CYTOCOMPATIBILITY OF PRESSURELESS SINTERED POROUS B_4C-CERAMICS ASSESSED *IN VITRO*

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The materials used to restore bone defets have a number of systemic limitations. The metal implants showing high mechanical strength have an insufficient osseointegration capability, while ceramic and polymer materials have better biocompatibility, but do not meet the requirements of mechanical reliability in the zones of considerable load. In this regard, the study of new classes of materials combining the strength characteristics with the osseogenic potential seems to be a promising area. The study aimed to assess cytocompatibility of the boron carbide (B_4C)-based porous ceramic material to confirm the possibility of its use for bone defect replacement. The B_4C semi-finished products were manufactured by pressureless sintering at 1900–2100 °C; ultrastructure of the resulting sample surface was examined by atomic force and scanning electron microscopy. Citotoxicity of the B_4C samples was estimated by an indirect method relative to human mesenchymal stem cells. The following cell survival rates were reported: 102.1% (24 h) and 99.1% (72 h) for the samples autoclaved; 110.0% (24 h) and 94.4% (72 h) for those treated with ethylene oxide. No significant intergroup differences were revealed (Mann–Whitney U-test). The findings allow us to consider B_4C ceramics as a promising solution for bone grafting. However, further research is required to assess its clinical potential, including the development of sterilization protocols for larger and complex-shaped samples.

Keywords: boron carbide, bone implants, ceramics, sterilization, biocompatibility

Funding: the study was supported by the Russian Science Foundation grant (project No. 25-25-00187).

Author contribution: Chepeleva EV, Khakhalkin VV — study concept and design; Chepeleva EV, Kozyr KV, Vaver AA, Khakhalkin VV — experimental procedure and data processing; Chepeleva EV — manuscript writing; Kozyr KV, Vaver AA, Khakhalkin VV — manuscript editing.

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Received: 10.09.2025 **Accepted:** 28.09.2025 **Published online:** 12.10.2025

DOI: 10.24075/brsmu.2025.044

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ЦИТОСОВМЕСТИМОСТЬ СВОБОДНОСПЕЧЕННОЙ ПОРИСТОЙ B_4C-КЕРАМИКИ ПРИ ИССЛЕДОВАНИИ *IN VITRO*

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Материалы, применяемые при восстановлении костных дефектов, имеют ряд системных ограничений. Металлические импланты, демонстрируя высокую механическую прочность, обладают недостаточной остеоинтеграционной способностью, в то время как керамические и полимерные материалы имеют лучшую биосовместимость, но не удовлетворяют требованиям по механической надежности в зонах значительной нагрузки. В этой связи перспективным направлением представляется исследование новых классов материалов, сочетающих прочностные характеристики с остеогенным потенциалом. Цель исследования — оценить цитосовместимость пористого керамического материала на основе карбида бора (B_4C) для подтверждения возможности его использования при замещении костных дефектов. Заготовки B_4C изготавливали методом свободного спекания при 1900–2100 °C, исследование ультраструктуры поверхности полученных образцов проводили методами атомно-силовой и сканирующей электронной микроскопии. Цитотоксичность образцов B_4C оценивали непрямым методом по отношению к мезенхимальным стволовым клеткам человека. Получены следующие показатели выживаемости клеток: для образцов после автоклавирования — 102,1% (24 ч) и 99,1% (72 ч); после обработки этиленоксидом — 110,0% (24 ч) и 94,4% (72 ч). Статистически значимых различий между группами не выявлено (*U*-критерий Манна–Уитни). Полученные результаты позволяют рассматривать B_4C-керамику как перспективное решение для костной пластики, однако для оценки ее клинического потенциала требуются дальнейшие исследования, включая разработку протоколов стерилизации для образцов большего размера и сложной формы.

Ключевые слова: карбид бора, костные импланты, керамика, стерилизация, биосовместимость

Финансирование: исследование выполнено за счет гранта Российского научного фонда (проект № 25-25-00187).

Вклад авторов: Е. В. Чепелева, В. В. Хахалкин — концепция и дизайн исследования; Е. В. Чепелева, К. В. Козырь, А. А. Вавер, В. В. Хахалкин — проведение экспериментов и обработка данных; Е. В. Чепелева — написание статьи; К. В. Козырь, А. А. Вавер, В. В. Хахалкин — редактирование статьи.

