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Systemic effect of alumina-coated titanium implants: histopathological analysis in rats

O. O. Bondarenko[A,B,C,D], **A. H. Bozhko**[B], **S. A. Kalmykova**[B,D], **I. O. Maltsev**[C,E], **I. S. Shponka**[E,F], **O. Ye. Loskutov**[A,E,F]

Dnipro State Medical University, Ukraine

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The systemic biocompatibility of implant materials is crucial for ensuring their safety, since materials such as titanium (Ti), hydroxyapatite (HAp) and, in particular, alumina (Al_2O_3) can affect vital organs beyond the site of implantation. While alumina-based coatings are valued for their mechanical stability, experimental studies suggest that aluminium ion release can cause toxicity to the liver and immune system.

The aim of the study is to evaluate the organ-specific toxicity of Ti bone implants, both with and without functional-protective coatings, by conducting a histopathological analysis of the liver, kidney and spleen in an experimental model.

Materials and methods. Cylindrical Ti pins, either uncoated, alumina-coated (Al), or HAp-coated, were produced and characterized previously. Ninety-five female Wistar rats were divided into four groups (Ti-, Al-, HAp-groups, and sham control). Implants were inserted into the right femur following by postsurgical treatment and observation. Liver, kidney, and spleen tissues were collected at 1, 2, 4, and 8 weeks and processed for blinded histopathological evaluation using a semi-quantitative scale (based on ISO 10993-11:2017). Statistical analysis utilized Kruskal–Wallis tests, with $p < 0.05$ denoting significance.

Results. In the first week after implantation, all groups showed hepatocellular swelling, sinusoidal congestion and moderate portal mononuclear infiltration in the liver. They also showed tubular epithelial swelling and focal lymphocytic infiltration in the kidneys and follicular hyperplasia in the spleen. By the second week, these inflammatory alterations persisted but generally decreased, showing no significant difference from the sham-operated control group. By the fourth week, hepatocyte swelling and periportal infiltration were evident primarily in the Ti-group, while the Al_2O_3- and HAp-coated groups showed only mild reactions. Renal infiltration remained more pronounced in the Ti-group. By the eighth week, liver morphology was almost normal in all groups, with only minimal residual periportal infiltration. The kidneys showed only slight tubular swelling. While most splenic changes had resolved, some Ti-group specimens retained follicular hyperplasia, indicating a prolonged systemic response.

Conclusions. This study confirms that all tested Ti-based biomaterials are acceptable in terms of systemic biocompatibility. No necrosis or irreversible organ damage was observed, indicating an absence of toxicity induced by the materials. The initial, transient histological changes were nonspecific responses to surgical stress. Systemic responses indirectly correlated with the implant surface. HAp coatings demonstrated the most favourable systemic profile due to their robust osseointegration, whereas uncoated Ti resulted in prolonged immune activation. This highlights the importance of coatings that promote rapid and complete osseointegration in minimizing long-term systemic effects.

Ключові слова: ортопедичні імплантати, функціонально-захисні покриття, корундова кераміка, оксид алюмінію, остеоінтеграція, біосумісність, системна токсичність, запалення, печінка, нирки.

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Системний вплив титанових імплантатів із корундовою керамікою: гістопатологічний аналіз у щурів

О. О. Бондаренко, А. Г. Божко, С. А. Калмикова, І. О. Мальцев, І. С. Шпонька, О. Є. Лоскутов

Системна біосумісність імплантаційних матеріалів має вирішальне значення для їх безпечного використання, оскільки такі матеріали, як титан (Ti), гідроксиапатит (HAp) і, зокрема, оксид алюмінію (Al_2O_3), можуть впливати на життєво важливі органи поза місцем імплантації. Хоча покриття на основі оксиду алюмінію цінують за їхню механічну стабільність, експериментальні дослідження показують, що вивільнення іонів алюмінію може мати токсичні ефекти для печінки й імунної системи.

Мета роботи – оцінити органоспецифічну токсичність кісткових імплантатів із титану (з функціонально-захисними покриттями та без них) шляхом гістопатологічного аналізу печінки, нирок і селезінки в експериментальній моделі.

Матеріали і методи. Циліндричні титанові штифти без покриття, з покриттям з Al_2O_3 або з покриттям з HAp виготовлено й схарактеризовано раніше. Експеримент здійснили на 95 самках щурів лінії Wistar, яких поділили на чотири групи: Ti, Al, HAp і контрольну – без імплантатів. Імплантати введено в праву стегнову кістку, надалі здійснили постопераційне ведення тварин і спостереження. Тканини печінки, нирок і селезінки взято через 1, 2, 4 і 8 тижнів, оброблено для сліпого гістопатологічного оцінювання, що передбачало використання напівкількісної шкали (на основі ISO 10993-11:2017). Статистичний аналіз здійснили за допомогою тесту Краскела–Волліса; при $p < 0,05$ відмінності визначено як статистично достовірні.

