

SUMMARY OF THE DOCTORAL THESIS

**Evaluation of the potential regeneration of the  
periimplant tissue depending on the  
physiological state**

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## Introduction

The use of biomaterials that are as well tolerated by the animal and human body as possible has been a permanent concern. They have been and are necessary for many medical activities, among which orthopedics and dentistry occupy a special place. These biomaterials must be tolerated by the body on the one hand but at the same time present biomechanical qualities. These qualities are necessary so that a biomaterial introduced into the intimacy of the tissues can remain there for a sufficient period of time to support their function. Of great importance is immune tolerability and the choice of the most suitable biomaterial for the respective intervention. Although biomaterials from animals have been used for a relatively long period of time, they have gradually been largely replaced by foreign biomaterials that imitate the structures of the body.

In addition to bioactive metals and ceramics, recently, polymeric substances with certain qualities have been increasingly researched.

The progress made in the field of polymers is great but the structural and functional complexity of natural polymers cannot yet be equaled. These polymers must possess the ability to release biomolecules used in cell signaling and regulate cellular behavior. It should be noted that not all polymers obtained at present have a suitable and advantageous structure for applications in the field of bone tissue regeneration. In order to be recommended and effective in bone tissue regeneration, only degradable biomaterials of hybrid polymers with osteo-conductivity, biomimetic elastomeric behavior and electro-activity can be used. It is also necessary to obtain high mechanical strength and at the same time with certain elastomeric qualities. Their antibacterial activity and bioimaging ability should not be neglected either. All these aspects will have to be taken into account in the design of the next generations of biomaterials. At present, it is difficult or even impossible to anticipate what the next major step will be in the evolution of implants, where everything is changing very quickly. Given that manufacturers of new materials sometimes pursue the economic aspect to a large extent and are not always able to appreciate a material from a bio-medical point of view, they are sometimes tempted to overestimate the qualities of the materials they produce. The clinician must critically assess what he intends to use, because in case of complications or failure, he is the only one to whom all accusations will be addressed, being the link between the manufacturer and the patient.

## THESIS STRUCTURE

The doctoral thesis entitled "**ASSESSMENT OF THE POTENTIAL OF PERIMPLANT TISSUE REGENERATION FUNCTIONING WITH THE PHYSIOLOGICAL STATE**" is prepared in compliance with the methodology for writing doctoral theses, both in terms of the relationship between components and the structuring by chapters. It comprises 113 pages and has the content argued with rich imagery, represented by 81 microscopic figures. The thesis comprises two parts: The current state of knowledge and the Personal Contribution.

The current state of knowledge is presented on 38 pages and is divided into two chapters with complete information from the specialized literature, relating to the topic addressed.

**Chapter 1**, entitled "**General notions about bones and osseointegration**", presents information from the specialized literature on bone biology and histophysiology, general data on osseointegration and the main factors that significantly influence the osseointegration of implants, namely the three main categories: patient-dependent factors, factors dependent on the qualities of the implant and factors involved in the surgical intervention.

**Chapter 2**, entitled "**General notions about biomaterials**", presents information on biomaterials, starting with a brief history, then data on each category of biomaterials. The immunological classification of biomaterials is presented, dividing them into four categories: autologous, homologous, heterologous and alloplastic, but also the classification according to their behavior in the interaction with the organism, being grouped from this point of view into four categories: biotolerated, bioinert, bioreactive and bioresorbable. According to structural criteria, biomaterials are divided into four major classes: metallic, ceramic, polymeric and composite. When assessing the qualities of a biomaterial, a multitude of aspects must be taken into account, the most important of which are the mechanical, thermal and surface properties, as well as the electrical, optical and diffusion properties.

The personal contribution comprises 80 pages and is systematized in 7 chapters. These chapters present the specific objectives of the research, then the materials and methods used to carry out the investigations, the histological investigations and the results obtained for each category of animals studied regarding the process of osseointegration of screws in the rabbit femur bone and all the events that accompanied this complex process, then the general conclusions that were drawn based on the results obtained. Based on an overall analysis, the originality and innovative aspects of the thesis were formulated, and at the end, the consulted bibliography is presented.

