Musculoskelet Surg (2009) 93:89–96
DOI 10.1007/s12306-009-0028-0

CASE REPORT

Major bone defect treatment with an osteoconductive bone substitute

Stefania Paderni · S. Terzi · L. Amendola

Received: 13 October 2008 / Accepted: 22 April 2009 / Published online: 16 June 2009

Abstract A bone defect can be provoked by several pathological conditions (e.g. bone tumours, infections, major trauma with bone stock loss) or by surgical procedures, required for the appropriate treatment. Surgical techniques currently used for treating bone defects may count on different alternatives, including autologous vascularized bone grafts, homologous bone graft provided by musculoskeletal tissue bank, heterologous bone graft (xenograft), or prostheses, each one of them dealing with both specific advantages and complications and drawbacks. The main concerns related to these techniques respectively are: donor site morbidity and limited available amount; possible immune response and viral transmission; possible animal-derived pathogen transmission and risk of immunogenic rejection; high invasiveness and surgery-related systemic risks, long post-operative. physical recovery and prostheses revision need. Nowadays, an ideal alternative is the use of osteoconductive synthetic bone substitutes. Many synthetic substitutes are available, used either alone or in combination with other bone graft. Synthetic bone graft materials available as alternatives to autogeneous bone include calcium sulphates, special glass ceramics (bioactive glasses) and calcium phosphates (calcium hydroxyapatite, HA; tricalcium phosphate, TCP; and biphasic calcium phosphate, BCP). These materials differ in composition and physical properties fro each other and from bone (De Groot in Bioceramics of calcium phosphate, pp 100–114, 1983; Hench in J Am Ceram Soc 74:1487–1510, 1994; Jarcho in Clin Orthop 157:259–278, 1981; Daculsi et al. in Int Rev Cytol 172:129–191, 1996). Both stoichiometric and non-stoichiometric HA-based substitutes represent the current first choice in orthopedic surgery, in that they provide an osteoconductive scaffold to which chemotactic, circulating proteins and cells (e.g. mesenchymal stem cells, osteoinductive growth factors) can migrate and adhere, and within which progenitor cells can differentiate into functioning osteoblasts (Szpalski and Gunzburg in Orthopedics 25S:601–609, 2002). Indeed, HA may be extemporarily combined either with whole autologous bone marrow or PRP (platelet rich plasma) gel inside surgical theatre in order to favour and accelerate bone regeneration. A case of bifocal ulnar bone defect treated with stoichiometric HA-based bone substitute combined with PRP is reported in here, with a 12-month-radiographic follow-up.

Keywords Bone defect · Hydroxyapatite · Bone substitute · Open fracture

Introduction

A bone defect can be provoked by several pathological conditions (e.g. bone tumours, infections, major trauma with bone stock loss) or by surgical procedures, required for the appropriate treatment. Surgical techniques currently used for treating bone defects may count on different alternatives, including autologous vascularized bone grafts, homologous bone graft provided by musculoskeletal tissue bank, heterologous bone graft (xenograft), or prostheses, each one of them dealing with both specific advantages and complications and drawbacks. The main concerns related

S. Paderni (✉) · S. Terzi · L. Amendola
UO Ortopedia e Traumatologia Ospedale Maggiore,
Largo Nigrisoli, 2, Bologna, Italy
e-mail: stefania.paderni@ausl.bologna.it

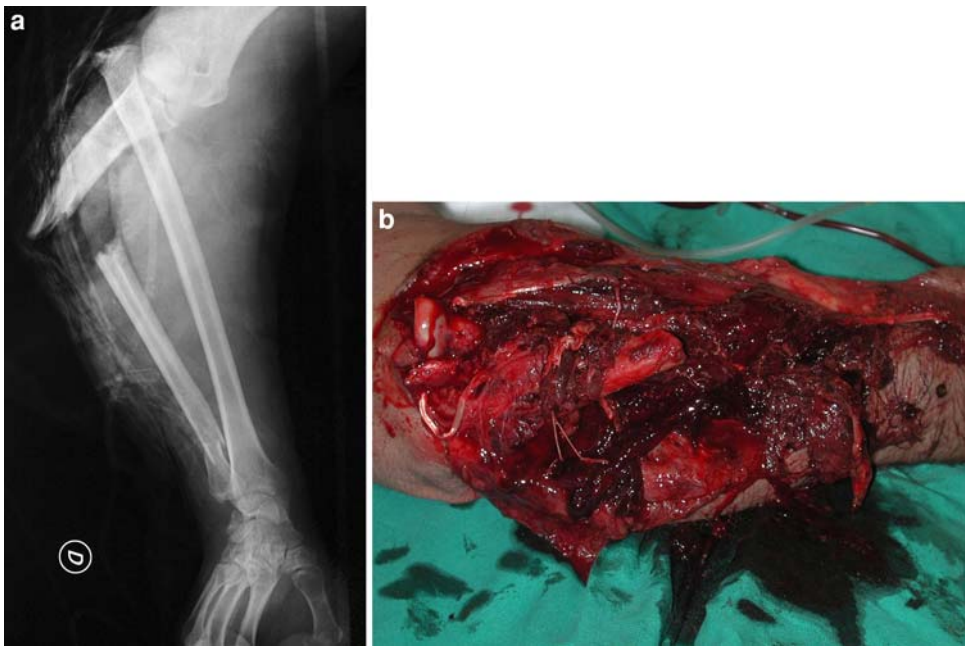

Fig. 1 Right Monteggia's injury, ulnar bifocal exposed fracture (IIIB degree) with wide contamination