Результати. У перший тиждень після імплантації в усіх групах визначено гідропічну дегенерацію гепатоцитів, венозний застій і помірну перипортальну мононуклеарну інфільтрацію в печінці. Виявлено також набряк тубулярного епітелію та фокальну інтерстиційну лімфоцитарну інфільтрацію в нирках і фолікулярну гіперплазію в селезінці. До другого тижня ці запальні зміни зберігалися, але загалом зменшилися; відмінності порівняно з контрольною групою невірогідні. На четвертий тиждень набряк гепатоцитів і перипортальна інфільтрація виражені передусім у групі Ti, а в групах із покриттям Al_2O_3 і HAp визначено лише помірні реакції. Запальна інфільтрація нирок залишалася більш вираженою в групі Ti. На восьмий тиждень морфологія печінки практично відповідала нормі в усіх групах, з мінімальною залишковою перипортальною запальною інфільтрацією. У нирках виявлено незначні гідропічні зміни канальців. Хоча більшість змін у селезінці зникли, деякі зразки у групі Ti зберігали фолікулярну гіперплазію, що вказує на тривалу системну запальну реакцію.

Висновки. Встановлено, що всі протестовані біоматеріали на основі Ti прийнятні в аспекті системної біосумісності. Не виявлено некротичних змін або незворотного пошкодження органів, що свідчить про відсутність токсичності, спричиненої матеріалами. Початкові, тимчасові гістологічні зміни – неспецифічні реакції на хірургічне втручання. Системні реакції опосередковано корелювали з типом поверхні імплантату. Покриття з HAp мали найсприятливіший системний вплив завдяки міцній остеоінтеграції, а імплантати без покриттів асоціювалися з тривалою активацією імунної системи. Це підтверджує важливість покриттів, що сприяють швидкій і повній остеоінтеграції, для мінімізації віддалених системних ефектів.

The biocompatibility of implant materials is critical to their long-term success in biomedical applications. Aluminium oxide (Al_2O_3), titanium (Ti) and hydroxyapatite (HAp) are widely used due to their favourable mechanical properties and inherent bioactivity in specific contexts [1,2]. While these materials are often considered to be either bioinert or bioactive at the implant site, their potential systemic effects on distant organs remain an important area of investigation. It is crucial to understand the systemic impact of implant materials on major organs such as the kidneys and liver, as well as on peripheral immune organs such as the spleen, in order to ensure the overall safety and efficacy of implant-based therapies [3].

The liver and kidneys play pivotal roles in maintaining systemic homeostasis, including the metabolism and excretion of various substances, including potentially released ions or nanoparticles from implant materials [3,4,5]. The liver, as the primary site of detoxification, is susceptible to alterations in its cellular structure and function in response to systemic exposure to foreign materials [4]. Similarly, the kidneys, responsible for filtering waste products from the blood, may be affected by circulating substances, leading to functional impairment and histological changes [5].

The biocompatibility of implant materials is a critical parameter for ensuring their safety and long-term performance in clinical settings. Ti and HAp are among the most widely utilized materials in orthopedic and dental implants due to their mechanical strength, corrosion resistance, and favorable interactions with bone tissue [2]. While these materials are generally considered bioinert at the site of implantation, the impact of Al_2O_3 on vital organs such as the liver, kidneys, and spleen remains controversial [6,7,8].

Laboratory rodent studies demonstrate that the liver and the immune system are the primary targets for toxicity of alumina-based biomaterials [6,7,8,9]. Liver damage is characterized by the hepatocellular degeneration and necrosis, liver sinusoid congestion, inflammation, and fibrosis. Systemic inflammation and impaired phagocytosis are the hallmarks of alumina-based toxicity, which was widely documented [7,8]. Particularly, it was reported that toxic effects have been attributed to Al^{3+} release leading to a number of adverse outcomes: oxidative stress, inflammation, mitochondrial dysfunction, genotoxicity, cell cycle dysregulation, and programmed cell death [7]. However, it is also evident that the spatial appearance of Al-based composites significantly affects their cytotoxicity [9,10,11]. Therefore, the studying specific models of alumina implant coating is required for clarification of its toxic effects mechanisms, as well as its potential adverse effects on human health.

