Int. J. Morphol.,
41(5):1317-1322, 2023.

Comparative Assessment of Contact Osteogenesis at the Titanium Implant-Bone Junction in Male Rabbits with Dissimilar Femoral Defects

Evaluación Comparativa de la Osteogénesis de Contacto en la Unión entre el Hueso y el Implante de Titanio en Conejos Macho con Defectos Femorales Diferentes

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DUMA, V.; GAL, A. F.; RUS, V.; MATEI-LATIU, M. C.; RATIU, C.; ALEXANDRU, B. C. & LATIU, C.; MARTONOS, C. & OANA, L. I. Comparative assessment of contact osteogenesis at the titanium implant-bone junction in male rabbits with dissimilar femoral defects. *Int. J. Morphol., 41(5)*:1317-1322, 2023.

SUMMARY: Traumatized bone tissue has the capacity to repair itself so that it eventually regains its almost original form, even in the case of artificially inserted implants. The process that stays at the base of the regeneration is represented by osteogenesis or remote osteogenesis. The major difference between the two types of bone formation is the location of the cement line, which is located on the surface of the implant for contact osteogenesis and on the surface of the bone defect for remote osteogenesis. The aim of the present study was to assess the contact osteogenesis in the case of inserted titanium screws in holes with diameters of 1.8 mm and 1 mm respectively. The obtained results show, in the case of the groove with 1.8 mm that the newly proliferated bone represents 73.85 % of the total area, while in the case of the groove with 1 mm in diameter the value of the newly proliferated bone is 26.15 %. In conclusion, the insertion of titanium screws by self-tapping into the hole smaller than the core of the screw is accompanied by bone proliferation by contact osteogenesis much more modest than in the case of insertion into the hole larger than the core of the screw.

KEY WORDS: Titanium implant; Osteogenesis; Bone repair.

INTRODUCTION

The bone has a remarkable regenerative capacity following a trauma, whether it is an accidental or an experimental one. Unlike most tissues in the body that repair themselves through scar tissue, the traumatized bone is able to repair itself so that it eventually regains its almost original form (Fratzl & Weinkamer, 2007). This is possible if the bone is adequately stabilized, sufficiently vascularized and if the biological factors are available. Stability must be ensured in such a way that the distance between the components is not more than 150 microns, since otherwise there is a risk that the repair will be performed through scar tissue (Szmukler-Moncler *et al*., 1998). The bone repair process is a complex one and is initiated by cellular and molecular interactions that lead to osteoblast recruitment, stem cell differentiation and mineralized matrix production (Jimi *et al*., 2012).

The repair process is similar in the case of a mechanically and chemically stable implant, which is finally completely embedded in the bone. After inserting the implant into the

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Received: 2023-06-07 Accepted: 2023-07-10

bone, interactions immediately occur between its surface and the environment. The surface of the implant comes into contact firstly with the blood and thus the exchange of ions and the adsorption of proteins begins. The blood brings platelets that release cytokines and growth factors such as platelet-derived growth factor (PDGF) and beta-transformer growth factor (TGF-b) (Tang *et al*., 2009; Xie *et al*., 2014; Oryan *et al*., 2016). They act as chemotactic factors, promoting the migration of osteoprogenitor cells from the bone marrow and the supply of blood to the surface of the implant (Fiedler *et al*., 2004). Thrombocytes initiate the cleavage of fibrinogen into fibrin and form with it a fibrinothrombocitary aggregate that will be absorbed on the surface of the implant (Green, 2006). Based on chemotactic signals, osteoprogenitor cells migrate to the surface of the implant through the fibrin network of the clot (Oprea *et al*., 2003; Davies, 2003). The osteoprogenitor cells that reach the surface of the implant, differentiate into osteoblasts. They initiate a bone proliferation directly on the surface of the implant, known as contact osteogenesis, which is the preferred form of bone proliferation. The first tissue that is deposited on the surface of the implant is a noncolagenic one that bears the name of cement line. If the osteoprogenitor cells do not come into direct contact with the surface of the implant, a bone proliferation called remote osteogenesis occurs. In the case of this type of osteogenesis, the new bone is initially deposited on the periphery of the bone defect, from where it gradually migrates to the implant (Davies, 1998, 2007). The major difference between the two types of bone formation is the location of the cement line, which is located on the surface of the implant for contact osteogenesis and on the surface of the bone defect for remote osteogenesis (Liddell & Davies, 2018).