to these techniques respectively are: donor site morbidity and limited available amount; possible immune response and viral transmission; possible animal-derived pathogen transmission and risk of immunogenic rejection; high invasiveness and surgery-related systemic risks, long post-operative. physical recovery and prostheses revision need.

Nowadays, an ideal alternative is the use of osteoconductive synthetic bone substitutes. Many synthetic substitutes are available, used either alone or in combination with other bone graft. Synthetic bone graft materials available as alternatives to autogeneous bone include calcium sulphates, special glass ceramics (bioactive glasses) and calcium phosphates (calcium hydroxyapatite, HA; tricalcium phosphate, TCP; and biphasic calcium phosphate, BCP). These materials differ in composition and physical properties from each other and from bone [1–4]. Both stoichiometric and non-stoichiometric HA-based substitutes represent the current first choice in orthopedic surgery, in that they provide an osteoconductive scaffold to which chemotactic, circulating proteins and cells (e.g. mesenchymal stem cells, osteoinductive growth factors) can migrate and adhere, and within which progenitor cells can differentiate into functioning osteoblasts [5]. Indeed, HA may be extemporarily combined either with whole autologous bone marrow or PRP (platelet rich plasma) gel inside surgical theatre in order to favour and accelerate bone regeneration.

A case of bifocal ulnar bone defect treated with stoichiometric HA-based bone substitute combined with PRP is reported in here, with a 12-month-radiographic follow-up.

Clinical case

A 55-year-old male was admitted in our Emergency Room in August 2005. He was a poly trauma patient, due to work accident, with multiple and diffuse penetrating wounds, severe chest trauma, right Monteggia's injury, ulnar bifocal open fracture (grade IIIB) and severely contaminated (Fig. 1a, b).

Surgical debridment, reduction and stabilization with an external fixator were immediately performed, but the external fixator was removed 20 days after surgery because of a bone/pin interface absorption. Skin and bone necrosis (at proximal ulna) also occurred. Both local tissues conditions and blood tests revealed a infection. For this reason, 5 cm long necrotic ulnar segment and radial head were resected and local antibiotic therapy (gentamycin beads) was administered into the ulnar bone loss. The wound was then covered by an autologous myocutaneous flap and an articulated elbow external fixation was applied to provide stability (Fig. 2a, b).

E.v. antibiotic therapy based on clindamycin and gentamycin was administered since admission, according to the standard surgical protocol for open fractures. Afterwards, on the basis of microbiological analysis results, antibiotic therapy was replaced by ciprofloxacin and ceftazidime followed by i.m. injection of teicoplanin and oral rifampicin for 45 days at a therapeutic range.

Two months after primary surgery, inflammatory field and blood laboratory parameters were normalized and skin conditions became satisfying, showing no persisting infection. Gentamycin beads were removed and the bone gap was