Aim

To evaluate the organ-specific toxicity of Ti bone implants, both with and without functional-protective coatings, by conducting a histopathological analysis of the liver, kidney and spleen in an experimental model.

Materials and methods

The manufacturing process of the implants, along with their physical and chemical properties, has been detailed in previous publications [12,13] and depicted briefly in *Fig. 1*.

The prepared cylindrical pins were intramedullary implanted into the right femurs of 95 female Wistar rats, with an average age of 17 weeks and a mean body weight of 250 g. Primarily, all animals were divided into seven groups based on implant type that is thoroughly described in our previous publications [12,13]. However, exclusively for the purpose of this study, we regrouped the animals according to the unique chemical compounds of the implants *(Fig. 1)*:

1) titanium-only implanted animals (Ti-group): includes the use of implants that contained the untreated titanium wire (Ti, n = 5), sandblasted titanium wire (TS, n = 5), sandblasted titanium wire sprayed with titanium powder (TSP, n = 5) or titanium wire (TSPT, n = 5) using the plasma torch;

2) animals implanted with alumina-coated implants (Al-group): sandblasted titanium wire sprayed with Al_2O_3 (TSPC, n = 10) or combined spraying with titanium wire and Al_2O_3 (TSPTC, n = 10);

3) implanted with HAp-coated implants (HAp-group, n = 20);

4) 15 more rats were used as a sham operated control group.

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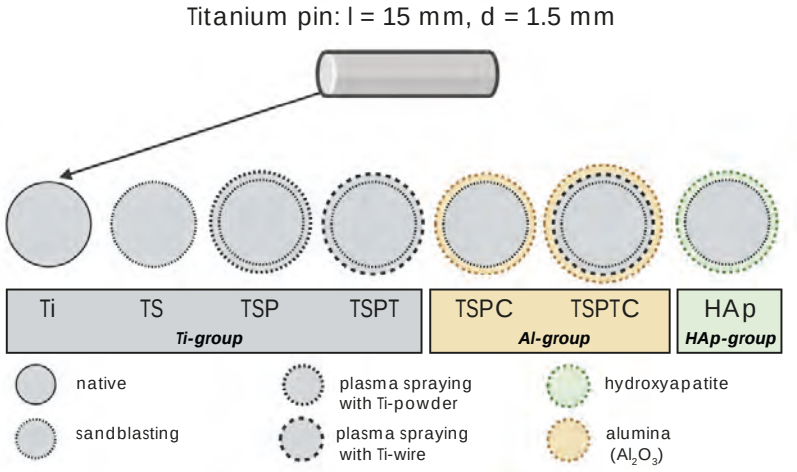

Fig. 1. Diagram of the implant surface modifications: schematic view of the implant cut surface with different coating applications, explained in the legend at the bottom, and the corresponding experimental group arrangement according to the chemical compounds of the most superficial layer.

All surgical procedures, anesthesia protocols, and pharmacological treatments, including euthanasia, were performed as previously described in our prior publications [12,13]. The rats maintained under standard laboratory conditions with a 12-hour light / dark cycle and had free access to water and a standard chow diet containing 10 % fat. All experimental procedures adhered to ethical standards as per the Law of Ukraine No. 3447-IV and the European Directive 2010/63/EU, with approval from the Biomedical Ethics Committee of Dnipro State Medical University (meeting minutes of the Biomedical Ethics Committee of Dnipro State Medical University No. 31, dated 15.10.2025).

After euthanasia, tissue samples from kidneys, livers, and spleens were harvested at 1, 2, 4 and 8 weeks post-implantation. To standardize the sampling process, only the left kidney from each rat was collected. The samples were fixed in formalin, then dehydrated through a graded isopropanol series (70 %, 80 %, 95 %, and three changes of 100 %, each for 90 minutes), cleared in xylene, and embedded in paraffin via two changes of molten paraffin, each lasting 120 minutes. The paraffin-embedded specimens were then mounted into blocks using a HistoStar embedding system (Thermo Fisher Scientific, USA).

Serial sections no thicker than 4 μm were cut using a Thermo HM 355S microtome (Thermo Fisher Scientific, Germany). Each tissue section was stained with hematoxylin and eosin for routine histological analysis.