The reaction of bone tissue to various implants is an intricate study field that requires a high level of know-how from practitioners in a vast range of areas. In view of that, the aim of the present study was to assess the contact osteogenesis in the case of inserted titanium screws in holes with diameters of 1.8 mm and 1 mm respectively.

MATERIAL AND METHOD

Biological material: This experiment was conducted with the agreement of the Institutional bioethics committee (Decision no. 219/10.07.2020). It was carried out in accordance with national (Law 43 of 2014) and European legislation (EU Directive 63 of 2010). The used animals were represented by 10 rabbits of the common breed, males, one-year-old and an average weight of 4.5 kg. The materials used were represented by titanium screws with a diameter of 2 mm and a length of 5 mm. The 10 rabbits were divided into two groups (n= 5/groups).

Experimental interventions: The intervention began with the anesthesia of animals with a mixture of xylazine 5 mg/kg + ketamine 40 mg/kg, im. After physical and chemical antisepsis of the intervention area, the incision of the skin and muscles was made, to highlight the femoral bone.

In the animals of group 1, a hole with a diameter of 1.8 mm was made. For group 2, the diameter of the orifice was 1 mm. Screws were inserted by self-tapping with the help of a special manually operated device, followed by the suture of the muscles and the skin. For postoperative prevention, treatment with enrofloxacin, sc, 20 mg/kg, for 5 days was followed. As an analgesic was administered Meloxicam, sc. 1 mg/kg, for 3 days. After 6 weeks the animals were euthanized and the portions of the femoral bone containing the screws were harvested and fixed in 10 % buffered formalin for 7 days.

Histological assessment. The pieces were then decalcified with 7 % trichloroacetic acid, included in paraffin and cut to 5 micrometers thick. The sections were stained using Goldner's trichrome method and examined with an Olympus BX41 microscope. The capture of microscopic images was done with an Olympus E-330 digital camera.

Morphometric evaluation. The morphometric evaluation of the bones was performed using ToupView software. The bone surface (μm^2) was measured from the two different groups (e.g. group 1 - 1.8 mm hole, group 2 – 1 mm hole; n=7/group). The measured surfaces were selected from the best fit intercepted by the histological sections.

Statistical analysis. The obtained data were statistically evaluated using GraphPad 8 software. To compare and analyze the mean surface of the proliferated bone, descriptive statistics and t-test (unpaired, two-tailed) were performed.

RESULTS

In the case of inserting the screws into the hole with a diameter of 1.8 mm, the interface is covered, after 6 weeks, with newly formed bone tissue, the thickness of which varies greatly from one area to another (Figs. 1A-C). The newly proliferated bone has the greatest thickness in the endosteal area of the interface, followed by the periosteal and then the central area. In the periosteal area, a relatively