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Статья получена: 10.09.2025 **Статья принята к печати:** 28.09.2025 **Опубликована онлайн:** 12.10.2025

DOI: 10.24075/vrgmu.2025.044

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The today's traumatology and orthopedics face the challenge of reconstructing the large bone defects resulting from injuries, tumor resection or degenerative disorders [1]. The key approach to treatment of bone defects is the use of implantable materials for replacement. An ideal bone grafting material must be biocompatible, it must ensure osteoconduction (the process, when the bone replacement material serves as a structural matrix for osteoblast migration and proliferation), osteoinduction (the process, though which mesenchymal stem cells and osteoprogenitor cells are activated to differentiate in the osteogenic direction), as well as preserve the structural and mechanical properties of the regenerated bone [2]. There is currently no universal approach to bone grafting, and selection of the optimal material should be based on the specific clinical situation, defect size, and functional requirements. The range of materials widely used for bone defect replacement includes polymer matrices, bioceramics, and structural metal alloys; bone autografts and allografts are used in certain clinical situations [2–4]. The analysis of the effectiveness of available solutions shows systemic limitations that vary depending on the material class (Table 1) [3–11].

Today, the approaches to bone tissue restoration are focused on overcoming the current limitations through the development of fundamentally new solutions, among which several key directions can be distinguished. Tissue engineering allowing one to produce biomimetic structures by combining biocompatible matrices, progenitor cells, and bioactive molecules for targeted stimulation of osteogenesis is one of the most promising [4, 12–14]. A significant potential arises from the use of additive technologies (3D printing, selective laser melting), ensuring fabrication of implants having the complex architecture, controllable porosity and showing full compliance with the defect anatomy, which is impossible when using conventional methods [3, 15, 16].

Boron carbide is conventionally used as a structural material due to high hardness (up to 48.5 GPa), relatively low density (~2.52 g/cm^3), and chemically inert nature [17]. The properties of B_4C as an independent implantable material are currently poorly understood, and the scarse research is focused mainly on its role as an auxiliary component (modifying additives, protective coatings).

The study aimed to assess biocompatibility of the boron carbide-based ceramic samples by assessing their cytotoxic effects on mesenchymal stem cells.

METHODS

The boron carbide semi-finished products were fabricated using the proprietary technology (patent No. RU 2 836 825 C1) [18]. During the technological process the source boron carbide powder (UNICHIM & EP, Russia) together with the adhesive agent was loaded into the XLB-3 atomizer dryer (Oriental Development Limited, China) for 1 h. Then the moulding powder was pressed using the SOROKIN 7.50 hydropneumatic press (Lekht, Russia) by cold pressing in order to produce a semi-finished product, from which parts of appropriate shape were fabricated by mechanical processing. To remove the adhesive agent, the moulded part was put in the EKPS-50 muffle furnace (Smolensk SKTB-SPU, Russia). Then the semi-finished product was placed in the HP W 250 hot pressing device (FCT Systeme GmbH, Russia), in which pressureless sintering occured at at temperature of 1900–2100 °C in 14 phases involving heating, interim passage, and evacuating. The source semi-finished products were cut into samples sized 5 × 5 × 30 mm using the diamond blades and cleaned of the dust formed during cutting in the CD-4830 ultrasonic bath (Codyson, China) in the ethanol medium, then triple washed with distilled water for 40 min. Samples of the same size made of the BT 1-00 titanium (TNMK, Russia) were used as a reference material.

The structure of the surface of boron carbide-based samples was examined using the KYKY-EM6900LV scanning

Table 1. Comparative analysis of the major classes of materials for bone grafting [3–11]

Material class	Examples	Benefits	Limitations
Biomaterials			
Bone tissue	Autograft	No risk of rejection, osteoconductivity, osteoinductivity	Limited material volume, additional surgical intervention and the associated risk of complications
	Allograft	No material volume limitation, osteoconductivity, osteoinductivity	Risk of immune rejection, risk of viral ot bacterial infection transmission, additional steps required for processing
Natural polymers	Proteins (collagen, fibrin, gelatin); polysaccharides (hyaluronic acid, chondroitin sulfate, alginate, chitosan)	Biocompatibility, biodegradability	Low mechanical strength, natural impurities, variability of properties
Natural minerals	Corals	Biocompatibility	Limited availability, slow resorption
Synthetic materials			
Metals	Titanium and alloys, tantalum, stainless steel, magnesium and alloys	High mechanical strength and wear resistance, biocompatibility	Low biodegradability, risk of toxicity due to release of metal ions, low resistance to cyclic loads
Bioceramics	Bioinert (ceramic aluminum oxide); biodegradable (hydroxyapatite, β-tricalcium phosphate, bioglass)	Biocompatibility, structural similarity to bone tissue, osteoconductivity/ osteoinductivity (depending on the structure and composition)	Brittleness, low bending and torsional strength, difficulty controlling the resorption rate
Polymers	Biodegradable (polycaprolactone, polylactic acid, polyglycolic acid)	Biodegradability, biocompatibility, versatility	Low mechanical strength, risk of inflammation due to degradation products
	Non-biodegradable (polyethylene, polyurethane)	Biocompatibility, versatility	
Composite materials	Hydroxyapatite-collagen matrices, calcium phosphate coatings on metals	Combination of mechanical properties and biocompatibility	Production complexity, high cost, possible structure heterogeneity

