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Bone and Soft Tissues Integration in Porous Titanium Implants (Experimental Research)

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Abstract

Aim. It's common that revision arthroplasty of the large joints demands replacing of bone defects of irregular geometrical shapes and simultaneous restoring of support ability and ability to integrate surrounding muscular and tendinous structures into an implant that is required for a complete restoration of joint function.

The purpose. To experimentally study the process of integration for muscular and bone tissue as well as tendinous and ligamentous structures into porous titanium materials.

Material and Methods. During in vivo experiment the authors created a standardized bone defect in 6 rabbits of chinchilla breed at the point of patella ligament attachment as well as a delamination area of muscular tissue in latissimus dorsi. Both knee joints and both latissimus dorsi were used in each animal. Study group included titanium implants with three-dimensional mesh structure. Control group — solid titanium implants with standard porosity. Titanium implants were produced by additive technologies with preliminary prototyping. The porosity corresponded to trabecular metal, striations — 0.45, pores size —100–200 microns. Study and control components were implanted in the identical conditions into the corresponding anatomical sites. Postoperative AP and lateral roentgenograms of knee joints were performed for all animals. Morphological research was conducted on day 60 after the implantation and strength properties were studied at day 90 after the implantation.

Results. The authors observed bony ingrowth into implant pores with minimal volume of fibrous tissue, a distinct connective integration was reported represented by a dense fibrous tissue in the pores of components implanted into the muscular tissue. Testing of fixation strength of the study implants demonstrated a clearly superior strength of soft and bone tissue integration into the experimental mesh implants produced using additive technologies.

Keywords: integration of soft tissue, bony integration, porous titanium implants, experimental model, bone defect, additive technologies.

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Introduction

During the last decades arthroplasty has become a widespread and efficient treatment for pathologies of hip and knee joints. The data of leading orthopaedic centers confirms a current routine increase in the number of surgeries for joint replacement [1–3]. However, increase of primary surgeries inevitably results in increase of revision procedures. Hip arthroplasty register of the Vreden Russian Research institute of traumatology and orthopaedics (RNIITO) revision rate in overall hip arthroplasty procedures amounts to 13–18% in the last few years [4]. The most frequent indication for revision joint replacement is the aseptic loosening of prosthesis components. Less frequently such procedures are performed in cases of infectious complications, recurrent dislocations, periprosthetic fractures and mechanical rupture of components [5]. Besides, the number of patients who underwent multiple revisions with severe bone defects is growing [4]. At the same time revision procedures become more complications due to scar alterations of para-articular soft tissues, structural bone changes as well as issues related to removal of previous implants [6].

Each subsequent surgery creates additional challenges for orthopaedic surgeons. E. Garcia-Cimbrelo et al reported that along with increase in size of a femoral defect the efficiency of joint replacement is declining [7].

There are several options for replacement of bone defects during revision surgery. Undoubtedly bone autografting yields better outcomes however it's limited by a restricted graft size and additional trauma to the donor site. Bone allografting is the most widespread option but it can't provide for complete defect replacement in all cases. It depends of the quality of host bone, defect size and method of harvesting [8–10]. At the same time there is a high probability of histoincompatibility and transfer of virus infections, mechanical strength of such grafts still remains an unsolved issue, and availability and regular replenishment of bone bank demands substantial organizational and economical expenses [11].

Use of carbon and ceramic implants is accompanied by a high rate of aseptic instability and osteonecrosis at bone-implant interface [11, 12].

At present, high porosity metal implants are becoming more favored and recognized among non-biological replacement options while such components have almost no limitations in size, have high mechanical strength and proven osteointegration potential. However, in case of irregular shape defects it's not always efficient to use standardized implants. A possible alternative could be the precision 3D-printing of customized components but there are only few studies in this area [13, 14].

No less important is the task to gain integration of surrounding muscular and ligamentous structures in the implant after replacement of complex defects without insertion point of muscles and ligaments. This sphere has not been yet sufficiently investigated and doesn't provide a clear answer in respect of implant choice for replacement of such bone defects [15, 16].

The present study raised the following questions:

1) will soft tissue (muscles, tendinous and ligamentous structure) and bone integration take place with the high porosity titanium implants produced by additive technologies?

2) in case of a verified integration into titanium implants what type of tissue be present at tissue-implant interface?

