Nonstoichiometric hydroxyapatite granules for orthopaedic applications

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A new method for the preparation of nonstoichiometric hydroxyapatite (HA) ''dense'' and porous granules, round in form and up to 8 mm in sizes designed for application in orthopaedic surgery has been developed. The ''dense'' granules' porosity was up to 32% and they only contained micropores. They differed from that kind of granules by increased values of compression strength (up to 48 MPa). The porous granules contained a system of interconnected micro- and macropores. The porosity value (up to 70%) and the porosity structure were similar to those in the mineral framework of a spongy bone. The compression strength of the porous granules (up to 25 MPa) was high enough for various kinds of application. Granules of both sorts were used in performing 42 operations on the locomotor system. Depending upon localization and supposed level of the injured area loading, ''dense'' or porous granules were used. The postoperative observations (up to four years in length) have attested to the high quality of the granules.

1. Introduction

Calcium phosphate materials based on hydroxyapatite (HA) have been successfully used in medical practice [1, 2]. They are usually produced as blocks of various form, coatings on metal implants and granules. HA granules are particularly convenient for filling bone defects. However, the main functional properties (such as the composition, form, value and structure of porosity, mechanical strength) of the granules, which are available on the market or were developed and tested by researchers, are not optimum. The market granules are often irregular fragments produced by crushing HA ceramic blocks; sometimes, the crushing is followed by a treatment (usually by rolling). The untreated fragments have sharp areas that adversely affect the osteogenesis [3]. The rolling destroys the structure of the surface layer of the fragments resulting in a significant difference in the state of the porosity in the surface layer and in the size of a fragment.

In both cases, the form of the fragments is not spherical. Hence, they cannot fill any bone defects as tightly as possible, which is one of the main requirements for an effective transformation of introduced HA into osseous tissue [4]. Spherical ceramic granules were produced by the vibration and rolling method [5]. The granules' porosity approached 12% and looked like a system of connected micro- and macropores. The granules' compression strength turned out to be sufficient for their successful application in dentistry. But the porosity of the granules was poor. Besides, this method was difficult for processing granules of the size (diameter) exceeding ≈ 2 mm. Larger and almost spherical granules were produced by methods based on dropping HA suspension into liquid nitrogen [6] or gypsum mould [7] followed by drying and sintering of ''green'' granules. The size of the obtained granules was increased up to ≈ 4 mm [6] and up to ≈ 6 mm [7]; the total porosity owing to micro- and macropores was $\approx 40\%$ and 50%, respectively. However, there was no information on mechanical properties of the granules [6, 7]. Spherical granulates were also manufactured by dispersion of a HA/foamer slurry in a mixture of liquid paraffins followed by some treatment and sintering. However, granulates of small sizes of 200–1000 μm could only be produced; the granulates were primarily suitable for dental and maxillofacial applications [8].

Recently, the process of healing an artificial defect made in a rat's femur and filled in with a domestic porous block of nonstoichiometric HA ceramic was investigated [9]. *In vivo* study at various stages of implantation revealed that the material had fine biocompatibility and bioactivity. Besides, some physics during densification of compacts of a nanodispersive HA powder were studied,

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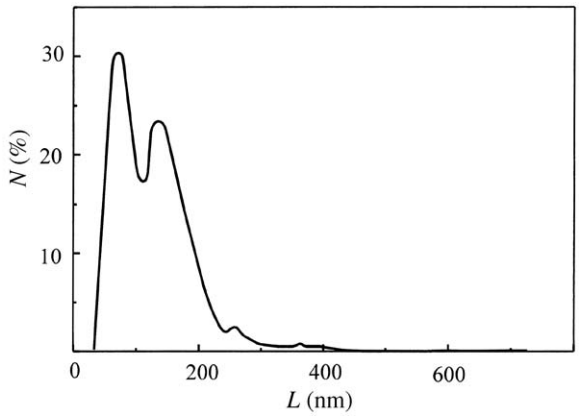


Figure 1 Particle size distribution in the nanodispersive HA powder.

and a few new approaches for strengthening HA ceramics were proposed and realised [10, 11]. The aim of this study was to develop, on the basis on the results obtained [9–11], spherical nonstoichiometric HA ceramic granules of rather large size, which would combine the physicochemical characteristics close to those in the mineral framework of a spongy bone and excellent biological properties with appropriate strength, and to test the granules in orthopaedic surgery clinically.

