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ORIGINAL ARTICLE

Radio-opaque polyethylene for personalized craniomaxillofacial implants

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Abstract
Objective This study aimed to present a new possibility to create radio-opaque implant material for craniomaxillofacial reconstruction.
Materials and methods The test disks made of the own compound of polyethylenes with addiction of 2, 4, and 6 % of weight TiO_2 was investigated for cytotoxicity [each group 15 disks respectively]. Next, computed tomography of the disks was performed in environment of muscle and fat. Hardness, tensile modulus and strength, and compressive modulus and strength were tested too.
Results Deterioration of mechanical properties of the composites containing titanium dioxide was observed [hardness, tensile modulus and strength, compressive modulus and strength, respectively: 56.7 ± 1.6 shore D, 354 ± 52, 22.5 ± 1.3, 21.8 ± 1.1, and 2995 ± 327 MPa as addiction of 2 % TiO_2; 52.0 ± 0.9 shore D, 347 ± 66, 18.0 ± 0.7, 14.2 ± 0.9, and 1396 ± 477 MPa as 4 % TiO_2; 51.3 ± 1.3 shore D, 316 ± 9, 17.4 ± 0.2, 13.6 ± 0.6, and 1100 ± 144 MPa as 6 % TiO_2 added]. The test disks revealed no cytotoxicity effect on human osteoblasts. The new material presents mild radio-opacity which was enough to observe the implant in relation to fat and muscle, but with no visible effect of beam hardening.
Conclusion In view of the performed tests, the polyethylene enriched by titanium dioxide seems to be a proper material to consider manufacturing of craniomaxillofacial implants.
Clinical relevance Maxilloafacial surgery is still looking for new implantologic materials. The proposed one is a new way to manufacture an implant visible in computed tomography which does not interfere with its shape in radiological examination and makes it possible to observe the surrounding soft tissues.

Keywords Maxillofacial implants · polyethylene · radiological opacity · personalized treatment

Introduction

Orbital reconstruction including individual implant [1, 2] is the main procedure in maxillofacial surgery (Fig. 1). They need correct positioning which is easy to check as the implant is a radio-opaque object [3] The same is in cranioplasty [4], but neurosurgeons prefer radio-translucent materials (polypropylene, polyetheretherketone, methacrylate) due to the need of observation of the soft intracranial tissues under the implant [5].

As far as precise personalized reconstruction is considered, the implant should be visible to evaluate the contact between the bone and the soft tissue. It is particularly important in orbital wall reconstruction [6] due to recognition of residual diplopia [7]. The increase of implant volume not present in reality caused by the beam hardening effect which is an issue around high absorbing species, i.e., metallic implant surface [8].

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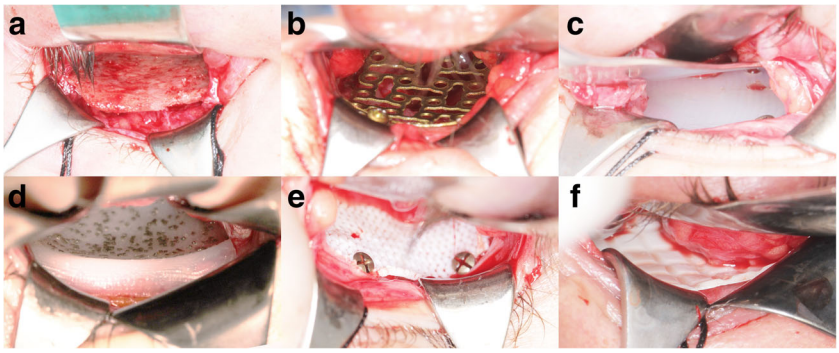

Fig. 1 Current examples of maxillofacial implants (one of the most frequent application is lower orbital wall implantation). **a** Autologous bone reconstruction is the golden standard; **b** titanium mesh is very often type of implant; **c** porous polyethylene also very popular; **d** ultrahigh molecular weight polyethylene enriched with titanium cubes for radiological visualization; **e** polypropylene implant; **f** full ceramic implant

The research status of this subject is advanced. The preliminary test and some clinical tests were performed for polyethylene covered with titanium grade 5 enriched with sonotroded titanium microcubes [9]. The new mixed material was revealed in patent pending 4 years ago [3]. As far as nuclei of heavy elements (i.e., pure titanium or titanium oxide) are concerned, titanium dioxide was the marking substance of choice and polyethylenes were the base material for maxillofacial implant.

