In Vivo Inflammatory Soft and Hard Tissue Response to Newly Developed Osteosynthesis Material for Pediatric Maxillofacial Traumatology in a Critical Size Bone Defect Model

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Abstract: Childhood trauma defects in the head and neck area are challenging in many aspects for patients and surgeons. One major issue is the still incomplete growth. Bone defect fixation measures have to consider biomechanical forces due to the bone growth from both sides, the bone growth possibly influencing and working against the fixation itself and vice versa. A solution will be the development of a stable but, at the same time, quickly degradable osteosynthesis system (OSS) specifically for the pediatric sector. Besides the physical demands, biocompatibility and low risk for unphysiological tissue response are exceptionally important. A newly developed PDLLA-derivate/chitosan hybrid material (PDLLA:CC:Mg+Chitosan) with promising features confirmed in vitro experimental set-ups has been tested in a critical size bone defect model in Wistar rats to confirm slow degradation and absence of unphysiological integration of the material, and of bone growth induced by the material itself. mCT and histologic analysis of implanted rat skulls after 1, 3, and 5 months confirmed slow degradation of the PDLLA:CC:Mg+Chitosan material without any unintended bone growth induction or morphologic changes due to the material. The results of this *in vivo* study confirmed the suitability of the material to serve as OSS in clinical practice.

Key Words: *In vivo* critical size defect model, pediatric traumatology, resorbable osteosynthesis

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In the field of pediatric oral and maxillofacial traumatology, osteosynthesis with titanium plates is the gold standard for treating fractures in the skull and facial area.[1,2] However, in children, metallic osteosynthesis systems (OSS) have the significant disadvantage of disrupting rapid bone growth,[3] necessitating their removal through additional surgical procedures.[4] This results in further suffering and health risks for the children.

Compared with metallic OSS, absorbable OSS have the significant advantage of eliminating the need for a second surgery to remove the material. However, the current absorbable OSS have material-related weaknesses that have hindered their widespread adoption in pediatric care.[5] One major weakness is their low primary stability. To achieve sufficient primary stability, OSS made from today's absorbable materials must be relatively large and thick. This poses a challenge for ensuring the rapid absorption required, especially in growing children. In addition, the high material volume increases the risk of inflammatory reactions in the soft tissue,[6] which may necessitate premature removal of the OSS. It is without any doubt necessary to address this issue to improve the small patient's treatment. As the material is the key element it is clear that a new type of material with an optimized composition needs to be developed.

Therefore, a recently reported project[7] aimed to develop a significantly improved absorbable OSS specifically for pediatric OMFS traumatology for juvenile patients of 1 to 11 years in age. For this a new composite material and novel plate structures were designed with the intention to eliminate the need for

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a second surgery for material removal. Materials composition was based on PDLLA (poly(D,L-lactide)), which was combined with calcium carbonate (CC), magnesium (Mg), and chitosan fibers (CH). PDLLA-based materials are promising materials for resorbable OSS; however, some limitations due to materials characteristics need to be taken into consideration.[7] The side effect of good resorbability is the accumulation of lactic acid, leading to a pH decrease in the proximity of the material. This can have a direct influence on the tissues' inflammatory response. The integration of calcium carbonate can act as a buffer to keep the pH at a value 7.4.

Magnesium is the second factor added to the material composition because of its stimulating osteogenic effect, leading to enhanced bone formation and bone healing.[8] Further it is biodegradable as well, so it does not interfere with the resorbability of the composite material.

Chitosan, gained by processing of the natural component chitin, the latter being part of for example, shrimp or crab shells, has been shown to have a promoting effect on wound healing.[9] With its well-suited characteristics of being biocompatible, non-antigenic, non-toxic, antimicrobial, and further biodegradable,[9] it is very interesting material to combine with PDLLA in a functional OSS.

