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The use of bone-graft substitutes in large bone defects: Any specific needs?

G.M. Calori *, E. Mazza, M. Colombo, C. Ripamonti

C.O.R., Orthopaedic Institute, G. Pini, University of Milan, Italy

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ABSTRACT

Introduction: The gold standard for restoring bone defects is still considered to be autologous bone grafting. However, clinical benefits are not guaranteed and donor-site complications and morbidity is not infrequent. Research is on-going for the development of alternative bone substitutes of both biological and synthetic origin. The purpose of this study was to evaluate the type of materials used and their efficacy for the treatment of large bone defects in traumatology and orthopaedic surgery.
Materials and method: A literature review was carried out of Embase and PubMed databases. Inclusion criteria were articles in English language focusing on the use of bone substitutes in trauma and orthopaedic surgery for the treatment of bone defects and included details on the structural, biological or biomechanical properties of the pure product. Furthermore, based on two clinical challenges, fracture non-union and impaction grafting we elaborated on the use of polytherapy for large bone defects as guided by the diamond concept.
Results: All the products indicated in this manuscript possess osteoconductive activities but have different resorption times and biomechanical properties. Bone graft substitute materials are used for a wide range of clinical applications even when the level of clinical evidence is low. The size and location of the defect and the local biological and mechanical environment as well as the biomechanical characteristics of the material determine the type of device that can be implanted in a bone defect.
Conclusion: Proper assessment of the biological and mechanical environment and accurate patient selection are necessary to judge the extent of therapy the injury warrants. A sound understanding of various aspects of biomaterial properties and their relation and influence towards bone healing is of utmost importance. We suggest the application of polytherapy for the treatment of large bone defects and advocate the use of the diamond concept as a guideline.

Introduction

The healing of fractures is a physiological process that results in bone union.[1] Studies have estimated that 5–10% of all fractures are associated with impaired healing, resulting in delayed union or non-union.[2–4] Bone defects are very challenging in orthopaedic practice; they can result from a high-energy traumatic event, from large bone resection for different pathologies such as tumour or infection, or from the treatment of complex non-unions (en-bloc resection). They can be considered critical in relation to the skeletal segment involved and the length of bone loss: 3 cm for the forearm, 5 cm in the femur and tibia, 6 cm in the humerus. Apart from the usual known techniques – such as distraction osteogenesis, autograft or arthrodesis – tissue engineering and regenerative medicine using biotechnologies can be very useful.[5]

Significant bone defects or post-traumatic complications may require bone grafting in order to fill the defect. Bone grafts fill spaces and provide support, and may enhance the biological repair of the defect. Bone grafting is a common surgical procedure; it has been estimated that 2.2 million grafting procedures are performed worldwide each year.[6,7]

The biological properties of bone grafts and bone graft substitutes are often described by the terms osteoinductivity, osteoconductivity and osteogenicity. Osteoinductivity is the ability of a graft to actively stimulate or promote bone formation.[8] Osteoconductivity is a property of the scaffold that allows the colonisation and ingrowth of new bone cells and sprouting capillaries due to its three-dimensional structure. Osteoconduction is mainly determined by the porosity properties of the scaffold and also in a lesser extent by its chemical and physical properties of the substrate that promote adhesion and cell growth.[9,42] The osteoconductive calcium phosphate bone graft substitutes allow attachment, proliferation, migration, and phenotypic expression of bone cells leading to formation of new bone in direct apposition to the biomaterial. Osteoconductivity is by definition a passive process.[42] Osteogenicity is related to the presence of bone-forming cells within the bone graft.[10]

* Corresponding author at: Reparative Orthopaedic Surgery Department, G. Pini, University of Milan, P.za Cardinal Ferrari 1, 20122 Milan, Italy.
Tel.: +39 02 58296903; fax: +39 02 58296905.
E-mail address: gmc@studiocalori.it (G.M. Calori).