3) what will be the fixation strength in case of tissue integration into such implants?

Material and Methods

Titanium implants were produced by additive technologies. Porosity corresponded to trabecular metal, pores size — 100–200 microns, striations (connections between pores) — 0.45. The choice of such pore size was conditioned by successful results of earlier experimental research [17]. Study and control implants were prepared for study in accordance with ISO 10933-12 (Fig. 1).

In vivo experiment was performed on 6 reproductive rabbits of chinchilla breed in vivarium of RNIITO. All animals were female. Mean age of animals was 7 months (from 6 to 8 months).

Mean body weight of animals was 2870 g (from 2700 to 3000 g). Management and use of laboratory animals corresponded to principles of the Declaration of Helsinki, revision 2013. Experiment was approved by the meeting of ethical committee of RNIITO (minutes No.10 dated 02.12.2016). All animals had veterinary certificates of quality and health and were fed and kept in the identical conditions.

Surgical technique. Procedure was performed simultaneously on both hind legs and latissimus dorsi of all animals.

Control groups included implants with non-porous surface (right side), study group — high porosity implants on the left side. Components of study and control groups were implanted in the same animal. Two plates were implanted into latissimus dorsi on both sides and one plate was implanted into the tibia — totally 24 research targets.

To study the integration process for experimental porous titanium implants in the bone defect, the surgery was performed on tibial bones of rabbits. The defect was created in the following manner: after splitting the patella ligament at the point of its attachment to tibial tubercle by a dental borer, a longitudinal trephine opening was formed with dimensions — length 3 mm, width 1 mm and depth 5 mm. Afterwards titanium implant was inserted into the created defect and split ligament: non-porous titanium component was implanted into the right tibia, and porous component — into the left tibia. Patella ligament fibers were fixed to the titanium component by sutures (Fig. 2).

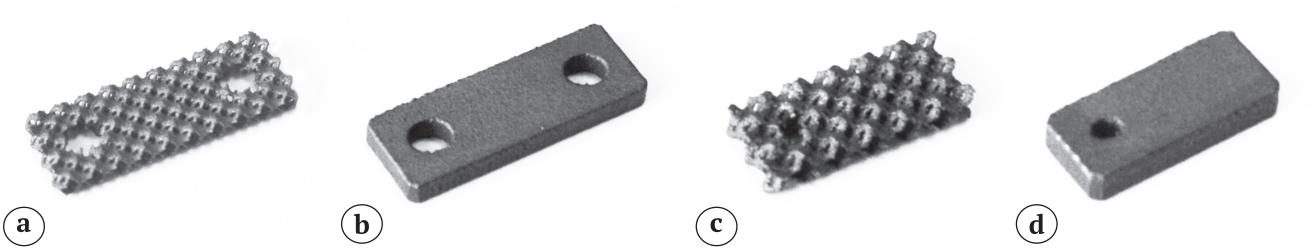

Fig. 1. Samples of titanium implants:
a — porous titanium implant for study of soft tissue integration;
b — non-porous titanium implant for study of soft tissue integration;
c — porous titanium implant for study of bony integration;
d — non-porous titanium implant for study of bony integration

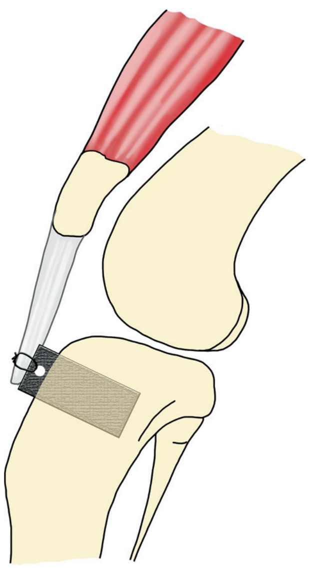

Fig. 2. Scheme of surgery on rabbit tibia

To study integration properties of muscular tissues into the titanium implants the authors performed procedure on latissimus dorsi of rabbits. Animals were placed in prone position. Skin incision was done 1 cm laterally to spinous processes Th_V–Th_{XII} on the right and left side. The authors performed fibers separation in the upper and lower thirds of the belly of latissimus dorsi and then implanted two versions of titanium components into the areas of dissociation, non-porous implanted on the right side and porous — on the left side. Wound was closed in layers.