Any material used for patients' treatment, especially if implanted, has to show biocompatibility and absence of enhanced risks due to genotoxicity or endoxicity characteristics.[10,11] It is also important that a modified material doesn't bear the risk for unwanted and thereby unintended bone growth due to the material modifications. It needs to stay inert besides being susceptible to a slow degradation process, the latter as well not inducing any unphysiological tissue reaction. In short, such material needs to meet all demands for medical devices, especially to confirm the absence of unphysiological events like inflammation, undirected bone formation induced by the material, or any other adverse events.[12] The former could already be confirmed in vitro using a complex human co-culture model system.[7]

However, with implanted materials in vivo experiments with respective microenvironment at a defect and/or implantation site cannot be fully replaced, yet. Especially in terms of defect regeneration observations in the head area where several complex tissue types are in close proximity to the bony defect, all with the capacity to be at risk for unwanted side effects. Investigation of any potentially unphysiological or adverse reactions in the field of bone regeneration, should, therefore, be analyzed in a bone defect model of the skull. Using a so-called critical size defect model, here in the rat calotte, which per definition won't fully regenerate within a certain time frame,[13] any unintended bone growth induction due to the application of a novel composite material can be well detected.

Therefore, aim of this study was to evaluate the degradation process and the risk for adverse events in terms of unphysiological degradation and unwanted side effects of the newly developed material in an in vivo critical size bone defect model.

MATERIAL AND METHODS

Study Design

Twenty-four male rats were divided into 3 groups with 8 animals per group. In each animal 2 critical size defects were set according to the surgery protocol with 1 sham defect without material, and 1 defect with material. Groups were sacrificed and analyzed at 1-month, 3-month, or 5-month post-surgery.

Ethics

The *in vivo* experiments were conducted according to EU Animal Protection Law 86/606 under the approval of the responsible authorities No. 390/23.11.2023.

Animals

Animal experiments were made in 12-weeks old wildtype Wistar Rat with a mean weight of ~350 g per rat. The rats were housed in cage accommodating 4 animals each, with access to food and water "ad libitum". The microclimate was maintained at 21 to 24 degrees, with a humidity level of 40% to 45%. Throughout the study, the rats received optimal care after laboratory animal welfare guidelines.

Material

The biomaterial used for evaluations was a newly developed composite material composed of PDLLA (poly(D, L-lactide)) with calcium carbonate, magnesium (PDLLA: CC + Mg), and chitosan (CH). The material was produced using biocomposite material PDLLA: CC from SchäferKalk (Hahnstätten, Germany) and magnesium alloy WE43. The latter was used as powder formulation (MeoTech) and combined in a speed mixer (Hauschild) at room temperature with mixing parameters (800–1200 rpm) in a final weight% formulation of 90% PDLLA: CC and 10% WE43. Chitosan raw material (DD = 90%) with a molecular weight of 110 kDa was manufactured and processed by the project-affiliated partner BioLog Heppe® GmbH.[14] Therefore, chitosan was dissolved in acetic acid before starting the spinning process using a solvent wet-spinning machine (FOURNÉ). For the combination of chitosan fibers with the polymer material (PDLLA: CC + Mg), multifilaments were manufactured with the following parameters (Yarn count: 224 tex, diameter: 32 μm, and tenacity: 14.1 cN/tex). For the osteosynthesis material combination with chitosan, the corresponding basis material that forms the matrix, PDLLA: CC, and the magnesium alloy was first weighed and mixed in the speed mixer. The chitosan endless fiber was stretched in the press frame before the mixed composite material was placed on the chitosan continuous fibers. At a temperature of 80 to 120°C and pressure of 100 to 200 bar for 10 to 30 min, the composite material was pressed and a wafer was produced. The wafer was further machined in a milling device (Chiron) and was milled into the coin-shape structure for *in vivo* implantation.

Surgical Protocol

Critical size defect model surgery was made under total anesthesia of the animal. Supportive care was applied was applied according to institutional guidelines. Anesthesia was performed by i.m. application of 20 UI ketamine and 30 UI xylazine into the thigh muscle. After anesthesia is confirmed by toe-pinch reflex test the temporo-parieto-occipital region was trimmed and shaved, followed by disinfection of the operating field with iodine solution. An anterior-posterior skin incision from the inter-orbital aspect to the cervical region was made, followed by periosteum exposure. Following were incision of the periosteum incision and exposure of the calvarial bone. The drilling of the critical size bone defects was made using a 5 mm diamond drill under continuous saline solution cooling. Defects were carefully prepared inter-orbital and frontoparietal without damaging the dura. One of the defects was filled with discs of the resorbable PDLLA:CC:Mg+Chitosan material, and the other remained unfilled as sham control (Fig. 1). After the material was placed into the defect site wound closure by suture was done using resorbable suture for deep layers and nylon for the skin. Finally, iodine solution was applied on the suture, and