## OBJECTIVES OF THE WORK

- *Morphological evaluation of the osseointegration of titanium screws over a period of 2 months in males;*
- *Evaluation of the osseointegration of titanium implants over a period of 2 months in nulliparous females;*
- *Morphological evaluation of the osseointegration of titanium implants over a period of 2 months in primiparous females.*

## MATERIALS AND METHODS

The materials used were self-tapping titanium screws, with a diameter of 2 mm and a length of 5 mm.

The animals used were 30 rabbits of common breed - 10 males and 20 females.

## RESULTS AND CONCLUSIONS

**Chapter 5 – Study 1**, was entitled “*Morphological evaluation of osseointegration of titanium screws over a period of 2 months in males*” and aimed to capture the dynamic evolution of the osseointegration process in male rabbits, over a period of 2 months. To achieve this goal, the following objectives were set:

- *Introduction of titanium screws by self-tapping into the femur of male rabbits;*
- *Evaluation of tissue integration of the screws at 4 and 8 weeks, respectively.*

The results obtained served to formulate the conclusions resulting from the investigation, as follows:

1. Histological evaluation of the proliferated tissues on the interface highlighted that they covered the entire interface, as early as four weeks, and increased quantitatively and qualitatively, at eight weeks.

2. The proliferation of new bone directly on the surface of the screws demonstrates that it was produced by contact osteogenesis, and titanium appears to stimulate this process.

3. The stimulation is illustrated by the fact that the newly proliferated bone has expanded on the surface of the screw, but also outwards and inwards, so that the interface has a fan-like appearance.

4. This increase in the interface is facilitated by the fact that the bone repair processes had two starting points, periosteal and endosteal, from where they gradually expanded.

5. In terms of the stage reached by the integration process after eight weeks, we found that the newly proliferated bone represents 90-95%, and the remaining bone, approximately 5-10%.

6. The connection between the proliferated bone and the one in the depth is different from one area to another, being achieved from 40%, in the middle area of the interface and approximately 80%, in the periosteal and endosteal portions.

7. If we take stock of the osseointegration process from a quantitative and qualitative point of view at eight weeks, we find that, although it has evolved appropriately, it is only approximately 40% resolved.

**Chapter 6 – Study 2**, was entitled “*Evaluation of osseointegration of titanium implants over a period of 2 months in nulliparous females*” and aimed to investigate the osseointegration process of titanium implants in nulliparous female rabbits, over a period of two months. In order to achieve the proposed goal, the following objectives were set:

**- Introduction of titanium screws into cortical bone in nulliparous female rabbits;**

**- Histological evaluation of osseointegration at 4 and eight weeks, respectively.**

The results obtained allowed the formulation of some conclusions regarding the dynamic development of the osseointegration process in this category of animals, as follows:

1. After four weeks, the interface is covered in a relatively large proportion with newly proliferated bone in contact with the screw surface, which demonstrates that it was formed by contact osteogenesis.

2. The thickest layer of newly proliferated bone is located in the endosteal area, followed by the periosteal area, while the middle area is only covered zonally with a thin and interrupted or absent layer.

3. The bone that predominates at this point in the experiment is the primary one, in different stages of consolidation, but in the endosteal area there are also a few outlines of trabeculae signaling incipient remodeling processes.

4. The degree of attachment of the bone proliferated on the interface to the bone structures in the depth of the interface is modest after four weeks, so the interface is still weak.

5. After 8 weeks, the amount of newly proliferated bone increases, the endosteal area also has the largest surface area and thickness, followed by the periosteal area, while the osseous area is not yet covered by stable bone.

6. If we compare the thickness of the newly proliferated bone on the interface in males and nulliparous females, we find a gap in the sense that in males, the thickness is significantly greater.

7. The processes of reshuffling and consolidation are clearly more advanced in males compared to nulliparous females, after two months after implant insertion.