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The mechanical properties of bone grafts and bone graft substitutes and their resistance to compression and torsion are influenced by their shape and size (massive, cortical or cancellous block, bone chips), the harvesting, processing and storage methods utilised, and the type of fixation used. The mechanical properties of bone graft substitutes are further dependent on their composition, shape, porosity properties and crystallinity.[42]

The optimal bone substitute should be osteoconductive, osteoinductive, osteogenetic, without risk of transferring infectious diseases, readily available, manageable, biocompatible, and bioresorbable. Moreover, it should induce minimal or no fibrotic reaction, undergo remodelling, and support new bone formation. From a mechanical point of view bone substitutes should have similar strengths to that of the bone being replaced. Finally, it should be cost effective and available in the quantity required.[15]

Medical scientists started to focus their research on enhancement of bone healing using other active biological substances as alternatives to autologous bone grafting (ABG) due to its limited availability, and to other problems in managing ABG such as the prolonged surgical time and the additional donor-site morbidity.[13,14,51–53] Technological evolution and better understanding of bone-healing biology resulted in the development of numerous alternative bone graft substitutes with various effects on bone healing.[41] Numerous products containing hydroxyapatite, tricalcium phosphate, dicalcium phosphate, calcium sulphate or bioactive glasses are currently available for use in trauma and orthopaedic surgery.[15]

The diamond concept[11,12] suggests that in order to achieve uneventful fracture healing four parameters (osteogenic cells, osteoconductive scaffold, growth factor and a stable mechanical environment) are mandatory. Later vascularity at the defect site was added as an important factor in the fracture healing process.[12] Several studies have applied some or all the principles of the diamond concept in the clinical setting with satisfactory results.[16–23]

However, an evidence-based guideline to assist surgeons in selecting the best product for specific clinical indications is not yet available. The purpose of this study therefore was to provide an overview of the use and efficacy of bone graft materials/substitutes for the treatment of such clinical challenges as bone defects, and non-union treatment.

Materials and methods

Bone graft and bone graft substitute materials were selected on the basis of the following criteria: (1) indicated for use in trauma and orthopaedic surgery; (2) available on the market at the time of this study; (3) they are biological bone substitutes such as demineralised bone matrix (DBM), allograft, or synthetic substitutes such as calcium phosphate, calcium sulphate or bioactive glass. Products were excluded if they were indicated for use only in craniomaxillofacial surgery.

Using the PubMed and Embase search engine, a search of the published series on bone substitutes was performed on 1st November 2010. The following keywords were used: "bone substitutes" OR "review" OR "bone defect" AND "biomaterials" OR "scaffolds" OR "calcium phosphate/sulphate" OR "growth factors" OR "mesenchymal stem cells" OR "autologous bone graft" OR "BMPs".

Brand names and composition of all products were used as search terms in the available online databases (Embase, PubMed). Titles and abstracts were screened and only papers that reported on structural, biological or biomechanical properties or on clinical indications in trauma and orthopaedic surgery were considered eligible. Exclusion criteria were: case reports or reports referring to children (age <16 years), editorials, and articles other than the English language. All references in the selected manuscripts were reviewed in order to ensure that no papers had been missed with the chosen search strategy. Data from the accumulated manuscripts were collected, mainly those addressing the issues of this review. Furthermore, based on two clinical challenges, non-union treatment and bone impaction grafting treatment, we elaborated on the use of polytherapy for large bone defects as guided by the diamond concept.

Results

The initial literature search resulted in more than 250 papers. After screening of all titles and abstracts and exclusion of duplicates a total of 200 eligible manuscripts were reviewed. After reading the full text of all eligible manuscripts, some papers were excluded and others were added based upon the reference list. Based on the manuscripts that fulfilled all the inclusion criteria a short overview of bone substitute materials and their key characteristics and indication areas is presented below.