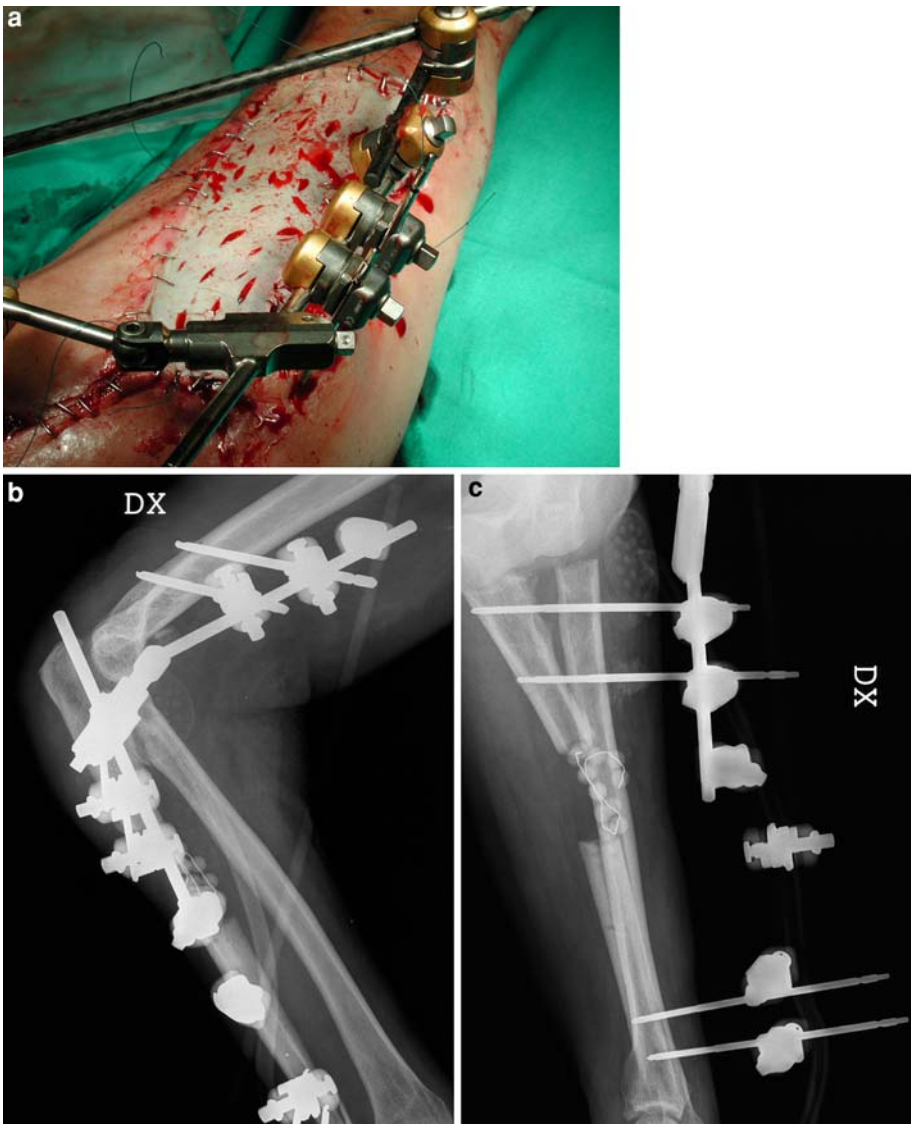

Fig. 2 **a** Wound covered by cutaneous preformed flap, articulated elbow external fixation applied to ensure stability. **b** Ulnar necrotic segment and radial head were resected. **c** Gentamycin ball chains was put inside the ulnar bone loss

filled with a custom-made 5 cm-long cannulated cylindrical highly porous (90%) scaffold, made up of biomimetic stoichiometric hydroxyapatite (HA) (Fin-Ceramica Faenza S.p.A.). The bone graft substitute consisted in a sterile cylinder made up of highly porous (90%) hydroxyapatite, with an external diameter of 1.6 cm and an inner diameter of 0.8 cm. The pores size diameter ranged from 200 to 500 μm (macroporosity), whereas the interconnection pores ranged from 80 to 200 μm (microposity). The cylinder was customized on patient needs, acquiring CT-scan image of the bone gap few weeks before the implant. The scaffold exhibited a compressive strength of 1.5 MPa, which is lower than human cancellous bone one [6]. In order to fix and stabilize the customized the siynthetic bone graft between proximal and distal bone remains, an intra-medullary Kirshner-wire (K-wire) was applied. To improve the healing process, the porous hydroxyapatite cylinder was loaded with autologous platelet rich plasma (PRP gel) (Fig. 3a–c).

Unfortunately, an additional fracture occurred during surgery in the proximal part of the bioceramic bone graft, therefore an immobilization of the elbow for 5 weeks was needed, by using an external orthesis hardware.

Two months after surgery K-wire was removed, but 3 weeks later a non-union was found at the proximal bone-graft interface, with loss of alignment. During the surgical revision, graft osteointegration was observed both at proximal and distal interfaces, with neo-vascularisation of the graft, coming from muscle connection. Migration and loss of alignment appeared where graft fracture previously occurred.

A rigid fixation with cortical LCD plate and screws was performed and additional PRP was introduced (Fig. 4a, b).