2. Processing of granules: Materials and methods

Commercial HA powders or those obtained by precipitation methods [12, 13] are widely used in manufacturing HA-based ceramic materials. The maximums in the size distribution curve for particles in these powders are within the interval of 1–100 μm [14, 15]. However, that kind of powder is not optimal for the production of porous ceramic granules. In this case, the formation of ''green'' granules is carried out without any pressing technique to avoid distortion in the given porosity structure [6, 7] that results in a ceramic product, lacking a required density and, consequently, having poor mechanical characteristics. It may be possible to strengthen ceramics, including HA ceramics, by using fine initial powders [11, 16]. Hence, if an ultrafine HA powder for manufacturing porous granules is used, the strength properties of the granules should improve owing to the increase in the density of their ceramic framework.

In order to prepare an ultrafine HA powder, we somewhat modified the known method [12] by adding a surface-active substance (SAS) to the reaction mixture; the SAS (hexanol) did not allow primary nanocrystals of HA to unite and form conglomerates. The particle size distribution curve for the powder finally obtained (Fig. 1) had two main peaks near 70 nm and 130 nm, and this testified that the powder was nanodispersive. IR spectrometry and X-ray diffraction analysis revealed that the powder was pure HA as no admixture ion groups and phases were fixed in it (Figs. 2(a) and 3(a)) within the sensitivity limits of the methods (approximately 5 wt % and 0.5 wt %, respectively).

Porous granules were produced using cellular polystyrene (CPS) in the form of balls as a foamer. The main particle size of the foamer was selected in such a way that

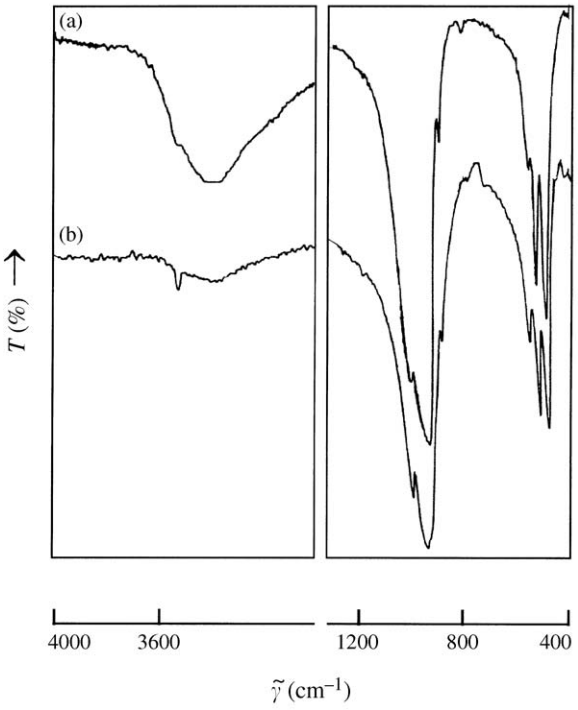


Figure 2 IR spectra of (a) the original powder and (b) granules sintered at 1150 °C for 2 h.

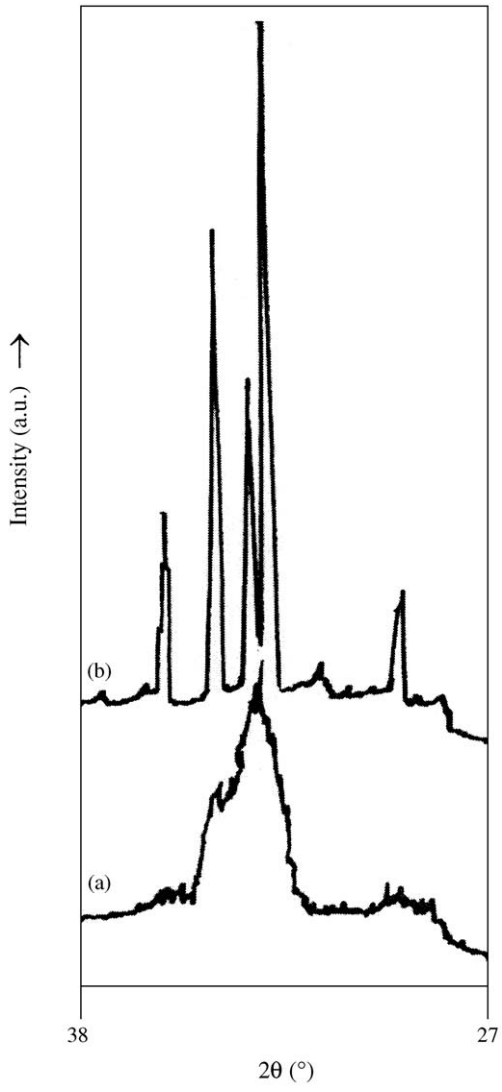


Figure 3 Diffractograms of (a) the original powder and (b) granules sintered at 1150 °C for 2 h.

