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Original article

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Prospects of low-modulus alloys of the TI-(15-20)NB-(5-10)TA system for engineering implants used in traumatology and orthopedics. A preclinical study

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Abstract

Aim Study of mechanical and biological properties of five variants of alloys of the Ti-Nb-Ta system. **Materials and methods** Five alloys were obtained from the system: Ti-(15-20)Nb-(5-10)Ta (at. %). Their mechanical tests were carried out by stretching on the INSTRON 3382 universal testing machine in accordance with GOST 1497-84. The biological properties of the resulting alloys were evaluated in in vivo experiments (implantation surgery) on white outbred male JCR mice. Histological study of the tissues of the limb with an implant, kidneys and liver was carried out at three time points: at 1, 4, 12 weeks after surgery, which corresponds to the early, middle and late phases after implantation. **Results** The samples showed ductility from 11.5 % to 14.6 %, strength from 549 to 673 MPa and Young's modulus from 42 to 50 GPa. The yield strength also varied depending on the composition of the alloy within 188 – 572 MPa. The inflammatory reaction was the least pronounced in the groups with Ti-20Nb-5Ta and Ti-15Nb-10Ta alloys implanted. **Discussion** Compared to the widely used TiAl6V4 alloy, the obtained alloys approximately correspond in terms of plasticity and have approximately 2 times lower Young's modulus, which should lead to better biomechanical compatibility between the implant and the surrounding biological tissues, preventing the effect of protection against stress and, accordingly, bone resorption. The relatively low tensile strength of the obtained alloys does not reduce the above-mentioned advantage over TiAl6V4, since this strength is quite sufficient for the proposed application. Histological study after 1, 4 and 12 weeks showed that the intensity of the local inflammatory reaction due to new alloys is higher than with the use of TiAl6V4, which requires further study and could be associated with a small sample size. **Conclusions** The way to create titanium alloys with a low Young's modulus may solve the problem of biomechanical compatibility of the implant with the surrounding tissues. The obtained and described alloys of the Ti-Nb-Ta system showed the neceary mechanical and, according to the initial assessment, acceptable biological properties that require further broader research.

Keywords: titanium alloy, Ti-Nb-Ta system, biocompatibility, mechanical properties, in vivo studies, Young's modulus, biomechanical compatibility

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INTRODUCTION

The desire to increase the quality and duration of human life may involve creation of artificial organs and tissues based on the invention of biocompatible materials. Of particular relevance are materials for surgical treatment of various skeletal diseases or injuries (fractures), which allow maintaining optimal conditions for bone tissue regeneration. Currently, metals and their alloys are most common materials used in traumatology and orthopedics [1].

Integration of the material into the bone in order to improve the stability and survival of implants is an important issue in traumatology and orthopedics is [2].

Bone loss caused by protective stress of metal implants is a concern as it could potentially lead to destabilization of the implant. Surface coatings and reduction of structural stiffness of implants are two ways to improve bone ingrowth and osseointegration. Additive manufacturing via selective laser sintering (SLS) or electron beam melting (EBM) of metal alloys provides production of porous implants with bone ingrowth spaces that improve osseointegration and, as a result, clinical outcomes [3].

Cobalt-based alloys are among the first biomaterials to be used in hip arthroplasty. However, these alloys have a number of shortcomings, and namely, high modulus of elasticity, biological toxicity, and high costs [4].

Magnesium-based alloys have good biocompatibility, low modulus of elasticity, and are biodegradable. However, do not forget about the shortcomings of this material such as low corrosion resistance, hydrogen release during degradation, as well as the possibility of their use only on skeletal parts that do not carry loads [5, 6].

Stainless steel is also used for fabrication of various metal fixators. Despite a number of disadvantages (high modulus of elasticity, frequent allergic reactions), stainless steel is an attractive material due to its low cost, easy availability, and acceptable biocompatibility [7].

Titanium (Ti, pure titanium – 98-99.6 %) is characterized by high corrosion resistance and biocompatibility. Pure titanium is more viscous and is used for porous coatings, total joint arthroplasty, and metal fixators; however, its disadvantages are associated with low wear resistance and high modulus of elasticity [8, 9]. The high elastic modulus of pure titanium (102-105 GPa) as compared to biological tissues (for example, with bone tissue, 4–30 GPa) can cause a low level of biomechanical compatibility between the implant materials and surrounding biological tissues and even cause rejection of the implant [10].