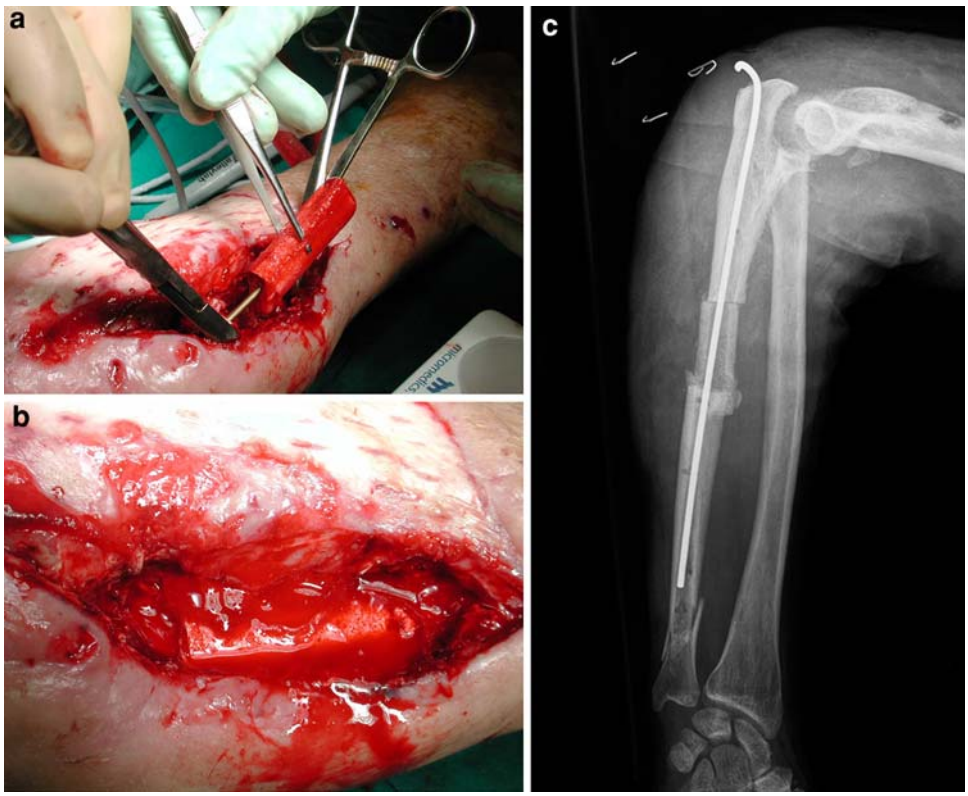

Fig. 3 **a** Gentamycin beads removal and bone defect filling with a 5 cm long-"custom-made" cannulated HA-based cylinder, fixed with an intramedullary K-wire; **b** bone substitute loaded with PRP; **c** post-operative. X-ray

At the end of surgery, an elbow articulated tutor was applied in order to ensure the highest protection. Post-operative course was regular without any sign of infection.

Thirty weeks after second surgery and one year since the trauma occurred, standard X-ray examination and 2D CT scan confirmed proximal and distal graft good osteointegration, with complete fracture healing (Fig. 5). Functional recovery was almost complete (Fig. 6).

Discussion

Bone defects treatments include many different surgical techniques and options, each with specific disadvantages and complications.

From a biological and an economical standpoint, the autologous vascularized bone graft is currently defined as gold standard, since it is not associated with any immunological related adverse reactions and possesses osteoconductive, osteoinductive and osteogenic potential. On the other side, long operating time, technically demanding surgical treatments and donor site specific morbidity represent the most concerning drawbacks. Moreover, it is difficult to obtain sufficient amount of bone tissue when a major bone loss stock has to be treated and an overall high incidence of complications is reported in literature [7–10].

Homologous bone grafts provided by accredited musculoskeletal tissue banks are not associated to donor site morbidity, and are available in sufficient amount; however, allogenic bone graft can elicit host's immune reactions and may increase the risk of infection. Heterologous grafts are associated with possible pathogen transmission and risk of immunogenic rejection; furthermore, graft integration requires longer time, with increased risk of fracture [11].

Different synthetic biomaterials have also been investigated and proposed as bone substitutes: calcium phosphate-based implants have the most similar composition to human bone, in particular those made of hydroxyapatite (HA) which usually show a calcium/phosphate (Ca/P) ratio of 1:67.

Synthetic hydroxyapatite exhibits a higher biocompatibility as it does not evoke any inflammation, immune reactions or infections and is gradually degraded through cellular phagocytosis and extracellular dissolution processes [12]. In addition, this material is always widely available and, thanks to its own structural and physico-chemical peculiarity, is characterized by high osteoconduction and osteopromotion. Indeed, porous HA provides an excellent environment for cells migration from host bone tissue, colonization, growth and eventually cells differentiation.

Osteoconduction is proportional to porosity and it improves in presence of an higher degree of total