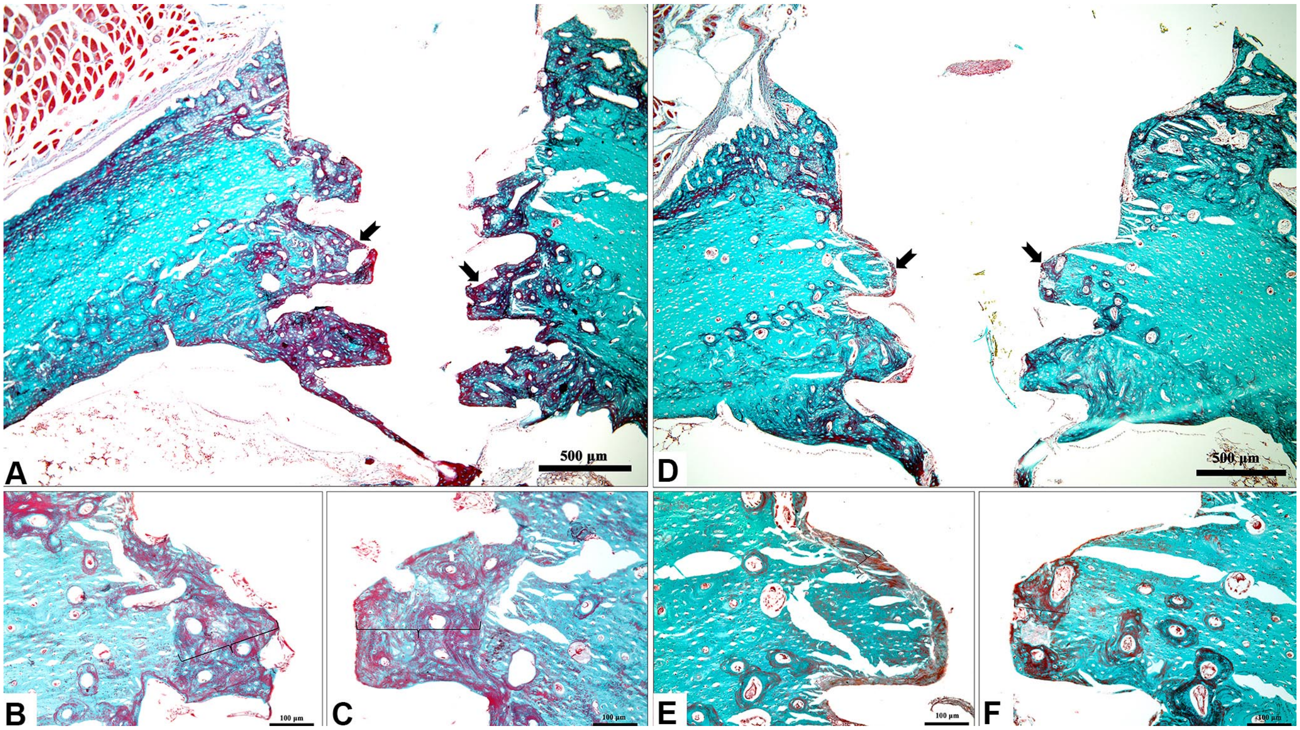

Fig. 1. Newly formed bone tissue at 6 weeks after screw insertion in a hole with a diameter of 1.8 mm (Group 1). A – overview of the groove and proliferated bone (black arrows); B, C – detail with the surface of the bone created by contact osteogenesis (accolades); D - Newly formed bone tissue at 6 weeks after screws insertion in a hole with a diameter of 1 mm (Group 2); E, F –newly proliferated bone present as a thin layer in the very early stage of organization and consolidation

thick layer of newly formed bone proliferated, extending to the surface, increasing the surface of the interface, but also laterally in the form of a well-represented layer that gradually thins as it moves away from the interface. The proliferated bone in the endosteal area also forms a thick layer that extends over the surface of the screw and lateral interface, in a manner comparable to the situation in the periosteal area. The expansion of the newly proliferated bone on the surface of the interface leads to its significant growth, which acquires the appearance of a fan.

On the interface area next to the bone wall that is the one between the periosteum and the endosteum, the thickness of the proliferated bone is very different from one area to another. Thus, next to the unfilled collar, the newly proliferated bone layer is very thin, and on the rest of the interface, it is thick in the grooves between the screw turns and thin next to the turns, so that the interface acquires here the appearance of saw teeth.

There are differences from one area to another and in the stage at which the newly proliferated bone is located. Next to the non-threaded collar, the newly proliferated bone layer, in addition to being very thin, is also in its early stage, being represented on certain portions only as a cement line and after as an osteoid. The rest of the interface predominates the primary bone in which there are limited areas of osteoid. In the case of the proliferated bone in the grooves between the turns, there is in some places a tendency to reshuffle towards the secondary bone, materialized by the existence of sketches of dispersed bone trabeculae.

In the case of inserting the screw into the hole with a diameter of 1 mm, the interface situation is different in many ways compared to the insertion into the hole with a diameter of 1.8 mm. The newly proliferated bone structures are in significantly smaller quantities and in a much earlier stage than in the case of inserting screws into the 1.8 mm hole. On the interface next to the bone wall is present newly proliferated bone in the form of a thin layer consisting of newly proliferated bone in the very early stage of organization and consolidation, on some portions only in the cement line stage (Figs. 1D-F). The situation of the bone proliferated by contact osteogenesis after 6 weeks after the insertion of titanium screws is presented in Table I.

The results obtained from morphometric analyses suggest that the average total area of the bone existing in the grooves between the turns records similar values in the

Table I. The area occupied by the bone proliferated by contact osteogenesis, in the grooves between the turns of the screw.