The addition of special alloying elements to titanium reduces the modulus of elasticity. Such alloying elements include tantalum, niobium, zirconium, vanadium, aluminum, and some others. The interaction of the implant with tissues and the internal environment of the human body can lead to the release of alloying elements, which, in turn, can cause an allergic reaction and leads to the need to remove such an implant [11-13].

Ti6Al4V alloy is one of the first titanium-based biomaterials for the manufacture of implants and is still one of the most commonly used materials for this purpose due to better mechanical characteristics compared to pure titanium and some alloys based on it. However, there is a huge shortcoming of the Ti6Al4V alloy associated with the cytotoxic effect. It is caused by the emission of aluminum and vanadium ions, which are poisonous and adversely affect human health. It should be noted that Ti6Al4V has a higher elastic modulus compared to bone tissue, which provokes the effect of protection against stress but causes bone resoption by contact with the implant, which, in turn, leads to its failure [14].

One of the new contenders for the leading positions in the creation of implants are titanium alloys being developed due to their very good mechanical and corrosion resistance and biocompatibility [15], which contain only non-toxic elements and meet the needs of an implant in terms of mechanical, anticorrosive and biocompatible properties, exhibit high mechanical strength and fatigue resistance, low modulus of elasticity and good wear resistance.

Thus, tantalum and niobium have high corrosion resistance and biocompatibility [16, 17]. They are also used as β-stabilizers in titanium alloys, which contribute to a decrease in the elastic modulus [10]. The study of Huifeng Wang et al (2014) used niobium as the basis, and titanium was used as an alloying element [18]. The investigation showed good biocompatibility, but insufficient elastic modulus. It can be concluded that titanium should be the main component to ensure the mechanical properties of the implant. It is also worth highlighting the work by Jue Liu et al (2017), in which the resulting Ti-Nb-Ta alloy showed a low elastic modulus and higher corrosion resistance compared to the Ti-6Al-4V alloy [19].

Thus, the development and study of the material alloy system Ti-Nb-Ta is of interest for the further development of materials for traumatology and orthopedics.

The **purpose** of the study was to investigate the mechanical and biological properties of five variants of alloys of the Ti-Nb-Ta system.

MATERIALS AND METHODS

Five alloys of the Ti-Nb-Ta system were studied in our investigation.

The alloys from the following range of compositions were selected: Ti-20Nb-10Ta, Ti-20Nb-7.5Ta, Ti-20Nb-5Ta, Ti-15Nb-10Ta, Ti-15Nb-5Ta (at. %). Titanium iodide, Nb-1 grade niobium, and HDTV grade tantalum were used as charge materials. The melting of the samples was carried out in an electric arc vacuum furnace with a non-consumable tungsten electrode L200DI manufactured by LEYBOLD-HERAEUS (Germany). Ingots weighing 30 g were obtained, which were fused into a single ingot weighing 180 g. Large ingots were additionally subjected to homogenizing annealing in a vacuum of 5×10^{-5} mm Hg at a temperature of 850 °C for 12 hours. The deformation of cast billets with a thickness of 10-12 mm was carried out by the method of warm rolling at a temperature of 600 °C on a two-roll mill DUO-300 to a final thickness of the billet of 1 mm.

The study of mechanical properties was carried out by stretching on an INSTRON 3382 universal testing machine with a stretching speed of 1 mm/min. Headed flat specimens were prepared from flat plates and cut out by EDM cutting. Samples were tested according to the methods of GOST 1497-84. The processing of test results in determining the characteristics of mechanical properties was carried out in accordance with GOST 1497-84 using INSTRON Bluehill 2.0 software. Five samples were tested per one experimental point. The values of relative elongation, conditional yield strength, tensile strength and Young's modulus were determined.

Biological properties were evaluated in experiments in vivo. Experiments in vivo were carried out on white outbred male JCR mice, the weight of animals at the time of inclusion in the experiment was 20-25 grams, the age was 2-3 months (n = 72). The animals were divided into 6 groups (12 mice per group). All animals underwent surgery to introduce implants in the thigh muscles (Table 1). The implant was a cylindrical alloy sample 1 × 1 × 8 mm in size (height × width × length).

