Chapter 2
Clinical Applications of Hydroxyapatite in Orthopedics

Hiroyuki Oonishi Jr., Hironobu Oonishi, Hirotsugu Ohashi, Ikuo Kawahara, Yoshifumi Hanaoka, Ryoko Iwata, and Larry L. Hench

Abstract This chapter describes since 1982 the use of porous synthetic hydroxyapatite (HA) granules (0.1 to approximately 1.5 mm) interposed at the cement-bone interface to enhance bone bonding, a surgical procedure labeled interface bioactive bone cement (IBBC). HA granules were smeared on the bone surface just before cementing. Because the HA granules used in IBBC were pure polycrystalline HA, they were scarcely absorbed and their osteoconductive activity can continue indefinitely even after the onset of osteoporosis due to aging and even in conditions of extremely low pathological activity of bone. The appearance rate of radiolucent lines and osteolysis was extremely low even over 30 years when IBBC was used. Since 1986, in an attempt to fill the massive bony defect in the acetabulum at revision surgery of total hip arthroplasty, a mixture of HA granules with a size between 0.9∼1.2 mm and 3.0∼5.0 mm was placed densely and firmly into the bone defects. Bone ingrowth was measured to be over 2.5 cm in full depth and the new bone was very stable. Long-term clinical results over 26 years were excellent. On the weight-bearing area, bone ingrowth over 2.5 cm in full depth can be expected. However, on non-weight-bearing area, bone ingrowth is only 0.5 cm in depth. In large cavities

H. Oonishi Jr., M.D. • H. Oonishi, M.D., Ph.D. (✉) • I. Kawahara, M.D. • Y. Hanaoka, M.D.
H. Oonishi Memorial Joint Replacement Institute, Tominaga Hospital, 1-4-48, Mintatomachi, Naniwa-ku, Osaka 556-0017, Japan
e-mail: oons-h@os.rim.or.jp

H. Ohashi, M.D., Ph.D.
Department of Orthopaedic Surgery, Saiseikai Nakatsu Hospital, 2-10-39, Shibata, Kita-ku, Osaka 530-0012, Japan

R. Iwata, Ph.D.
Olympus Terumo Biomaterials Corporation, Shinjuku Monolith, 3-1, Nishi-Shinjuku 2-chome, Shinjuku-ku, Tokyo 163-0941, Japan

L.L. Hench, Ph.D.
Department of Biomedical Engineering, Florida Institute of Technology, Melbourne, FL 32901, USA

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after resection of bone tumors, or after removal of pathological fatty bone marrow at joint replacements, excellent stability to provide long-term strong bony support was obtained by filling HA granules firmly into the defects.

Keywords Bioceramics • Hydroxyapatite • Orthopedics • Rheumatoid arthritis • Total hip arthroplasty • Osteoconduction • Interface bioactive bone cement (IBBC)

2.1 Introduction

Bioceramics have been widely used as bone replacement materials in orthopedic surgery. In particular, calcium phosphate ceramics such as synthetic hydroxyapatite (HA) have been applied as bioactive ceramics with bone-bonding capacities. Since 1982, we have used HA in the bony defect area at total hip and knee arthroplasty, sometimes in extremely progressed atrophic cancellous bone area of rheumatoid arthritis at joint replacement to get firm bony support. HA has also been used as bone filler in the area of bone deficiency after resection of bone tumors. In order to obtain physicochemical bonding between bone and implant, HA coatings on implants had been used for about 15 years. However, HA coatings were absorbed within 15 years after implantation due to the amorphous HA present in the HA coatings.

In order to protect from loosening of prostheses, osteoconduction has to be maintained at the interface between bone and implant even after onset of osteoporosis. Therefore, non-resorbable polycrystalline HA has to be used to obtain long-term stability. For this reason, we have been using the interface bioactive bone cement (IBBC) technique which involves interposing non-resorbable crystalline HA granules at the interface between bone and bone cement at the time of cementing during surgery.

2.2 Clinical Applications in Orthopedic Surgery: Interface Bioactive Bone Cement (IBBC)

Cemented total hip arthroplasty (THA) has been one of the most successful procedures in orthopedic surgery, since J. Charnley applied polymethylmethacrylate (PMMA) to fix the components [1–11]. Efforts to improve the mechanical bonding at the bone-bone cement interface have been pursued for many years by many teams or researchers. Even with these contemporary techniques, cement fixation is often limited with respect to long-term stability of the bone-cement interface. Furthermore, the physicochemical bonding cannot be expected in addition to the mechanical bonding for traditional cement fixation, since the bone cement is not osteoconductive [1–11].

To augment the bone-bone cement bonding, we investigated a new cementing technique to achieve the long-lasting physicochemical bonding at the bone-bone cement interface by interposing osteoconductive crystalline HA granules. In this technique, bone cement is covered by polycrystalline porous HA granules at the interface, thereby achieving essentially custom-made HA-coated cemented implants. HA granules for our technique were pure polycrystalline HA; thus they were scarcely absorbed and their osteoconductive activity continued indefinitely even after the onset of osteoporosis due to aging. We call this technique interface bioactive bone cement (IBBC) [7–28].

2.2.1 Materials and Methods

The IBBC method involves placing less than 2–3 layers of porous polycrystalline HA granules 0.3–1.5 mm in diameter with a porosity of 35–48 % (average 42 %) between the bone and cement (Fig. 2.1a). Although HA granules of 0.3–0.5 mm in diameter were used initially, they were later reduced to 0.1–0.3 mm, as it was found those sizes adhere to bone more easily. HA must be used on the surface of completely hemostatic bone. On the areas with slight bleeding, HA particles larger than 0.6 mm are more appropriate, as granules smaller than 0.3 mm will be covered by the blood. As a result, blood will be present between the HA and bone cement. Additionally, low-viscosity bone cements should not be used with HA granules, because the HA granules will sink into it. We used CMW-type I as the PMMA bone cement.

2.2.2 Experimental Studies

2.2.2.1 Histological Studies

Holes with a diameter of 6 and 10 mm in depth were made in both femoral condyles of mature rabbits, and HA granules of 300–500 μm in diameter were smeared in less than two layers over the bone surface of the hole, and the hole was filled with bone cement (Fig. 2.1b). In groups of three, rabbits were sacrificed at 2, 3, 4, 6, 12, and 24 weeks and at 3 years after implantation. Non-decalcified hard tissue specimens were prepared and examined by optical microscopy, scanning electron microscopy (SEM), and backscattered electron imaging.

One week after surgery, new bone began entering the first to second layer and adhering to the HA granules (Fig. 2.1c). At 2–3 weeks after surgery, new bone had entered a majority of the spaces in the second layer (Fig. 2.1d). After 6 weeks or more, all spaces were filled with new bone, thus forming a unified body, as illustrated in Fig. 2.1e at 8 months postsurgery. Three years after surgery (Fig. 2.1f),

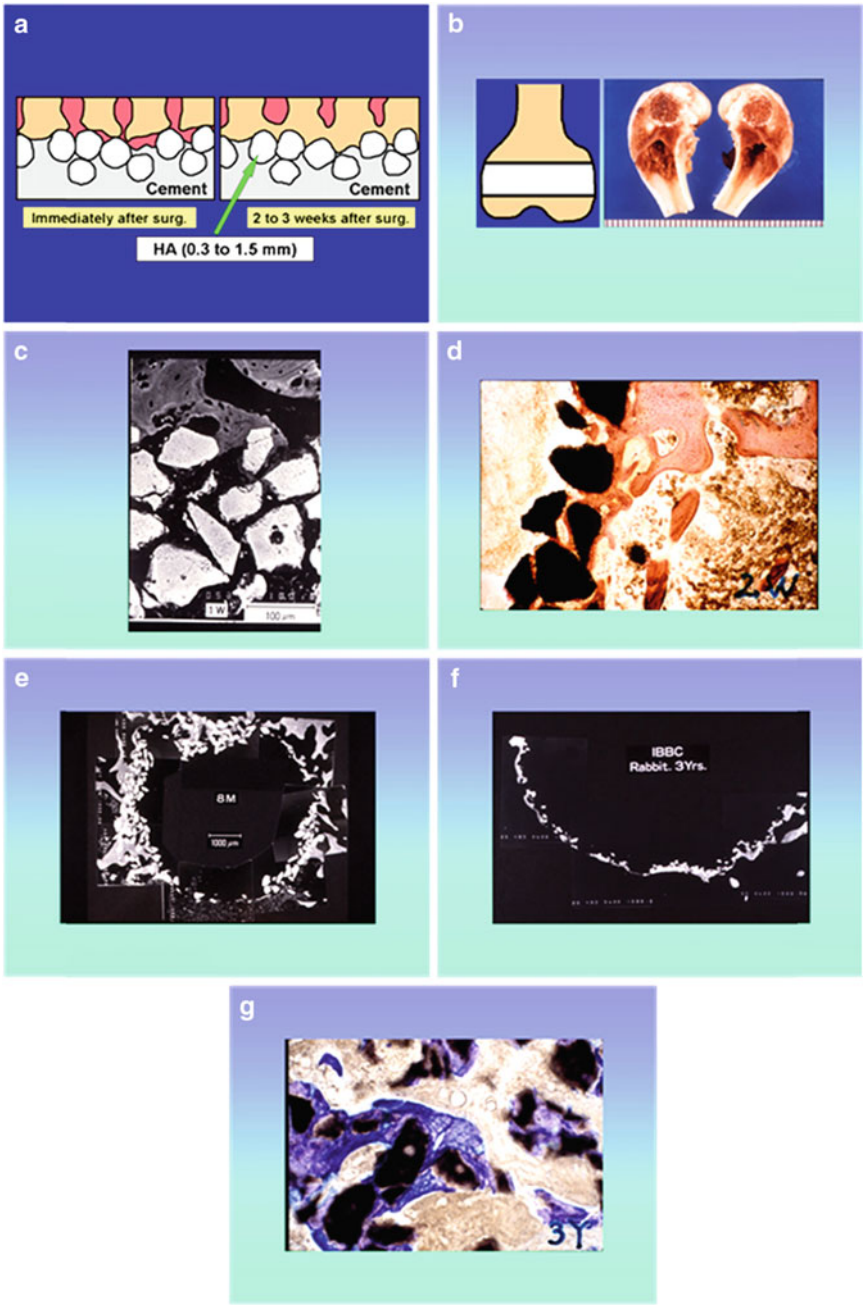

Fig. 2.1 (**a**) Scheme of IBBC at immediately after surgery and 2–3 weeks after surgery. (**b**) Animal experiment of IBBC cross section of femoral condyle of the rabbit performed with IBBC. (**c**) Animal experiment of IBBC 1 week after surgery. (**d**) Animal experiment of IBBC 2 weeks after surgery. (**e**) Animal experiment of IBBC 8 months after surgery. (**f**) Animal experiment of IBBC 3 years after surgery. (**g**) Higher magnification of Figure (**f**)

bone ingrowth into the spaces of HA granules was the same as that seen at 6 weeks and 8 months (Fig. 2.1e). The bone was retained only in the place where HA granules were smeared. There was no bony tissue in other place due to aging (Fig. 2.1f, g).