Biological substitutes

In this category autograft, allograft and demineralised bone matrix have been included

Autograft

The use of ABG is still considered the gold standard for augmentation of bone healing. Theoretically, it possesses all three desirable properties of graft materials: osteogenicity, osteoinductivity and osteoconductivity. However, failure rates have been reported to be as high as 50%, and this can be explained by different types of harvesting, handling, the implantation method used, and differences between patient conditions and bone vitality.[50] The reported healing rates where ABG has been used as a biological stimulant for the treatment of large bone defects shows a range of 60–100%.[23,50]

Nevertheless autologous bone grafting has some significant disadvantages. Firstly, the harvesting process has been associated with perioperative and post-operative complications and morbidity. Secondly, a prolonged surgical and anaesthesiological time can cause a proportionally increased risk of infection.[51,52] Finally, the cost of harvesting can be equivalent to the cost of commercial available bone graft substitute products.[14,51–53]

Allograft

Allograft is a good alternative to ABG; avoiding donor-site morbidity and pain. It is relatively easy to obtain and manage. The major risk and disadvantage in using allografts is viral disease transmission and bacterial infection, especially when fresh implantations are performed. Recognised as "non-self", the allograft is attacked by the immune system. Allografts primarily showed osteoconductive power and less frequently osteoinductive properties due to the variable presence of growth factors. Allograft offers optimal osteoconductive and biomechanical characteristics due to its three-dimensional structure similar to that of human bone and the presence of collagen type 1 with all its above-cited biological properties. This characteristic depends on the type of allograft and the processing methods used to prepare, sterilise, and store it. It is important to realise that allograft quality is donor dependent and therefore will not always result in the same clinical outcome. Allografts, once implanted, follow the kinetics of physiological bone-tissue remodelling, the process achieving complete remodelling and replacement of the graft by newly formed bone. Incorporation of allograft bone begins with passive osteoconduction, and it differs according to the type of graft used; cortical grafts are usually incorporated by creeping substitution

through the process of intramembranous bone formation, whilst cancellous grafts are incorporated by enchondral bone formation along the osteoconductive framework. Allografts can be processed as a powder, granules, cancellous or cortical chips, wedges, strips or blocks. Potential applications in the trauma setting include reconstruction of large bone defects, augmentation in fracture repairing, and treatment of non-unions. They can be used as fillers (in chips) or as a mechanical support (wedge, block or strips).

Allograft has been used quite frequently with the bone impaction grafting technique. The bone impaction grafting technique offers a biological solution for coping with bone stock loss during revision THA and was first described by Slooff and colleagues for the acetabular side.[72] The bone impaction grafting technique has three main characteristics: first of all, the closure of all segmental bone defects with metal meshes (secured with bone screws) in order to contain these defects. Secondly, restoration of bone stock by filling the bone defect with vigorously impacted morselized cancellous bone grafts (MCB) using various shaped impactors and a metal hammer. Next, bone cement is introduced in the reconstruction and pressurised to force it into the bone graft layer. Finally, a new acetabular cup is implanted in the reconstruction to complete the technique. In general this technique has led to excellent short- and long-term clinical results.[73–76]

Due to the expected shortage of bone grafts for surgical procedures in the future and the risk of virus transfer when using allograft bone, there has been an increased interest in bone substitutes.[6] From a biological point of view ceramic calcium phosphates, such as tri-calcium phosphate (TCP) and hydroxyapatite (HA) are widely considered as promising bone graft substitutes.

Mixtures of MCB and TCP-HA granules combined with the bone impaction grafting technique have been mechanically studied in both acetabular and femoral in vitro models. In general, the implant stability on both the acetabular[77,78] and femoral[79,80] side improved relative to reconstructions with pure allograft bone. In an animal model swift osteointegration and absence of third body wear was observed.[81] Clinically good short-term results of bone impaction grafting with ceramic bone graft substitute materials were obtained.[67,68] Non-surprisingly these results were obtained with following the four domains of the diamond concept and providing vascularity by means of burr holes in the acetabular socket.