Table 1

Types of implants used in the studied animals

Group	Implant type	Number of animals
1	Ti-20Nb-10Ta	12
2	Ti-20Nb-7,5Ta	12
3	Ti-20Nb-5Ta	12
4	Ti-15Nb-10Ta	12
5	Ti-15Nb-5Ta	12
6	TiAl6V4*	12

* – this alloy is frequently used in medicine and was a control material

Preparation for surgery

The operation was performed under general anesthesia: Zoletil 8 mg/kg (active ingredients – zolazepam hydrochloride, tiletamine hydrochloride in equal proportions) and xyl 0.42 ml/kg (active ingredient – xylazine hydrochloride 2 % solution) intraperitoneally. Before implantation, the hair in the perioperative area was removed with Veet cream, the skin was treated with an antiseptic.

Antibiotic therapy included injection of 0.4 mg of ceftriaxone intraperitoneally immediately before surgery, and 0.8 mg of ceftriaxone intraperitoneally after surgery.

An incision was made in the skin and fascia of the thigh along the lateral surface. Muscle fibers were moved apart and experimental samples were placed deep into the wound. The wound was sutured and treated with an antiseptic (Fig. 1).

Histological study

For histological study, the animals were euthanased by introducing a lethal dose of the anesthetic Zoletil, 200 mg/kg of body weight.

The limb with the implant, kidneys and liver were sent for histological study.

Histological study of tissues was carried out at three time points: 1, 4, 12 weeks after surgery, which corresponds to the early, middle and late phases after implantation. There were 3 mice per observation point.

The material to be studied (limb, kidneys, liver) was fixed in 10 % neutral (buffered) formalin for 10-24 hours. After cutting, tissue fragments were processed in a Leica TP1020 histoprocessor (Leika Microsystems, Germany) according to a standard protocol, after which they were embedded in paraffin blocks. Histological sections with a thickness of 3-5 μm were obtained using a Leica RM2245 microtome (manufactured by Leika Mikrosystems, Germany). The histological preparations were stained with hematoxylin and eosin in a Leica Autosteiner XL histotainer (manufactured by Leika Microsystems, Germany). Additional staining was carried out according to Van Gieson to study the structure of the connective tissue, as well as to assess the stages of fibrin. The resulting histological preparations were examined under a Leika DFS 295 light microscope (Leika Microsystems, Germany).