8. The quantitative and qualitative evaluation of the bone proliferated on the interface in nulliparous females leads to the conclusion that osseointegration is resolved after two months, in a proportion of 30%.

9. If we compare the stages of osseointegration in males with nulliparous females, we find that the same stages are completed, only that the speed of development is higher in males.

**Chapter 7 - Study 3**, was entitled "*Morphological evaluation of the osseointegration of titanium implants over a period of 2 months in primiparous females*" and aimed to verify the development of the osseointegration process in females that have gone through a period of gestation and lactation, and to achieve this goal, the following objectives were established:

**- Self-tapping insertion of a titanium screw into the femur of primiparous female rabbits;**

**- Histological assessment of osseointegration in primiparous rabbits compared to nulliparous ones and males.**

Based on the results obtained, the following conclusions were formulated:

1. After 4 weeks from the insertion of the titanium screws, the newly proliferated bone on the interface is relatively well represented in the endosteal portion, little and very young, in the periosteal one and absent, in the osteal one.

2. The attachment of the newly proliferated bone on the interface to the bone structures in the depth of the interface is very weak after four weeks, it being more seated than attached to the underlying bone structures.

3. It is found that the osseointegration of titanium screws in the femoral bone of primiparous rabbits is somewhat more modest than in the case of nulliparous ones and significantly weaker than in males.

4. At the time of eight weeks, the osseointegration processes are clearly more advanced in the endosteal and periosteal portions, but the osteal is still not covered with newly proliferated bone.

5. The stage at which the reparative processes have reached after eight weeks in primiparous rabbits is close to that observed in nulliparous ones, but still some gap is observed.

6. At eight weeks, the interface has a fan-like appearance, as was also observed in the other two categories of animals studied, but it is smaller than in nulliparous females and especially compared to males.

7. The stages through which the osseointegration process goes are the same in the animals studied, but the speed of development differs, being the highest in males, followed by nulliparous females and then primiparous ones.

**Chapter 8** is entitled "**General Conclusions**" and contains a synthesis of the conclusions that emerged from each chapter, reflecting the general results obtained from the investigations carried out:

1. The newly proliferated bone is arranged in direct contact with the surface of the titanium screws, which demonstrates that titanium is very well tolerated by the body and seems to stimulate bone proliferation.

2. By extending the newly proliferated bone onto the surface of the titanium screw, the surface of the interface increases greatly, taking on a fan-like appearance, which is the largest in males, followed by nulliparous and primiparous females.

3. After 8 weeks, the interface is completely covered with new bone only in the case of males, while in females, the central area is not yet covered, and the difference between nulliparous and primiparous females is not very large.

4. The thickness of the bone layer existing at the interface after 8 weeks is particular to each area, being the greatest in the endosteal portion, then in the periosteal, and in the osteal area, it is present only in males.

5. The newly proliferated bone layer on the surface of the interface is the thickest in males, obviously thinner in nulliparous females and much thinner in primiparous ones.

6. The connections of the proliferated bone on the interface with that in the depth are best achieved in males, much weaker in nulliparous females and modest in primiparous females.

7. Regarding the stage at which osseointegration reaches after eight weeks, it is achieved in a proportion of 40% in males, 30% in nulliparous females and approximately 20% in primiparous ones.

8. The osseointegration process follows the same stages in the three categories of animals, but differs greatly in terms of the speed of development, being the highest in males, followed by nulliparous females and then primiparous ones.

**Chapter 9** entitled "**Originality and innovative contributions of the thesis**", includes the particular aspects that emerged from the results obtained and their comparison, as follows:

- the newly proliferated bone extends onto the implant surface exceeding the initial thickness of the bone, so that the interface gradually acquires a fan-like appearance;

- the fan-shaped proliferation suggests that titanium may have a stimulating effect on bone proliferation and remodeling at the interface level;

- the osseointegration process goes through certain successive stages, which follow each other in the same way, in the three categories of animals studied;

- the highest speed of osseointegration was found in males, followed by nulliparous females and the lowest in primiparous females.

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