Demineralised bone matrix

DBM is produced by specific demineralisation (using acid extraction) of allograft, and it contains type-1 collagen, non-collagenous proteins, and a small amount of osteoinductive growth factors such as BMPs, transforming growth factor beta (TGF-β 1-2-3), and insulin-like growth factor (IGF).[24] All of these factors, when implanted, are able to work in combination in order to create a potential osteogenic response.[60–64] A large number of demineralised bone matrix formulations are available on the market, differing in refinements and manufacturing processes. These are available as granules, strips, putty, gel and freeze-dried powder. They can be used alone or in combination with other materials such as allogeneic bone chips and calcium sulphate granules. In animal studies they have been shown to have osteoinductive effects, but there are no level-I studies in humans. Moreover, in large bone defects and non-unions there is a lack of clinical and scientific evidence. However, DBM has demonstrated a lower osteoinductive capacity compared to ABG[25] and has shown a high and questionable variability of the concentration of BMP-2 and BMP-7 in some products,[26] depending on the manufacturer and manufacturing process.[27]

Synthetic bone graft substitute materials

Synthetic bone graft substitute materials are mineral structures similar to the mineral content of human bone including calcium phosphate or calcium phosphate ceramics such as hydroxyapatite (HA), coralline hydroxyapatite, tricalcium phosphate (TCP) and biphasic calcium phosphate (BCP = HA + TCP). They are made from inorganic, non-metallic materials with a crystalline structure, usually processed at a high temperature (sintering). Most synthetic bone substitutes are hard, porous yet brittle. They have only osteoconductive properties.[42]

Calcium phosphate

Calcium phosphate such as TCP and HA were introduced for clinical use in the 1980s.[28] Nowadays, different calcium phosphate grafts are available on the market. They can be separated into HA, TCP and biphasic materials on the basis of their chemical composition.

Structural properties are related to the method of production; they allow us to distinguish between ceramics and cements. A ceramic is defined as an inorganic phase solid prepared by thermal treatment and subsequent cooling. For calcium phosphate ceramics thermal treatment is called sintering. The sintering process removes volatile chemical constituents and increases the size of crystallisation, thus resulting in a porous and solid material. Cements consist of a mixture of calcium phosphates which can be applied as a paste that usually gets hard at the application site due to precipitation or exothermic reactions. Cements, unlike ceramics, have a solid structure characterised by limited porosity and pore size. They have been shown to induce a biological response similar to that of bone.[29] In general, calcium phosphates are considered to be osteoconductive.

The osteoconductive properties of these materials depend on the pore size, porosity and degradation potential of the bone substitute. The optimal pore dimension for ingrowth of new bone is between 150 and 500 μm in size (macroporosity).[43,44] Based upon their structures, HA and TCP ceramics offer a suitably macroporous structure to facilitate new bone ingrowth. Microporosity (e.g. pores <5 μm) is considered important for the bioresorbable properties of the material and the diffusion of nutrients.[45]

Bioresorption by dissolution or cell mediated by osteoclast, macrophages or giant cells of HA seems to be related to its manufacturing process (i.e. crystallinity, sintering temperature), surface area and porosity properties (% porosity, interconnected or surface porosity) whereas the calcium phosphate cement seems to only to be mainly degraded by osteoclasts.[30–34] Calcium phosphates generally provide limited biomechanical support due to their low tensile resistance. TCPs are less brittle than HA; however, during degradation (TCP faster degradation than HA) there is a subsequent loss of mechanical strength. TCP and calcium phosphate cement composites are degraded by osteoclasts within approximately 1 year (TCP) or 2–5 years (HA).[29]

Clinical indications are related to specific structural, biological and biomechanical properties of the graft. TCP ceramics are useful to fill small bone defects after bone tumour resection or after bone loss in fresh fracture in e.g. tibia, humerus, calcaneus, radius and vertebral surgery, but they are not indicated in large bone defects.