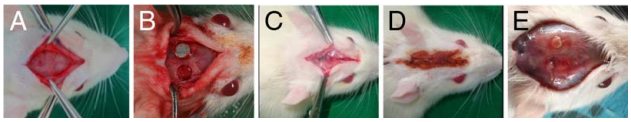

FIGURE 1. Critical size defect model. Implantation of newly developed osteosynthesis material PDLLA:CC:Mg CH into rat calotte. (A) Representation of the rats calotte and planned area of implantation. (B) Critical size defects with implanted material (left side of calotte) and sham defect (control, contralateral defect site). (C) Approximation and suture of wound margins. (D) Defect post-surgery. (E) Defect site at 1-month post-surgery.

animals were kept under surveillance until fully recovery from anesthesia. Animals were then kept under veterinary care during follow-up period in the institutional animal facility.

mCT analysis

After the defined follow-up period of 1, 3, or 5 months the subjects were euthanized with an overdose of anesthetic (150–200 mg/kg ketamine and 10–15 mg/kg xylazine). Animal skulls were prepared for mCT for evaluation of the bone mineralization at the implant site and the degradation pattern of the biomaterial. mCT analysis was done using a SKYSCAN microCT, model 1172 (Bruker). The bone tissue was harvested and fixed in 10% formaldehyde solution for micro-CT analysis. After a fixation period of 5 days, the sample was prepared for the scanning process. The scans were conducted at an intensity of 80 kV, using a rotation step (deg) of 0.400, no filter applied and the resulting images exhibited a resolution of 2000 pixels, a pixel size (μm) of 13.56116. The scanned images were subjected to the reconstruction process, using the NRecon (Bruker) software (version 1.6.9.9). After reconstruction, all results were extracted with the help of CTAn (Bruker) software (version1.14.4.1).

Radiologic evaluation of material degradation *in vivo* was done by evaluation of bone mineral density (BMD). For this a disc-like volume corresponding to the original material geometric characteristics, 3 or 5 mm in diameter and 1 mm in height, has been defined and the density of residual material within this predefined volume was measured in mCT recordings. mCT scan and evaluation of plain material pre-implantation were done accordingly.

Histologic Analysis

Post-mCT analysis the calvarian samples were harvested and processed for histologic staining and analysis. For histologic analysis, the retrieved specimens will be fixed with 4% (v/v) paraformaldehyde for at least 30 minutes at room temperature and placed in PBS for 15 minutes before decalcification. The fixed biopsies underwent a processing procedure consisting of decalcification in 10% tris-buffered ethylenediamine tetraacetic acid (EDTA) (Carl Roth) at 37 °C for 14 days in an ultrasonic decalcifier (Medite), followed by dehydration in alcohol in a series of increasing concentrations and, finally, in xylol. Subsequently, the processed biopsies were embedded in paraffin. Sections of 2 to 4 μm were cut from the biopsies' central region with a microtome (Leica). The slices were stained with hematoxylin and eosin, and trichrome Masson Goldner, according to standard protocols.

The histologic evaluation was performed after a standardized study protocol using a research scanning microscope in combination with NIS-Elements software (Nikon). Images of the total implantation beds ("total scans"), that is, of the biomaterial and their corresponding peri-implant tissue and surrounding structures, were digitized using a DS-Fi1/Digital camera connected to an Eclipse 80i histologic microscope (Nikon) that was equipped with an automatic scanning table (Prior).

