

Early weight bearing of porous HA/TCP (60/40) ceramics in vivo: A longitudinal study in a segmental bone defect model of rabbit

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Received 4 August 2006; received in revised form 12 April 2007; accepted 16 April 2007

Available online 15 June 2007

Abstract

Porous interconnected hydroxyapatite (HA) and HA/tricalcium phosphate (TCP) (60/40) ceramics are promising materials for hard tissue repair. However, the mechanical properties of these materials have not been accurately determined under weight-bearing conditions. In this study, newly developed HA and HA/TCP (60/40) ceramics were used with intramedullary fixation in segmental bone defects of rabbits. Early radiological, histological, densitometric and biomechanical changes were evaluated. The mean radiological grade of healing and bonding to bone was higher in HA/TCP (60/40) ceramics than that of pure HA ceramics but the difference was not statistically significant. The densities of both implanted ceramics improved with time, supported by the histological evaluation of bone matrix ingrowth into ceramic pores, whereas the densities at the bone–ceramic interface decreased gradually. Flexural resonant frequencies and three-point bending strength increased, revealing an increase in mechanical stability during this early critical time interval where implant and/or bone–implant interface failures occur frequently. It can be concluded that both HA and HA/TCP (60/40) ceramics have a limited application in the treatment of load-bearing segmental bone defects but did not fail at the early stages of implantation.

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Keywords: Hydroxyapatite; Calcium phosphate ceramic; Early weight bearing; Bone defect; Biomechanics

1. Introduction

Healing of segmental bone defects remains a difficult problem in orthopedic and trauma surgery. One reason for this difficulty is the limited availability of bone material to fill the defect and promote bone growth. Autograft bone transplantation to the defect site is the current standard; however, the amount of transplant is usually limited and donor site morbidity is a major concern [1,2]. Allografts

alone or combined with autografts to extend the graft volume are used in current clinical practice, though these pose a risk of transmission of bacterial and viral diseases [3,4], and legal, religious and cultural limitations exist [5].

Matrix-based tissue-engineering approaches aim to use structural implants and/or materials to replace the defective bone [6,7]. These approaches depend on the recruitment of endogenous osteoinductive factors and migration of osteogenic cells to regenerate the load-bearing segmental bone defect [8–11]. Even though quite a large number of biomaterial-based approaches have been developed for segmental bone defect repair and used with inconsistent success, none of them have proved ideal [12–15]. In early

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attempts, synthetic materials such as hydroxyapatite (HA) and tricalcium phosphate (TCP) were only conformable to fill non-weight-bearing bone cavities [16]. Improved processing techniques have allowed the production of biologically and mechanically stronger ceramics that can withstand loading conditions of weight-bearing bones [9,17,18]. The ideal bioceramic for replacement of segmental bone defects should have complete biocompatibility, adequate biodegradation rate and mechanical stability, and should be replaceable by bone cells [19,20]. HA/TCP ceramics alone [21] or in combination with osteogenic cells [22,23] and/or local regulatory factors [24,25] are currently being studied for this application. Nevertheless, the ideal load-bearing ceramic with appropriate mechanical properties has yet to be defined. It was assumed that new formulation and compositions of interconnected porous pure HA and/or HA/TCP ceramics would overcome mechanical problems in load-bearing segmental bone defects and allow early mobilization with minimal internal fixation and acceptable biocompatibility. Such ceramics can then be used as scaffolds and/or carriers of biologically active cells and mediators [26].

This study aimed to evaluate early radiological, densitometric, biomechanical and histological changes in newly developed, biocompatible and interconnected porous implants that are pure HA and/or HA/TCP (60/40) composite ceramics following implantation into load-bearing segmental bone defects created in rabbit tibia with intramedullary fixation and immediate load bearing following surgery.

2. Materials and methods

2.1. Ceramics

Two types of biodegradable porous ceramics were produced. The materials used for the production of ceramics were calcium phosphates, either in the form of pure HA or as composites of HA and TCP. The calcium phosphate precursors were synthesized by a conventional homogeneous precipitation technique involving the use of aqueous solutions of calcium nitrate and diammonium hydrogen phosphate. Merck-grade $\text{Ca}(\text{NO}_3)_2$ and $(\text{NH}_4)_2\text{HPO}_4$ were the starting materials. The ceramics were shaped by a modification of the conventional slip-casting technique, the details of which are described elsewhere [27].

The slips used in manufacturing the porous ceramics were made as slurries of HA powders or as HA/TCP powders suspended in water and stabilized with Dolapix PC33. Polymethyl methacrylate (PMMA) beads in the size range of 220–300 μm were added into the slip as agents to generate the requisite porosity. The amount of PMMA was adjusted so that the final product would have about 65% porosity of the total volume [28].

Green ceramic rods were dried thoroughly by keeping them at room temperature for 2 days, and then the polymeric beads were eliminated by heating the cast pre-forms

to 500 °C in a muffle furnace. This process was carried out carefully under a neutral gas atmosphere so that no cracks would be generated during polymer removal. The ceramics were densified by sintering them in a muffle temperature. Pure HA ceramics and HA/TCP composites were sintered at 1170 and 1100 °C, respectively. The soak period for both types of ceramic was 4 h. Phase development in the sintered ceramics was monitored and verified by qualitative and quantitative powder X-ray diffraction (XRD) analyses using a Rigaku D-MAX/B powder diffractometer with monochromatic Cu K_α radiation at 40 kV and 20 mA.

Sintered ceramics were characterized in terms of their pore morphology and strength. The pore structure was examined throughout the fracture surfaces of ceramics under a JSM 6400 scanning electron microscope (JEOL Ltd., Japan). The geometry of the implants had to be similar to that of the bone, and therefore 10 mm long tubular-shaped ceramics were prepared with an outer diameter of about 7.5 mm and a inner diameter of about 2.5 mm. Any surface defects on the ceramic implant were removed by soft grinding. Compression tests were performed on the selected standalone porous ceramics to determine their mechanical strength. HA and HA/TCP ceramic groups ($n = 6$) were compressed between compression plates at a constant deformation rate of 3 mm min^{-1} using Lloyd LS500 Material Testing Machine (Southampton, UK). The remaining ceramics were autoclaved to sterilize them and kept in sterile conditions until the experiments.

2.2. Animals and surgical protocol

Thirty-eight local 4-month-old white rabbits weighing 1942 ± 259 g were used. Four of the rabbits were reserved for histological analysis to be evaluated at 4 and 8 weeks. The remaining 34 rabbits were divided into three time groups; each time group was further separated into two according to the type of the ceramic implantation employed. Ceramic-implanted rabbits were followed for 6, 12 and 18 weeks. Food and water were supplied at 15 cm above cage basement for load bearing of hind limbs during feeding. Animals were allowed to move freely immediately after surgery without external fixation to ensure normal loading conditions. All procedures were fully compliant with Turkish Law 6343/2, Veterinary Medicine Deontology Regulation 6.7.26 and with the Helsinki Declaration of Animal Rights.

Anesthesia was induced with an intramuscular (i.m.) injection of ketamine (35 mg kg^{-1}) and xylazine (5 mg kg^{-1}). Local anesthetic (0.5 ml lidocaine) was provided routinely at the cutaneous site of surgery. In the pure HA ceramic group the ceramics were implanted into the left and in the HA/TCP (60/40) composite group the ceramics were implanted into the right tibiae for the ease of determination of groups throughout the experimental period. The opposite normal tibia of each animal established the control. A 1 cm long segment was removed from the central third of the tibia. After the ceramics were placed

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