2.2.2.2 Bonding Strength of the HA Granule Layer to Bone

IBBC was tested on mature rabbits. Holes with a 6 mm diameter and a depth of 10 mm were made in both femoral condyles. The rabbits were sacrificed in groups of three at 2, 4, 6, 12, and 24 weeks after implantation, and a push-out test was performed. HA coating applied to a smooth titanium surface was used as a control.

A relatively strong initial fixation was obtained immediately after implantation using the IBBC technique. Two weeks after implantation, the bonding strength of IBBC was higher than that of the HA coating, but at 6 weeks after implantation, the bonding strength of IBBC became similar to that of HA coating. The fractures resulting from the push-out test occurred in the HA granule layer from 2 to 6 weeks after implantation and occurred in both the HA granule layer and the surrounding bone layer after 12 weeks. These results indicated that the strength of the HA granule layer gradually increased after surgery and reached almost the same level as the bone around the HA granule layer after 12 weeks. In these experiments, the bonding strength of bone cement to bone by interposing HA granules was found to be adequate (Fig. 2.2).

Stress shielding was not found in subsequent clinical trials. When cement fixation using PMMA bone cement was performed, excellent initial fixation can be obtained. However, after a period of time, a connective tissue membrane may form between the bone and bone cement, particularly in the acetabulum. This may lead to component loosening.

When cementless fixation with a HA-coated component was performed, micromotion of the component may occur if the initial fixation is insufficient. Therefore, we are confident that IBBC combines the fixation advantages of both conventional PMMA bone cement and HA coating in early stage.

2.2.3 Clinical Studies

2.2.3.1 Surgical Technique

A cobalt-chromium alloy femoral component (KC, Kyocera Co. Ltd. Kyoto, Japan) with a 28 mm alumina head was used in combination with an all-polyethylene acetabular component. All operations were performed by the senior author (H.O.) through an anterolateral approach in supine position.

HA granules were manufactured by sintering at 1,200 °C in Sumitomo Osaka Cement Co. Ltd., Chiba, Japan. Porous HA granules with 300–500 μm in diameter were used. For acetabular side, several small anchor holes for initial fixation were

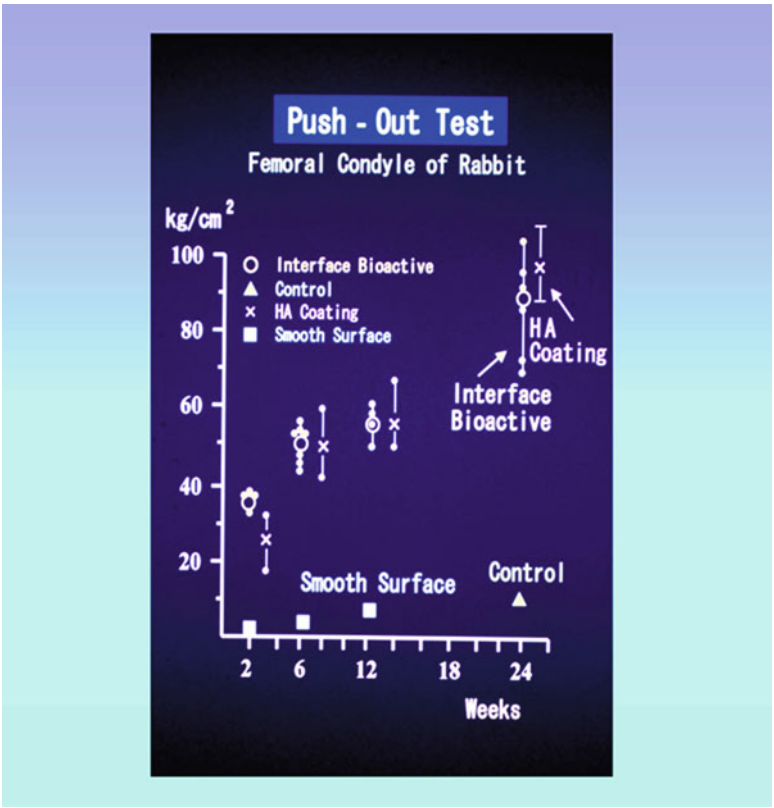

Fig. 2.2 Push-out test: Comparison of adhesive strength to the bone of IBBC and HA coating

made and intensive care was taken for sufficient hemostasis by means of hypotensive anesthesia (approximately 90 mmHg), temporal compress at the bleeding points with bone paste obtained by acetabular reaming, and a rinse with hydrogen peroxide followed by compressive gauze packing. HA granules (2–3 g) were smeared on the bone surface just before cementing of the acetabular component. CMW-I bone cement (C.M.W. Laboratories Ltd., Blackpool, UK) was used in all cases. Porous HA granules could easily adhere on the wet bone surface (Fig. 2.3a, b). For the femoral side, hemostasis was achieved in the same manner and HA granules (2–3 g) were smeared on the inner surface of the prepared femoral canal using a half-tube silicone rubber (3–5 cm in length) clamped by a long-straight Kocher's hemostatic clamp (Fig. 2.3c, d). The femoral component was fixed with second-generation cementing technique using an intramedullary bone plug and cement gun. These procedures resulted in the presence of less than 2–3 layers of HA granules in most of the bone-bone cement interface, while bone cement directly contacted with bone without interposition in some part. The same cementing technique was applied for the conventional THA procedures except for using HA granules.

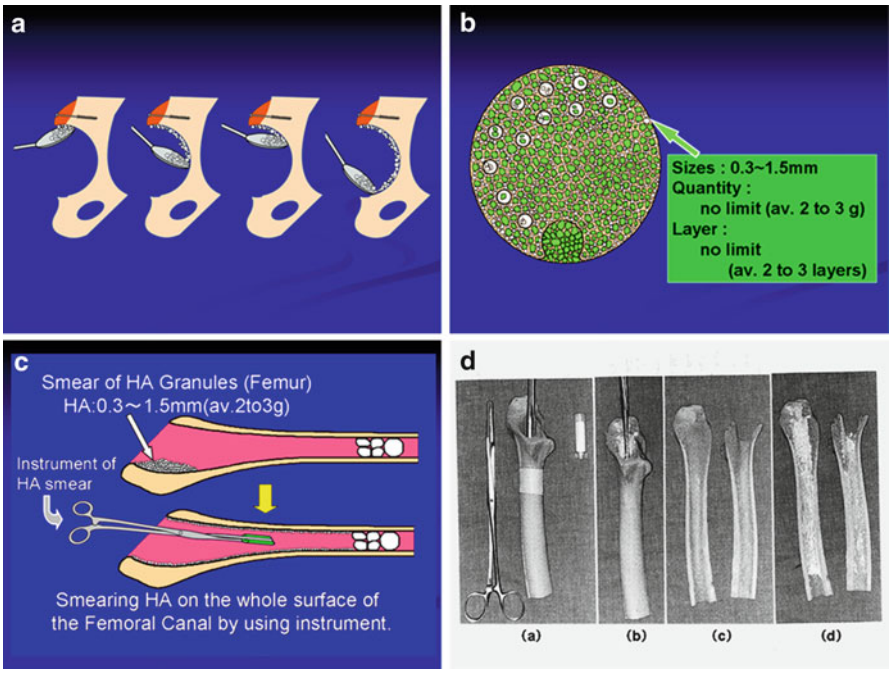

Fig. 2.3 (**a**) Smearing procedures of HA granules on the acetabulum. (**b**) After smearing of HA granules on the acetabulum. (**c**) Smearing procedures of HA granules on the inner surface of the femur. (**d**) Experimental studies of smearing of HA granules on the inner surface of the femur. (**d**–[*a*]) Homemade instrument to smear HA granules. (**d**–[*b*]) Smearing HA granules by using the instrument. (**d**–[*c*]) Inner surface of the femur before smearing HA granules. (**d**–[*d*]) Inner surface of the femur after smearing HA granules

The key points of surgical procedures were as follows:

1. Hemostasis immediately before cementing is very important.
2. Several small anchoring holes for initial fixation are necessary.
3. HA impregnated by antibiotics as a drug delivery system is very effective for prevention of infection.

2.2.3.2 Changes of IBBC Technique

In the first generation, from 1982 to 1988, HA granule size of 0.3–0.5 mm in diameter was used, and several small anchoring holes of 3 mm in diameter were made. In the second generation, from 1989 to 1997, HA granules of 0.1–0.3 mm were used because a smaller size of HA granules adhered more easily to the interface. However, as a smaller size of HA was covered easily by blood in the bleeding area, the connection of the bone cement with HA was prevented. As the result, a space appeared between bone cement and HA.

Consequently, in the third generation, from 1998 to 2001, HA granules of 0.3–0.5 mm were used again and several numbers of anchoring holes of 6 mm in diameter were made for stronger initial fixation. In the fourth generation, since 2001, HA granules of 0.3–0.5 mm with 1.0–1.5 mm were used and several layers of anchoring holes more than 6 mm in diameter were made, thereby enhancing safety even if IBBC was performed in the bleeding area.

2.2.3.3 Long-Term Clinical Results for 24–31 Years

Long-term clinical cases were classified into three groups. In group (1), 1982–1985, IBBC was performed in 12 joints as trials and conventional bone cement (non-IBBC) in 79 joints. In group (2), 1985–1986, IBBC was performed on one hip joint and non-IBBC was performed on the other hip joint in the same patient. These were performed in 25 patients. In group (3), 1986–1989, IBBC was performed in all cases in 285 joints (212 patients) (Fig. 2.4).