HA is a common material and is available in non-absorbable or absorbable solid forms and as granules and it has been used successfully in larger bone defects.[67,68] Limitations of these materials are that ceramics are available only in the form of powder, cements or porous implants, and they have some disadvantages such as difficulty in implanting, usually a long time required for complete integration and replacement by newly formed bone, and the inability to fill irregular gaps. They are

therefore not very useful when used alone in the treatment of atrophic non-unions of long bones due to lack of growth factors.[35] However, they have proven their worthiness in the restoration of large bone defects with the bone impaction grafting technique revision THA.[67,68]

Calcium sulphate

Calcium sulphate has been used as bone void filler since the late 1980s. It is available in a dry powder produced by heating gypsum; it can be hardened by crystallisation in an exothermic reaction following the addition of water. It has resorbable osteoconductive properties due to the three-dimensional structural framework which is useful for angiogenesis and osteogenesis; however, it lacks osteogenic and osteoinductive properties. Calcium sulphate is considered to be biocompatible and is fully dissolved within 6–12 weeks.[36] There are no relevant data on structural or biomechanical properties of calcium sulphate grafts in the literature. Calcium sulphate grafts are mainly used to replace bone loss after tumour resection surgery or to graft bone defects of the distal tibia, patella, calcaneus, ileum, femur and humerus; they can also be used to treat both proximal and distal tibia fractures.[37,38] However, calcium sulphate may not provide sufficient biomechanical support and osteoconductive efficacy in large bone defects for calcium sulphates are generally dissolved within 6–12 weeks.[46]

Bioactive glasses

These can be defined as hard, solid materials consisting of sodium oxide, calcium oxide, silicon dioxide and phosphorous in various proportions, available as soluble and non-resorbable grafts.[39] Bioactive glasses can be manufactured as microspheres, fibres and porous implants.

They display mainly osteoconductive properties and have few osteoinductive properties.[10] Reported bioactivity depends upon the presence of silicon oxide. A silicate-rich layer is produced when it comes into contact with human fluids such as blood, creating a bond between bone and glass upon which a new layer of HA is deposited. There are no relevant data on structural or biomechanical properties of bioactive glasses in the literature, but they show a superior mechanical strength compared with calcium phosphate products as a result of strong graft–bone bonding.[10]

The resorption of bioactive glass is variable and depends upon the relative amounts of the different constituents. Clinically, bioactive glasses have been applied for craniofacial reconstructive surgery and for dental and trauma or orthopaedic surgery.[69–71]

Case 1: Bone impaction grafting for revision Total Hip Arthroplasty. The bone impaction grafting technique offers a biological solution for coping with bone stock loss during revision THA and was first described by Slooff and colleagues for the acetabular side.[72] The bone impaction grafting technique has three main characteristics: first of all, the closure of all segmental bone defects with metal meshes (secured with bone screws) in order to contain these defects. Secondly, restoration of bone stock by filling the bone defect with vigorously impacted morselized cancellous bone grafts (MCB) using various shaped impactors and a metal hammer. Next, bone cement is introduced in the reconstruction and pressurised to force it into the bone graft layer. Finally, a new acetabular cup is implanted in the reconstruction to complete the technique. In general this technique has led to excellent short- and long-term clinical results.[73–76]

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Discussion

Bone regeneration in large bone defects resulting from trauma or other diseases remains an important and unsolved problem in trauma and orthopaedic practice. Treatment strategies depend upon the size, the segment involved and the location (epiphyseal, meta-epiphyseal, diaphyseal) of the defect.

The size and location of the defect and the local biological (i.e. vascularisation and presence of stem cells) and mechanical (load) environment as well as the type of device implanted are the main factors relevant to the requirements of an optimal bone substitute.

Our review focuses on the use of bone substitutes in large defects. The past decade has seen an increasing number of bone substitute materials becoming available for use in trauma and orthopaedic surgery. The structural, biological and biomechanical properties of bone grafts are very important for their clinical success. All the products we have analysed (DBM, allograft, synthetic bone graft substitutes and bioactive glasses) possess osteoconductive properties and variable (high to none) osteoinductive properties.

Besides biological properties, bone graft substitutes should offer optimal biomechanical strength, especially in those segments – such as femur and tibia – that are under high weight-bearing loads, or forearm and humerus that are subjected to high torsion forces. The biomechanical strength is a result of a complex interplay between the bone and the bone graft substitute material. In an ideal situation a bone substitute material may offer the same biomechanical strength as the bone being replaced.