After creating the model of functional bone defect involving muscular and ligamentous attachment points into the defect the animals were followed up for 3 months from the moment of surgery until removal from the experiment. The authors watched over the general status of animals (activity, appetite, physiological functioning) as well as evaluated the condition of postoperative wound. Special attention was given to movement of animals and joint function.

X-ray examination. X-rays of knee joints in AP and lateral views was done in experimental animals of study and control groups on day 1 after creating the bone defect, on day 60 and 90 after the procedure.

Animals were placed in supine position while roentgen rays were centered at the area of knee joints. Lateral roentgenography was made with animal in lateral decubitus. X-rays were performed in two standard planes in control terms using Philips Diagnost system. Image conditions: 42 kV, 5.00 mAs, 22.9 ms. Focal distance was 1 m.

During imaging the authors assessed either absence of bone resorption at implant interface or signs on bone ingrowth into the implant.

Dissection technique. Dissection was done on day 60 after the surgery. Necropsy specimen containing studied implants were fixed in 10% solution of neutral formalin. After that the material was dehydrated in ascending alcohols and saturated by methyl methacrylate Technovit 4004 (Kulzer, Germany), then placed into polypropylene test tubes and perfused by new mixture of polymer and monomer of methyl methacrylate Technovit 4004 in proportion 1:1. After that test tubes were placed into thermostat at t +60°C where the final polymerization into blocks took place. Specimen fixed in plastic were cut by parting machine IsoMet HS (Buehler, USA) along vertical axis of implants and then machine grounded on Metaserv 250 (Buehler, USA) basing on established procedures of preparing non-decalcified bone micro sections [18, 19]. Specimens were stained by hematoxylin and eosin. Microscopic examination was performed using a light microscope AxioScope A1 (Carl Zeiss, Germany).

During dissection of muscular and ligamentous micro specimens the authors evaluated:

– nature of the tissue at the interface with implant;

– tissue integration or absence of such into the implant;

– cellular response of tissues surrounding the implant.

Evaluation of cancellous and cortical bone integration into the titanium implant was evaluated upon the following criteria:

– presence or absence of fibrous capsule around the implant;

– presence of bone tissue in the pores of study implants.

Video analysis software VideoTesT 4.0 was used for quantifying tissue elements:

– fibrous tissue perimeter around the implant;

– blood vessels area.

Testing of strength properties. Strength properties were examined at day 90 after the surgery using a universal machine for mechanical testing AG-100X Plus (Shimadzu Corp., Japan). Tensile testing was done with deformity control in accordance with ISO 6892-2009 and JIS Z2241-2010. Tissue samples integrated into titanium plates (solid or porous) were testing in uniaxial tension mode. To fix specimens in the flat clamp tissues were sewn by surgical suture and the suture ends were placed into the clamp. Opposite side of the specimens (titanium) was also fixed by suture fed through the hole at the end of the plate. Deformation rate was 100 mm/min. Deformity curves of the specimens were reflected in coordinates "clamp transfer (mm) — tensile loading (H)". It was impossible to identify specific units of deformation and mechanical strain during testing while not only specimen tissue (or interface area "titanium-specimen") but also sutures were deformed during tensioning. Thus, it was not realistic to separate the specimen deformity as such during the procedure. Calculation of strains demanded a precise value of specimen section — the tissue receiving the load in the process of deformation. In result, the only significant criteria identified during testing was the maximum load (in newton) recorded during tensioning. While testing strength properties of bone integration the authors assessed the rupture forces for soft tissues at the area of attachment to the implants.

Statistical analysis. GraphPad Prism 6.0 software was used for statistical analysis of data: the authors calculated arithmetical mean and its errors (M±m), variances were evaluated by Welch's t-test. Critical level of significance *p* was taken less or equal to 0.05.

Results

The animals were followed during the whole postoperative period until removal from experiment. During day 1 after the surgery the authors clinically observed loss of appetite and activity of experimental animals. Starting from day 2 all animals demonstrated normalization of activity and appetite. Surgical wounds healed without any inflammation signs (hyperemia, edema, mobility abnormalities) in animals of all experimental groups.

X-ray examination. No signs of bone resorption around the implant or it's migration was observed on x-rays on day 60 and 90 after the surgery in both groups. On day 90 after the implantation bone tissue around titanium components had no signs of resorption in both groups (Fig. 3).