	Mean area (μm^2) of the grooves between the turns	Percentage (%) of new bone proliferated by contact osteogenesis, from the total surface area of the grooves	Percentage (%) of old bone in the total area of grooves
Group 1	466455.6979	73.85	26.69
Group 2	436817.4548	26.15	73.31
		Group 1 vs. Group 2 $p<0.0001$ for T test	

case of the 2 groups (466455.6979 μm^2 for the drill bit of 1.8 mm and 436817.4548 μm^2 for the drill bit of 1 mm). The mean area of the bone proliferated by contact osteogenesis records different values (342892.9721 μm^2 of the total for group 1 and 115265.2381 μm^2 for group 2). Thus, in the case of group 1, the newly proliferated bone represents 73.85 % of the total area, respectively 26.15 % for group 2 (Table I). The results of the t-test also suggest that the surface area of the proliferated bone differs significantly when comparing group 1 with group 2 ($p<0.0001$ for the t-test).

DISCUSSION

In the case of reparative processes around an implant (screw) inserted into the bone, the preferred way of repair is contact osteogenesis. It begins by organizing an aggregate rich in fibrin and thrombocytes that will be adsorbed on the surface of the implant (Green, 2006). Based on the chemotactic signals released by platelets, osteoprogenitor cells proliferate and differentiate from osteoblasts that migrate through the fibrinous aggregate and reach the surface of the implant. In the first phase they synthesize a noncolagenic matrix that is deposited on the surface of the implant in the form of a thin layer called the cement line. The cement line is made up of noncolagenic proteins such as integrins, glycoproteins, osteopontin, bone sialoprotein and proteoglycans (Baht *et al*., 2008). These proteins are involved in the organization of hydroxyapatite crystals, respectively, the mineralization of the cement line, which intimately follows the surface contour of the implant. The next stage is that of osteoid formation, a stage in which osteoblasts synthesize collagen precursors that are assembled extracellularly. On account of the osteoid, the primary bone is formed, which from a structural point of view has a less orderly organization (plexiform). The primary bone is then subjected to the remodeling process to replace this originally deposited bone with a more resistant one. Remodeling is not just a process specific to the repair of bone defects, but a normal one that unfolds throughout life. It is a complex process that aims to replace worn components, but also to optimize bone architecture to more efficiently support the loads to which it is subjected (Martin & Seeman, 2008). Bone remodeling goes through the same steps as bone regeneration, but the major difference between them is the time frame in which they unfold. If bone regeneration proceeds in a short time (in a hurry), bone remodeling is a much slower process, but it leads to the direct formation of secondary bone. The formation of osteons gives the bone a much higher strength compared to the primary, non-spot bone (Liddell & Davies, 2018). Also through such a process is replaced the periinplantar bone more or less affected by necrosis that can occur up to 1 mm of implant (Roberts, 1988) as a result of the lesions that accompany the procedure of inserting implants, the applied pressure and the interruption of the blood supply. When the remodeling is completed, the bone reaches homeostasis, and the strength of the bone-implant interface reaches a balance in terms of strength (Liddell & Davies, 2018). Homeostasis can be negatively influenced by certain factors with systemic action such as diabetes, smoking, excessive alcohol consumption and the action of some stressors (de Souza *et al*., 2006; Petru?iu *et al*., 2014; Tomina *et al*., 2022).

During the osseointegration process of titanium screws, both bone regeneration and bone remodelling processes take place (Marcu *et al*., 2022). The regeneration ones consist mainly of the proliferation of new bone on the surface of the implant, through the process of contact osteogenesis. In the 6 weeks that have passed since the insertion of the screws in the rabbit femur, we found the presence of newly proliferated bone on the surface of the interface next to the bone wall, in the case of both groups. However, the difference between them was significant in terms of the amount of newly proliferated bone, which was significantly less in the case of the 1 mm hole. We believe that this difference is due to the fact that in the case of the 1 mm hole, there is practically no space left between the surface of the screw and the bone wall so the grooves between the turns are occupied by residual bone. In the version with a 1.8 mm hole, only one-third of the groove surface is occupied by residual bone. The blood that invades the area will occupy the available space, which is significantly larger in the case of the 1.8 mm hole. The fibrinoleukocyte aggregate will thus, have a much greater thickness in the version with a 1.8 mm hole and through it, the osteoblasts will migrate more easily to reach the surface of the screw. Moreover, osteoblasts reaching the surface of the screw initiate the synthesis of new bone, but it will expand on the available surface, i.e. it will occupy the existing space between the surface of the screw and the remaining bone wall at the interface. So, the newly proliferated bone is arranged in a thin layer in the case of the 1 mm hole (Group 2) and significantly thicker, especially near the grooves, in the case of the 1.8 mm hole (Group 1). Moreover, the proliferated bone in the thicker layer more rapidly goes through the stages of organization and remodelling, which are present at an early stage in the case of the 1.8 mm hole, but not in the case of the 1 mm hole. Results somewhat similar to those found by us were also reported by other authors who found that the newly proliferated bone was preferentially deposited in the concavities of the thread (the grooves between the turns) (Scarano *et al*., 2014). According to some authors, an explanation of the preferential growth of the bone in the concavities of the implant would be due to the increase in the concentration of platelets (Moreo *et al*., 2009a,b). By degranulation, platelets release a number of growth factors such as PDGF and TGF-b, along with vasoactive factors such as serotonin and histamine. These factors play an important role in regulating the healing cascade (Davies, 2003).