2.2.3.4 Group (2): (1985–1986, 25–26 Years After Surgery)

Group 2 has 16 patients with survival in both hips. In non-IBBC hips, the prostheses were loosened in five hips in the acetabulum and in two hips in the femur within 20 years. The radiolucent line and the osteolysis increased gradually and their appearance time was indefinite. Seven hips were revised within 15–20 years.

In IBBC hips, the radiolucent line and the osteolysis appeared in only small limited areas and did no progress. The rich new bone formation was maintained at the interface of bone and bone cement by interposing HA granules (Fig. 2.5a–c). In the survival cases of hips with both IBBC and non-IBBC, wide radiolucent lines and osteolysis and loosening were seen in non-IBBC cases; however, only few radiolucent lines and osteolysis were seen in the small limited areas in IBBC hip replacements (Fig. 2.5d, e).

2.2.3.5 Group (3): (1986–1989, 22–25 Years After Surgery)

In this group, IBBC technique was used in all cases in 285 joints (212 patients). The radiolucent line and osteolysis appeared in only small limited areas and did no progress (Fig. 2.6a). Extensive new bone formation was seen at the interface of bone and bone cement by interposing HA granules (Fig. 2.6b, c). In groups 1–3, when IBBC was performed in the bleeding area, the spaces appeared between bone cement and HA several months after surgery on the X-ray figure (Fig. 2.6d). However, the spaces did no progress (Fig. 2.6e). When the space appeared in the large area, the partial separation of bone cement from HA at the interface of HA and bone cement occurred in two cases (Fig. 2.6f). HA incorporated with the bone at the interface

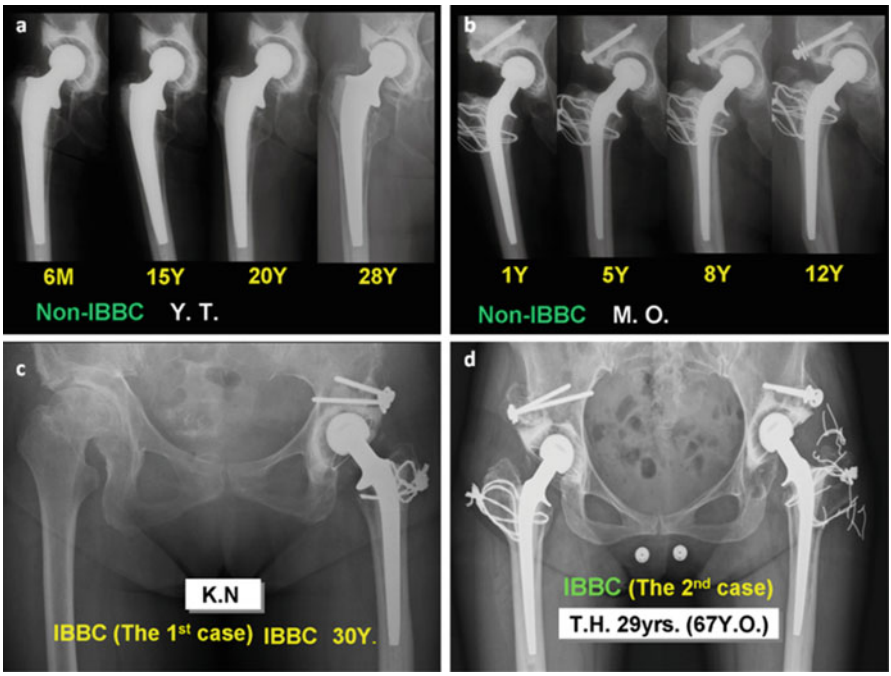

Fig. 2.4 (**a**) Clinical course of X-ray figure after THA with conventional bone cement (non-IBBC). Osteolysis was seen in the femur 15 years after THA. Osteolysis and radiolucent line were seen in the acetabulum and the femur 20 years after THA, and they progressed 28 years after THA. (**b**) Clinical course of X-ray figure after THA with non-IBBC radiolucent line was seen in the acetabulum 5 years after THA. Stem loosening was seen 8 years after THA and it progressed and radiolucent line progressed in the acetabulum and stem loosening progressed 12 years after THA. (**c**) This is the first case of THA with IBBC. Thirty years after THA, polyethylene socket wear increased in high degree. However, neither radiolucent line nor osteolysis was seen. (**d**) This is the second case of THA with IBBC in bilateral hips 29 years after THA. She has worked as a dancer for 28 years. Radiolucent line and osteolysis were seen in only small limited area

(Fig. 2.6g). In non-IBBC cases with only conventional bone cement, when wear particles of polyethylene increased, phagocytosis occurred and osteolysis appeared on the radiograph.

From the long-term clinical results of IBBC, the rate of formation of space or voids between HA and bone cement was less than 2 %. They appeared at the limited areas in both the acetabulum and the femur for the first- and second-generation IBBC procedures. The spaces were not radiolucent lines. They appeared at a rather higher rate in the second generation than in the first generation because the HA granule size in the first generation was bigger than that in the second generation.

The appearance rate of osteolysis was extremely low, less than 1.5 %, appearing in few restricted areas. The separation between bone cement and HA occurred in the acetabulum in the second generation in two joints that is 0.8 %. There was

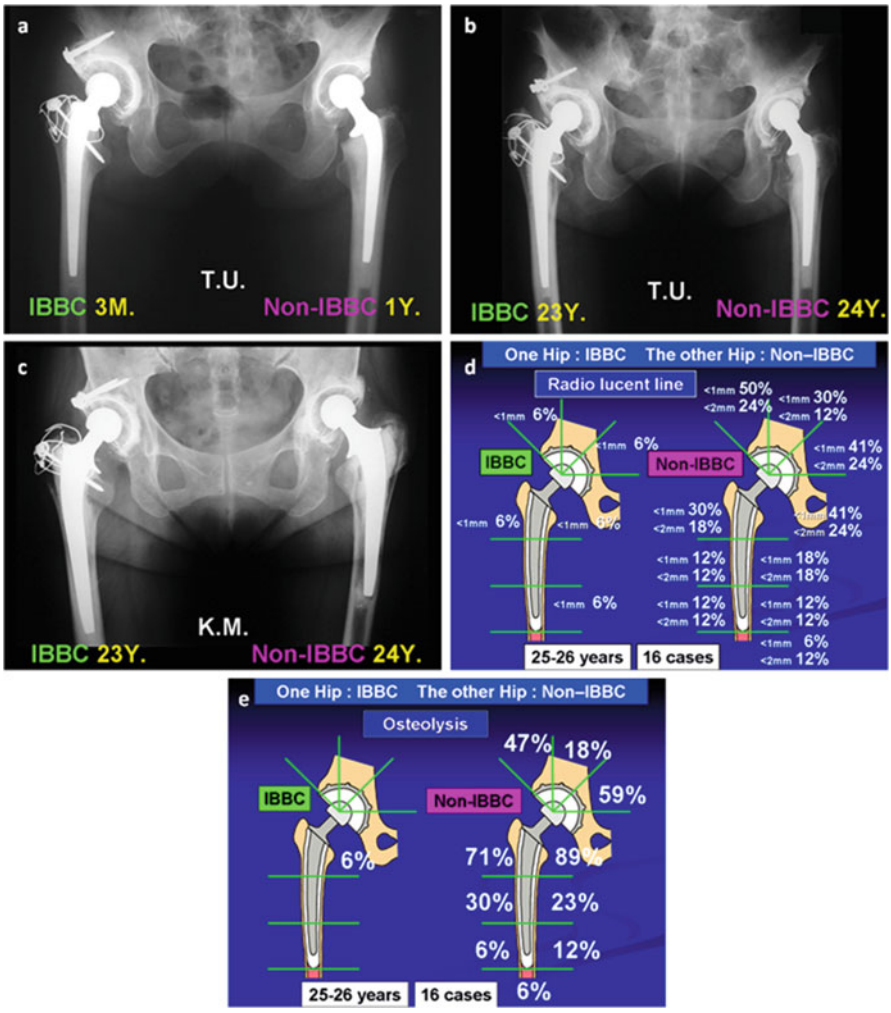

Fig. 2.5 (**a**) One year after THA with non-IBBC in the left hip and 3 months after THA with IBBC in the right hip. (**b**) In the right hip with IBBC, neither radiolucent line nor osteolysis was seen 23 years after THA in spite of progress of polyethylene wear. In the left hip with non-IBBC, both radiolucent line and osteolysis progressed in both acetabulum and femur 24 years after THA. (**c**) In the right hip with IBBC, neither radiolucent line nor osteolysis was seen 23 years after THA. In the left hip with non-IBBC, 24 years after THA, both radiolucent line and osteolysis were seen in the acetabulum, and osteolysis and stem loosening were seen in the femur. (**d**) Comparative appearance rate of radiolucent line 25–26 years after THA with IBBC and non-IBBC performed in the same patient. (**e**) Comparative appearance rate of osteolysis 25–26 years after THA with IBBC and non-IBBC performed in the same patient

no loosening between bone and bone cement. Since 2001, in order to prevent the occurrence of the spaces and the separation between bone cement and HA, several anchoring holes over 6 mm in diameter were made in the acetabulum and HA granules of 0.3–0.6 mm and 1.0–1.5 mm were smeared on the bone surface.

In the IBBC procedure, there was no loosening between bone and bone cement in groups 1, 2, and 3 for 27 years. However, in non-IBBC hip replacements, loosening occurred in over 80 % of cases, a high rate, for 31 years (Table 2.1).

2.2.4 Histological Studies on Retrieval Cases

2.2.4.1 Materials and Methods

In 14 patients, specimens containing a well-fixed bone-cement interface were retrieved during revision surgery. The diagnosis was degenerative osteoarthritis in ten hips and in one knee, rheumatoid arthritis (RA) in two, and osteonecrosis after radiation therapy for portio cancer in one. The causes of revision were dissociation of the metal-back socket from the bone cement in nine hips, aseptic loosening of the socket in one, and late infection in four.

At the revision surgery, the specimens were carefully cut out using a surgical osteotome or oscillating bone saw to retrieve the bone-cement composites without breaking the bone-cement interface. In the acetabulum, six specimens were retrieved from the superior wall, which was considered to be the principal weight-bearing site, and ten specimens were retrieved from the inferomedial wall, which was considered to be the auxiliary weight-bearing site. Three specimens were retrieved from sites where the HA granules failed to be smeared. In the femur, two specimens were retrieved from the greater trochanter and femoral neck. In the femoral condyle, two specimens were retrieved.