Results of dissection. During dissection of muscular tissue specimens at day 60 after the surgery in the group where non-porous titanium components were implanted the authors observed formation of a thin connective tissue capsule around the implant without any inflammation signs. Fibrous tissue perimeter around the titanium was 86417.5±17939.1 mkm. No integration with soft tissues was observed. Single blood vessels were detected at periphery with the area of 2754.5±499.4 mkm^2. In the experiment group of porous titanium components implanted into the muscular tissue the authors observed ingrowth of mature tissue with ordered fibers into metal pores with irregular localization of heterogeneous vessels without any cellular reaction. Fibrous tissue in experimental group demonstrated full component thickness ingrowth (Fig. 4).

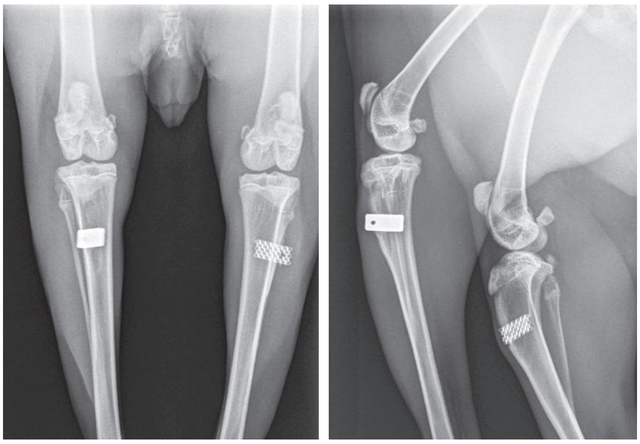

Fig. 3. AP and lateral X-rays on day 90 after implantation. No radiolucency observed around the implants, surrounding bone without any pathological changes