electron microscope (KYKY Technology Co., Ltd., China) at an accelerating voltage of 20 kV and electron beam amperage of 120 μA. The sample surface topography was assessed with the NTEGRA II atomic microscopy system (NT-MDT Spectrum Instruments, Russia) in the semi-contact mode using the HA_FM A silicon ultra-sharp cantilever (NT-MDT Spectrum Instruments, Russia) at the scan frequency of 0.7 Hz. The Nova-Px software (NT-MDT Spectrum Instruments, Russia) was used to produce the 3D topographic images.

Two methods widely used in laboratory and clinical practice were chosen for sample sterilization: physical (autoclaving) and chemical (ethylene oxide) ones. Before using in the experiment, a half of boron carbide samples and titanium samples were sterilized in an autoclave (Youjoy BES-12L-B-LED, China) at a temperature of 121 °C, pressure of 1.1 atm. for 45 min. The remaining samples were subjected to ethylene oxide sterilization in the Steri-Vac 5XL gas sterilizer/aerator (3M, USA) with the ethylene oxide concentration of 750 mg/L, temperature in the chamber 37°C, 70% humidity for 3 h. Aeration was carried out at the sterilization temperature for at least 8 h.

Cytotoxicity of samples was estimated by an indirect method involving assessment viability of the MSC-DP-1 human mesenchymal stem cells, MSCs (the shared research facility "Vertebrate Cell Culture Collection", Institute of Cytology RAS), in the extract obtained by incubation of the test samples in the DMEM/F12 culture medium (Servicebio, China) at 37 °C in the humid atmosphere with 5% CO_2 throughout 72 h in accordance with GOST ISO 10993-12-2023 [19]. Since MSCs are osteoblast progenitors that play a key role in bone tissue regeneration, the use of these makes it possible to estimate the extent, to which the test material would be compatible with the target biological medium *in vivo*.

The MSC-DP-1 cells were cultured in the DMEM/F12 medium (Servicebio, China) supplemented with 10% fetal calf serum (PanEco, Russia), 100 U/mL penicillin (Thermo Fisher Scientific, USA), 100 U/mL streptomycin (Thermo Fisher Scientific, USA), and 2 mmol/L L- glutamine (PanEco, Russia) at 37 °C in the humid atmosphere with 5% CO_2. To assess cytotoxicity of the extracts, the cells were sown on the flat bottom 96-well culture plates, 2×10^4 cells per 200 μL of medium in each well, and incubated throughout 24 h. Then the medium was replaced with 200 μL of the extract. After incubation in extracts at 37 °C in the humid atmosphere with 5% CO_2 under standard conditions throughout 24 and 72 h, cell viability was measured using the EZcount™ XTT Cell Assay Kit for cell proliferation assessment (HiMedia Labs, India). Optical density of the well content was measured at the wavelength of 450 nm and reference wavelength of 690 nm using the Stat Fax-2100 microplate photometer (Awareness Technology, Inc., USA). The cells cultured in the DMEM/F12 complete medium were used as a control. The number of repetitions per group was 5. Cell viability was calculated as a ratio between optical density in experimental groups and the control group (A):

$$\text{Cell viability} = (A_{\text{experimental group}}/A_{\text{control}}) \times 100\%.$$

The sample was considered non-toxic when the cell viability index was greater than 70% (GOST ISO 10993-5-2023) [20].