The retrieved tissues were immediately fixed with neutral buffered formalin (10 %) and dehydrated in increasing concentration of ethanol up to 100 % at room temperature. A polyester resin solution (Rigolac; Mixture of resin no. 2004 and resin no. 70 °F, 80/20 (wt.%/wt.%); Showa Highpolymer Co., Ltd., Tokyo, Japan) was used for embedding. To prevent complete loss of the bone cement, the treatment in the first resin solution was minimized. Finally, the resin solution was kept in a chamber at 60 °C for 8 h and polymerized. The cured blocks were cut into slices 300–500 μm thick using a metal cutting saw and then ground down to sections 50–80 μm thick. Sections were examined by backscattered electron microscopy (SEM) and conventional light microscopy after staining with methylene blue or toluidine blue.

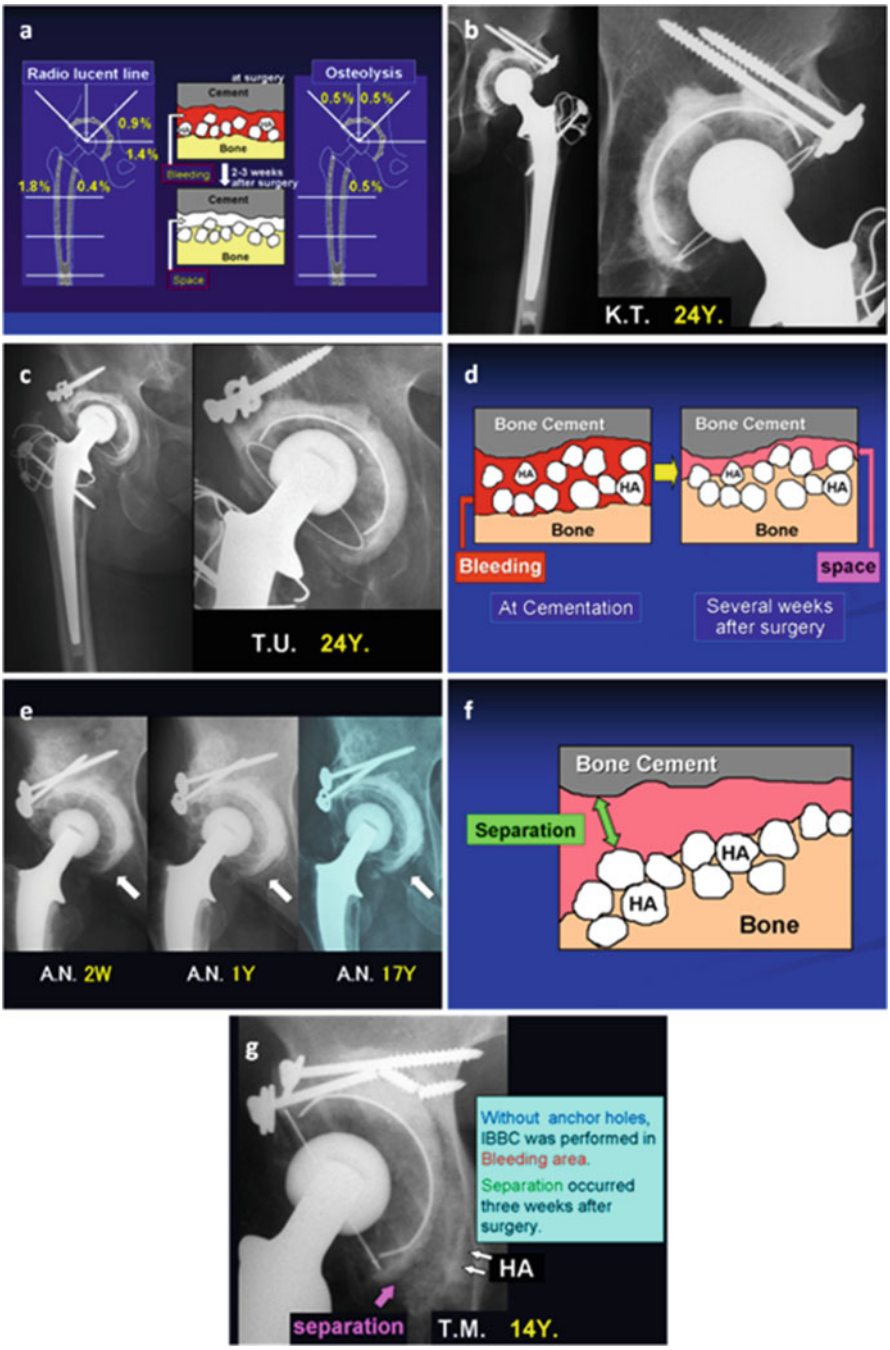
a
Radio lucent line
0.9%
1.4%
1.8%
0.4%
at surgery
Cement
Bone
Bleeding
2-3 weeks after surgery
Cement
Bone
Space
Osteolysis
0.5% 0.5%
0.5%
b
K.T. 24Y.
c
T.U. 24Y.
d
Bone Cement
HA
HA
Bone
Bone Cement
HA
HA
Bone
Bleeding
space
At Cementation
Several weeks after surgery
e
A.N. 2W
A.N. 1Y
A.N. 17Y
f
Bone Cement
Separation
HA
HA
Bone
g
Without anchor holes, IBBC was performed in Bleeding area.
Separation occurred three weeks after surgery.
HA
separation
T.M. 14Y.

Table 2.1 Summary of results of loosening rate between bone and bone cement in groups 1, 2, and 3

	Non-IBBC		IBBC	
	79 Joints		**12 Joints**	
G. 1	R.L.L.	7 Joints not loosened	R.L.L.	Extremely low rate no progress
	O.L.		O.L.	
	L.	6 Joints not revised	L.	0
	Revision, death, and lost	65	Death	3 Joints
			Lost	3 Joints
G. 2	Total: 25			
	Survival in both hips for 25–26 years: 16 patients			
	Loosening within 20 years	Acetabulum: 5 hips	L.	0 (except for separation between HA and cement)
		Femur: 2 hips		
G. 3				285 Joints
			R.L.L.	Extremely low rate no progress
			O.L.	
			L.	0

2.2.4.2 Results

Bone ingrowth was observed in all interfaces where the HA granules were interposed on the living bone. Dense bone ingrowth was present in all specimens retrieved from the superior wall of the acetabulum. Among specimens from the inferomedial wall of the acetabulum, cancellous bone ingrowth was recognized in nine specimens and dense bone ingrowth was recognized in one (Fig. 2.7a). Cancellous bone ingrowth was also recognized in specimens from the femur. On the

Fig. 2.6 (**a**) Clinical results of THA with IBBC 22 to 25 years after THA. Appearance rate of radiolucent line and osteolysis was extremely low. Radiolucent line appeared between bone cement and HA, because the cementation was performed in the bleeding area. This line was not a radiolucent line but a space in correct. (**b**) THA with IBBC was performed in dysplastic acetabulum 24 years after THA. Neither radiolucent line nor osteolysis was seen in both acetabulum and femur. Rich new bone formation was seen on the hole around the bone cement. (**c**) THA with IBBC was performed in dysplastic acetabulum 24 years after THA. Wear of polyethylene socket highly increased; nevertheless, neither radiolucent line nor osteolysis was seen. (**d**) Scheme of the condition performed IBBC in the bleeding area. Spaces appeared between bone cement and HA several weeks after THA on the radiograph. It did no progress. (**e**) IBBC was performed in the bleeding area. A *space* appeared several weeks after THA. It did no progress. (**f**) Separation between bone cement and HA after THA with IBBC in the bleeding area and without sufficient anchor holes. (**g**) IBBC was performed in the bleeding area without sufficient anchor holes. Separation occurred between bone cement and HA 3 weeks after THA. However, fixation of bone to the bone cement was continued by interposing HA granules (IBBC) at the laterosuperior area

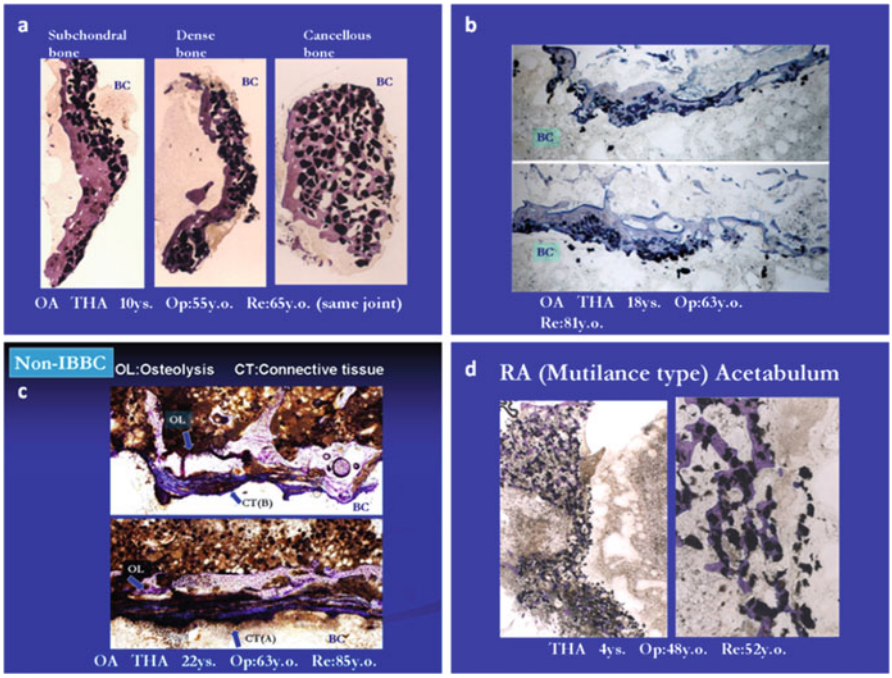

Fig. 2.7 (**a**) Photomicrographs of bone-cement interfaces. These three specimens were retrieved from the same joint. THA was performed on an OA hip joint at 55 years old and retrieved 10 years after surgery at 65 years old. Dense bone ingrowth is observed in superior wall of the acetabulum and cancellous bone ingrowth is observed in inferomedial wall of the acetabulum. (**b**) Photomicrographs of bone-cement interfaces. These two specimens were retrieved from the same joint. THA was performed for an OA hip joint at 63 years old and retrieved 18 years after surgery at 81 years old. This was implanted for 18 years. These were retrieved from the acetabular superior wall. (**c**) Photographs of interface without the HA granules. THA was performed for an OA hip joint at 63 years old and retrieved 22 years after surgery at 85 years old. These specimens were retrieved from acetabular inferior medial wall. Connective tissue (*CT*) interposition and osteolysis (*OL*) are observed at the interface (*BC* bone cement, *CT* connective tissue). (**d**) THA was performed for an RA hip joint at 48 years old and the specimen was retrieved 4 years after surgery at the age of 52 years old from the inferomedial wall of the acetabulum. New bone ingrowth around and between HA granules was formed and cancellous bone was made with HA granules only in the area where HA granules were smeared relatively sparsely

area in which thick layers of HA granules were smeared on the bone, thick and rich bone layer with HA granules was present. On the area in which even one layer of HA granules was smeared sparsely on the bone, a very thin new bone layer was formed (Fig. 2.7b).