the granules, after drying and firing, had macropores of 400–600 μm that correspond to those in the human spongy bone [2]. As foamers, we also tested graphite (hoping the granules would be carbonised; the carbonate-containing porous HA ceramics showed increased dissolution and caused faster ingrowth of bone tissue *in vivo* [17, 18]) and polyvinylbutyral; however, these attempts were not successfull. CPS was foamed, and a fraction of particles of 500–1000 μm in size was selected. The ultrafine HA powder was thoroughly mixed with the selected fraction of the foamer and, by adding distilled water, an elastic paste was prepared. Small portions of the paste were spinned between two parallel-plane discs, which had one axis and rotated in opposite directions, to prepare rounded (almost spherical) green granules of 6–8 mm in diameter. After drying at 100–120 °C for 24 h, the green granules were subjected to preliminary annealing (calcination) at 800 °C in water vapour (to prevent dehydroxylation of HA and its transformation into tricalcium phosphate), and were sintered at 1100–1150 °C for 2 h. The size of the green granules reduced in the process of sintering. As a result, porous and ''dense'' granules (in case of the ''dense'' granules, no foamer was used) of 4–6 mm in diameter were manufactured (Fig. 4).

In order to study value, structure and degree of ''transparency'' (interconnection) of the porosity, the granules were impregnated with a liquid media (an epoxy solution and stained distilled water, having different viscosity, were used). The granules were put into a vacuum chamber, and the air was evacuated up to the pressure of 10^{-1} Pa in the chamber; then the granules were thrown off into the liguid in vacua, and air was let into the chamber. For both epoxy solution and distilled water, complete filling of the pores were observed.

Compression strength testing of the granules was carried out utilising an Instron-type compression unit with a capacity of 3 tonnes (precision = 1% of the measured force) and at a crosshead speed of 0.5 mm min^{-1}. As it was difficult to determine the compression strength of the granules with acceptable accuracy because of their rounded form, proper discs of 8 mm diameter by 3 mm height, manufactured under the same conditions as the granules, were used. Ca/P ratios of the samples were determined by standard EDTA titration for Ca and phosphomolybdate techniques for PO_4. The estimated error in a Ca/PO_4 value was $\pm$ 2%. Standard SEM techniques were used for microstructure observation.

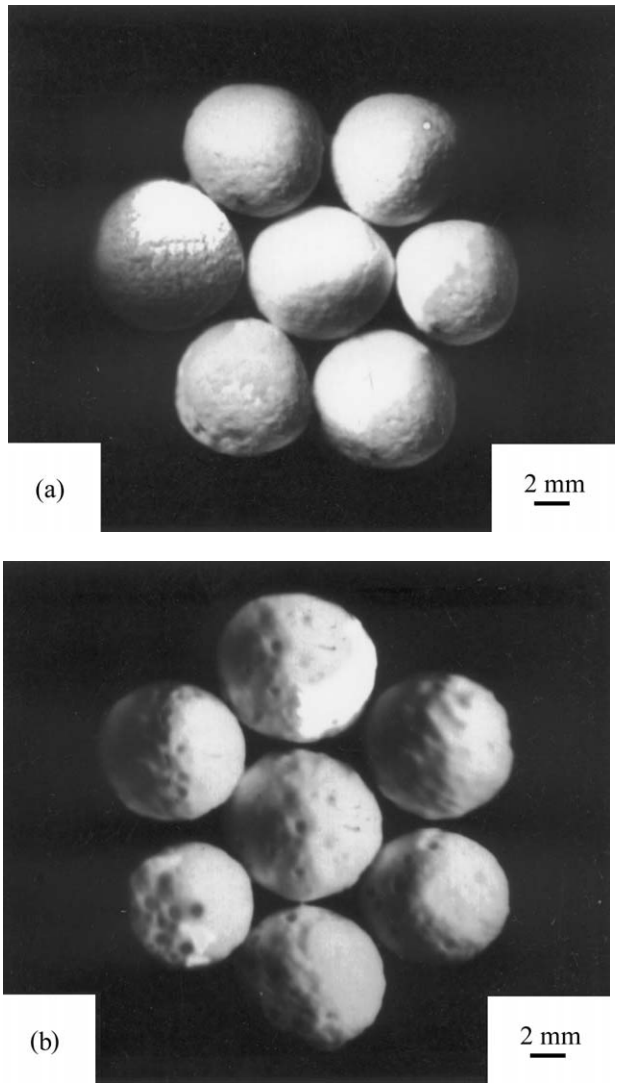


Figure 4 Appearance of (a) ''dense'' and (b) porous HA granules.