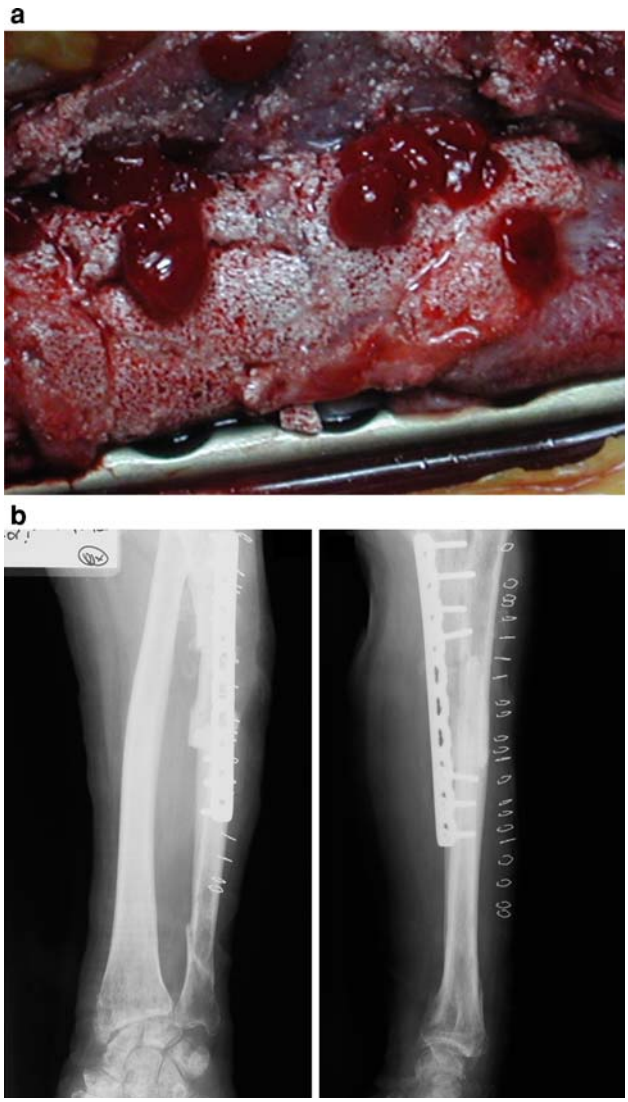

Fig. 4 **a** Rigid internal osteosynthesis with plate and screws and further PRP apposition. **b** X-ray after the revision surgery

porosity with a bimodal distribution (macro- and micro-porosity) [13, 14]. High porosity and presence of interconnections help new bone formation, osteoprogenitor cells distribution and neoangiogenesis [15], otherwise osteoconduction decreases when magnesium and carbonic impurities are present inside bioceramic scaffolds [16]. On the other hand, low scaffold density causes a reduction of bone substitute mechanical strength and an increase of graft fracture risk. For this reason, a fracture occurred inside bio-ceramic graft implanted in our patient during surgery and lead to the loss of alignement and delayed union.

Despite of being osteoconductive, the HA is not osteoinductive: in order to achieve a satisfying bone ingrowth, further factors should be added, such as multipotential stromal stem cells or PRP growth factors [17].

Several studies carried out on bioceramic scaffold implanted under myocutaneous flap of athymic mice, showed that new bony tissue was produced only in the hydroxyapatite cylinder loaded with bone marrow stromal cells, whereas in the control acellular scaffold a new-vascularization with mesenchimal tissue formation was noticed [18, 19]. Another study showed that when an HA-based scaffold was used to fill a surgically induced bone stock loss in a sheep model, new bone formation was evident also in the non-loaded cylinder [15].

Kon et al. in 2000 proved that whereas in scaffold loaded with bone marrow stromal cells the new bony tissue was observed in the macroporous and on the cylinder surface, in the scaffold without stromal cells loading bone formation was limited to the external surface and the bone scaffold unit mechanical strength turns out inferior [20].

Many authors have studied the effect of different growth factors on marrow stromal cells proliferation and differentiation: Martin et al. showed that FGF-2 promotes bone marrow stromal cells proliferation in vitro, maintaining cells in a more immature state. Moreover, they found out that combination between stromal cells and bio-ceramic scaffold allowed cells in vivo differentiate and form bone tissue [21].

Therefore, HA, whose chemical composition is very similar to the inorganic component of human bone, may be used in regenerative medicine with the purpose of either filling bone defect (osteoconductive function), carrying growth factors (osteoinductive potential) or cells (osteogenic potential) [22]. The hydroxyapatite scaffold is manufactured in different shapes and dimension/volumes: paste, granules or chips, blocks and cylinders, even customized or loaded with cells or antibiotics.

HA used in case of limited bone defect has been studied by several authors and in different fields, such as odontostomatology [23, 24], neurosurgery [25–27], and particularly orthopaedics [28, 29]. For instance, metaphyseal defects resulting from reduction of tibia compression fracture [30, 31] and bone cavities caused by courettage of benign tumour [32, 33] can be successfully filled with HA graft. Moreover, osteomyelitic cavities following surgical debridment can be packed with HA blocks combined with antibiotics powder; femoral peri-prosthetic bone defects can be reconstruct using HA granules to limit the amount of allogenic tissue required to increase stability in case of femoral revision arthroplasty [34, 35].