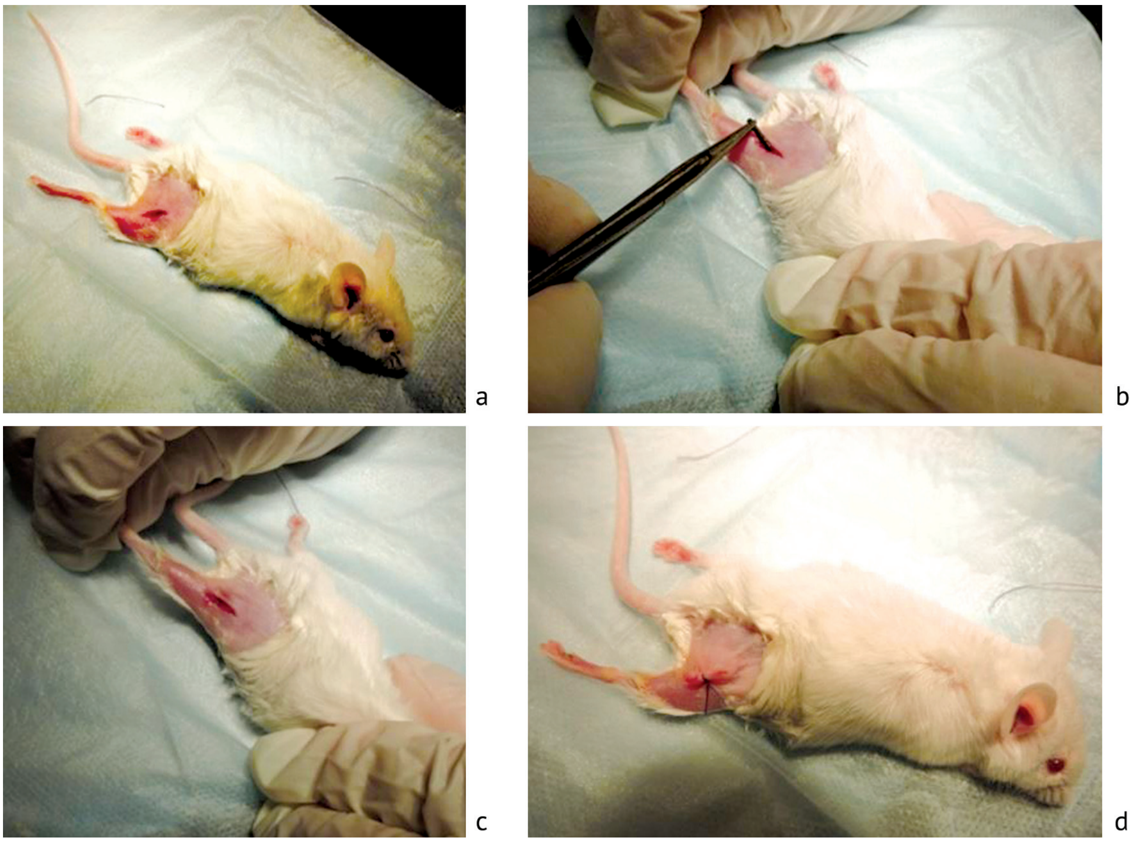


Fig. 1 Stages of implantation

RESULTS

Mechanical properties of the alloys studied

Mean values of tests are presented in Table 2.

Table 2

Mechanical properties of alloys

Alloy type	Relative elongation (%)	Yield strength (MPa)	Tensile strength (MPa)	Young's modulus (GPa)
Ti-15Nb-5Ta	11.6 ± 0.5	572 ± 7	673 ± 8	42 ± 2
Ti-15Nb-10Ta	14.6 ± 0.5	212 ± 3	608 ± 6	50 ± 2
Ti-20Nb-5Ta	11.5 ± 0.5	189 ± 3	592 ± 6	48 ± 2
Ti-20Nb-7,5Ta	12.4 ± 0.5	188 ± 3	569 ± 6	44 ± 2
Ti-20Nb-10Ta	11.8 ± 0.5	296 ± 4	549 ± 6	49 ± 2
TiAl6V4 (contol material)	11.5 ± 6.5	900 ± 20	925 ± 25	108.5 ± 4.5

Based on the data obtained, it can be concluded that all samples have good plasticity (from 11.5 to 14.6 %), strength (from 549 to 673 MPa) and Young's modulus ranging from 42 to 50 GPa. The yield strength also varies within 188-572 MPa and depends on the composition of the alloy.

The Ti-15Nb-5Ta alloy has the highest strength, which also has a minimum Young's modulus, high yield strength, and good ductility. It should also be noted that the Ti-15Nb-10Ta alloy is the next alloy in terms of strength with a plasticity index higher than that of Ti-15Nb-5Ta. It can also be seen that with an increase in the proportion of niobium, the tensile strength of the material decreases, i.e. alloys containing 20 % of niobium have the lowest strength.

Compared to TiAl6V4, the alloys are approximately similar in terms of plasticity and have approximately two times lower Young's modulus, which should provide better biomechanical compatibility between the implant and the surrounding biological tissues, preventing the effect of protection against stress and, accordingly, bone resorption. The relatively low tensile strength of the alloys does not reduce the above-mentioned advantage over TiAl6V4, since this strength is quite sufficient for the intended application.

Assessment of biological properties of the alloys *in vivo*

Surgical treatment and postoperative care

Interventions were successfully completed on all animals. In the early postoperative period, one lethal outcome was noted in the Ti-20Nb-7.5Ta group, associated with anesthesia, which was 1.4 %. Four cases of death occurred due to infection and sepsis in groups Ti-20Nb-10Ta, Ti-20Nb-7.5Ta, Ti-20Nb-5Ta, Ti-15Nb-10Ta. The overall mortality was 6.9 %. Histological preparations of tissues of animals that died due to inflammatory reaction are shown in Figure 2.