3. Results and discussion

X-ray and IR spectrometry examinations revealed that CPS decomposed into ammonia and benzene during annealing at about 200 °C. When the temperature increased, they evaporated, and there were no admixture phases in the green granules above 440 °C. Comparative analyses of spectrograms and diffractograms of the granules (Figs. 2(b) and 3(b)) and of the microporous block which had been produced earlier under the same sintering conditions as the granules and had been implanted into rat's femur to study the process of bone tissue formation [9], revealed that the data obtained did not go beyond the acceptable experimental error. Additionally, material in these sintered products (i.e. in the granules and in the block) was polycrystalline with grains of about 0.5 μm in size. The ratio of Ca/P = 1.65 ± 0.03 in the material was very close to the theoretical value of Ca/P in HA (1.67). However, the lattice constants (in Å units) of the material $a = 9.412 \pm 0.003$ contracted and $c = 6.887 \pm 0.003$ expanded in comparison with those for stoichiometric HA by the ASTM data ($a = 9.4160$ and $c = 6.8830$). This meant that, in both cases, the ceramic material was a nonstoichiometric (partially dehydroxylated) HA with vacancies located in hydroxyl positions [19]. The study of the porosity showed that the ''dense'' granules' porosity was within the limits of 25–32%. The porous granules had two kinds of pores: micropores and quasi-spherical macropores. The micropores formed a network of interconnected channels with a transverse size of a few microns (Fig. 5(a)). The value of microporosity was within 25–35%, i.e. the characteristics of the micro-porosity were practically the same as those in the ''dense'' granules. The macropores were 350–600 μm in diameter (Fig. 5(b)) and were formed as a result of escape of water vapor during drying and products of decom-position and burning of the foaming agent, as well as (to a less degree) owing to incomplete sintering of the

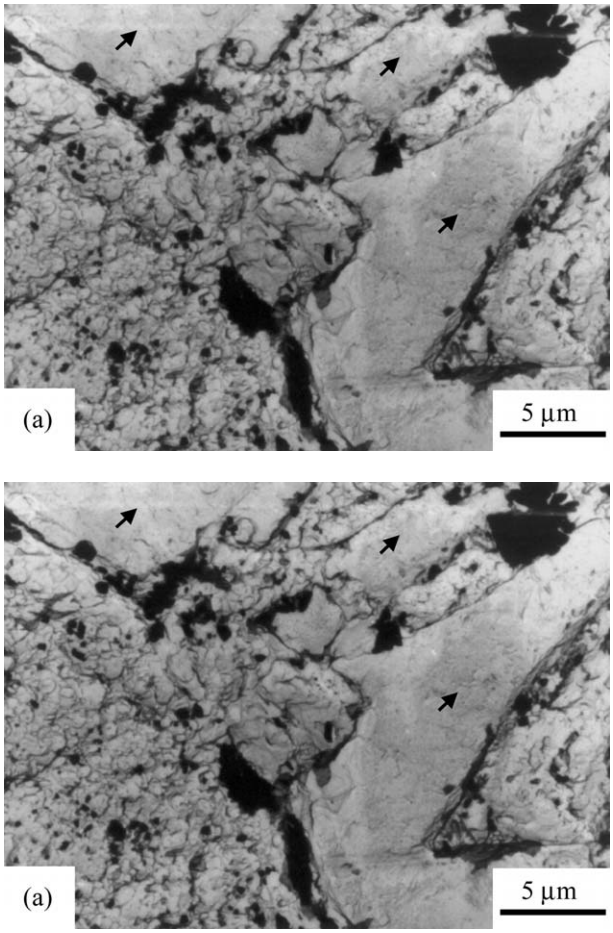


Figure 5 Microphotograph of the section of a porous HA granule filled with a stained liquid medium. (a) Micropores and (b) macropores are indicated by arrows.

powder particles. The volume of the macroporosity could be increased up to 80% and was given by the amount of CPS introduced. The total porosity was usually from 40% to 70% ($\pm$ 5%) that was similar to the porosity of human spongy bone.