The aim of this study is to present a new possibility to create radio-opaque implant material for craniomaxillofacial reconstruction.

Materials and methods

Manufacturing of the test disk of modified polyethylene

The injection mold was designed and manufactured for a series of polymer trials (Fig. 2). Own compounds made of density series of polyethylene (PE) enriched by addition of 2, 4, and 6 % of weight titanium dioxide [3] were used in the experiment. Injection molding machine Arburg Allrounder 420C 1300-675 was used to manufacture the test disks (1.8 × 18mm). The titanium dioxide was added as a material to improve disks' opacity in computed tomography. Data of the injection process are as follows: a masterbatch as a concentrated mixture of 75 %TiO_2 and 25 %PE was made using heat process and cut into a granular shape afterwards. Then, the masterbatch was added to the PE obtaining a PE mixture with 2, 4, 6, or 10 % TiO_2. This process was analogical to adding color pigments to plastic material. After that, the material was poured into the injection molding machine. Before each new mixing with higher concentration of the masterbatch, the previous material was removed. These operations were carried out to ensure the control over the consistency of the material. The parameters of the injection were as follows: temperature of injection 250 °C, pressure of injection 500 bars, pressing of injection mold 350 bars, operative time of injection 15 s, and temperature of injection mold 30 °C.

Physical property tests

The samples (15 disks in each group) were tested in an automatic motorized Digi-Test II Shore D durometer (Zwick/Roell, Germany), equipped with a hardened steel rod (ø = 1.1–1.4 mm, 30° conical point, and 0.1 mm radius tip), providing a load of 44.6 N during 5 s. The results from 15 measurements for each material were averaged.

The tensile and compressive tests were performed on universal testing machine Zwick/Roell Z020 under axial loading. The tensile experiments were conducted at a constant

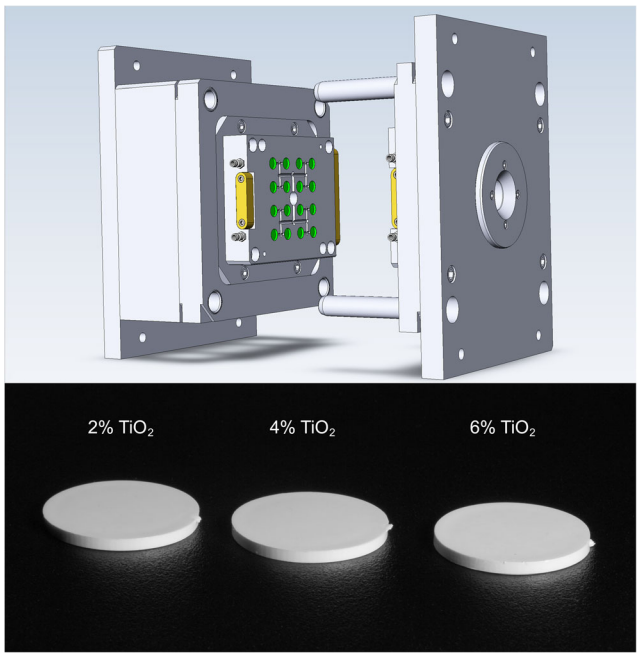

Fig. 2 The design of injection mold used for production of test disks of polyethylene compound enriched by titanium dioxide and manufactured test disks (*below*)

crosshead speeds: 50 mm/min for the tensile strength determination; 1 mm/min for the elasticity modulus determination. The compressive experiments were conducted at constant crosshead speeds: 10 mm/min for the compressive strength determination and 1 mm/min for the compressive modulus determination. Tensile strength, elasticity modulus, compressive strength, and compressive modulus for each specimen were obtained from the automatic computerized chart recorder and analyzed using TestXpert® II software.