A blinded method was used for the histopathological examination, which was verified by two independent experts using an optical light Axio Imager 2 microscope (Zeiss, Germany) at magnifications of ×100, ×200, and ×400. The systemic (liver and kidney) biocompatibility of the coatings was assessed, taking into account the presence of the following histopathological phenomena: inflammatory infiltrate (polymorphonuclear and mononuclear cells), fibrosis and vascular congestion (fibroblasts and blood vessels). In addition to these tissue changes, cellular swelling, micro- and macrovesicular steatosis, necrosis and apoptosis were also considered when assessing the inflammatory response in the liver and kidneys.

According to the ISO 10993-11:2017 specification [14] and based on tissue responses stimulated by different coatings and the sham group, tissue inflammation was classified using well documented semiquantitative scoring system [15,16] as follows: G0 – absent; G1 mild – up to 25 inflammatory cells per field of view (FOV); G2 moderate – 26-125 inflammatory cells / FOV; and G3 severe – more than 125 inflammatory cells / FOV. Evaluations were performed at 4 and 8 weeks of observation to exclude the non-specific tissue responses related to the post-surgical stress.

A statistical analysis of the semiquantitative histopathological evaluation was conducted using GraphPad Prism version 8.0.2 (263) for Windows (GraphPad Software, San Diego, California, USA; www.graphpad.com). The non-parametric Kruskal–Wallis and post hoc Dunn's tests were used to compare evaluated histopathological data. A significance level of $p < 0.05$ was used as a reference point.

Results

In the first week following the implantation, swelling of hepatocytes in the periportal zones and moderate, diffuse mononuclear infiltration of the portal tracts were observed in the livers of animals in all study groups. Congestion of the central veins with sinusoidal dilatation and focal, microvesicular steatosis of hepatocytes were also observed in the periportal zones. Among all the groups investigated, only the kidneys showed significant changes in the form of swelling of the convoluted tubule epithelium with foci of stromal lymphocytic infiltration during the first week. By the end of the first week, hyperplasia of lymphoid follicles with the formation of germinal centers was evident in the spleen tissue.

At the end of the second week after the surgery, the aforementioned changes were evident in all experimental