In contrast, connective tissue interposition and osteolysis were observed at the sites where HA granules were not present (Fig. 2.7c). No foreign body reaction or proliferative granuloma formation was observed in any specimen.

The specimens were retrieved from 13 hips over 1–22 years, as well as 5 months in one knee after the initial operation. Considering the interval between the

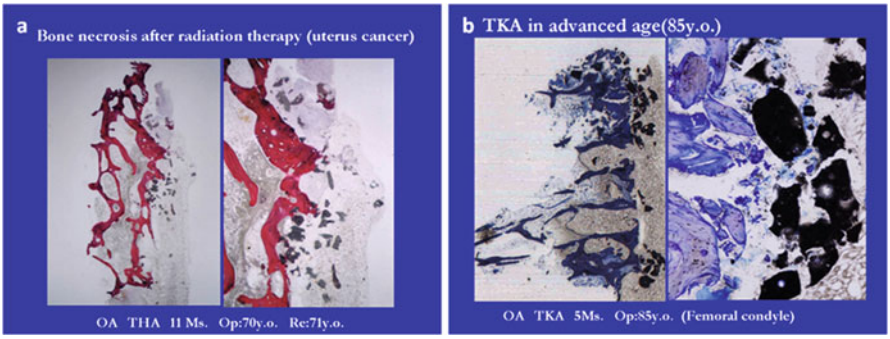

Fig. 2.8 (**a**) THA was performed for patient with bone necrosis after radiation therapy to portio cancer. Bone necrosis was found in iliac bone and hip joint. The joint replacement was performed at 71 years old and the specimens were retrieved 11 months after surgery from the inferomedial wall of the acetabulum at the age of 71 years old. IBBC was performed in scanty bleeding area due to bone necrosis. However, new bone formation was found to be relatively rich. (**b**) TKA was performed for an OA knee at the great age of 85 and the specimen was retrieved due to infection 5 months after surgery from the femoral condyle. New bone ingrowth was found around HA granules and between HA granules. However, speed of bone formation is rather slow

initial operation and revision, there was no difference in bone ingrowth except for the specimen from the knee joint. All specimens were retrieved from female patients, except for knee specimens, over 50 years of age. Although postmenopausal osteoporosis was observed in the host bone of the hip joint for the female patients, the findings of bone ingrowth around the HA granules were similar (Fig. 2.7b).

Considering patients with RA, new bone ingrowth around and between HA granules was formed and cancellous bone was formed in low density with HA granules only in the area where HA granules were smeared.

In this type of RA, cancellous bone was extremely atrophic and contained a large quantity of fatty marrow; thus, it was inevitable that HA granules were smeared in a thick layer in low density of bone (Fig. 2.7d). However, there was no new bone formation where host bone was observed necrotic.

On bone with extremely low osteoconductive ability, and scanty bleeding due to bone necrosis after radiation therapy for cancer, new bone formation was found (Fig. 2.8a). TKA was performed in an osteoarthritic (OA) knee at the great age of 85. The specimen was retrieved from the femoral condyle. New bone ingrowth around HA granules was found. However, speed of bone formation is rather slow due to the advanced age of the patient (Fig. 2.8b).

2.2.5 Discussion

In the IBBC technique, HA granules exist on the surface of cement mantle. This seems to be an HA-coated prosthesis-bone cement composite. In cementless

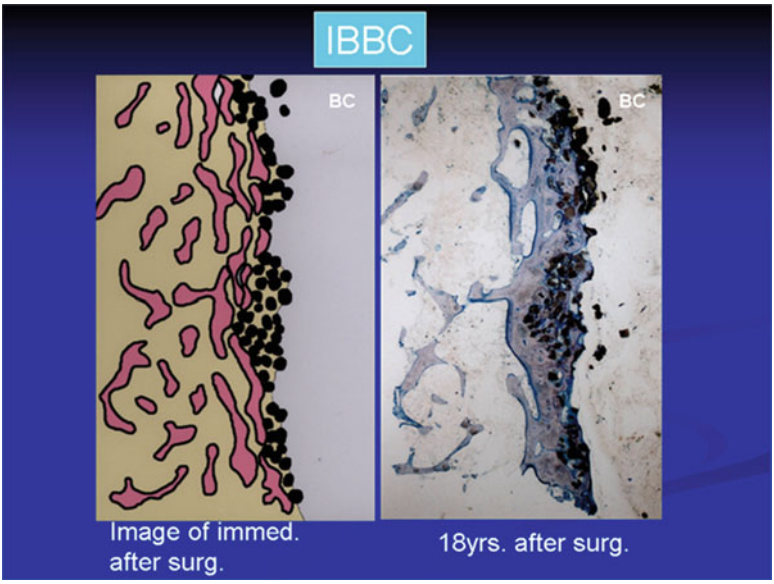

Fig. 2.9 Hypothetical time course of periprosthetic bone condition: immediately after THA (*left figure*) and 18 years after THA (*right figure*)

stems, it was reported that HA coating increases the amount of bone ingrowth and attachment leads to better bone fixation and enhanced the stability of the stem. The same effects can be expected for the cemented stem when the bone cement is coated with HA using IBBC technique. The clinical results using the IBBC technique were reported to be excellent. The characteristics of HA coated on a cementless prosthesis and HA granules for IBBC technique are different. As HA coated on prosthesis contains amorphous HA, HA resorbs with time.

In contrast, HA granules in our technique were pure polycrystalline HA phase and thus they were scarcely absorbed. We could not detect any sign of HA resorption in the retrieved specimens. It is expected that osteoconductive activity can continue indefinitely even after the onset of osteoporosis due to aging. Figure 2.9 shows our hypothetic time course of periprosthetic bone conditions; pre-osteoporotic bone smeared by HA granules at immediately after surgery and thick bone layer around HA granules surrounded by osteoporotic bone at 18 years after surgery.

In histological studies, dense bone ingrowth was observed in all specimens retrieved from the superior wall of the acetabulum, which was considered to be the principal weight-bearing site. Cancellous bone ingrowth was observed in specimens retrieved from the inferomedial wall, which was considered to be the auxiliary weight-bearing site. Connective tissue interposition and osteolysis were observed at the sites where HA granules failed to be smeared. The findings of bone ingrowth in the hip joints were similar regardless of the interval between the initial operation and revision or patient age at retrieval. New bone ingrowth was found around HA

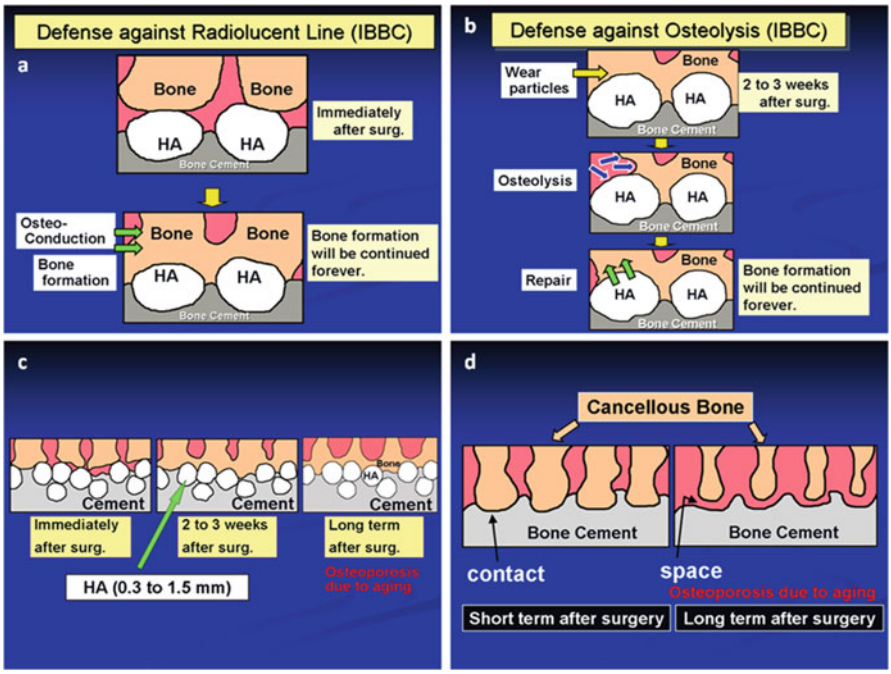

Fig. 2.10 (**a**) Scheme of effect of crystalline HA endures osteoconduction in IBBC. No radiolucent line appeared enduringly on radiograph due to osteoconductive effect of HA. (**b**) Scheme of effect of crystalline HA enduring osteoconduction in IBBC. Immediately before occurrence of osteolysis due to reaction of wear particles, it will be repaired by the osteoconductive effect of HA. (**c**) Scheme of the conditions cemented by IBBC at immediately after THA, 2–3 weeks after THA and long term after THA shifting to osteoporosis due to aging. (**d**) Scheme of the condition cemented using conventional cementation (non-IBBC) at short term after THA and long term after THA shifting to osteoporosis due to aging

granules and between HA granules, even when IBBC was performed at the great age of 85. However, speed of bone formation was understandably slow for this patient.

On the area in which thick layers of HA granules were smeared on the bone, thick and rich bone layers over the HA granule layer were formed. This bone layer with HA granules formed new bone around the HA granules that was fixed to the bone cement providing steady support to the prosthesis. Even on the area in which one layer of HA granules was spread sparsely, thin layer of new bone formation was found. However, at an interface where the bone was completely dead, there was no new bone formation.