As it had been expected [20], the dependence of compression strength upon porosity of the samples was described by a drop-down curve (Fig. 6). The first left point in the curve corresponded to a dense ceramics produced by usual uniaxial moulding of the powder at 20 MPa and subsequent thermal treatment of the powder compact simultaneously with the green granules. The porosity of the dense ceramics was about 7%, and the crushing strength was 100 MPa. The group of points in the center of the curve corresponded to the compression strength of 35–48 MPa for the ''dense'' granules, and the

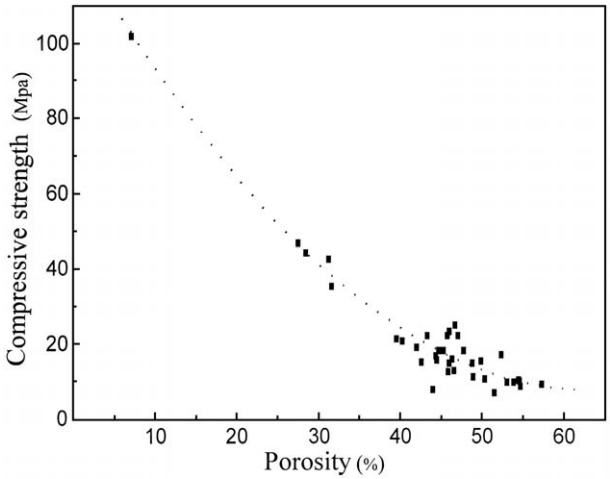


Figure 6 Dependence of compression strength upon porosity in HA ceramic products.

right group of points – of 7–25 MPa for the porous granules. The comparison of the compression strength values with those for human cortical (88–164 MPa) and spongy (40–60 MPa) bones [13] revealed that the ''dense'' and porous HA granules had good prospects to be utilized as filling agents for partially loaded and unloaded bone defects, respectively.

4. Clinical application

About 42 patients (22 women, 20 men from 15 to 72 years, average age of 39 years) were treated using two types of HA ceramics (''dense'' and porous granules) with a follow-up from three to 43 months. Localisation of the bone defects underwent to the plasty is represented in Table I. Taking into account that ceramics does not possess osteoinductive properties and only stimulates and improves the quality of the newly formed bone, we prepared a recipient site thoroughly. Before implanting the ceramics, we removed all necrotic tissues to provide as much intimate contact as possible between the ceramics and the patient's bone itself. In the post-operative period, except for the hip re-endoprosthesis, all flexion and shear forces were excluded by means of adequate immobilization.

In 10 patients with aseptic bone necrosis (in nine cases the process was localized in the femoral head, and in one case in the humeral head), HA was applied in combination with cancellous autograft to fill the defect after necrectomy. Aseptic necrosis was evaluated according to the International Classification of

TABLE I Some data on operations

Localization of affected area	Number of operations with the use of granules			Total
	''Dense''	Porous	''Dense'' + porous	
Acetabulum	3	2	10	15
Femoral (humeral) head	7	3	—	10
Proximal third of femur (tibia)	2	9	—	11
Distal third of femur (tibia)	1	2	—	3
Pubic bone	1	—	—	1
Radius	—	1	—	1
Metatarsal 1st	—	1	—	1
Total	14	18	10	42

Osteonecrosis of the Femoral Head. In the I–II stages of the process (four cases), tunnellization of the bone was produced with the help of the hollow milling cutter to destruct sclerotic zone around the nidus and remove necrotic mass by the curettage spoons. The column of autospongiosa extracted was turned to 180° and placed subchondrally. The remained defect was filled with HA ceramics. In the II–III stages aseptic necrosis (six patients), flexion intertrochanteric femoral osteotomy was performed in order to eliminate the load in the affected femoral head. After the necrosis nidus excochleation, the plasty of the defect was performed in the same way. In most cases taking into account that femoral neck and head belong to the loaded zones, we used ''dense'' granules resistant to mechanical compression.

In 10 patients, a revision of hip endoprosthesis was performed. Instability of both components was found in all the cases. Cementless reendoprosthesis was performed to three patients, and seven patients underwent the cemented one. Revision constructions were chosen from the standard endoprostheses set taking into account individual patient's peculiarities. Granuloma, fibrous tissues and particles of polyethylene were completely removed in every case. According to the offered technique, acetabular cavity defects were filled with HA granules. HA granules were separately used in cemented re-endoprosthesis, in cementless – in combination with cancellous autotransplants in the form of chips. The application of HA in the latter case allowed to decrease the amount of the automaterial used (and thus, to lessen the risk of possible complications) as well as to provide a possibility of distributed loading on the extremity up to complete bone transplants reconstruction. The hollow defects were tightly filled with HA granules, and hip endoprosthetic component was set in after that. The cement was applied in the thinnest layer possible to provide necessary rigidity and exclude filling into the spaces between ceramic granules. In one case, we used a support ring placed on the ceramics and fixed by screws. Large press-fit cups were set in cementless re-endoprosthetics. We used combination of ''dense'' and porous granules in all the patients. It was conditioned by the necessity of functional loading, on the one hand, and that of providing optimal terms for reparative osteogenesis, on the other.