However, the biomechanical behaviour of a bone substitute implanted is a result of in vivo interactions (integration, incorporation and bioresorption). Human cortical bone has a compressive strength of 130–290 MPa and a tensile strength of 90–190 MPa, whereas the compressive strength of cancellous bone is in the range 2–38 MPa.[47] None of the included bone substitutes offers a biomechanical strength similar to that of cortical bone. Calcium phosphate grafts possess compressive strengths comparable to those of cancellous bone, but have limited resistance to tensile and shear forces. Calcium sulphates provide only minimal structural support. Bioactive glass has a compressive strength of 91–197 MPa but its tensile strength does not reach values comparable to that of cortical bone.[48] Thus from a mechanical point of view these bone substitutes would appear to be unsuitable for grafting of significant cortical bone defects without additional support.

Calcium phosphate grafts may be used to fill metaphyseal bone defects at various locations of the lower limbs (calcaneus, proximal tibia, distal tibia, and proximal femur) where they reach at least a level II of evidence. In the lower extremity, calcium sulphate is rarely used. Calcium phosphate grafts are most frequently used in the upper extremity, as supported by level-II evidence.

In our study we have analysed only one aspect of the diamond/pentagon concept; what should be the characteristics of an osteoconductive scaffold. This may provide an adequate support

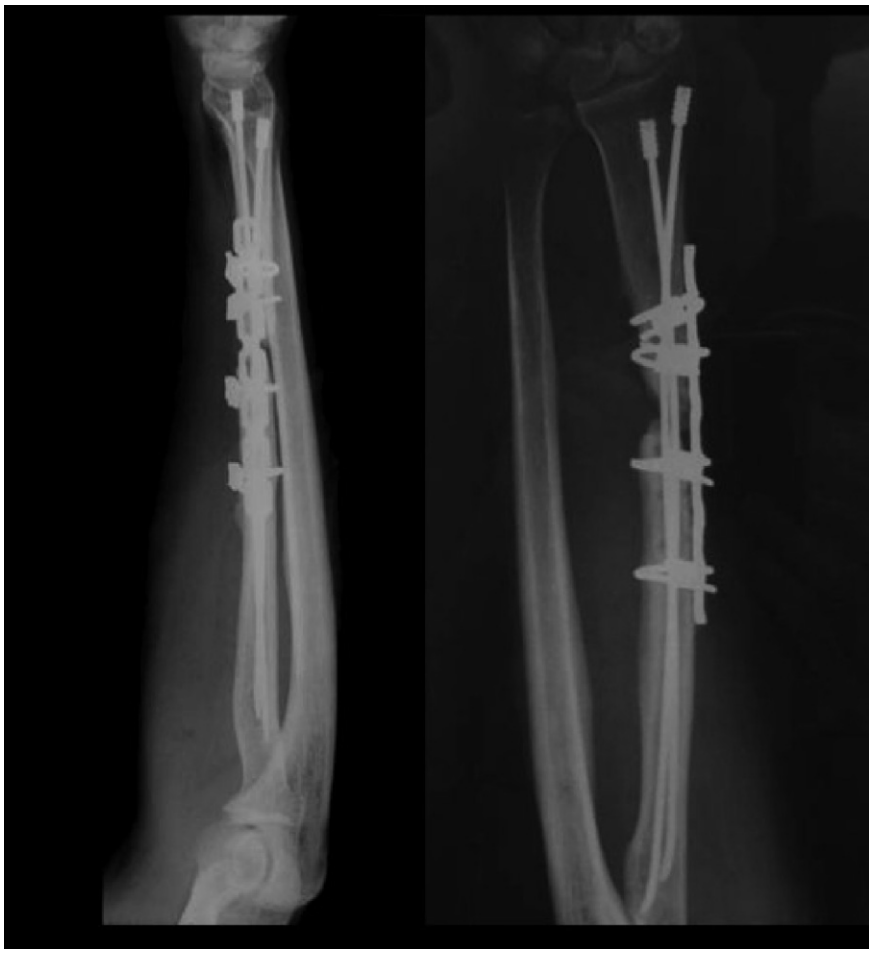

Fig. 1. Pre-operative X-ray image. Male, 34 years old, NUSS = 68. First trauma: motorcycle accident, left radial fracture. Current situation: atrophic non-union with critical bone defect.