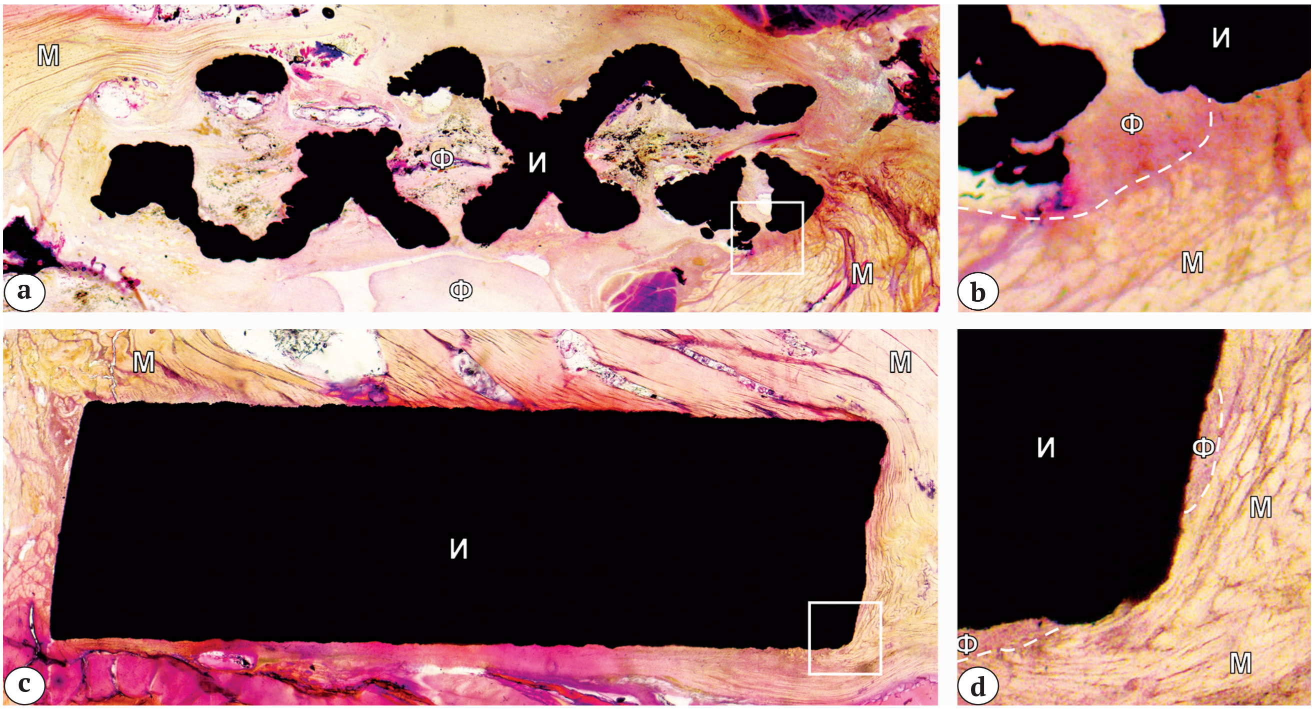

Fig. 4. Microslides of muscular tissue in the experiment groups on day 60 after implantation:
Ф — fibrosis;
М — muscle;
И — implant;
a — ingrowth of fibrous tissue into implant pores with heterogeneous blood vessels located unevenly;
b — mature fibrous tissue on implant surface;
c — non-porous titanium implant within muscular fibers;
d — thin connective tissue capsule around the non-porous implant.
Staining by hematoxylin.
Mag.: a, c — ×40; b, d — ×80

Fibrous perimeter at interface with implant was 185482,7±89906,6 mkm. Single heterogeneous vessels were observed in the depth of the implant with the area of 14978.08±14441.7 mkm^2.

During dissection of titanium specimens implanted at the site of patella ligament attachment to tibia on day 60 the authors reported osteointegration in both groups. New bone had a firm adherence to the implant surface (Fig. 5). Porous implant surfaced in experiment group demonstrated thin areas of fibrous tissue with periphery of adherence was 10555.04±2173.13 mkm, and fibrous tissue mainly was located in areas of patella ligament adjacency. In the control group the perimeter of fibrous tissue contact with implant surface was 5723.82±974.81 mkm. Fibrous tissue was also detected at the areas of contact with patella ligament fibers. It should be noted that in the experiment group with porous titanium apart from osteointegration the authors observed an intimate and firm integration of connective tissue with ordered fibers to the titanium component at the point of contact with patella ligament with an interlayer of fibrous tissues (Fig. 6).

