Zr and Ti-Cp in the periods studied. Regarding the interaction force evaluated by the removal torque, it is possible to state that the alloy presents osseointegration comparable to commercial Ti-Cp implants. In the histological analysis, there was new bone formation in both types of implants. Compact bone is observed with numerous Haversian systems, formed by concentric bony lamellae arranged around a central canal. The lamellae with osteocyte gaps, also arranged in concentric rings, which were interconnected by canaliculi. In both implants, in the lower and upper regions of the cortical bone, signs of new bone formation were observed, suggesting osseointegration over longer periods. The delimitation of the area of newly formed bone tissue and the pre-existing cortical bone was also observed.

Despite the initial difficulties in machining the alloy due to Niobio's malleability, it was possible to manufacture dental implants in the dimensions and parameters of commercial Ti-Cp implants.

Finally, the results obtained in this research demonstrated that the Ti-35Nb-7Zr implant induces osteogenesis and osseointegration, being biocompatible and biofunctional, which makes it a promising biomaterial to be used as an intraosseous implant, not only in dentistry, but also in other bones prostheses areas.

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Author's Contributions

FZDM: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Validation, Visualization, Writing – Original Draft Preparation. LMRV, SGS: Conceptualization, Investigation, Methodology, Project Administration, Software, Supervision, Validation. DCRM: Data Curation, Formal Analysis, Investigation, Methodology, Validation. MNV: Formal Analysis, Investigation, Methodology, Validation, Writing – Review & Editing.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Regulatory Statement

This research was approved by the Research Ethics Committee of the School of Dentistry of São José dos Campos/UNESP protocol nº 007/2016 and was carried out in accordance with the Ethical Principles for Animal Experimentation, adopted by the National Council of Control of Animal Experimentation (CONCEA).

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