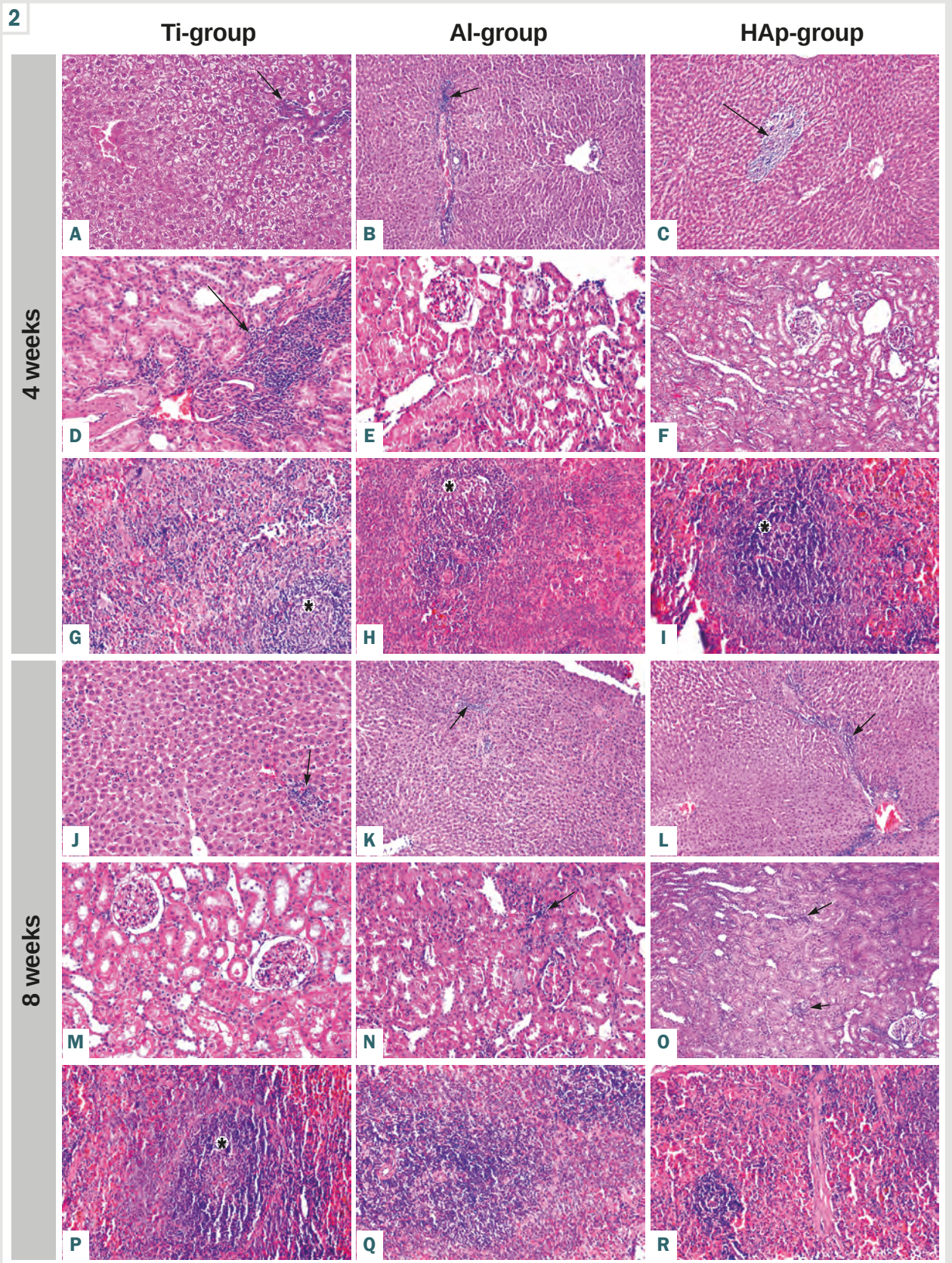

Fig. 2. Histopathological changes in liver (**A–C**, **J–L**), kidneys (**D–F**, **M–O**), and spleen (**G–I**, **P–R**) following the implantation of the investigated materials after 4 and 8 weeks of the experiment. Notable cellular swelling in the liver, which is still present in some samples from Ti-group (**A**). Chronic interstitial inflammation (**arrows**) occurs in all specimens from different groups with variable severity. Follicular hyperplasia with formation of germinative centers (**asterisk**) is visible in all specimens following 4 weeks of the implantation (**G–I**); in Ti-group they are still present after 8 weeks (**P**). Hematoxylin and eosin staining; magnification: ×100 (**B**, **C**, **F–I**, **K**, **L**, **N–R**), ×200 (**A**, **D**, **E**, **J**, **M**).

Table 1. Assessment of the inflammatory response in the liver specimens.

Implant material	Inflammation grade								p (4–8 weeks)
	4 weeks				8 weeks				
	G0	G1	G2	G3	G0	G1	G2	G3	
Sham	10	4	1	0	12	3	0	0	1.000
Ti-group	1	7	12	0	9	11	0	0	0.0005*
Al-group	0	14	5	1	10	10	0	0	0.0056*
HAp-group	1	16	3	0	12	8	0	0	0.021*
p (groups)	<0.0001*				0.1849				–

*: statistically significant difference.

Table 2. Assessment of the inflammatory response in the kidneys.

Implant material	Inflammation grade								p (4-8 weeks)
	4 weeks				8 weeks				
	G0	G1	G2	G3	G0	G1	G2	G3	
Sham	4	9	2	0	6	9	0	0	1.000
Ti-group	1	6	11	2	8	11	1	0	<0.0001*
Al-group	0	11	8	1	10	9	1	0	0.0001*
HAp-group	1	12	7	0	5	14	1	0	0.0901
p (groups)	0.0051*				0.4946				–

*: statistically significant difference.

groups and the sham-operated group. However, there was a tendency towards decreased inflammatory infiltration in the liver and kidney stroma, as well as reduced splenic lymphoid follicle hyperplasia. However, no significant histological differences were found between the investigated groups and the specimens from the sham-operated animals.

By the fourth week, swelling of hepatocytes was only still observed in the Ti-group *(Fig. 2A)*, and moderate lymphoplasmacytic infiltration was detected in the periportal tracts *(Table 1)*. Meanwhile, the "coated" groups (Al and HAp) and the sham group exhibited mild lymphohistiocytic infiltration of the periportal tracts, with minimal pathological changes observed in the hepatocytes. Interstitial lymphoid infiltration was also present in the renal stroma, though it was more pronounced in some samples from the Ti group *(Fig. 2D, Table 2)*. Lymphoid follicular hyperplasia was observed in spleen specimens from all experimental groups *(Fig. 2G–I)*, but not in the sham-operated group.

After eight weeks, there were no significant pathohistological changes in liver tissue in any of the groups with implants or the sham-operated group, except for minor lymphoplasmacytic infiltration of the periportal tracts *(Fig. 2J–L)*. In the kidneys, there was slight swelling of the convoluted tubule epithelium and scarce diffuse lymphocytic infiltration of the stroma *(Fig. 2M–O)*. Splenic tissue showed germinal centre involution, except in a few specimens from the Ti-group where hyperplastic follicles were still present *(Fig. 2P)*.