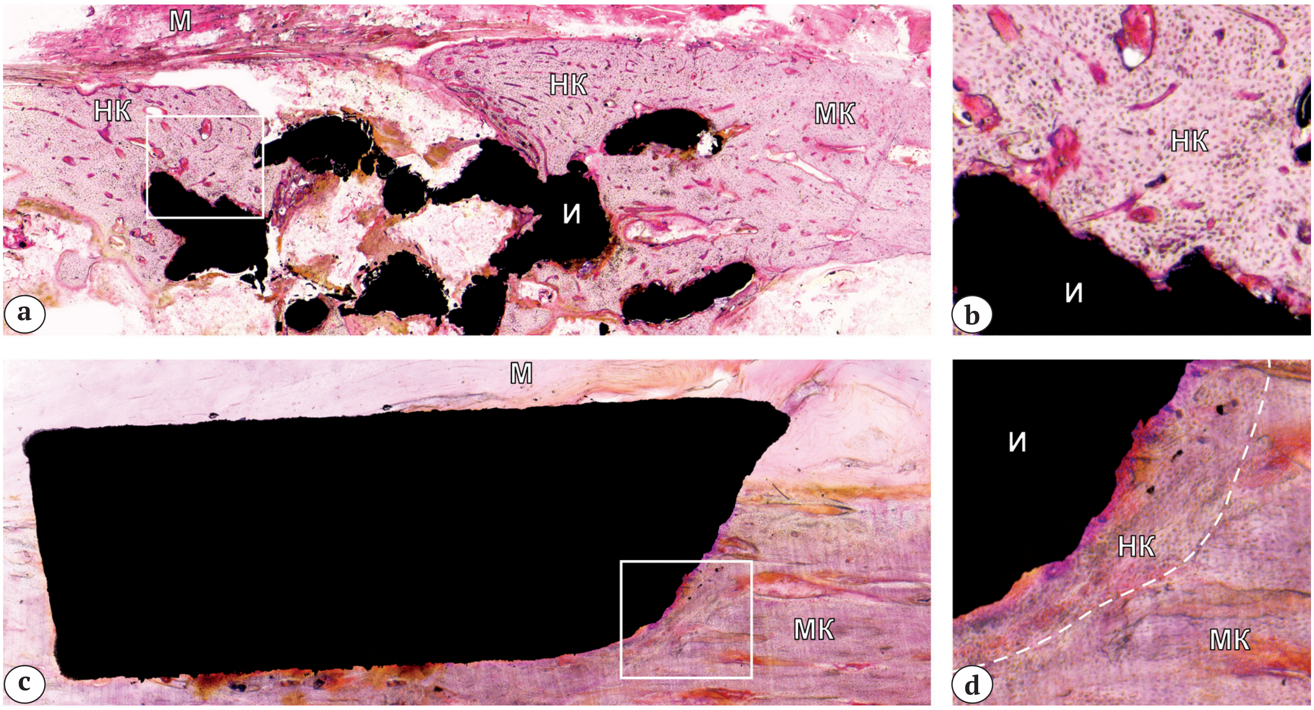

Fig. 5. Microslides of bone tissue on day 60 after implantation:
Ф — fibrosis;
М — muscle;
И — implant;
МК — host bone;
НК — new bone;
a — porous titanium implant at the site of tibia tubercle;
b — ingrowth of new bone into the three-dimensional pore of porous titanium implant;
c — non-porous titanium implant at the site of tibia tubercle;
d — adherence of new bone to implant surface.
Staining by hematoxylin.
Mag.: a, c — ×40; b, d — ×80

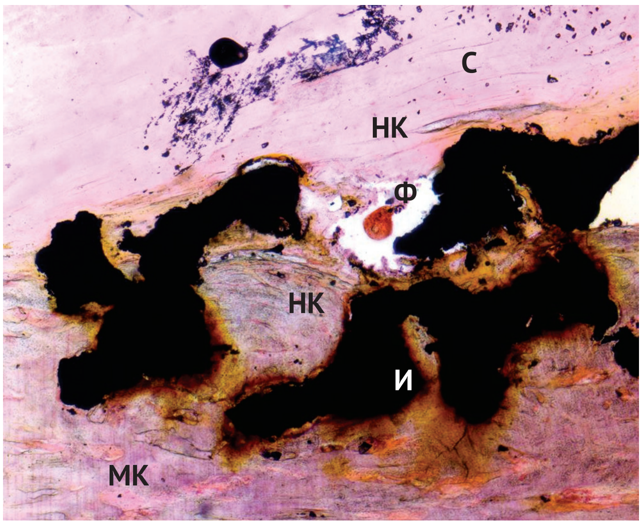

Fig. 6. Patella ligament adjacent to the implant is intimately attached to titanium surface with an uneven interlayer of thin fibrous tissue:
Ф — fibrous tissue;
С — tendon;
И — implant;
МК — host bone;
НК — new bone.
Staining by hematoxylin.
Mag. ×80

Results

Testing of strength properties. Strength properties of muscular tissue fixation to titanium components were examined at day 90 after the surgery in both groups. Rupture force in control groups of non-porous component was 8±2.9 N. By applying such force in control group the authors observed detachment of fibrous tissue from titanium implants without any damage to muscle fibers. In the experiment group (porous titanium component) rupture force was 26±6.5 N which lead to failure of muscular fibers apart from contact area with titanium implant. Fibrous capsule around the test experiment porous implants was intact and continuous. Rupture force in experiment group was significantly higher than in control group ($p<0.05$). One of the four test macro-specimens in experiment group had a friable fibrous capsule around titanium implant and contained serous fluid. During strength testing the implant slipped out of the capsule at rupture force of 13 N (illustrated on the chart, Fig. 7).

During strength properties testing of fixation in bone tissue for implants in both groups the rupture force in control group was 108±21 N against 147±6.1 N in experiment group ($p = 0.07$) (Fig. 8). Recorded data demonstrate superior strength properties of integration of soft tissues and bone into the experimental mesh implants produced by additive technologies.

Discussion

Implants integration in the human body is closely related to biophysical and biochemical processes in surrounding tissues. Protein absorption with following adhesion of cellular structures to the metal components surface which occurs after the implantation further leads to adhesion of soft tissues or bone matrix. In presence of micromotion and absence of adhesion a connective tissue capsule is formed which surrounds the liquid-filled cavity between the implant and tissues. J.S. Hayes et al have proven by the experiment on rabbits that most often the capsule is formed in case of using polished implants. Micro-cracks on implant surface facilitate a better tissue adhesion which improves integration of surrounding tissues without formation of a dense fibrous capsule [20].