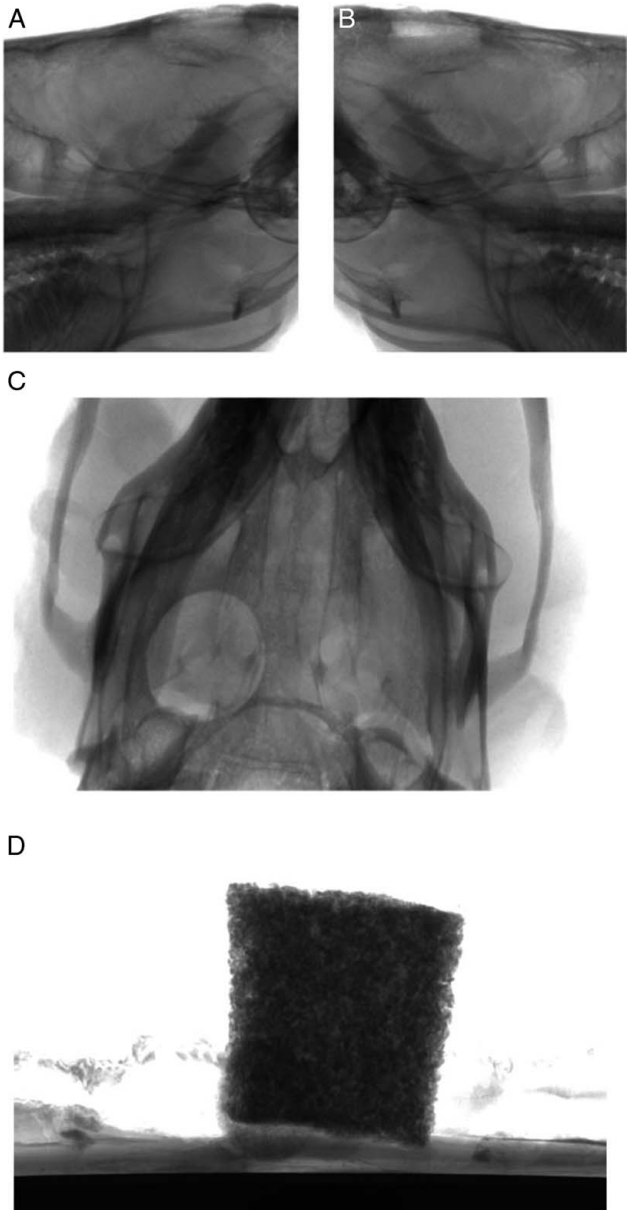

FIGURE 2. mCT imaging of material pre-implantation and implanted critical size defect. (A–C) microCT-analysis of critical size bone defect w/ (A, C) and w/o (B, C) implanted PDLLA:CC:Mg CH material in vivo (representative image taken at 3 months post surgery). (D) microCT image of PDLLA:CC:Mg CH material before implantation.

RESULTS

For the evaluation of the developed material in the critical size model PDLLA:CC:Mg CH scaffolds of different sizes were provided as discs with a diameter of 3 or 5 mm and implanted as described before and shown in Figure 1. After 1, 3, and 5 months, tissue samples of the respective region were harvested and examined radiologically and histologically. As the aim of this in vivo model was to investigate potentially adverse reactions in the field of bone regeneration, 2 main

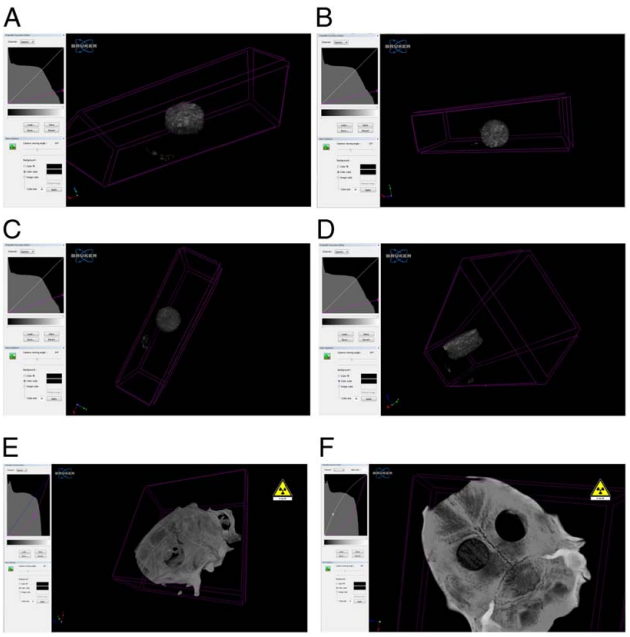

FIGURE 3. mCT imaging and 3D reconstruction of material pre-implantation and 3D mCT imaging of critical critical size defect in rat calotte. (A–D) microCT-analysis-based reconstruction of the PDLLA:CC:Mg CH material in different orientations. (E, F) microCT image of critical size defect in rat calotte with implanted PDLLA:CC:Mg CH material (left) and control defect (right).

investigational approaches were made. First of all, total mCT scans of the skull and the implanted area were made to analyze the 3D structure of the (former) defect area (Figs. 2,3), most importantly any signs of either necrotic or dysplasia event. In addition, degradation of the material by radiologic evaluation of the material density was made (Fig. 4). To get a deeper insight into the structure of the residual material, and further of the tissue type and morphology histologic evaluations (hematoxylin and eosin, trichrome Masson Goldner; Fig. 5) of the same areas were made.