On the contrary, only few papers describe the clinical use of massive graft made of HA-based scaffolds. Marcacci et al. treated four patients affected by massive segmental bone defect, through a bio-engineered tissue approach: mesenchymal stem cells were collected from autologous bone marrow were first in vitro culture expanded, then loaded into bioceramic scaffold [29]. Authors published

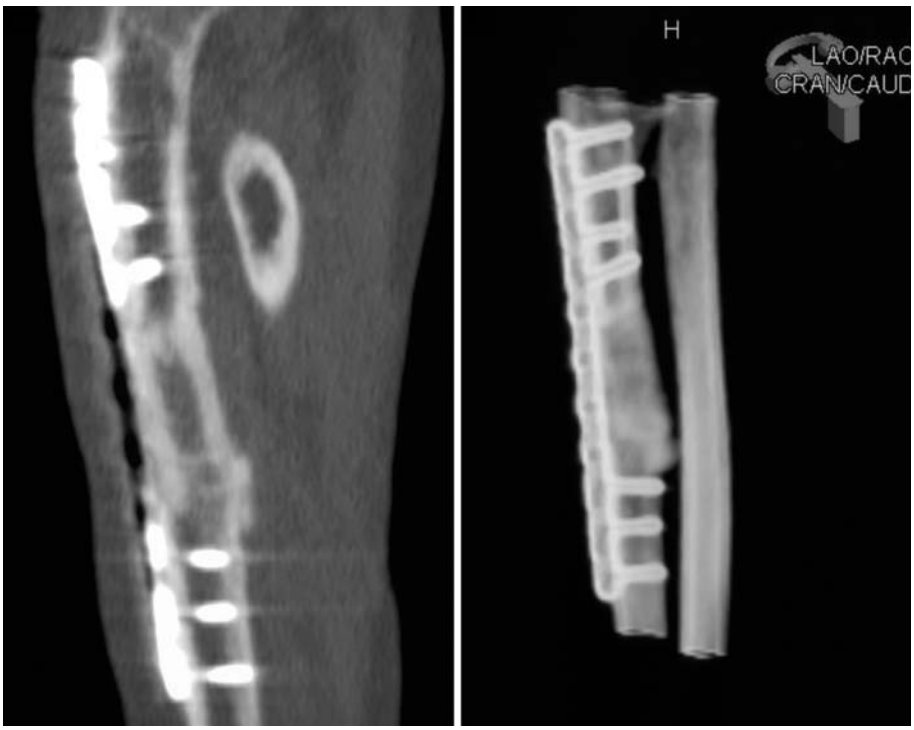

Fig. 5 Thirty weeks after second surgery and 1 year since the trauma occurred, standard X-ray and 2D CT scan confirmed proximal and distal graft osteointegration, with fracture healing