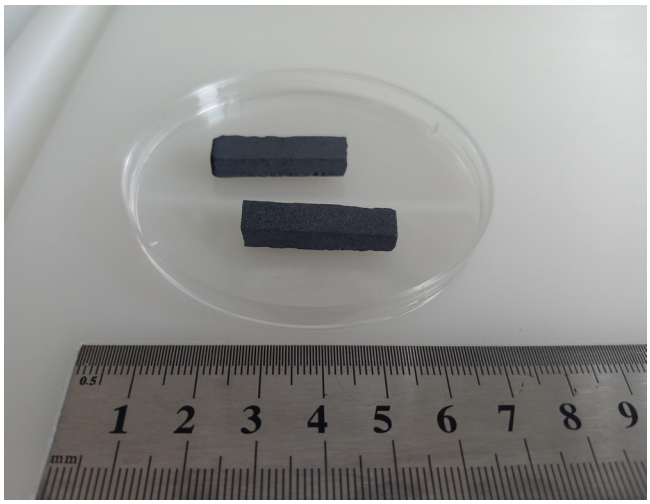

Fig. 1. Overall appearance of the B_4C ceramics samples produced by pressureless sintering

Statistical data processing was performed using the Statistica 10.0 software (StatSoft, USA). The data distribution was tested for normality using the Shapiro–Wilk test. The Mann–Whitney U-test was used to identify intergroup differences. The study results are presented as Me (25%; 75%), where Me is the median, and interquartile range represents the values of the 25th and 75th percentiles. Bonferroni correction was applied to adjust for multiple comparisons; after adjustment the significance level was as follows: $\alpha = 0.0125$; the intergroup differences were considered significant at $p < 0.0125$.

RESULTS

The overall appearance of the boron carbide-based porous ceramic samples sized 5 × 5 × 30 mm is presented in Fig. 1. The material main technical characteristics are provided in Table 2.

Microphotographs of the surface of the sintered boron carbide-based samples show a typical polycrystalline structure with the pronounced granular organization, the average granule size is 40 μm (Fig. 2). The granules that are located tightly, without significant gaps, are mostly of angular morphology with rounded margins. The margins have a complex configuration, including twin structures and areas of incomplete fusion. The surface has a highly porous structure of the interconnected pores that are mostly roundish or oval with the average size of 30 μm. The analysis of interconnections between pores revealed the branched channels and chains forming the interpore communication system. The distribution of pores in the material volume is relatively even, with local clusters and the zones of increased porosity. The pore walls have a smooth surface with microroughness and partial fusion of adjacent structures.

Topographic analysis of the test sample structure demonstrates complex morphology of the relief showing the pronounced mucrostructure heterogeneity; the root-mean-square roughness of the samples is 0.203 ± 0.037 μm, the elevational gradient is 1.563 ± 0.607 μm (Fig. 3). On the surface

Table 2. Characteristics of the B_4C ceramics samples produced by pressureless sintering [18]

Technical characteristics	Value
Raw material particle size	3 μm
Density	1.8 g/cm^3
Bending strength	250–300 Mpa
Open porosity of the semi-finished product	50–60 %

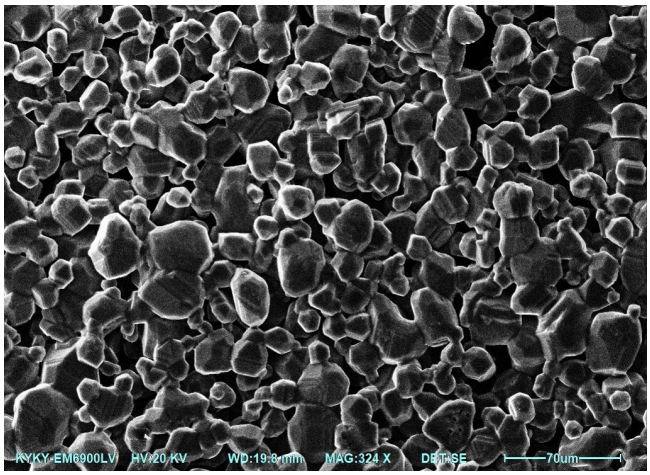

Fig. 2. Microstructure of the surface of the B_4C ceramics produced by pressureless sintering. Scale bar — 70 μm

the elements can be seen represented by both submicron-sized elevations and shallow depressions of various configurations. Uneven distribution of the altitude characteristics with formation of local hilly structures and the areas of increased roughness is reported.

When assessing viability of the MSCs cultured with the boron carbide sample-derived extracts, no toxic effects were revealed in both experimental and comparison groups (Fig. 4). The semi-finished products made of the BT 1-00 titanium were used as negative controls, which confirmed the method reproducibility and compliance of the biological response in the test system with the specified requirements. No effect of the sterilization method on the cell viability was also reported (Fig. 4).