At the sites where HA granules failed to be smeared, connective tissue interposition and osteolysis were observed. From these results, it can be concluded that the osteoconductive ability of HA prevents the occurrence of unmineralized connective tissue and osteolysis (Fig. 2.10a, b).

In a comparison of the interface with and without HA granules, bone ingrowth was observed at the interface with the HA granules (Fig. 2.10c), and the interface was interposed by connective tissue at the interface without the HA granules (Fig. 2.10d). Thus, the longevity of the bone-cement bonding for all these patients was attributed more to the interposed HA granules.

We retrieved the specimens between 5 months to 22 years after the initial operation. The HA granules were still present in the specimens after this long-term follow-up as the resorption of crystal HA is extremely slow and the bone directly contacts the HA granules.

In terms of patient age and postmenopausal osteoporosis, most of the patients were over 60 years of age at the time of the revision surgery. The histological findings were similar between elderly patients and patients less than 60 years of age. In addition, the specimens from the patients with rheumatoid arthritis and post-radiation osteonecrosis, conditions in which bone formation activity is considered to be very low, showed similar findings in the area where HA granules were smeared. These results indicate that HA granules have osteoconductive activity even in conditions of poor bone formation activity. When HA granules were smeared on the bone of a patient at the age of 85, the activity of osteoconduction was relatively low. However, relatively slow new bone formation was found in this patient.

In general, dense bone ingrowth was observed when HA granules were smeared on the dense bone and cortical bone. Cancellous bone ingrowth was observed when HA granules were smeared on the cancellous bone.

Further in the acetabulum, dense bone ingrowth was observed in specimens retrieved from the superior wall of the acetabulum, and cancellous bone ingrowth was observed in specimens retrieved from the inferomedial wall of the acetabulum; in both locations, the HA granules were evenly smeared. Assuming that the superior wall is the principal weight-bearing site and the inferomedial wall is the auxiliary weight-bearing site in the acetabulum, bone formation around the HA granules may be affected by mechanical conditions as an additional factor.

The use of HA granules in THA has some possible drawbacks, including loss of interdigitation of cement with bone, foreign body reaction, and third-body wear. For cement fixation, the strength of the cement-bone interface depends on the physical properties of the bony surface, the contact area, and the extent of penetration of cement into the bony trabeculae. In the IBBC technique, the HA granules cover the trabecular bony structure and prevent cement penetration following loss of interdigitation of cement. Consequently, the creation of small anchor holes in the acetabulum is recommended for initial fixation. No foreign body reaction was present at the interfaces with and without interposition of the HA granules. Although it has been reported that HA granules with a diameter of less than 10 mm cannot be incorporated, the HA granules used in the present study were 0.1–1.5 mm in diameter. Third-body wear is another potential risk. The retrieved polyethylene cups were not investigated for wear measurement and surface observation.

In a previously reported radiological study using an alumina head with IBBC technique in 111 hips, the linear wear rate depended on the thickness

of the polyethylene and was compatible with other reported results. There were no untoward clinical complications attributed to the use of the HA granules.

Histological examination of the specimens containing well-fixed bone-cement interface 5 months to 22 years after THA and TKA with the IBBC technique showed bone ingrowth between the HA granules. Because bone ingrowth between the HA granules was observed in the specimens retrieved more than 20 years after the initial operation, the longevity of the bone-cement bonding was attributed more to the interposed HA granules. The histological findings were not affected by the pathological bony conditions associated with aging, postmenopausal osteoporosis, and diseases that lead to extremely low osteoconductive ability.

The histology showed there was no connective tissue interposition and no osteolysis in the area interposed by HA granules (Fig. 2.10a, b); however, they were found in the area without HA granules (Fig. 2.10c). From these results, there was long-term direct contact between the bones and HA granules and long-term longevity could be expected in patients receiving implants with IBBC (Fig. 2.10b).

2.3 Clinical Application: Reconstruction Surgery of the Acetabular Huge Bone Deficiency by Filling HA Granules at Revision Total Hip Arthroplasty

2.3.1 The First Generation

Before 1985, in the bony defect even in the massive bony defect at revision THA, the bony wall defect was covered by metal mesh and the bony defect was filled by bone cement (Fig. 2.11a, b). On the other hand, freeze-preserved, non-pathological allografts of the bone have been used in cases of massive bone deficiencies during revision total hip arthroplasty (THA) for more than 25 years in Europe and in the USA, and excellent results have been reported [1–4]. Cases using allografts have also been reported in Japan [5], although in Japan, materials other than femoral heads, partial femoral condyles, and partial tibial plateaus from patients undergoing arthroplasty are still very difficult to obtain. On the other hand, increasing interest in bioactive ceramics, particularly in HA over the past 30 years, has resulted in a significant increase in its clinical application during this period [6–32]. Under these circumstances, we began to use sintered HA granules clinically.

As a material, sintered HA is not resorbable, binds to the bone physicochemically, and is strong enough as bone defect filler. We obtained good results in three revision cases by placing fine HA granules (300–500 μm) between the bone cement and the bone graft on the deficiencies of the femur in 1984. In addition, since 1985, massive bone deficiencies have been filled with HA granules [26–28].

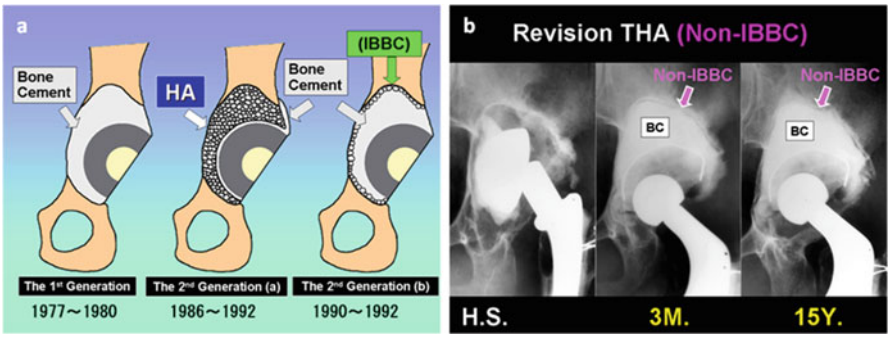

Fig. 2.11 (**a**) Revision THA in the acetabulum with massive bone deficiency. The 1st generation: deficiency was filled only by bone cement. The 2nd generation (a–a): deficiency was filled by HA granules. The 2nd generation (a–b): deficiency was filled by bone cement with IBBC. (**b**) Revision THA in the acetabulum with massive bone deficiency. Deficiency was filled only by bone cement (non-IBBC). *Left figure* is before revision THA. Radiolucent line was seen immediately after revision THA (*center figure*), and the component with bone cement was moving little by little superiorly (*right figure*: 15 years after revision THA)

2.3.2 The Second Generation (a) (1986–1992)

2.3.2.1 Materials and Methods

HA granules of 0.3–0.6 mm (G-2), 0.9–1.2 mm (G-4), and 3.0–5.0 mm (G-6) are mixed at a ratio of 10:45:45. Physiological saline is added to the mixture to increase the mixing density and to facilitate the adhesion of granules with each other due to the porous characteristic of the granules. This results in firmer adhesion and more stable shape formation. The acetabulum is filled with the mixture. If the same size of HA granules is used, the mixing density decreases, a firmer and more stable filling cannot be obtained, and the shape easily breaks.

A hemispherical compressor 2 mm larger than the outer diameter of the socket is then inserted successively into the previously determined space for the socket installation and firmly struck into the acetabulum using a plastic hammer while continuously making adjustments to determine the best socket location (Fig. 2.11a).

When cementing the socket, a 2–3 mm thickness of cement of paste-like condition is placed on the entire surface of the acetabulum and compressed with a compressor 2 mm larger than the outer socket diameter until the cement hardened. When a bone defect extended over a large area on the superior periphery of the acetabulum and it was not possible to fill the defect sufficiently with HA granules, additional HA granules were placed in this region and fixed using a 1–2 mm thickness of cement.

Before the socket was cemented, the hardened cement surface was dried, and the socket fixed with cement in a sticky condition on the hardened cement. This procedure facilitates binding the cements together.

2.3.2.2 Clinical Case

Between 1986 and 1992, we carried out this procedure on 40 hips. Whole peripheral segmental and cavitary deficiencies with medial walls intact were found in 13 joints (33 %), and peripheral cavitary deficiencies over the whole area with the medial wall absent were found in 18 joints (45 %). They were very unstable cases after revision surgery. There were 2 men and 38 women, and their ages at operation ranged from 35 to 81 years. The follow-up period was from 18 to 24 years. Our original revision THR was performed in osteoarthritis in 33 patients, rheumatoid arthritis in 5, avascular necrosis in 1, and systemic lupus erythematosus in 1. In 36 joints, this was the first revision, in 3 it was the second, and in 1 it was the third.

2.3.2.3 Results: X-Ray Evaluation

When HA granules are firmly packed, a stable filling is attained, similar to a stone wall. Although narrow spaces were observed in areas at the interface between HA granules and bone immediately after surgery, these spaces gradually disappeared within 3 months following surgery. This was probably due to new bone formation into the space between the HA granules and the subsequent binding with HA granules. Sclerotic bone surrounding loose components changed to cancellous bone over a period of 1–3 years following revision surgery.

Our radiographic evaluation showed neither morphological changes nor decreases in volume (Fig. 2.12a) except for some cases with very specific complications. In a case with a considerable cavitary and peripheral deficiency and a medial wall defect, HA granules were overfilled in the medial area of the acetabulum, and the socket settled laterally. Not only was there no detrimental effect radiographically or clinically, but the filled HA granules were also very stable following surgery.

In two cases, spaces were observed between HA granules near the bone at the laterosuperior lesion. If the superior peripheral deficiencies had been covered with an allograft plate, such as tibial plateau, HA granules could have been filled sufficiently in the superior peripheral region and, as a result, the appearance of the spaces could be avoided.

In two patients after the second revision and in one patient after third revision, the large part of the medial wall was absent and the overall deficiency was too great to allow stable filling of the granules. The packed HA granules broke and the prostheses migrated (Fig. 2.12b).