Cell culture

Human osteoblast cell line Saos-2 was obtained from American Type Culture Collection (ATCC) and maintained in McCoy's 5A Medium (ATCC) supplemented with fetal bovine serum (Biological Industries), 100 U/ml penicillin, and 50 μg/ml streptomycin (Biological Industries). The cells were cultured under 100 % humidity and 5 % CO_2 at 37 °C in standard polystyrene flasks (TPP, 75 cm^2). The culture medium was changed every 48 h and the cells were transferred to new flasks at confluence of 80 %. Cells were tested between passages 5 and 10. Additionally, cells were tested on mycoplasma contagion using mycoplasma test EZ-PCR Kit (Biological Industries) according to the manufacturer's protocol.

Preparation of liquid extracts from materials

Sample materials (15 disks in each group) were placed in 6 well-culture plates and McCoy's 5A Medium (ATCC); penicillin/streptomycin (Sigma Aldrich) was added. The extraction process was conducted in the temperature 37 °C. After 24 h of extraction, medium containing substances released from test disks was added to the cell culture. As the negative control non-treated cells were used, positive control constituted cells treated with 50 % ethanol. The procedure was done in accordance with ISO 10993-5: 2009.

Cytotoxicity—LDH assay

Two variants of experiments were run. The first one included cells seeded directly onto the sample surface, whereas the second one employed earlier prepared extracts of substances released from the samples. For the first assay, the cells (Saos-2) were seeded on surfaces of examined materials, placed in 12 wells of culture plates (TPP), at a number of 1×10^5 cells/well in 2-ml medium. For the second assay, the cells were first cultured under standard conditions for 24 h, and then the supernatant was replaced with the same volume of earlier prepared extracts. In both assays, incubation was continued for 24 h, and then the supernatant was removed and centrifuged at 600×*g* for 5 min. The supernatant was then used to determine the activity of LDH according to the manufacturer's protocol (Sigma Aldrich). The absorbance was measured at 490 nm with the use of multitasking microplate reader Victor X.

Radiological investigation

Test disks (15 disks in each group) were inserted into meat-fat mixture and scanned in Multi-slice VCT, GE Lightspeed 64-slice scanner (equipped with AW Volume Share 5 adw 4.6 workstation), which simultaneously acquires 64 slices of 0.625 mm over a max 40-mm thick region, according to the following protocol: 0.625-mm layers, gantry tilt 0°, matrix 512 × 512—the typical for high-resolution in vivo scanning of craniofacial/orbital area. Five regions of interest (ROIs) were defined in the investigated object (Fig. 3): (1) transversal cut by polyethylene disk enriched by 2 % titanium dioxide (PE + 2%TiO2), (2) transversal cut by polyethylene disk enriched by 4 % titanium dioxide (PE + 4%TiO2), (3) transversal cut by polyethylene disk enriched by 4 % titanium dioxide (PE + 4%TiO2), (4) fat, and (5) muscle. Measurement of radio-opacity was performed 20 times on the surface area of each ROI and noted in Hounsfield's units (HU). The next focus of evaluation was to assess image artifacts caused by the alloplastic material within the surrounding structures and the evaluation of potential interference with small gas bubbles visible along the disks.

Statistical analysis

ANOVA (Tuckey post hoc *t* test) was applied to evaluate cytotoxicity. F-test multiple regression was performed for mechanical properties. The influence of titanium dioxide to

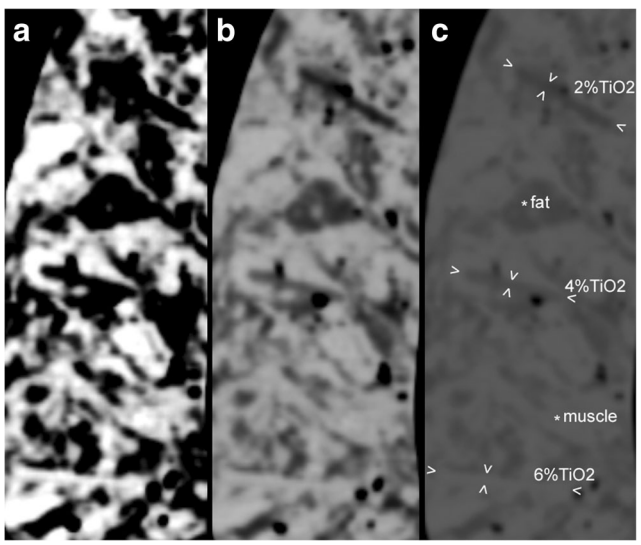

Fig. 3 Computed tomography of polyethylene disks in fat-muscle mixture. **a** Window level 40 HU and window width 80 (typical for brain evaluation), **b** window level 30 HU and window width 300 (the best visualization of the test disks), **c** window level 300 HU and window width 1500 (used for orbit evaluation). *Arrows* indicate the test disks