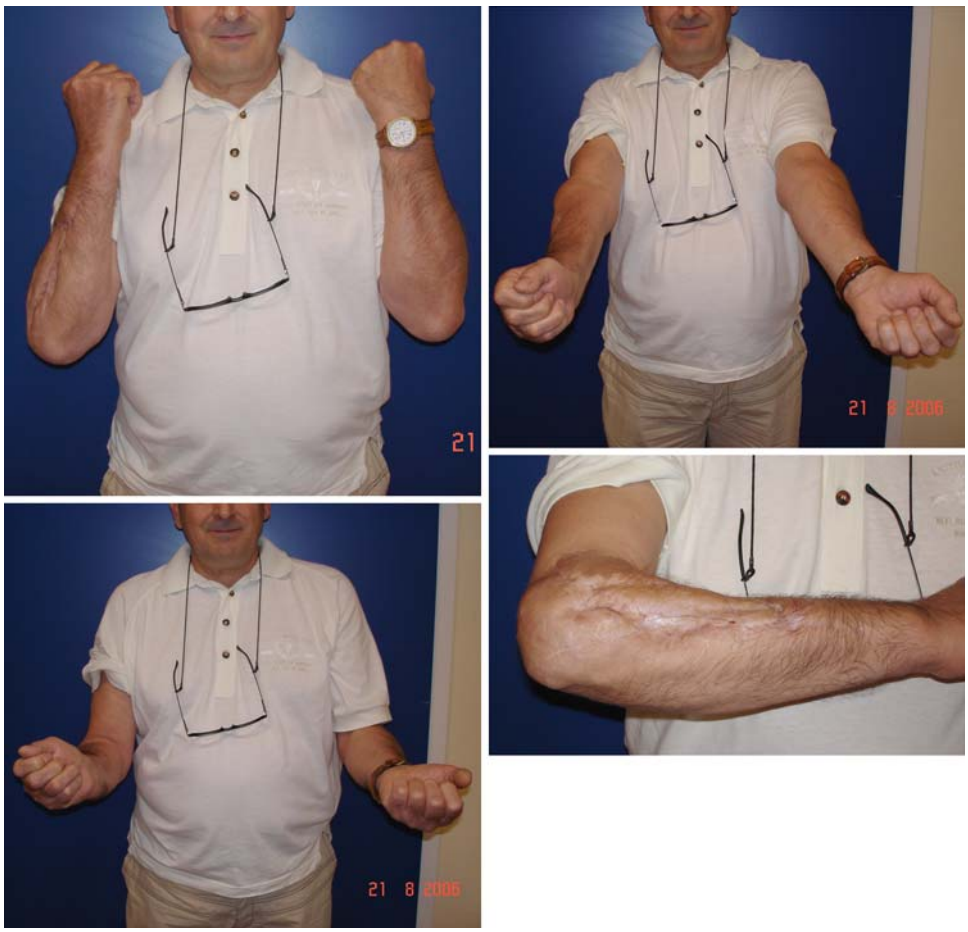

Fig. 6 Functional recover was almost complete

very promising short- [28] and long- [29] term results: total absence of complication and adverse events related to the bio-ceramic, evidence of a complete bone-scaffold union, long-term clinical and radiographic effectiveness (up to 7 years follow-up).

The patient we have treated was affected by severe open ulnar fracture combined with contamination and necrosis of soft tissue, periosteal devascularisation, and consequent bone necrosis whose debridment provoked a 5 cm-long bone defect.

Nowadays, combination of mature stromal cells and HA-based scaffolds represent the most useful tissue regeneration approach to be used in a clinical setting: unfortunately, when a considerable amount of progenitor stem cells is needed, it is rather difficult to keep cells in an in vitro undifferentiated stage and consequences of their in vivo implantation are not totally known.

Therefore, the HA-based scaffold we decided to implant was not loaded with marrow stromal cells, but just PRP, which is rich in growth factors and can stimulate bone ingrowth. The clinical use of HA to fill bone defects and then induce an effective tissue regeneration has been deeply studying in last years and future prospective sounds very promising.

Conflict of interest statement The authors declare that they have no conflict of interest related to the publication of this manuscript.

References

1. De Groot K (1983) Ceramics of calcium phosphates: preparation and properties. In: De Groot K (ed) Bioceramics of calcium phosphate. CRC Press, Boca Raton, FL, pp 100–114
2. Hench LL (1994) Bioceramics: from concept to clinic. J Am Ceram Soc 74:1487–1510
3. Jarcho M (1981) Calcium phosphate ceramics as hard tissue prosthetics. Clin Orthop 157:259–278
4. Daculsi G, Bouler JM, Legeros RZ (1996) Adaptive crystal formation: in normal and pathological calcification, in synthetic calcium phosphate and related biomaterials. Int Rev Cytol 172:129–191
5. Szpalski M, Gunzburg R (2002) Bone void fillers in trauma surgery. Orthopedics 25S:601–609
6. Eijkelkamp MF, Hayen J, Veldhuizen AG, van Horn JR, Verkerke GJ (2002) Improving the fixation of an artificial intervertebral disc. Int J Artif Organs 25:327–333
7. Taylor GI (1983) The current status of free vascularized bone grafts. Clin Plast Surg 10:185–209
8. Vail TP, Urbaniak JR (1996) Donor-site morbidity with use of vascularized autogenous fibular grafts. J Bone Joint Surg Am 78(2):204–211
9. Marcacci M (2004) Impiego della bioingegneria per la rigenerazione del tessuto osseo e cartilagineo. Minerva Ortop Traumatol 55(5):209–226
10. Martinetti R, Belpassi A, Nataloni A, Biasimi V, Martignani G (1999) Porous hydroxyapatite as synthetic bone graft: physico-chemical characterisation. Atti Biomateriali, Roma
11. Donati D, Giacobini S, Gozzi E, Di Bella C, Mercuri M (2003) The results of the surgical treatment of bone tumors using massive homoplastic grafts. Chir Organi Mov 88(2):115–122
12. Nizard R, Bizot P, Kerboull L, Sedel L (1996) Biomatériaux orthopédiques. Encyclopédie Médico Chirurgicale 44-003:1–15
13. Martinetti R, Belpassi A, Nataloni A, Piconi C (2001) Porous hydroxyapatite cell carrier for tissue engineering. Key Engineering Materials 192–195:507–510
14. Martinetti R, Dolcini L, Belassi A, Quarto R, Mastrogiacomo M, Cancedda R, Labanti M (2004) Inspired porousity for cells and tissues. Key Engineering Materials 254–256(109):5–1098
15. Mastrogiacomo M, Muraglia A, Komlev V, Peyrin F, Rustichelli F, Crovace A, Cancedda R (2005) Tissue engineering of bone: search for a better scaffold. Orthod Craniofac Res 8:277–284
16. Cazalbou S, Bastiè C, Chatainier G, Theilgaard N, Svendsen N, Martinetti R, Dolcini L, Hamblin J, Stewart G, Di Silvio L, Gurav N, Quarto R, Overgaard S, Zippor B, Lemure A, Combes C, Reyi C (2004) Processing of Ca–P ceramics, surface characteristics and biological performance. Key Engineering Materials 254–256(83):3–836
17. Boyde A, Corsi A, Quarto R, Cancedda R, Bianco P (1999) Osteoconduction in large macroporous hydroxyapatite ceramic implants: evidence for a complementary integration and disintegration mechanism. Bone 24(6):579–589
18. Casabona F, Martin I, Muraglia A, Berrino P, Santi P, Cancedda R, Quarto R (1998) Prefabricated engineered bone flaps: an experimental model of tissue reconstruction in plastic surgery. Plast Reconstr Surg 101(3):577–581
19. Mastrogiacomo M, Cedola A, Komlev VS, Peyrin F, Burghammer M, Giannoni P, Cancedda R, Rustichelli F, Lagomarsino S (2004) Advanced X-ray micro-analysis of bone regenerated by bone marrow stromal cells. In: Proceeding 9th meeting ceramics, cells and tissues
20. Kon E, Muraglia A, Corsi A, Bianco P, Marcacci M, Martin I, Boyde A, Ruspantini I, Chistolini P, Rocca M, Giardino R, Cancedda R, Quarto R (2000) Autologous bone marrow stromal cells loaded onto porous hydroxyapatite ceramic accelerate bone repair in critical-size defects of sheep long bone. J Biomed Mater Res 49:328–337
21. Martin I, Muraglia A, Campanile G, Cancedda R, Quarto R (1997) Fibroblast growth factor-2 supports ex vivo expansion and maintenance of osteogenic precursor from human bone marrow. Endocrinology 138(10):4456–4462
22. Fabbri M, Nataloni A, Celotti GC, Ravaglioli A (1995) Production and characterization of hydroxyapatite-based porous bodies for medical applications. Fourth Euro Ceramics 810:9–116
23. Ferraz MP, Mateus AY, Sousa JC, Monteiro FJ (2007) Nano-hydroxyapatite microspheres delivery system for antibiotics: release kinetics, antimicrobial activity, and interaction with osteoblasts. J Biomed Mater Res A 81(4):994–1004
24. Carey LE, Xu HH, Simon CG Jr, Takagi S, Chow LC (2005) Premixed rapid-setting calcium phosphate composites for bone repair. Biomaterials 26(24):5002–5014
25. Staffa G, Servadei F, Nataloni A, Martinetti R (2003) Design of custom-made porous hydroxyapatite devices for the reconstruction of the skull: 6 years multicentric experience. J Appl Biomater Biomech 1:214
26. Staffa G, Nataloni A, Compagnone C, Servadei F (2007) Custom made cranioplasty prostheses in porous hydroxy-apatite using 3D design techniques: 7 years experience in 25 patients. Acta Neurochir 149:161–170
27. Van Havenbergh T, Berghmans D, De Smedt K, Arcangeli E, Nataloni A (2007) One step neuronavigated cranial vault tumor resection and porous hydroxyapatite custom made prosthesis reconstruction: a case report. In: Proceeding 11th meeting ceramics, cells and tissues