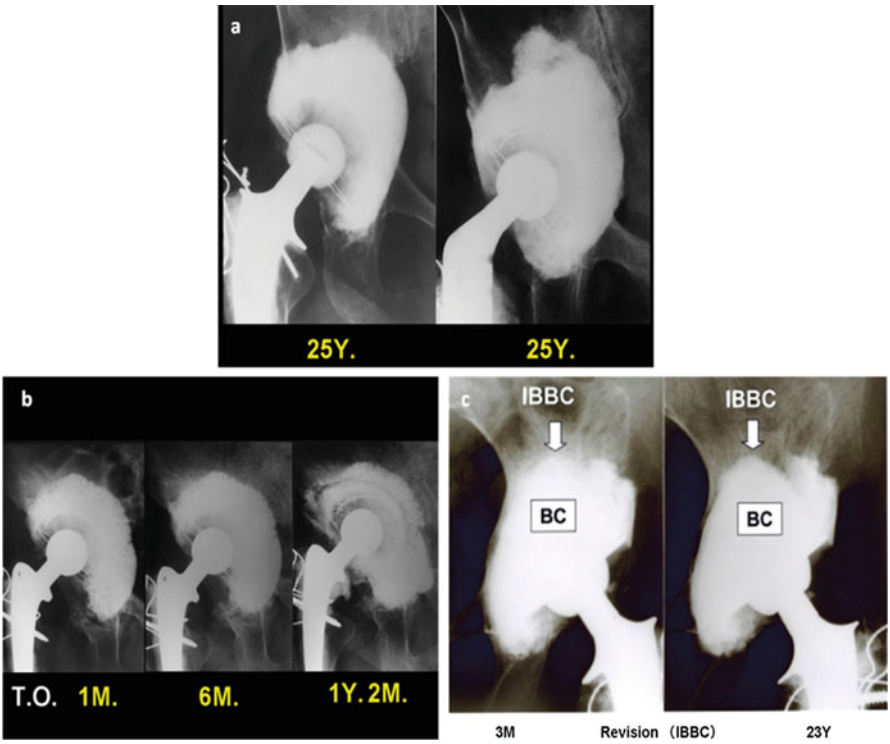

Fig. 2.12 (**a**) Revision of THA in the acetabulum with massive bone deficiency. Deficiency was filled by HA granules. Both *left* and *right* figures are 25 years after surgery. (**b**) Packed HA granules mass disintegrated after 1-year and 2-month revision THA. (**c**) IBBC was applied in a follow-up revision. The *left* figure shows 3 months and the *right* 23 years after revision surgery showing neither radiolucent line nor osteolysis

In these cases, peripheral bony wall deficiency should be covered by allograft bone to obtain stable HA granule filling [27, 28].

2.3.3 The Second Generation (b) (1990–1992)

In the old-age patients over 70 years old, bone cement was filled by using the IBBC technique in the huge cavity. In this case, a thicker layer of HA granules (3–5 layers) was smeared on the surface of the bone and soft tissue in the area of bone defect (Fig. 2.12). A very stable condition could be obtained immediately after surgery by using this technique (Fig. 2.12b, c). On the radiograph over 23 years after surgery, there was neither radiolucent line nor osteolysis (Fig. 2.12c).

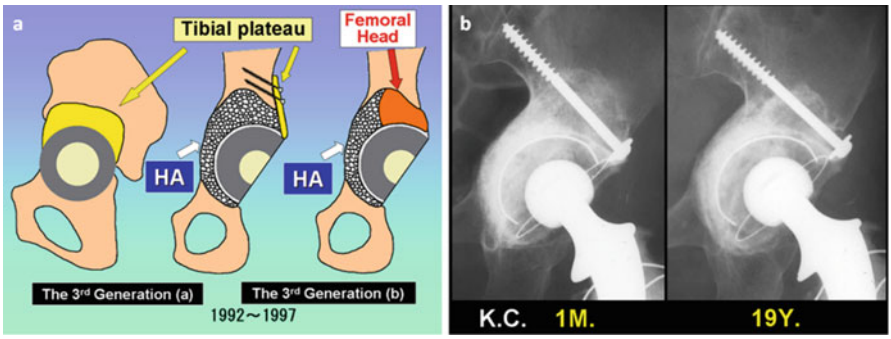

Fig. 2.13 (**a**) Scheme of the revision THA in the third (a) (b) generation. (**b**) Revision THA was performed by the third (**b**) generation. One month (*left figure*) and 19 years (*right figure*) after revision THA

2.3.4 The Third Generation (a) (Since 1992)

2.3.4.1 Materials and Methods

In the third generation, since 1992, peripheral segmental deficiencies were covered with allograft bone from the femoral head of patients undergoing arthroplasty to allow stable filling of HA granules. In some cases with a large cavitary deficiency combined with a large peripheral segmental deficiency, a large block of the femoral head was used. Since 1995, laterosuperior large peripheral deficiencies were covered with an allograft plate from the tibial plateau (Fig. 2.13a).

As a filler in the cavitary deficiency, mixtures of G-4 (0.9–1.2 mm) and G-6 (3.0–5.0 mm) HA granules were filled as in the first generation, and in some cases, mixtures of HA granules of 0.9–1.2 mm (G-4) and small bone chips at a ratio of 30:70 or 50:50 were filled. From 1995 to 1997, the Kerboull metallic cross-plate was used. However, after the Kerboull cross-plate had broken at the hook in 30 % of cases, it was discontinued.

2.3.4.2 Clinical Cases

In 1992–1997, 48 hips have been operated on using the procedure. The follow-up period was 14–19 years. Of the 48 hips, it was the first revision for 43, in 4 hips it was the second revision, and in 1 hip it was the third revision. They were very unstable cases, with great peripheral segmental and cavitary deficiencies, as in the first generation.

2.3.4.3 Results and Complications

In general, when the whole peripheral segmental deficiency was covered with allografts, filled HA granules were very stable. In one case filled with mixture of HA granules and bone chips, a slight volume change was observed. However, there were no clinical symptoms, and the change did not increase. There was no difference radiographically between HA alone and a mixture of HA and bone chips as fillers when the peripheral segmental deficiency was covered with allografts (Fig. 2.13b).

2.3.5 The Third Generation (b) (2002–Present)

In patients over 70 years of age, bony defects at the superolateral area were covered by using allograft of tibial plateau and huge bone defect was filled by bone cement by using IBBC technique. In these IBBC cases thicker layers of HA granules (3–5 layer) were smeared. This technique was the same as the first generation (b). A very stable condition was obtained immediately after surgery by using this technique. Clinical results were excellent with neither radiolucent lines nor osteolysis appearing.

2.3.6 Comparative Histological Studies of Retrieved Specimens Under a Loaded Condition and the Specimens from Animal Experiment Under an Unloaded Condition

2.3.6.1 Retrieved Specimens Under Loaded Condition

As Kerboull cross-plates as cup supporters broke in many cases, in two cases HA granule masses of approximately 2.0 and 2.5 cm in thickness were retrieved at 2 and 2.5 years after revision THA, respectively. They contained whole thickness of HA granules. Non-decalcified ground thin specimens stained by toluidine blue were observed by optical microscopy, and non-decalcified ground blocks were observed by backscattered electron image.

In clinical cases, in the weight-bearing condition, at the second revision THA, it was very difficult to drill into the HA granule mass and to cut the mass with a chisel. In histological studies, a large amount of dense bone ingrowth from the base of dense bone (Fig. 2.14a) and a large amount of cancellous bone ingrowth from the base of cancellous bone (Fig. 2.14b) were found in the whole spaces between HA granules into the whole depth, respectively. New bone adhered to HA directly.

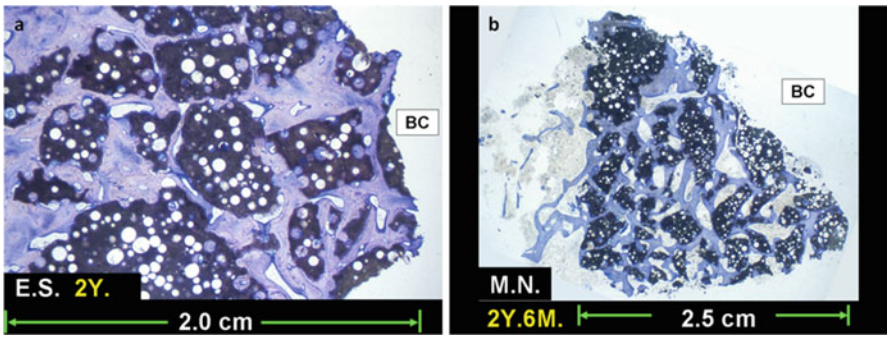

Fig. 2.14 (**a**) Retrieved specimen. Two years after revision THA. (**b**) Retrieved specimen. Two and a half years after revision THA

2.3.6.2 Animal Experiment in Bone Defect Cavity Under Unloaded Condition

Mixtures of G-4 (0.9–1.2 mm) and G-6 (3.0–5.0) HA granules as in clinical cases were filled into the cavity of 2 cm in diameter and 10 cm in length made at the proximal end of the tibia of goat (Fig. 2.15a). The proximal part of the tibia was cancellous bone and the distal part was cortical bone. Eighteen months after implantation, the animal was sacrificed, and radiographs by X-ray of A-P view and lateral view and the cross section of several levels were taken (Fig. 2.15b). From these specimens non-decalcified hard sections were made. A small amount of the new bone had entered from the periphery (Fig. 2.15c, d). As the quantity of bone ingrowth was small, some HA granules that filled the cavity dropped out while making non-decalcified hard tissue specimens and some HA granules dislodged from the specimens.

In a clinical case, HA granules were filled in the weight-bearing area. However, in experimental studies HA granules were filled in non-weight-bearing areas. From these results, it can be assumed that in the weight-bearing area, a great amount of new bone entered into the spaces of the HA granules and moved to the deep area. However, in the non-weight-bearing area in animal experiment, bone ingrowth could be expected only at the peripheral area of the cavity to approximately 5 mm in depth and not dense.