polyethylene mechanical properties was investigated by ANOVA. In all the investigated regions, mean densities presented in Hounsfield's units were compared by *t* test to one another. Data were defined as independent samples and the difference in density considered as significant if $p < 0.05$. Statgraphics Centurion XVI was applied for the analysis.

Results

Analysis of the mechanical properties of the studied materials revealed that the increase in TiO_2 concentration caused a slight decrease in tensile strength and modulus, together with a significant decrease in the compressive strength and compressive modulus of the composites.

There was a statistically significant ($p < 0.0001$) relationship among the investigated polymer properties (radiopacity, hardness, tensile modulus, tensile strength, compressive strength, and compressive modulus). Measured mean hardness was 56.7 ± 1.6 Shore D in PE + 2%TiO2, 52.0 ± 0.9 Shore D in PE + 4%TiO2, and 51.3 ± 1.3 Shore D in PE + 6%TiO2. Application of more than 2 % titanium dioxide reduced polymer hardness significantly ($p < 0.05$). The amount of the addition did not change polyethylene hardness. The gradual addition of TiO_2 evoked directly proportional decrease of tensile strength ($p < 0.05$ after each increase of TiO_2 contents in polyethylene): 22.5 ± 1.3 MPa in PE + 2%TiO2, 18.0 ± 0.7 MPa in PE + 4%TiO2, and 17.4 ± 0.2 MPa in PE + 6%TiO2. Tensile modulus maintained its value for addition of 2 and 4 % TiO_2 at the same level, and only the highest enrichment decreased it (but not significantly: $p = 0.06$): 354 ± 52 MPa in PE + 2%TiO2, 347 ± 66 MPa in PE + 4%TiO2, and 316 ± 9 MPa in PE + 6%TiO2. Compressive strength gradually decreased directly proportional to increase of TiO_2 addition ($p < 0.05$ after each increase of TiO_2 contents in polyethylene): 2995 ± 327 MPa in PE + 2%TiO2, 1396 ± 477 MPa in PE + 4%TiO2, and 1100 ± 144 MPa in PE + 6%TiO2. The same was observed in compressive modulus values ($p < 0.05$), but higher addition than 4 % did not make statistically significant decrease of the modulus: 21.8 ± 1.1 MPa in PE + 2%TiO2, 14.2 ± 0.9 MPa in PE + 4%TiO2, and 13.6 ± 0.6 MPa in PE + 6%TiO2.

The cytotoxicity test revealed no toxic effect of investigated material to human osteoblasts (Fig. 4). Direct assay with cells cultured on the disk surface indicated the lack of cytotoxic effect and no statistically significant differences between the test samples. The percentage of alive cells, calculated versus negative control was 39.0 ± 4.9 in the positive control, 104.7 ± 3.6 in PE sample, 106.2 ± 3.9 in PE + 2%TiO_2, 96.3 ± 3.7 in PE + 4%TiO_2, and 94.3 ± 4.9 in PE + 6%TiO_2, respectively. The assay involving the extracts gave a little increase in the number of living cells. It was 34.5 ± 3.0 in the positive control, 132.4 ± 3.6 in PE, 138.8 ± 1.1 in PE + 2%TiO_2, 138.4 ± 0.5 in PE + 4%TiO_2, and 116.5 ± 3.8 in PE + 6%TiO_2, respectively.