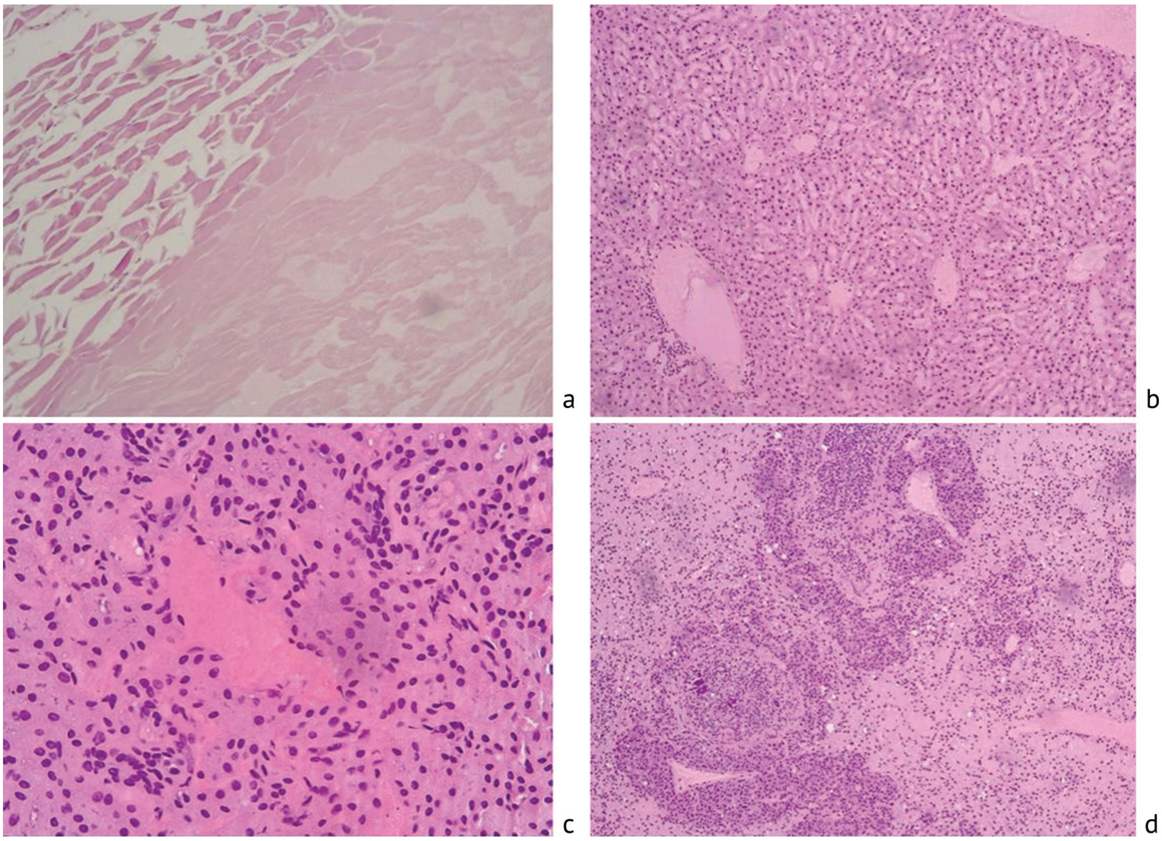


Fig. 2 Histological preparations: *a* soft tissues of the thigh with colliquat necrosis; Hematoxylin-eosin, ×200; *b* signs of acute heart failure in the liver tissue (degeneration of hepatocytes, centrilobular plethora); hematoxyly-eosin, ×100; *c* signs of acute heart failure in the kidney tissue (degeneration of the epithelium of the renal tubules, venous plethora, foci of hemorrhages in the interstitium); hematoxylin-eosin, ×400; *d* myelosis of the red pulp, reactive follicular centers in the septic spleen; hematoxylin-eosin, ×200

Histological study

The results of the study of the biological properties in vivo of the sheet samples of the Ti-Nb-Ta system alloy, based on a semi-quantitative assessment of the activity of inflammation, showed the following signs: the activity of inflammation of varying severity (from low to high) was noted in all experimental groups, except controls, in the first week of the experiment (Fig. 3).