In 14 cases, the ceramics was used when treating benign tumours and tumour-like diseases (aneurysm benign bone, fibrous dysplasia, gigant cell tumours, chondromyxoid fibroma, xanthoma, enchondroma). After the curettage, the defect was filled with HA granules. If it was located in the loaded zone, ''dense'' granules were used. HA granules were packed into the cavity and tightly pressed. In order to prevent any migration and stimulate osteogenesis, the fragments of cortical autobone and demineralised bone matrix were used.

Besides, in four cases, HA porous granules were used to fill the cancellous bone defect for fractures and its complications. In three cases, HA was used for the bone defects plasty after the removal of metallic constructions and in one case after taking a bone autograft. The cortical bone defects were filled with dense HA granules, and cancellous bone defects – with the porous ones.

In all these cases, there were no complications in the postoperative period. No signs of inflammation, allergy or ceramics rejection were observed, all the wounds healing in primary tension.

On the basis of our experience of using HA granules in patients with variable locomotoriun pathologies, we should note that the period of ceramics biodegradation roentgenological signs emergence depends on the chemical composition, structure and porosity degree of the material applied as well as the value of the functional load. For the ''dense'' ceramics, this period is one year, for the porous ceramics, it is six months. Roentgenologically, the process of biodegradation was manifested in intensity weakening of implants shadow; it was particularly seen in the border ''bone-ceramics'' where marginal sharpness was gradually weakening and the replacement by bone tissue was observed. Roentgenological evolution of mechanically stable ''dense'' HA granules should be considered separately. A rather fast integration stimulated by loading in early rehabilitation was clearly observed. However, it is difficult to suggest the process of resorption in the depth of ceramics. Absence of roentgenological density changes in the centre of the cavity filled with ceramics makes complete biological ceramics degradation doubtful even three or four years later. The follow-up is too short to account for the slow speed of remodelling. This problem should be discussed in 10–15 years' time, which is also confirmed by other researchers. The influence of the distributed functional load on the speed of ceramics biodegradation is clearly seen on the example of acetabular cavity defects plasty when revising hip endoprosthesis.

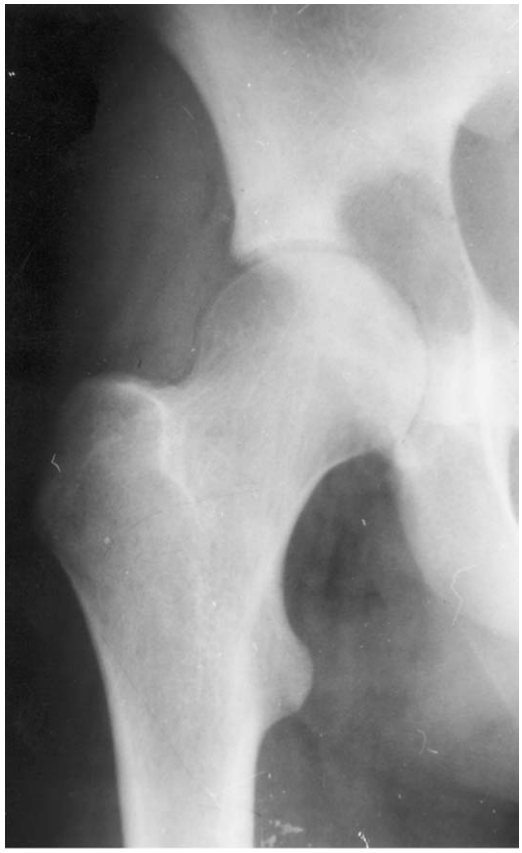
We obtained good results in all the patients due to different kinds of HA granules contributed to this matter. The results obtained confirm the high efficiency of using these synthetic bone substitutes for bone cavities plasty.

To illustrate this, we furnish clinical examples. (a) Antioperative, (b) postoperative and (c) two years nine months later, X-rays of aneurysmal cyst of the ilium in a 15-year-old boy. Thorough curettage of pathologic nidus was performed. The granules were tightly packed in the place of implantation. To prevent the granules' migration and to stimulate the bone formation, a demineralised bone matrix was used. As the site of a bone tissue defect belongs to the loaded ones, ''dense'' HA granules were taken (Fig. 7).

Patient S, 34-year-old male, diagnosis: idiopathic aseptic necrosis of the head of the right hip, stage II. The operation: tunnelling of the intertrochanteric area, the femoral neck and head, necrectomy, the bone autoplasty, the porous granules plasty (Fig. 8).