Post-Surgical Progression

All individuals of the 3 groups (1-month, 3-month, and 5-month follow-up) showed good recovery from surgery without any unusual changes in behavior. No wound infection or other clinical findings were observed post-surgery in any of the rats.

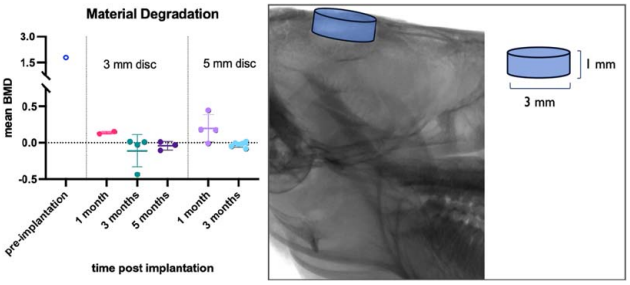

FIGURE 4. Radiologic evaluation of material degradation in vivo. Degradation evaluated by changes of bone-like material density (BMD) compared with pre-implantation material has been measured in the region of residual material within a predefined volume (right) in mCT recordings of implanted rat skulls. Continuous degradation over time can be observed for 3 and 5 mm implanted material (left). Data are shown as mean ± SD, n (3 mm discs): 1 month n = 2, 3 months n = 4, 5 months n = 3; n (5 mm discs): 1 months n = 4, 3 months n = 6.

Regeneration in Sham Defects

The regeneration of the control defects without material influence showed the expected regeneration pattern according to the definition for a critical size defect model. An early regeneration of the tissue in the defect area, especially in the area of the periphery adjacent to the residual bone tissue, was visible, but by no means a complete regeneration within the follow-up up to 5 months was observed. Pathologically inflammatory reactions, like pathologic lymphocyte infiltration, enhanced numbers of multinucleated foreign body cells, or further morphologic abnormalities, were absent in all control samples.

Regeneration in Defects with PDLLA:CC: Mg+Chitosan

The radiologic (mCT, Figs. 2–4) and histologic evaluation (Fig. 5) of the defect areas with PDLLA:CC:Mg+Chitosan after 1, 3, and 5 months showed a slow degradation of the material without unphysiological induction of bone tissue in the location of the material itself. Further, no inhibition of the beginning endogenous bone regeneration in the defect periphery was observed. The histologic evaluation of trichrome Masson Goldner bone tissue staining confirmed the absence of unphysiological bone formation induced by the material in the region where the residual material was found (Fig. 5A-D). Already after 1 month between the fibers of the material in the conjunctival capsule, fine septa that tend to surround each individual fiber of the material are visible (Fig. 5E).

A connective tissue encapsulation without pathologic induction of a foreign body reaction, like pathologic lymphocyte infiltration, was observed in the histologic preparations

Material Degradation In Vivo

Material degradation was evaluated in mCT recordings (Figs. 2 and 3) through changes of material density (BMD, bone-like material density) analyzed in a defined cylindrical volume centrally of the defect. A clear degradation of the material compared with pre-implantation was shown. Further, both sizes of material implanted, 3 and 5 mm, a continuous degradation over time can be observed (Fig. 4). Whereas the 5 mm discs showed, due to the higher material content, a higher density after 1 month, implanted material of both sizes (3 and 5 mm) reached a mean BMD value of approximately zero after 3 months. However, material degradation was not completed yet, as confirmed by histologic evaluations (Fig. 5A-D). Further, trichrome Masson Goldner histologic staining showed active material degradation by multinucleated giant cells (Fig. 5F).

DISCUSSION

Bone regeneration of trauma defects in children, especially in the head and neck area, is very challenging. The surgeon always has to keep in mind, that the facial bone in need of surgical fixation procedures with osteosynthesis systems (OSS) is still growing.[15] Using conventional non-resorbable systems, for example, titanium plates, will lead first of all to a need for a second surgery for OSS removal.[16] Besides the burden for the small patient, physiologically and psychologically, it has to be very well timed. The OSS needs to be kept as long as stabilization of the defect area is still necessary, on the other hand it has to be removed before it impairs the natural bone growth and extension in any way. To choose the right system further biomechanical features of the defect area should be taken into consideration as well.[17] Using a resorbable system is for sure not a novel idea.[18] However, the here developed material is char-