and framework to create new bone formation by the invasion of nearby bone-forming cells, but it may be not enough in real critical bone defects and in those patients characterised by a poor biological environment. In these cases all the elements of the diamond/pentagon concept must be provided (polytherapy) in order to achieve bone regeneration (Figs. 1–3).[12,49]

Also the local and general risk factors that may impair fracture healing must be studied, as should other patient characteristics

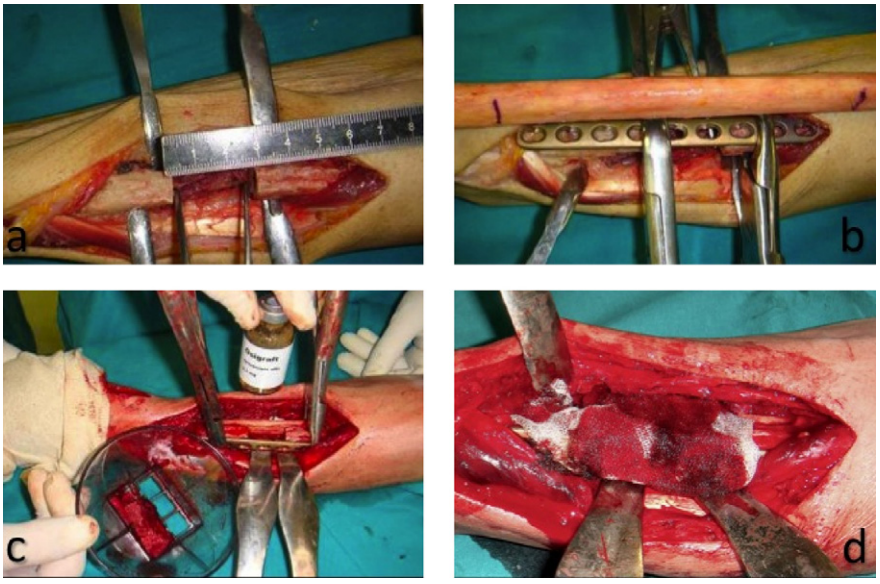

Fig. 2. Intra-operative images. (a) Treatment performed: radical resection of fibrous tissue (3 cm) and creation of the "biological chamber"; (b) mechanical stability obtained using a locking compression plate (LCP) + allograft implant; (c) implantation of growth factor and a scaffold with concentrated bone marrow aspirate (polytherapy); (d) closing of the "biological chamber" superiorly with a haemostatic agent (surgical).