5. Conclusions

An ultrafine original powder was used for the production of high-quality ''dense'' and porous HA granules combining large porosity and proper strength properties. The powder was prepared by the known method of ''wet synthesis'' with some change in the process of crystallization at the final stage of the precipitation. As a foaming agent, a few substances were tested, and cellular polystyrene proved to be the most appropriate of them. Green granules were prepared by an original technique



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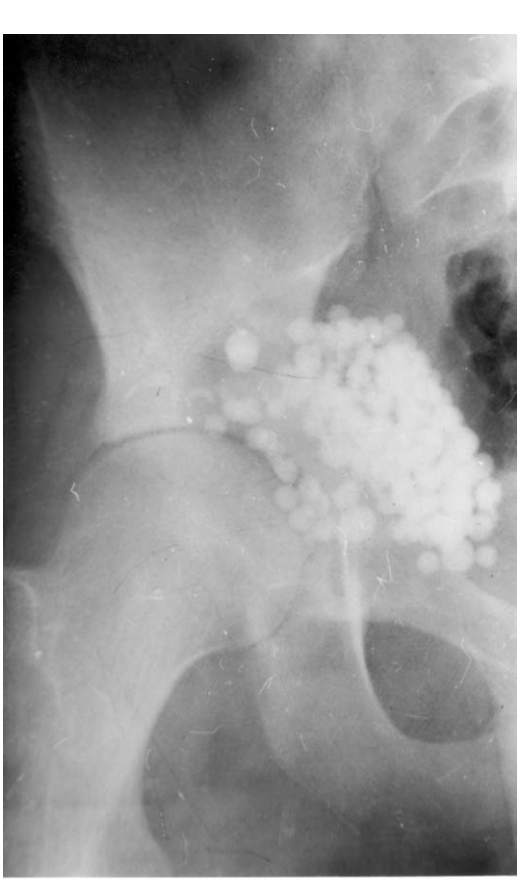

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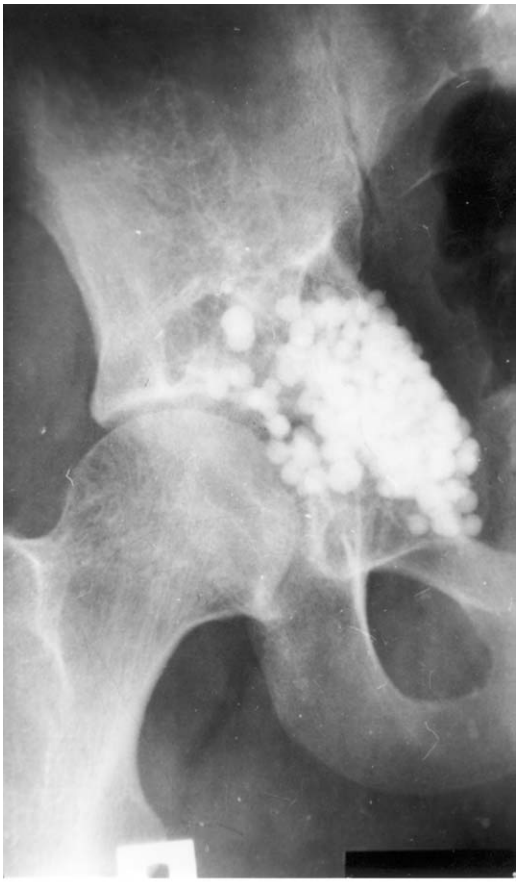
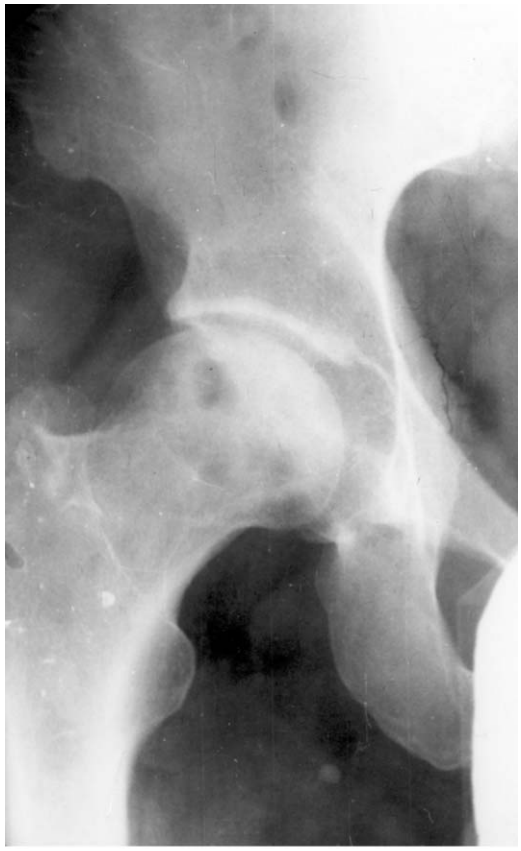


(c)

Figure 7 Aneurysmal cyst of the ilium in a 15-year-old boy. X-rayograms (a) before the operation, (b) after it and (c) 14 months later; the bone defect was filled, the pathological fracture was remodelled.