Subjective radiological evaluation in typical CT window level for orbital observation (B: window level 30 HU and window width 300) allows to recognize the location and shape and allows to measure diameters of the disks. This was easy for disks with 2 % TiO2 and 4 % TiO2concentration, as they turned out to be quite distinctively hypodense in comparison to fatty tissue. The disk with 6 % TiO2concentration was almost isodense on the fatty background and recognizable only thanks to its regular shape within the mixed irregular structure of the meat-fat. In the window level 300 HU and window width 1500, the so-called bony window (typically used for orbital bony walls evaluation), our disks with 2 and 4 % TiO2 remained still visible, but according to the wide

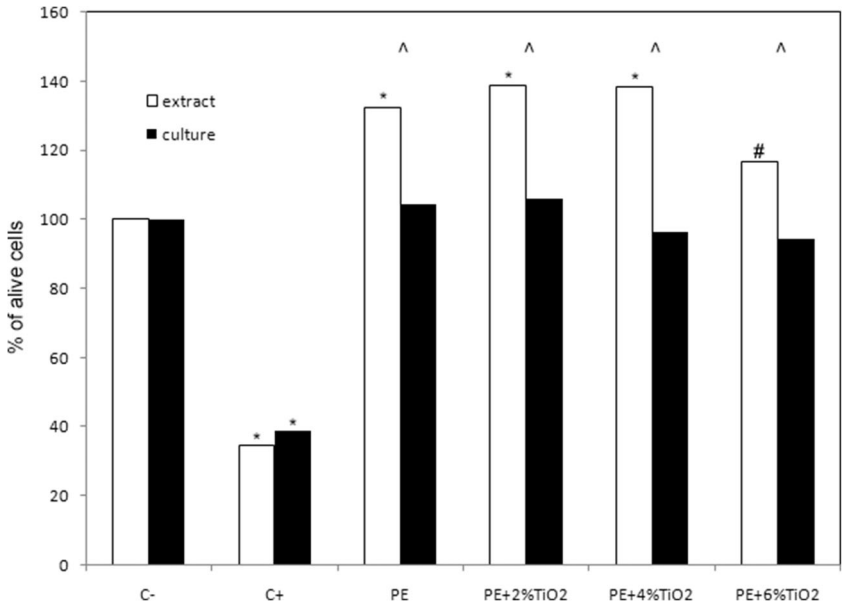

Fig. 4 Cytotoxicity of polyethylene compound enriched by titanium dioxide. Abbreviations: *PE* high and low molecular weight polyethylene compound, *significance versus negative control, #significance versus PE, ^significance of extract versus cell culture on the surface, $p < 0.05$

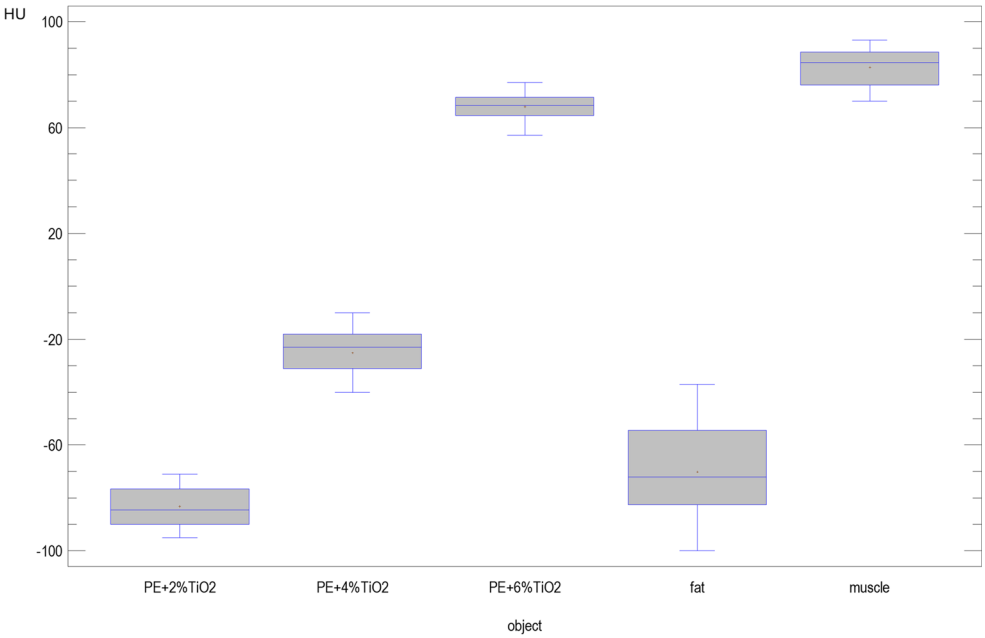

Fig. 5 Radio-opacity of investigated objects. The density in Hounsfield's units (HU). *PE* polyethylene compound. *TiO2* titanium oxide addition