Discussion

The present study aimed to evaluate the systemic effects of intraosseous titanium implants with functional protective coatings containing alumina ceramics. The objective of this assessment was to determine the safety and biocompatibility of these materials in comparison with conventional HAp-based coatings. A histological examination of the liver, kidneys, and spleen were conducted to identify possible systemic responses beyond the local bone–implant interface.

During the first and second weeks following implantation, the observed morphological alterations in the examined organs exhibited uniformity across all the experimental groups, including those that underwent a sham operation. These early changes, characterized by hepatocellular and tubular epithelial swelling, moderate interstitial inflammation and lymphoid follicular hyperplasia, are likely to reflect non-specific postoperative responses to surgical trauma, anesthesia and antibiotic treatment [17,18]. The uniformity of these findings across groups indicates that they were not directly related to the implant materials.

However, at four weeks following the surgical procedure revealed that hepatocellular swelling was observed in the Ti group exclusively. This pattern may indicate a systemic stress response associated with immune activation, rather than a direct hepatotoxic effect of titanium. Furthermore, persistent lymphoid follicular hyperplasia was observed in the Ti group up to eight weeks, suggesting prolonged activation of the adaptive immune system in response to ongoing interaction with the implant surface. This finding is consistent with the data obtained from the peri-implant tissues of the same animals, as described in a previous publication [12]. The study demonstrated the lower stability of titanium implants lacking functional protective coatings, the increased formation of wear particles and the more pronounced peri-implant fibrogenesis observed in this group (Ti, TS and TSP) [12]. Notwithstanding these observations, titanium remains a well-established biocompatible material [2].

The absence of sinus histiocytosis or particle-laden macrophages in lymphoid tissues in this study supports the stability of the implant surface and low degradation

rates. Nonetheless, the continued presence of mild follicular hyperplasia in the Ti group following a period of four weeks may be indicative of delayed osseointegration and incomplete implant stabilization. This, in turn, could lead to mechanical irritation of the peri-implant tissues during movement, a phenomenon that is in accordance with prior reports documenting this occurrence [19].

In contrast, titanium implants coated with Al_2O_3 induced only mild and transient hepatic alterations that had largely resolved by eight weeks, suggesting a weaker and short-lived systemic response. This finding provides further support for the hypothesis that mechanical stability and satisfactory osseointegration are characteristic features of alumina-coated implants. In the present study, the most favourable systemic profile was demonstrated by HAp-coated implants, which showed minimal organ responses at later stages. This finding is consistent with the well-recognized bioactive and osteoconductive nature of HAp coatings.

Of particular significance was the absence of any necrotic or irreversible changes observed in any organ, thereby confirming the absence of specific toxic effects of the materials that had been tested. The histological alterations detected appear to represent a transient systemic immune response to the presence of a foreign body in bone tissue, rather than toxicity induced by the materials. Furthermore, coatings that promoted faster osseointegration were associated with milder systemic responses, which further highlights their biological compatibility.

Overall, the mild lymphoid hyperplasia in the spleen and the limited inflammatory changes in the liver and kidneys reflect a transient, regulated immune activation involving both innate and adaptive mechanisms. The liver and kidneys are particularly susceptible to circulating inflammatory mediators due to their central roles in metabolism and detoxification. Notwithstanding the non-existence of toxic degradation products, surgical implantation in itself has been demonstrated to elicit systemic cytokine and stress responses, resulting in temporary histological alterations. In order to ensure the validity of the interpretation of biocompatibility studies, it is essential to distinguish these non-specific changes from material-specific effects. This is corroborated by the observation of comparable outcomes between experimental and sham-operated animals at early time points, with significant differences emerging only after a four-week implantation period ($p < 0.0001$ for the liver and $p = 0.0051$ for the kidneys; refer to *Table 1, 2*). These findings underscore the necessity for the implementation of proper control groups, rigorous timing methodologies, and standardised conditions in the realm of biocompatibility research. Furthermore, the value of systemic histological evaluation is highlighted, not only to confirm the absence of toxicity, but also to elucidate the broader biological responses to implant materials. This information can inform future improvements in implant surface design and clinical safety.

Conclusions

The present study highlights the systemic histological responses of major organs, including the liver, kidneys and spleen, to the implantation of titanium-based biomaterials with varying surface modifications.