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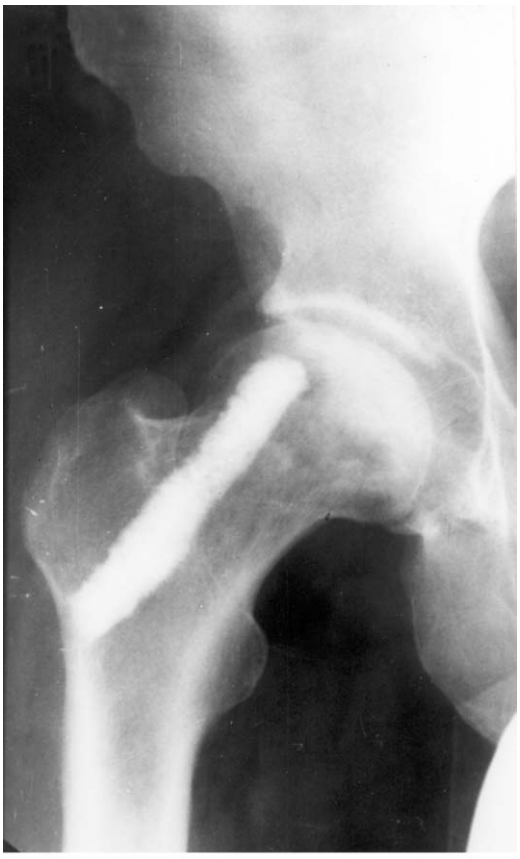

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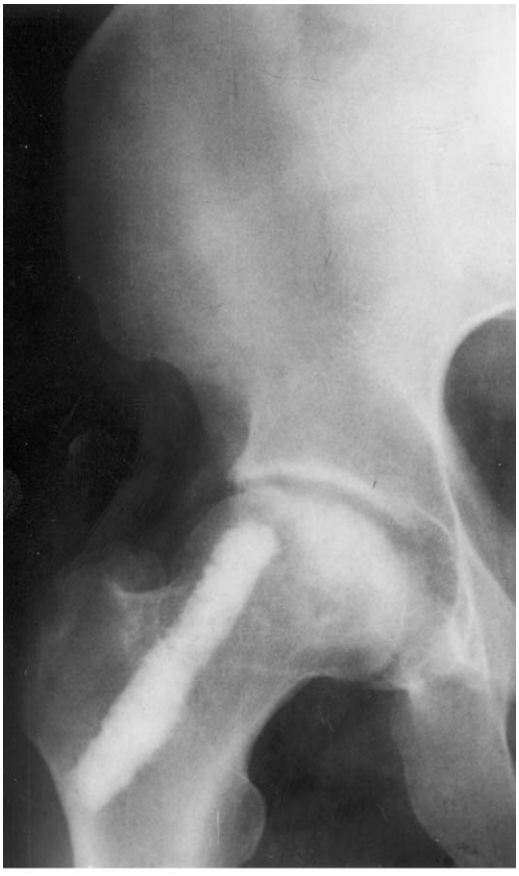

(c)

Figure 8 Idiopathic aseptic necrosis of the femoral head in a 34-year-old male patient. X-rayograms (a) before the operation, (b) after three months and (c) 11 months later; weaker intensity of the shadow of the implants and a less defined outline on the ''bone-ceramics'' border are noted.

without pressing, and then they were calcinated in a humid atmosphere and sintered in air. The ''dense'' granules were produced without the foamer, and the porous ones were prepared with it. The ''dense'' granules were microporous, while the porous ones contained a system of connected micro- and macropores. The material of the granules was a defective (non-stoichiometric) HA. Owing to the high density of the framework in the sintered granules, the compression strength for both kinds of them exceeded all known data in case when other characteristics were similar.

After a positive animal laboratory test, the granules were used in orthopaedic surgery. Two approaches were studied. Either ''porous'' or dense granules were used in operations with the same diagnosis in order to find out which kind is better. If the circumstances did not allow utilizing either kind of the granules, the one which by its functional characteristics optimally corresponded to the localization, state and the degree of the supposed loading of the affected area was selected. A detailed comparative analysis of the operation results will be performed after a longer postoperative period. However, the observations performed have attested to very successful results of the operations with the use of the developed granules both at immediate and in postoperative periods (one month to four years long).

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