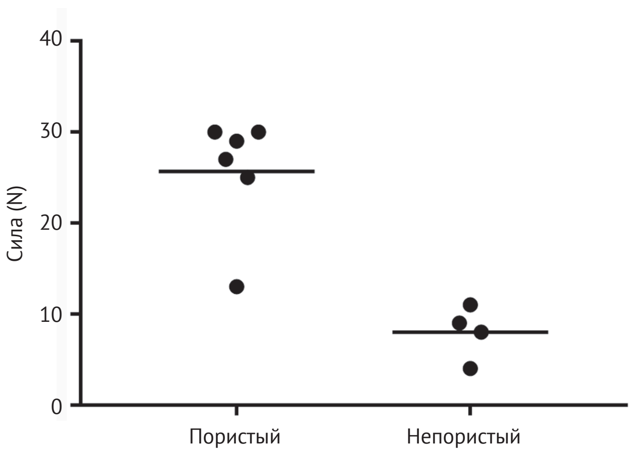

Fig. 7. Fixation strength of titanium samples in the muscle tissue of experimental and control animals

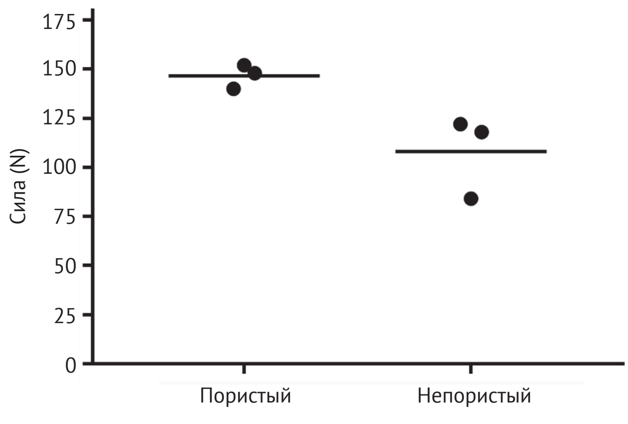

Fig. 8. Fixation strength of titanium samples in the bone tissue of experimental and control animals

Thus, the following conditions are required to obtain a good osteointegration with implant: porosity, solid primary fixation of the implant. Further research in this area is aimed at investigation of the optimal conditions providing better osteointegration. I.A. Van Dijk et al. used titanium components with hydroxyapatite coating for improvement of cellular structures adhesion [21]. M. Yamada et al. reported improvement in osteointegration after implant surface treatment by combination of anodizing and sandblasting [22]. N. Tsukimura et al as well as T. Ueno et al. established that coarse implant surface accelerates osteointegration at early stages and allows to increase contact surface implant-bone [23, 24].

Currently implants from trabecular metal are widely applied in orthopaedics while these components are known for its osteointegration properties [25]. The literature also describes the use of patella prosthesis made of trabecular metal after patellectomy or for revision surgery with massive bone defect in patella when patella component is implanted into the soft tissues of quadriceps tendon and patella ligament [26–28]. Such papers demonstrate a possibility for soft tissues integration with a good functional outcome.

E. Rieger et al. studied soft tissue integration into the implants surface which was previously treated by anodizing as compared to coarse materials. As a result previously treated components had a higher hydrophilia and protein absorption was higher than in control group [29]. Some studies established that microporous surface of titanium nickelide threads have matrix properties [30, 31]. V.A. Lanshakov et al. in their study demonstrated that in case of sewing tendons to reinforced mesh implant made of titanium nickelide threads the guided growth of connective tissues along the threads is stimulated [32]. J.D. Bobyn et al. in their study on animals established that size of tantalum block pores from 50 to 200 mkm is the optimal for integration of soft tissues [33]. M. Chvapil et al. suggested that size of pores above 100 mkm facilitates ingrowth of more differentiated tissues due to possibility of capillaries penetration. Less differentiated cells are formed in pores of smaller size due to limited tissue nutrition [17]. Thus, the optimal pores size for soft tissues integration is 100–200 mkm providing for bone ingrowth for 2–3 mm and allowing a good fixation of component. For this reason the authors of the present study used the implants with such porosity.

The present study using custom made implants confirmed a possibility to achieve a solid fixation of mesh titanium implants in the bone tissue. Tensile strength was 147±6.1 N which proves gaining of solid osteointegration.