1. The systemic biocompatibility of the implant materials tested (uncoated titanium, alumina-coated titanium, and hydroxyapatite-coated titanium) was found to be satisfactory. Observations conducted over a period of up to eight weeks revealed no evidence of necrosis or irreversible organ damage in any of the groups. This finding serves to confirm the absence of material-induced toxicity. The initial histological changes observed were non-specific, transient responses to surgical stress, which resolved or diminished uniformly across all groups at early time points.

2. The effectiveness of the implant surface was directly correlated with the systemic responses. Hydroxyapatite-coated implants exhibited the most favourable systemic profile, inducing the mildest and most transient responses due to their pronounced osteoconductive properties. Conversely, the uncoated Ti-group demonstrated protracted systemic immune activation, which is presumably indicative of delayed osseointegration and consequent chronic mechanical irritation. This finding indicates that the utilisation of coatings that facilitate rapid and complete osseointegration is imperative in order to minimise long-term systemic repercussions.

Perspectives of subsequent scientific research. In the subsequent publication, we will present the results of an immunomorphological study of diverse biomarker expression, as well as ELISA analysis of collected serum samples. It is anticipated that these findings will reveal the molecular mechanisms of peri-implant bone healing.

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Information about the authors:
Bondarenko O. O., MD, PhD, Associate Professor of the Department of Pathological Anatomy, Forensic Medicine and Pathological Physiology, Dnipro State Medical University, Ukraine.
ORCID ID: 0000-0002-9739-9219
Bozhko A. H., MD, Teaching Assistant, Department of Trauma Surgery and Orthopedics, Dnipro State Medical University, Ukraine.
ORCID ID: 0000-0002-1054-7574
Kalmykova S. A., undergraduate student, Dnipro State Medical University, Ukraine.
ORCID ID: 0009-0000-4681-5246
Maltsev I. O., MD, PhD, Associate Professor of the Department of Pathological Anatomy, Forensic Medicine and Pathological Physiology, Dnipro State Medical University, Ukraine.
ORCID ID: 0000-0002-3503-0790
Shponka I. S., MD, PhD, DSc, Professor of the Department of Pathological Anatomy, Forensic Medicine and Pathological Physiology, Dnipro State Medical University, Ukraine.
ORCID ID: 0000-0002-7561-6489

Loskutov O. Ye., MD, PhD, DSc, Professor, Head of the Department of Trauma Surgery and Orthopedics, Dnipro State Medical University, Ukraine; Academician of NAMS of Ukraine.
ORCID ID: 0000-0003-0579-5642

Відомості про авторів:
Бондаренко О. О., канд. мед. наук, доцент, каф. патологічної анатомії, судової медицини та патологічної фізіології, Дніпровський державний медичний університет, Україна.
Божко А. Г., асистент каф. травматології та ортопедії, Дніпровський державний медичний університет, Україна.
Калмикова С. А., студент, Дніпровський державний медичний університет, Україна.
Мальцев І. О., канд. мед. наук, доцент, каф. патологічної анатомії, судової медицини та патологічної фізіології, Дніпровський державний медичний університет, Україна.
Шпонька І. С., д-р мед. наук, професор, каф. патологічної анатомії, судової медицини та патологічної фізіології, Дніпровський державний медичний університет, Україна.
Лоскутов О. Є., д-р мед. наук, професор, зав. каф. травматології та ортопедії, Дніпровський державний медичний університет, Україна; академік НАМН України.