DISCUSSION

The findings showing the lack of significant cytotoxic effects of moulded boron carbide on the MSCs are consistent with the data of previous studies focused on the material biocompatibility. However, in these studies boron carbide was tested as a powder or single particles. It was earlier shown that the B_4C nanoparticles produced by solvothermal synthesis

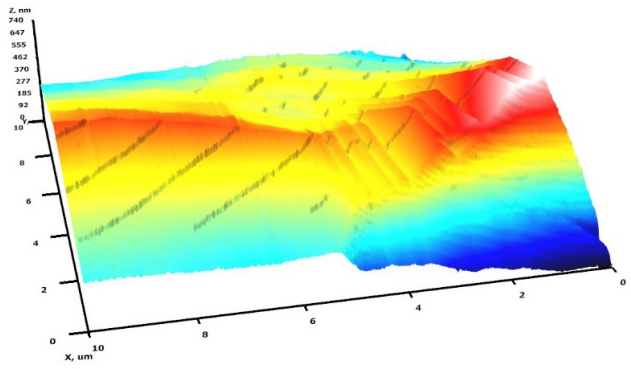

Fig. 3. AFM image of the relief of the surface of the B_4C ceramics produced by pressureless sintering. Field size 10 × 10 μm. Scale of the Z axis: 0–0.74 μm

have no toxic effect on the HeLa (cervical cancer) and HEK-293 (human embryonic kidney) cells in the concentrations of 100–800 μg/L [21]. Biocompatibility of amorphous boron carbide powder when contacting both somatic (Hs680 fibroblasts) and immune (RAW 264.7 macrophages) cells was also reported [22]. The lack of significant differences in cell viability between groups subjected to autoclaving and ethylene oxide sterilization suggests stability of the B_4C sample properties and tolerance of samples to sorption of toxic compounds during processing. It should be noted that in this study small boron carbide samples (5 × 5 × 30 mm) were used. In the future, further research may be required to select the conditions for sterilization of the larger and/or more complex-shaped samples, since the material porous structure can hinder diffusion of the sterilizing agents and contribute to accumulation of condensate in deep zones.

Currently, the vast majority of papers in the field of the boron carbide medical use are focused on using the B_4C nanoparticles as the highly effective carriers for targeted boron-10 isotope delivery within the framework of the boron neutron capture therapy of malignant neoplasms [23]. In contrast to the extensively studied therapeutic use, the issues related to the use of B_4C as a biocompatible material for implants are poorly undestood. The use of B_4C as an additive when making porous ceramic matrices of aluminum oxide results in improvement of their mechanical properties and cytocompatibility [24], but the

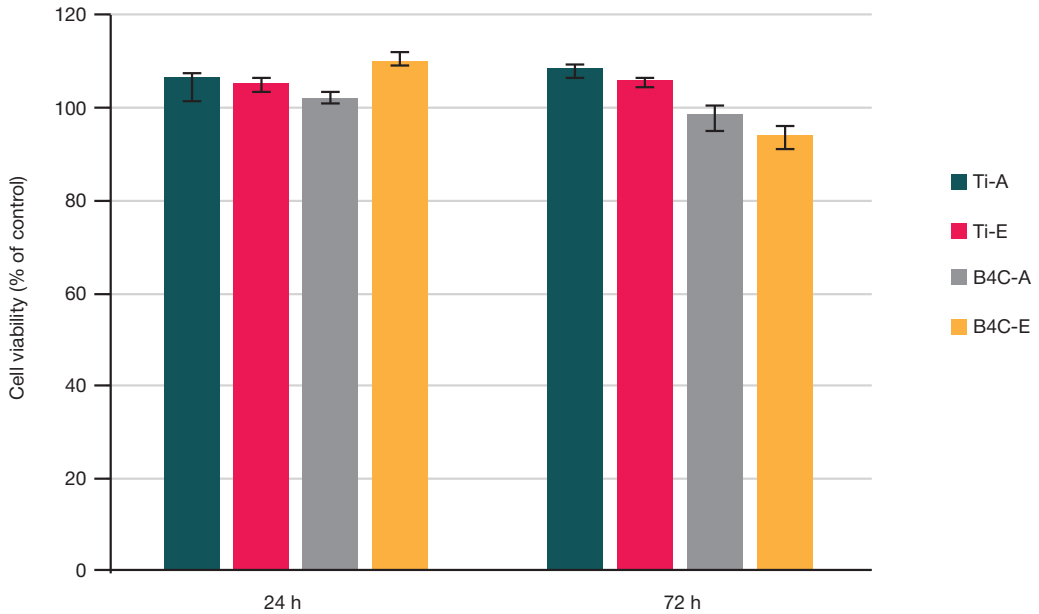

Fig. 4. Viability of the MSC-DP-1 mesenchymal stem cells after culturing for 24 and 72 h with the extracts obtained from the boron carbide (B_4C) and titanium (Ti) samples sterilized by autoclaving (A) or with ethylene oxide (E). Me (25%; 75%), Mann–Whitney U-test

detailed mechanisms underlying these effects require further investigation.