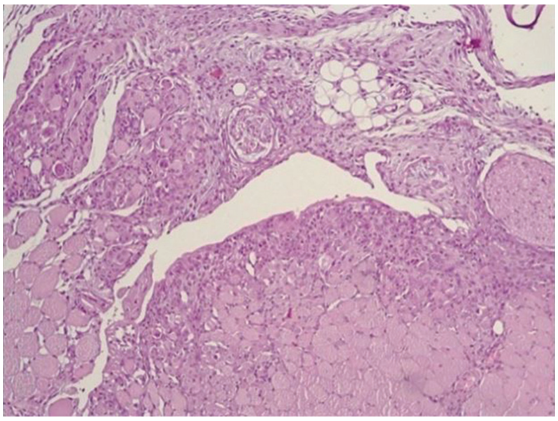


Fig. 3 Ti-20Nb-5Ta samples one week after the start of implantation: in the area adjacent to the implant, the thigh muscles show signs of acute inflammation. Hematoxylin-eosin, ×200

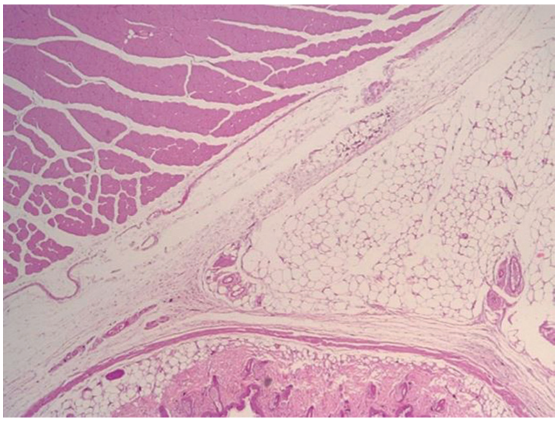


Fig. 4 Soft tissues of the thigh with morphological signs of inflammation in the proliferation phase. Hematoxylin-eosin, ×200

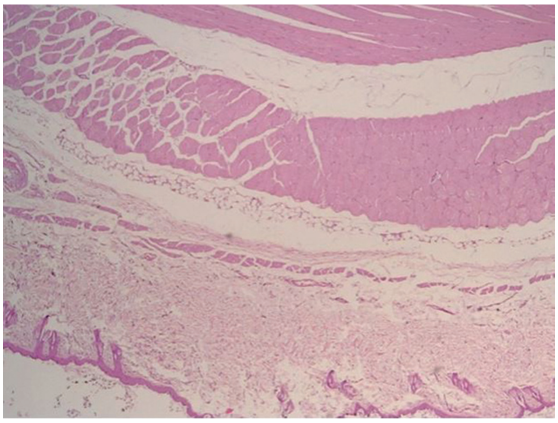
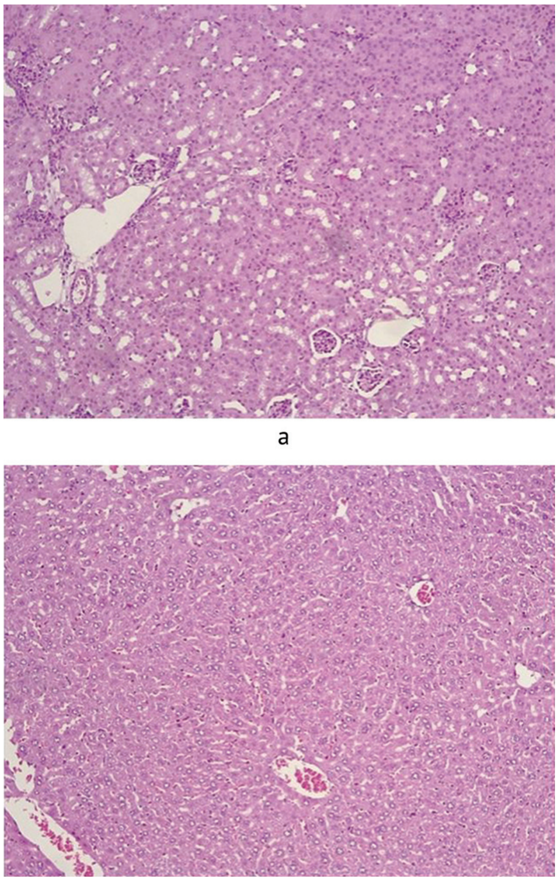


Fig. 5 Week 12: soft tissues of the thigh, regeneration phase. Hematoxylin-eosin, ×200



a

b

Fig. 6 Dystrophy of parenchymal organs: kidneys (*a*), liver (*b*). Hematoxylin-eosin, ×200

The dynamic study of biological properties in vivo of sheet samples of an alloy of the Ti-Nb-Ta system show preference to Ti-20Nb-5Ta and Ti-15Nb-10Ta alloys, since the severity of inflammation decreased (Table 3).