width of the window (1500 HU), the gray scale difference between them and the fat was poor. The disk with 6 % TiO2 concentration again was almost isodense, but this time, the area looked too homogenous to depict its margins. The third window level (A 40 HU and window width 80) is typical for brain evaluation and because of the narrow width (80 HU) did not present the inserted disks satisfactorily.

The presence of gas around test disks (like around implant in an orbit after injury and reconstruction) weakly influenced the perimeter of the polymer image. In any case, the presence of the implant was visible. All measured mean densities (Fig. 5) differed with one another ($p < 0.01$). PE + 2%TiO2 was the least radio-opaque material (−83.2 ± 7.7HU), investigated fat was a little more dense (−70.1 ± 19.2HU), next was PE + 4%TiO2 (−25.2 ± 8.2), and the highest values were for PE + 6%TiO2 (67.9 ± 5.2) and muscle (82.65 ± 7.1HU).

Simple regression shown in the linear graph revealed that the squared-X model (radio-opacity = −101.51 + 4.72*%TiO_2^2) is proper to describe the relationship between radio-opacity and TiO_2 contents in the implant material

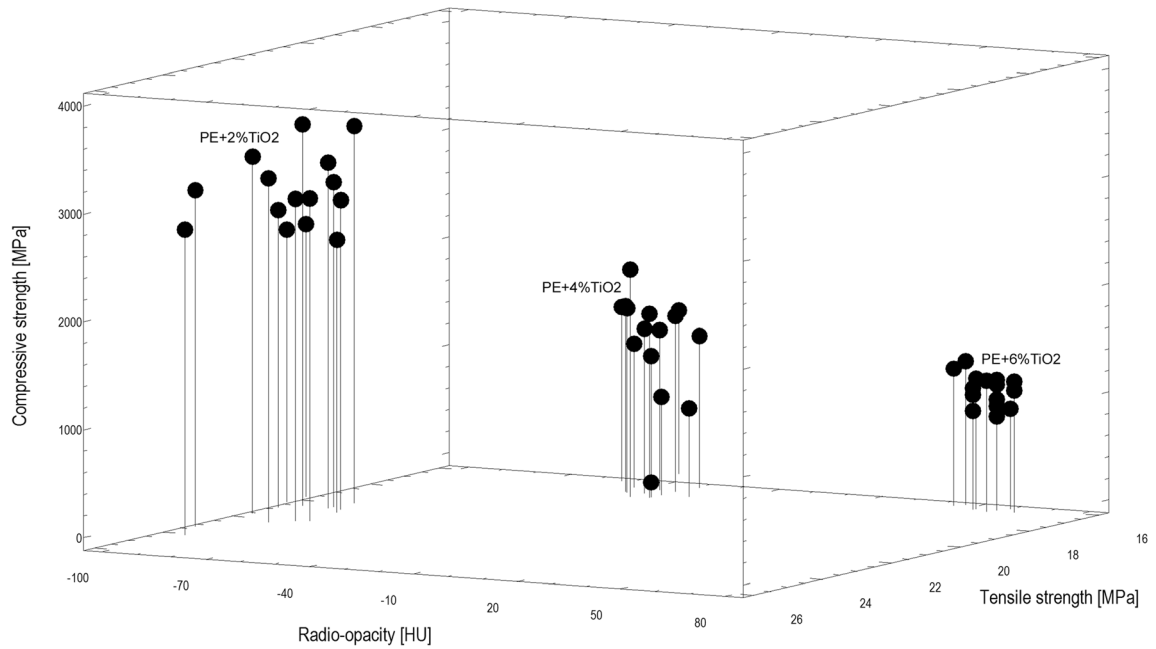

Fig. 6 Relation of implant radio-opacity (in Hounsfield's units) to contents of titanium dioxide in polyethylene compound and main mechanical properties

($R^2 = 99.99$, correlation coefficient = 0.99, $p < 0.01$), relatively strong relation between radio-opacity and the amount of titanium dioxide addition to the polyethylene (Fig. 6). Extrapolation for 8%TiO_2 is related with 200 HU, and for 10%TiO_2, 370 HU, respectively.