Above mentioned is confirmed by literature. J.S. Reach et al sutured supraspinatus tendon to high porous titanium implants which in turn were fixed to cancellous bone by a screw. Authors demonstrated that tensile strength at point of tendon attachment to titanium implant was 149 N at the average, and in 16 weeks it was comparable with strength of a healthy tendon, depth of collagen tissue ingrowth was 2.80–3.00 мм [34]. Similar experiment was undertaken by a group of authors on dogs, where patella tendon was sutured to tibia using two porous tantalum washers. Mechanical strength of tendon attachment was 76% from native tendon strength during 6 weeks, but it did not increase in time. During dissection it was established that fibrous tissue occupied ½ of available space in porous tantalum washers [35]. In another experimental study S.A. Hacking et al. implanted tantalum porous plates in the lumbar area of dogs in the space between subcutaneous fat and fascia. In 4, 8 and 16 weeks the strength of fixation to porous tantalum plates was 61, 71 and 89 g/mm respectively. Histology demonstrated full growth of tissue through the whole tantalum implant. Blood vessels were seen at the interface and inside of porous tantalum. This research demonstrated that vascularized soft tissue grows in faster into the porous coating of tantalum resulting in solid fixation of soft tissues [36]. Fixation strength in research of J.D. Bobyn et al. was 27.5 g/mm in 16 weeks after implantation. Dissection data confirms formation of good bone in the inter-trabecular space of implant [33].

Experimental cadaveric research of strength of muscular-tendon-bone complex demonstrated that muscles have been the weakest part of this system. However, it should be noted that measuring of the true muscle strength can be obtained only on such a model where neuro-reflex links of muscular-tendon complex to the body are preserved. T.A. Wren in his study of tendon lesions established that force resulting to Achilles tendon rupture amounts to 5000 N. In the present experimental study the force leading to full damage of ligament structures was clearly less [37] considering the fact that thickness of human Achilles tendon in AP plane is average of 6,6mm and thickness of patella ligament of rabbit is 1.2–1.5 mm. Data on strength and rigidity in the paper of N. Inoue et al demonstrate that supraspinatus tendons of dogs have a mean absolute strength and rigidity values of 1098.5 N and 100 N/мм respectively [38]. The literature doesn't provide a single threshold rupture force value for muscular and ligamentous structures due to various diameters of tendons used during experiments.

In the present experiment for muscular integration into titanium porous implants during strength testing the authors demonstrated solid fixation of titanium samples. Muscular tissue rupture occurred outside of contact area with implant and this can be considered as a confirmation of adequate rigidity of fixation. In authors opinion the area of contact between titanium high porosity materials with soft tissues is of key importance. The present research established that spatial pores of components produced by additive technologies contained fibrous tissue with heterogeneous blood vessels along the full depth. At the same time there were almost no hollow spaces at the contact point with implant which in turn enhances fixation strength in soft tissues.

Research conducted earlier in respect of soft tissues integration into porous metal implants demonstrated high strength properties of soft tissue integration. In the present study the authors evaluated a possibility of such integration into implants produced by additive technologies. The results of the present experiment offers new possibilities for clinical use of custom made implants intended to replace bone defects of complex geometry involving muscle attachment, tendons and ligaments during revision procedures and surgeries for complex orthopaedic pathologies.

Integration of high porosity titanium implants into the bone tissue has been well studied, however the authors of the present research aimed not only to find out possibilities to replace bone defects but also to evaluate a possibility to restore muscle attachment sites using a high porosity surface of titanium component. Additive technologies provided for development of such implant surface which allows not only to ensure solid integration with bone bed but facilitates integration of soft tissues and ligamentous structures. Competed dissection of titanium implants produced with additive technologies demonstrated bone ingrowth into implant pores with minimal volume of fibrous tissue which proves a high capacity for osteointegration of porous surface produced by 3D-printing. The authors observed a clear connective tissue integration represented by a dense fibrous tissue in pores of component implanted into the muscular tissue. Strength of tissues fixation in titanium porous implants in experimental group was significantly higher than fixation criteria in control group (rough titanium block).

The present research brings up broad perspectives for application of high porosity titanium implants produced by 3D-printing in reconstructive and revision surgery for bone defect replacement as well as for restoration of injured muscles.

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