Olexandr Bondarenko (Олександр Бондаренко)
bondarenko.olexandr@dmu.edu.ua

References

1. Farhan-Alanie OM, Hrycaiczuk A, Tinning C, Jones B, Stark A, Bryceland K. Alumina ceramic-on-ceramic hybrid total hip arthroplasty. A median of 15 years follow-up. Eur J Orthop Surg Traumatol. 2022;32(6):1127-36. doi: 10.1007/s00590-021-03087-w
2. Gil J, Manero JM, Ruperez E, Velasco-Ortega E, Jiménez-Guerra A, Ortiz-García I, et al. Mineralization of Titanium Surfaces: Biomimetic Implants. Materials (Basel). 2021;14(11):2879. doi: 10.3390/ma14112879
3. Murthy S, Effiong P, Fei CC. Metal oxide nanoparticles in biomedical applications. In: Metal Oxides, Metal Oxide Powder Technologies. Elsevier; 2020. p. 233-51.
4. Vilas-Boas V, Vinken M. Hepatotoxicity induced by nanomaterials: mechanisms and in vitro models. Arch Toxicol. 2021;95(1):1-21. doi: 10.1007/s00204-020-02940-x
5. Zhao H, Li L, Zhan H, Chu Y, Sun B. Mechanistic understanding of the engineered nanomaterial-induced toxicity on kidney. J Nanomater. 2019;2019:2954853. doi: 10.1155/2019/2954853
6. Park SH, Lim JO, Kim WI, Park SW, Lee SJ, Shin IS, et al. Subchronic Toxicity Evaluation of Aluminum Oxide Nanoparticles in Rats Following 28-Day Repeated Oral Administration. Biol Trace Elem Res. 2022;200(7):3215-26. doi: 10.1007/s12011-021-02926-5
7. Aschner M, Skalny AV, Lu R, Santamaria A, Paoliello MM, Tsatsakis A, et al. Toxic effects of aluminum nanoparticles: a review. Nanotoxicology. 2025;19(4):413-52. doi: 10.1080/17435390.2025.2511694
8. Maisanaba S, Pichardo S, Puerto M, Gutiérrez-Praena D, Cameán AM, Jos A. Toxicological evaluation of clay minerals and derived nanocomposites: a review. Environ Res. 2015;138:233-54. doi: 10.1016/j.envres.2014.12.024
9. Denes E, Barrière G, Poli E, Lévêque G. Alumina Biocompatibility. J Long Term Eff Med Implants. 2018;28(1):9-13. doi: 10.1615/JLongTermEffMedImplants.2018025635
10. Maccauro G, Cittadini A, Magnani G, Sangiorgi S, Muratori F, Manicone PF, et al. In vivo characterization of Zirconia Toughened Alumina material: a comparative animal study. Int J Immunopathol Pharmacol. 2010;23(3):841-6. doi: 10.1177/039463201002300319
11. Rahmati M, Mozafari M. Biocompatibility of alumina-based biomaterials-A review. J Cell Physiol. 2019;234(4):3321-35. doi: 10.1002/jcp.27292
12. Loskutov O, Shponka I, Bondarenko O, Bondarenko N, Bozhko A. Histological and histochemical assessment of short-term events in peri-implant bone for osteoinductivity evaluation of functional-protective implant coatings. Medicni Perspektivi. 2021;26(3):4-10. doi: 10.26641/2307-0404.2021.3.241875
13. Bondarenko OO, Bozhko AH, Skoryk MA, Bondarenko NS, Shponka IS, Loskutov OY. Peri-implant osteogenesis on alumina-coated titanium implants in rat femur: morphological and elemental analysis of implant surfaces. Pathologia. 2024;21(2):132-140. doi: 10.14739/2310-1237.2024.2.306822
14. ISO. ISO 10993-11:2017; Biological Evaluation of Medical Devices – Part 11: Tests for systemic toxicity. Geneva: International Organization for Standardization; 2017. [cited 2025 Oct 9]. Available from: https://www.iso.org/obp/ui/es/#iso:std:iso:10993:-11:ed-3:v1:en
15. Garcia LD, Huck C, Magalhães FA, Souza PP, Souza Costa CA. Systemic effect of mineral aggregate-based cements: histopathological analysis in rats. J Appl Oral Sci. 2017;25(6):620-30. doi: 10.1590/1678-7757-2016-0634
16. Ataş O, Bılge K, Yıldız S, Dundar S, Calik I, Gezer Ataş A, et al. Systemic effect of calcium silicate-based cements with different radiopacifiers-histopathological analysis in rats. PeerJ. 2023;11:e15376. doi: 10.7717/peerj.15376
17. Chen FH, Yu CF, Yang CL, Lin YC, Lin G, Wang CC, et al. Multimodal imaging reveals transient liver metabolic disturbance and sinusoidal circulation obstruction after a single administration of ketamine/xylazine mixture. Sci Rep. 2020;10(1):3657. doi: 10.1038/s41598-020-60347-1
18. Pakfetrat Z, Janfeshan S, Masjedi F, Rafiei M, Karimi Z. Involvement of oxidative stress and toll-like receptor-4 signaling pathways in gentamicin-induced nephrotoxicity in male Sprague Dawley rats. Drug Chem Toxicol. 2022;45(6):2568-75. doi: 10.1080/01480545.2021.1977024
19. Freitag L, Spinell T, Kröger A, Würfl G, Lauseker M, Hickel R, et al. Dental implant material related changes in molecular signatures in peri-implantitis – A systematic review and integrative analysis of omics in-vitro studies. Dent Mater. 2023;39(1):101-13. doi: 10.1016/j.dental.2022.11.022