When constructing porous ceramic matrices for bone replacement, the main task is to optimize their architecture that must ensure both mechanical stability and the conditions contributing to effective diffusion of nutrients and oxygen [25]. Based on the results of a number of studies, the optimal percentage of porosity is within the limits of 40–90% [3]. A fundamental contradiction emerges: on the one hand, the material porosity contributes to adhesion, proliferation, and differentiation of MSCs into osteoblasts, but on the other hand high porosity limits mechanical strength, which results in the need to search for the compromise between these parameters [6]. As for the dense matrix made of hydroxyapatite, the most common ceramic-based alloplastic material, the bending strength limits are within 38–250 MPa; as for the porous matrix, the bending strength limit depending on the pore shape and concentration is 2–11 MPa, which is considerably lower compared to that of the bone tissue (135–193 MPa) [26]. Despite the fact that there numerous methods to modify the calcium phosphate ceramics, this material is still inferior to the bone tissue in flexibility, elasticity, and strength. Due to brittleness, such implants are not used to restore the bones that bear a significant load [6]. In such cases (for example, when manufacturing the components of the hip joint endoprosthesis), the class A ceramic aluminum oxide (Al_2O_3) can be used as an alternative material [27]. The boron carbide-based porous ceramics can theoretically be used for implants as an alternative to the ceramic aluminum oxide-based materials in order to reduce the load on the joint, since it has lower density (approximately 1.8 g/cm^3), which is comparable with the cortical bone tissue density, while the density of the aluminum oxide-based ceramics is 3.94 g/cm^3 [6]. It should be noted that the ceramic aluminum oxide bending strength is higher than that of the sintered boron carbide-based ceramics (500 MPa and 250–300 MPa, respectively). One technological solution to improve the porous B_4C matrix strength can be the aluminum impregnation accomplished through application of metal powder on the matrix and repeated sintering at the temperature above the aluminum melting point (above 660 °C). The ceramic composite produced in this way has a specific gravity of 2.2–2.6 g/cm^3 and the bending strength of at least 600 MPa [18].

The pore geometry and the material surface roughness are additional factors affecting adhesion and cell proliferation in the implantation site [28]. The pore complex spatial organization not only increases the area for cell adhesion, but produces mechanical stimuli for cell differentiation. The surface roughness, in turn, contributes to adhesion of the extracellular matrix proteins via integrin receptors, and the surface hydrophilicity associated with microrelief ensures the optimal wettability, thereby contributing to the nutrient diffusion and cell migration [29]. It has been shown that osteoblast adhesion and proliferation on the hydroxyapatite surfaces increase with increasing surface roughness from 0.733 ± 0.203 to 4.680 ± 0.433 μm [30]. In this study we did not assess cell adhesion and proliferation on the surface of the boron carbide-based ceramics to determine the optimal material processing method; further research is planned.

CONCLUSIONS

The study conducted has shown cytocompatibility of the ceramic samples made of boron carbide by pressureless sintering, which makes this material a promising candidate to be used for medical implants. However, the study limitations associated with small sample size require validation in further experiments involving large or complex-structured semi-finished products. In clinical practice, the material developed can be used to produce personalized implants for replacement of bone tissue defects in maxillofacial surgery and orthoperdics, especially in the cases requiring the combination of mechanical strength and bone tissue integration capacity. It is reasonable to use the B_4C ceramics as a component of the combined constructs for arthroplasty, in which its low density makes it possible to reduce the total endoprosthesis weight. To improve the boron carbide-based porous matrix strength, it is a far-reaching approach to produce composite materials by impregnation of semi-finished products with molten metals. Further directions of assessing the B_4C ceramics biocompatibility include estimation of the effect of miscrostructure (particle size, porosity) on the surface adhesive properties and osteogenic activity *in vitro*, study of the material long-term stability under physiological conditions, as well as investigation of the stress-corrosion behavior with the cyclic load mimicking the natural biomechanics, which is especially important for joint replacement.

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