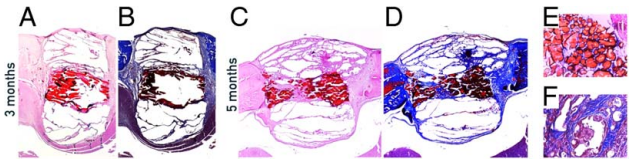

FIGURE 5. Histologic evaluation of material degradation, tissue reaction, and inflammatory response in vivo. Changes of material were evaluated in histologic staining's (A, C, E: H/E staining; B, D, F: trichrome Masson Goldner) of paraffinized tissue sections. (A, B) Three-month post-implantation degradation of material is clearly visible with soft tissue encapsulation around the material. (C, D) the same is true after 5 months, but with further progressed degradation, but not yet completed degradation. (E) Encapsulation of residual material by fine septa is already visible 1 month after implantation. (F) Ongoing material degradation by multinucleated giant body cells, 3 months post implantation.

acterized that it enables designing a resorbable OSS fixation plate with predefined breakage sites. So, the material degradation does not have to fit to the individual regeneration time of the bone, but can undergo a slowly degradation when the defect healing itself is complete and stabilization is no longer necessary. The concept allows for slow independent degradation and the OSS will break at predefined positions when the growth force becomes too strong. The bone can then extend as naturally given, whereas the material will further degrade over time. Ideally a second surgery won't be necessary anymore.

Nevertheless, it is very important that the material for this meets all demands for medical devices,[11] especially to confirm the absence of unphysiological events like inflammation, undirected bone formation induced by the material bearing a risk for displacement of the OSS,[19] or any other adverse events due to the material modifications. It needs to stay inert beside being slowly degraded, the latter as well not inducing any unphysiological tissue reaction. Even though that biocompatibility and osteogenic potential was confirmed in vitro in a co-culture model consisting of primary osteoblast and dermal microvascular endothelial cells,[7] the in vivo microenvironment in the implant area can have a tremendous effect on the cellular and immunological response to a material. Therefore, a final conclusion regarding an implanted materials performance in vivo cannot be solely made by in vitro evaluations. To investigate any potentially unphysiological or adverse reactions in the field of bone regeneration, the newly developed PDLLA:CC:Mg+Chitosan material was examined in a so-called critical size defect model in the rat calotte.[13]

The model is a standard model suitable and used for biomaterial investigations, especially with regard to their interactions with neuroectodermal bone tissue and related regeneration capabilities.[13] For this, 2 defects were set in 4 animals per time point. One defect presented the control without material and the second defect was filled with a disc-shaped sample of the material. Besides the important issue to minimize the need for animals according to the 3R principle, the approach provided information about individual regeneration without material influence. The radiologic (mCT) and histologic analyses of the defect areas after 1, 3, and 5 months showed a slow degradation of the material used.

The model confirmed the in vivo compatibility of the material even in a massive bone defect area, without unwanted induction of excessive inflammatory tissue response or induction of bone tissue in the material area itself. The latter is of crucial importance for later use to stabilize bone defects. A (partially) load-bearing osteosynthesis system should stabilize the defect until regeneration and degrade as a resorbable system, but not be integrated into newly formed bone tissue in the sense of a hybrid bone tissue. Further, it is known that due to the physiological bone growth in juvenile patients a risk for displacement of OSS can occur.[4,19] Likewise, no unphysiological foreign body reaction should be induced, and regeneration should thus be negatively influenced.[12,20] This could be confirmed in the histologic analysis. Further there were no signs of a pathologic foreign body reaction in the histologic samples observed. Most importantly, the presence of the material did also not negatively affect the beginning of natural bone regeneration in the defect environment.

However, it is important to note, that the here used critical size defect model in the rat calotte is only sufficient to provide a first insight into the in vivo tissue response to this novel material composition. Even though that it confirms our previous observations in vitro, showing a good biocompatibility,[7] it is not suitable for performance investigations regarding defect stabilization and functionality of the before-described intended disintegration at predefined breakage sites. For further in vivo investigations, the PDLLA:CC:Mg CH material should, therefore, be further characterized in the appropriate geometry for the stabilization of bone defects, for example, in the femoral or mandibular defect model, before introducing the material to clinical testing and aiming for approval for clinical use in humans.

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