28. Marcacci M, Kon E, Quarto R, Kutepov SM, Mukhacev V, Lavroukov A, Cancedda R (2001) Repair of large bone defects by autologous human bone marrow stromal cells. Key Engineering Materials 192–195(105):3–1056
29. Marcacci M, Kon E, Mukhacev V, Lavroukov A, Kutepov S, Quarto R, Mastrogiacomo M, Cancedda R (2007) Stem cells associated with macroporous bioceramics for long bone repair: 6- to 7-year outcome of a pilot clinical study. Tissue Eng 13(5):947–955
30. Huber FX, McArthur N, Hillmeier J, Kock HJ, Baier M, Diwo M, Berger I, Meeder PJ (2006) Void filling of tibia compression fracture zones using a novel resorbable nanocrystalline hydroxyapatite paste in combination with a hydroxyapatite ceramic core: first clinical results. Arch Orthop Trauma Surg 126(8):533–540
31. Helbert MU, Ulrich C (2000) Metaphyseal defect substitute: hydroxylapatite ceramic. Results of a 3 to 4 year follow up. Unfallchirurg 103(9):749–753
32. Baer W, Schaller P, Carl HD (2002) Spongy hydroxyapatite in hand surgery—a five year follow-up. J Hand Surg (Br) 27(1): 101–103
33. Yamamoto T, Onga T, Marui T, Mizuno K (2000) Use of hydroxyapatite to fill cavities after excision of benign bone tumours. Clinical results. J Bone Joint Surg Br 82(8):1117–1120
34. Fujishiro T, Nishikawa T, Niikura T, Takikawa S, Nishiyama T, Mizuno K, Yoshiya S, Kurosaka M (2005) Impaction bone grafting with hydroxyapatite: increased femoral component stability in experiments using Sawbones. Acta Orthop 76(4):550–554
35. Nich C, Sedel L (2006) Bone substitution in revision hip replacement. Int Orthop 30(6):525–531