Discussion

Intraoperative three-dimensional radiological imaging allows to make the final control and to validate the outcome of the surgery. It helps to avoid malpositioning of implants assuring the quality of complex operations and reducing the number of necessary secondary interventions [10]. But, the condition is to insert the radio-opaque implant.

One of the most popular and easy-to-use methods of orbital reconstruction is application of titanium mesh [11, 12]. Advantages of this reconstructive technique are radio-opaque, universal applicability (craniofacial, orbital, sinus defects, comminuted fractures); easily performed three-dimensional reconstruction of complex anatomic structures; possible combination with bone or cartilage grafts; and very low susceptibility to infection [12]. But, it is easy to deform the mesh during surgery [13], and the radiological deformation [13, 14] of the tissue image which surround the implant is observed in CT (blurring of horizontal and vertical borders of implant for each beam projection arrays) and MR (radiofrequency-shielding effect). More and more frequently, it competes with polyethylene [2, 15].

Moreover, high-density metallic implants can introduce considerable uncertainties in proton therapy treatment planning in oncology. These uncertainties eventually translate into proton range errors, which may cause significant underdosing to the target volume or overdosing to normal tissue beyond the target [16]. Polyethylene is free of that adverse effect and there is a polymer material enriched by antioxidants, dedicated for implantation in patients who will be irradiated [2].

Polyetheretherketone (PEEK) is the proper alloplastic material for craniomaxillofacial reconstructions because of resistance for ionizing radiation, biocompatibility, biomechanical similarity to native bone, and being non-ferromagnetic for postoperative monitoring of the surrounding tissue [17]. But, PEEK is invisible in CT. On the other hand [18], opaque PEEK is only theoretically available (Invibio Ltd.), but a scientific publication concerning the material is not available.

It is possible but difficult to find polyethylene implants (even ultrahigh molecular weight one), in the orbit after reconstruction [19] in MR and in CT as well. The attempts to make visible individual implants in CT were made. The method of ultrasound welding to connect the titanium cubes to the ultrahigh molecular weight polyethylene polymer surface was developed recently [9]. Unfortunately, it is a labor-intensive method.

In this study, a little amount (6 %) of TiO_2 addition to implant mass do not produce the problem of X-ray energy-dependent absorption [20]. Thanks to separate densities and anatomical structure of the orbit content, implant manufactured with polyethylene enriched by 6 % of titanium dioxide can be recognized and located in the orbit, as by visual inspection as well as by HU measurement. The complication of malpositioned implant particularly affecting the extraocular muscles could be easily diagnosed because of the anatomical layer of fat that normally separates the extraocular muscle from the orbital wall. And, the wall should be covered by the implant, and the implant should not be in contact with the muscle. Moreover, cranial vault implant can also be manufactured with that polyethylene compound due to the fact that the brain observation can be performed (no high opaque plate in the cranium).

Although the obtained results confirmed deterioration of mechanical properties of the composites containing titanium dioxide, the resulting values do not exclude the use of these materials for manufacturing of maxillofacial implants, since the tensile strength of the bone tissue usually reaches the values of 20–30 MPa. [21]. Additionally, contrary to the bone tissue, the studied materials exhibited a higher ductility and better resistance to fracture at impact loads. That is, the protective feature of the implant for surrounding tissues, i.e., impacted implant, will bend in a haphazard way but will not penetrate into the human body. Titanium plates and solid implants (made by direct metal laser sintering) may jeopardize a patient in such circumstances.

Conclusion

In view of radio-opacity, polyethylene compound enriched by titanium dioxide seems to be a proper material to consider craniomaxillofacial implant manufacturing.

Compliance with ethical standards Compliance with ethical standards is fulfilled by in vitro polymer investigations.

Conflict of interest The authors declare that they have no conflicts of interest.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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