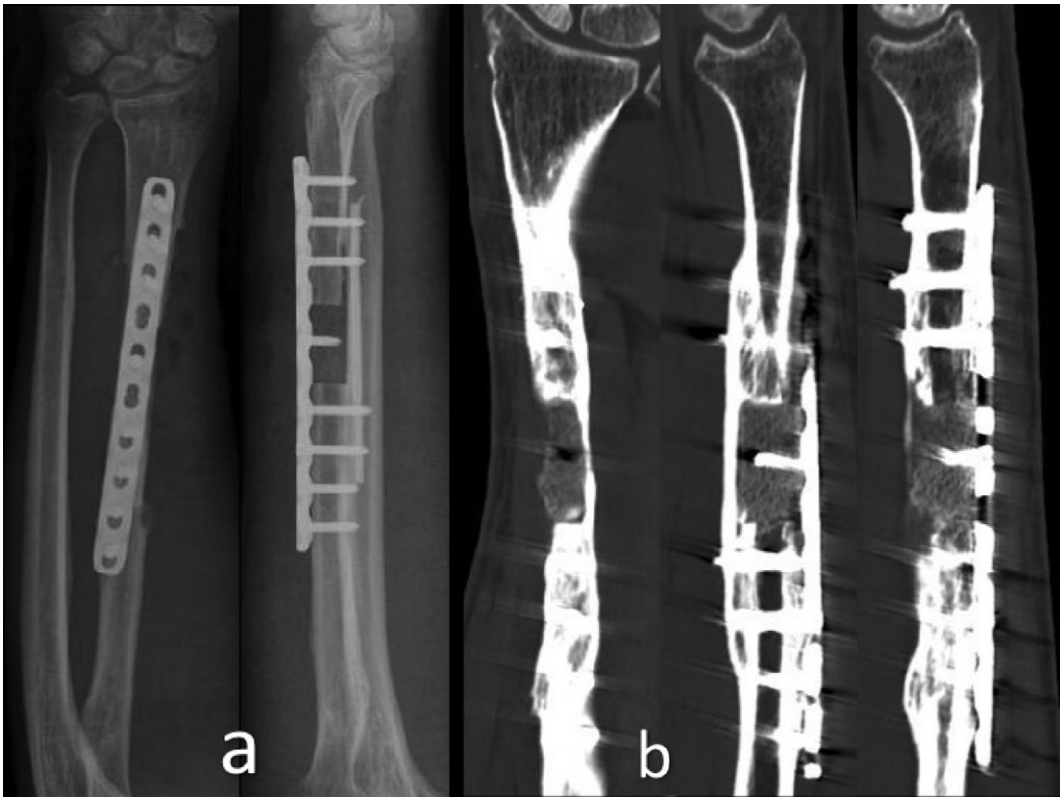

Fig. 3. (a) Post-op X-ray image; (b) CT images at 9 months.

that include bone quality, soft tissue status and the presence of comorbidities (such as diabetes, osteoporosis, vasculopathy and drugs).[2] For this reason we have developed a classification system called NUSS (non-union scoring system) that is an innovative approach to the problem, as it interprets the multifactor reasons for failure.[40]

Several studies over the years have shown that the implantation of one single bone graft material has been associated with different success rates ranging between 50% and 90%[17,19–21,23,54–58]: for this reason the idea of "polytherapy" is arising in the orthopaedic field and consists in the utilisation and simultaneous implantation of all three fundamental components of the diamond concept MSCs, growth factors and scaffolds.[12,59]

Polytherapy therefore may be a logical option, especially in individuals of advanced age with associated co-morbidities and a limited capacity for tissue regeneration. In such cases, it could potentially accelerate fracture healing, facilitate early mobilisation of patients, and reduced morbidity, health-care costs and complications associated with ongoing cases of impaired fracture healing.

Conclusions

Bone substitutes have different structures and chemical compositions. Patient conditions, the skeletal segment involved, and the size and location of the bone defect determine the choice of bone-grafting material and shape. There is a definite link between the type of osteosynthesis needed and the topography of the defect. Different situations require different solutions. So we can further distinguish between scaffolds that meet the biological requirements from scaffolds that possess mechanical properties to correct the spectrum of stability necessary for the healing of the bone defect.

The structural, biological and biomechanical properties of the graft itself are very important. It is very difficult to affirm whether there is any special need in a large bone defect. What we can say is that, based on our experience, the application of a scaffold alone is not enough for restoring large bone loss, particularly in complex non-unions in difficult patients characterised by a high NUSS score.

In addition, the importance of vascularity in bone regeneration should not be forgotten.[65,66]

In order to improve decision making regarding which bone substitute has to be used to treat large defects properly, more standardised studies are necessary to better understand the use of the grafts discussed above. Additional level-I scientific evidence is required in order to adequately state the clinical efficacy of those products.

The data present in the literature show that materials with similar chemical and physical compositions do not necessarily possess the same structural, biological and biomechanical properties or follow the same resorption pathway or even result in the same healing characteristics.

Therefore, proper assessment of the biological and mechanical environment and accurate patient selection are necessary to judge the extent of therapy the injury warrants in the clinical setting. A sound understanding of various aspects of biomaterial properties and their relation and influence towards bone healing is of utmost importance.

In conclusion we suggest the application of polytherapy for the treatment of large bone defects and advocate the use of the diamond concept as a guideline.

Conflict of interests

The authors have no conflicts of interest to declare. No financial support has been received by the authors for the preparation of this manuscript.

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