If we comparatively analyze the results obtained in the two groups, we find that the newly proliferated bone is significantly more in the variant with a 1.8 mm hole (Group 1). We consider that in the case of the variant with a 1 mm hole (Group 2), several factors intervene and negatively influence (delay) the osseointegration process. The first is that the somewhat forced insertion by self-drilling into a hole smaller in diameter than the core of the screw creates pressure on the surrounding bone, which amplifies the lesions that accompany the implant insertion operation. This aspect is supported by other authors who state that moderate compressive forces are beneficial but excessive ones can cause extensive bone resorption (Chamay & Tschantz, 1972). The second aspect is the one pointed out by us, namely that the newly proliferated bone occupies the space it has at its disposal, which is significantly larger in the case of the 1.8 mm hole. The advantage is that the space in the groove left unoccupied by the remaining bone is filled with a blood clot, in which bone fragments resulting in the course of the self-tapping process also remain. This mixture of blood and bone fragments constitutes an excellent autologous augmentation material that stimulates bone proliferation (Ratiu *et al*., 2022). Moreover, this bone is also in a somewhat more advanced stage of organization and consolidation compared to the proliferated one in the case of insertion into holes smaller than the core of the screw. Also, in the case of the hole with a diameter greater than the diameter of the screw core, the bone in the depth of the interface is comprised, at 6 weeks, of more obvious reshuffle processes. In this context, we can say that at 6 weeks, the interface is in the stage of restoration more advanced in the case of the hole wider than the diameter of the core of the screw, compared to the one below its diameter.

In conclusion, the insertion of titanium screws by self-tapping into the hole smaller than the core of the screw is accompanied by bone proliferation, by contact osteogenesis much more modest than in the case of insertion into the hole larger than the core of the screw. The appearance is due to the fact that on the one hand, additional harmful pressure is exerted on the insertion area, and on the other hand the remaining space between the surface of the screw and the neighboring bone, is very small and does not allow the proper conduct of contact osteogenesis.

DUMA, V.; GAL, A. F.; RUS, V.; MATEI-LATIU, M. C.; RATIU, C.; ALEXANDRU, B. C.; LATIU, C.; MARTONOS C. & OANA L. I. Evaluación comparativa de la osteogénesis de contacto en la unión entre el hueso y el implante de titanio en conejos macho con defectos femorales diferentes. *Int. J. Morphol., 41(5)*:1317-1322, 2023.

RESUMEN: El tejido óseo traumatizado tiene la capacidad de reparar en forma espontánea, de modo que eventualmente recupera su forma casi original, incluso en el caso de implantes insertados artificialmente. El proceso que queda en la base de la regeneración está representado por la osteogénesis u osteogénesis a distancia. La principal diferencia entre los dos tipos de formación ósea es la ubicación de la línea de cemento, que se encuentra en la superficie del implante para la osteogénesis de contacto y en la superficie del defecto óseo para la osteogénesis remota. El objetivo del presente estudio fue evaluar la osteogénesis de contacto en el caso de tornillos de titanio insertados en forámenes con diámetros de 1,8 mm y 1 mm respectivamente. Los resultados obtenidos muestran, en el caso del surco de 1,8 mm que el hueso neoproliferado representa el 73,85 % del área total, mientras que en el caso del surco de 1 mm de diámetro el valor del hueso neoproliferado es del 26,15 %. En conclusión, la inserción de tornillos de titanio por autorroscantes en el foramen menor que el núcleo del tornillo se acompaña de una proliferación ósea por osteogénesis de contacto mucho más modesta que en el caso de la inserción en el foramen mayor que el núcleo del tornillo.

PALABRAS CLAVE: Implante de titanio; Osteogénesis; Reparación ósea.

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