Table 3

Biological properties in vivo samples of alloys of Ti-Nb-Ta system

Alloy/week	Week 1	Week 4	Week 12
Ti-20Nb-10Ta	+++	+/–	–
Ti-20Nb-7,5Ta	++	++	–
Ti-20Nb-5Ta	++	+	–
Ti-15Nb-10Ta	+	–	–
Ti-15Nb-5Ta	+++	–	–
TiAl6V4 (control)	–	–	–

Criteria for semi-quantitative assessment of the severity of inflammation activity:

– low "+" fewer than 10 neutrophils in the field of view;

– moderate "++" more than 10, but fewer than 30 neutrophils in the field of view;

– high "+++" more than 30 neutrophils in the field of view;

– no active inflammation "–";

– the prevalence of chronic inflammation "+/-".

DISCUSSION

The growth in the number of primary hip and knee arthroplasties leads to an increase in revision surgeries. The reasons for revision arthroplasty are associated with complications that occur intraoperatively, in the early and late postoperative periods. There is an early and late aseptic instability. Early aseptic instability of the endoprosthesis includes all cases of aseptic instability detected within 5 years after the installation of the artificial joint. Late aseptic instability includes all cases that are detected more than five years after the primary arthroplasty. The share of revisions performed within 5 years after previous arthroplasty in the overall structure of revision operations is up to 33 %. Revision arthroplasty is indicated within 5 to 10 years after the primary operation in 25–60 % of cases of the total number of operations performed [20].

Complications that occur in the early postoperative period are usually associated with errors in the preoperative planning due to underestimation of bone quality and anatomical features of the proximal femur and acetabulum; underestimation of the patient's weight and physical activity, the wrong choice of the implant and the technology of its fixation.

In the late postoperative period, complications are associated with the operation and technical features of the endoprosthesis (material quality and defects in the manufacture of the endoprosthesis, design features, tribological characteristics of the friction pair, destruction of the endoprosthesis elements, loss of strong fixation of the components to the underlying bone) [21].

The solution to the problem of the destruction of the elements of the endoprosthesis lies in the plane of materials science and manufacture of endoprostheses. The reasons for the loss of strong fixation of the components are multifactorial, the processes are multifaceted and not fully understood [22].

Compared to the widely used TiAl6V4 alloy, the alloys under study approximately correspond in plasticity and have approximately two times lower Young's modulus, which should provide better biomechanical compatibility between the implant and the surrounding biological tissues, preventing the effect of protection against stress and, accordingly, bone resorption. The relatively low tensile strength of the alloys does not reduce the above-mentioned advantage over TiAl6V4, since this strength is quite sufficient for the intended application.

CONCLUSION

The way to create titanium alloys with a low Young's modulus can solve the problem of biomechanical compatibility of the implant with the surrounding tissues. The alloys of the Ti-Nb-Ta system described above showed the required mechanical and, according to the initial assessment, acceptable biological properties that require further broader research. The Ti-15Nb-5Ta alloy has the highest strength, which also has the minimum Young's modulus, high yield strength, and good ductility. The Ti-15Nb-10Ta alloy was the next strongest alloy with a ductility index higher than that of Ti-15Nb-5Ta and demonstrated the best biological properties in vivo, low inflammation activity in the first week and its complete absence by the fourth. Moreover, it should be noted that in the group with the implanted Ti-20Nb-5Ta alloy, a moderate inflammatory reaction was recorded in the first week and its gradual disappearance by the twelfth week. Histological examination after 1, 4 and 12 weeks showed that the intensity of the local inflammatory reaction due to new alloys is higher than with the use of TiAl6V4, which requires further investigation and could be associated with a small number of cases studied.

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