2.3.6.3 Discussion

The advantages of HA are as follows: (1) HA is osteoconductive and bonds to the bone physicochemically; (2) immunoreactions can be completely ignored; (3) postoperative morphological changes and volume decreases do not occur if a

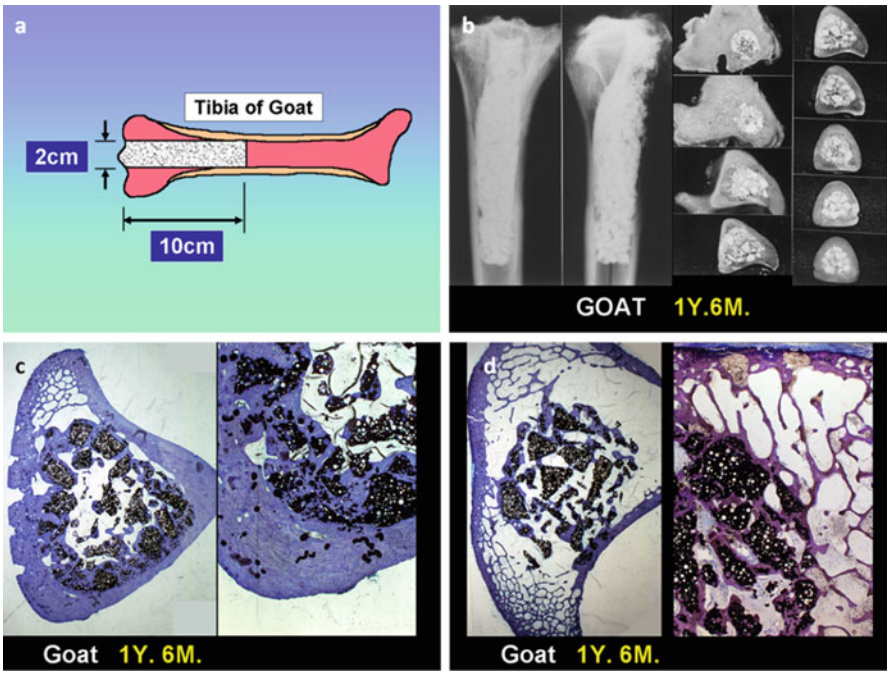

Fig. 2.15 (**a**) Scheme of animal experiment under unloaded condition as a control. (**b**) Radiograph. A-P view and lateral view (on the *left*) and cross sections (on the *right*). (**c**) HA granules were impacted into the cortical bone area. (**d**) HA granules were impacted into the cancellous bone area

mixture of adequate granule sizes is packed densely and firmly during surgery; (4) postoperative HA absorption, if any, is extremely small in amount and extremely slow; consequently, osteoconductivity can be continued; and (5) the occurrence of osteolysis by polyethylene wear particles at the interface of the bone is extremely few, because osteolysis can be recovered by osteoconduction of HA. We suggest that the reason for the marked pain-relieving effect is that there were neither changes in the shape of packed HA granules nor movement of the component, as HA granules were packed firmly and stably, bonded to the bone physicochemically, and fixed with bone cement mechanically.

The empty space or void at the interface between HA granules and bone immediately after surgery gradually disappeared within 3 months because new bone tissues entered into the space between the HA granules from the surface of the bony cavity. After filling HA granules into the cavitary deficiency, the sclerotic bone around the loosened socket changed to cancellous bone over a period of 1–3 years following revision surgery. This could be explained by the fact that bone ingrowth into the spaces of HA granules from the surrounding sclerotic bone was obtained, and the HA granules may have physicochemically bonded to the entire surface of the sclerotic bone wall. This phenomenon was very similar to bone union after nonunion of fracture.

On the retrieved studies, HA granules had formed a homogeneous mass, which was difficult to make a drill hole in or to cut with a chisel, and it adhered to the bone very firmly. Histologically, bone ingrowth was obtained 2 years and 2.5 years after surgery in the majority of the spaces between HA granules to the entire depth of about 2 cm and 2.5 cm, respectively. Consequently, if HA granules were filled very firmly and stably, a very strong new acetabulum could be reconstructed.

In the retrieved case, HA granules were filled in the weight-bearing area. However, in an animal experiment using a tibia of a goat, HA granules were filled in the non-weight-bearing area, and much less bone ingrowth into the spaces of HA granules was obtained. Consequently, excellent results can be expected when a mixture of several grain sizes of HA is packed densely and firmly during surgery into the massive defect of the bone in the weight-bearing area.

In conclusion, bone ingrowth over 2.5 cm in depth could be expected in weight-bearing area. However, it could not be expected over 5 mm in non-weight-bearing area.

As one of the complications, spaces between HA granules at nearby bone at the laterosuperior lesion (zone I) appeared. In this case the filling of HA granules may not have been dense near the bone base at the laterosuperior lesion (zone I), because the superior peripheral deficiency was covered with bone cement after filling with HA granules. As a result, continuous micromotion probably caused occurrences of the gaps before sufficient bone growth could provide bonding. If the superior peripheral deficiency had been covered by an allograft plate, such as tibial plateau, the HA granules would probably have filled the spaces more satisfactorily.

In the second generation, complications due to spaces between granules and the neighboring bony base at the laterosuperior lesion of the acetabulum have not been observed, and there was no socket migration, although breakage of the hook of Kerboull cross-plate was observed.

2.4 Other Clinical Applications

2.4.1 Bony Defect After Resection or Curettage of Bone Tumor

Bone ingrowth behaviors into the spaces of HA granules filled in the massive bony cavity are different in the weight-bearing area and in the non-weight-bearing area.

In the weight-bearing area, as shown in the clinical cases of massive bony defect of the pelvis at revision surgery, bone ingrowth could attain into the deep area. However, as shown in animal experiment of the massive bony defect of the tibia of the goat, bone ingrowth could not attain into the deep area in the non-weight-bearing area. Firm and stable filling of HA granules into the cavity is indispensable in both weight-bearing area and non-weight-bearing area. Otherwise, bone ingrowth could not be expected.

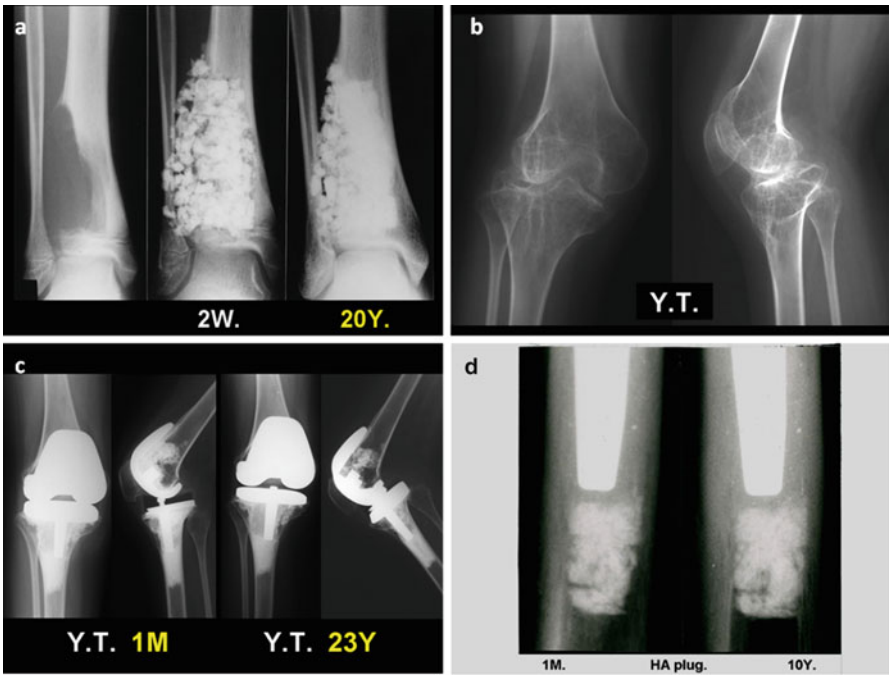

Fig. 2.16 (**a**) HA granules were filled into the cavity after resection of bone tumor in the tibia (*left*) before surgery, (*middle*) 2 weeks after surgery, and (*right*) 20 years after surgery. (**b**) Juvenile rheumatoid arthritis (*JRA*). 8 years old. Before surgery. (**c**) JRA. One month after surgery (*left figure*) and 23 years after surgery (*right figure*). A-P view and lateral view. (**d**) HA blocks were used as plugs at the distal end of the stem at THA. One month (*left figure*) and 10 years (*right figure*) after THA

2.4.1.1 Clinical Case 1: Giant Cell Tumor at the Distal End of the Tibia

This patient was operated on at 14 years old. HA granules were filled into the bony cavity and overfilled into the outside of the tibia, 20 years after surgery; on the radiograph in the weight-bearing area, bone ingrowth could be obtained densely into the whole spaces of HA granules. However, in the outside area of the tibia, which was non-weight-bearing area, dense bone ingrowth could not be obtained into the spaces of HA granules and the HA granules were retained (Fig. 2.16a).

2.4.1.2 Clinical Case 2: Juvenile Rheumatoid Arthritis (JRA)

This patient suffered from JRA since 8 years old. The multiple joints were destroyed, especially hip and knee bilaterally. This patient could not walk over 10 years due to flexion contracture of the knee bilaterally. This patient was operated on with total knee arthroplasty bilaterally. At surgery, cortical dense bone changed

to very thin and cancellous bone changed to fatty marrow bone completely in both femur and tibia, especially in tibia (Fig. 2.16b). At surgery, HA granules were filled steady after removing fatty marrow, and HA granules were filled firmly into the bony cavity and atrophic bone marrow.

In this case, HA granules were filled into the weight-bearing area. Twenty-three years after surgery, bone ingrowth was obtained into the whole spaces of HA granules and very stable condition was continued on the radiograph (Fig. 2.16c). This patient could walk in the room after surgery.

2.4.1.3 Clinical Case 3: Bone Plug at the Distal End of the Stem in Cemented Total Hip Arthroplasty

In order to fill the bone cement strongly into the femoral canal, a bone plug is used at the end of the stem. For bone plug, bone block or plastic plugs are used, but a plastic plug is not stable. When we have no bone block, HA blocks are used. When a few number of small HA blocks are used, a very stable condition can be obtained.

In this case, as the HA blocks are filled in the weight-bearing area, bone ingrowth into the whole spaces of HA granules can be obtained (Fig. 2.16d).

2.4.2 Discussion

Stable bone condition could be made and continued, after HA granules were filled into the bone base even after bone marrow changing to fatty marrow due to degeneration by disease. Because crystalline HA exhibits excellent osteoconduction and is not resorbable, when used in the IBBC technique, osteoconductivity develops and continues for the lifetime of the patient. Such an excellent function was found in only the crystalline HA-based IBBC technique.

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