An overview of dental bone graft materials

In search of the "optimal" material for dental bone grafting

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The range of dental bone graft materials currently available to the implant dentist is wide and varied. Although autologous bone is still widely regarded as the "gold standard" graft material, the number of practitioners who regularly employ it in day-to-day surgery is small. The majority of surgeons apply a number of alternative grafting options, carefully chosen from a range of commercial sources. The ever-increasing number of commercial products makes this decision a challenge, and it is important to apply a critical eye to manufacturer's claims and peer-reviewed scientific literature before using a graft material that can have a critical/fundamental effect on clinical outcome. The majority of dental bone grafts are promoted on the basis that they possess the ideal properties to support new bone growth through the presentation of optimized characteristics. The parameters widely accepted as fundamental to the bone-regenerative capacity of a graft material are material composition, particle size, pore size, porosity, surface area and surface modification. From the examination of a combination of peer-reviewed and commercial literature, this article attempts to determine the range of parameters to identify what makes a bone graft "optimal".

Composition

A number of materials are commonly used for the manufacture of dental bone graft materials, and a common differentiator used to distinguish these is the original source of material. From the review of a range of commercial products commonly used in Europe and the United States, it is evident that a range of material compositions are available (Table 1).

However, the variety of material shows recurrent constituents that are often blended together in different combinations. Overall, these material compositions can be categorized into three broad areas: synthetic, human-derived and animal/plant-derived.

In Europe, the latter of these has traditionally been the most commonly implanted dental bone graft. Bovine-derived hydroxyapatite is widely used, and there are significant peer-reviewed publications to support its performance in a number of indications. Despite this, its use is not without controversy. Sterilization processes to remove organic animal material are well established, with the risks of disease transmission minimal [1,2]. However, these fears continue to linger amongst the patient population, as regulations require us to inform them as part of the patient consent procedure before surgery with these materials. In addition, when presented in granular form, these materials require the use of a membrane to prevent soft-tissue infiltration [3-5]. These membranes are also frequently animal-derived bovine and porcine collagen, compounding the concerns with animal tissue as they are by their nature not fully cleansed of animal protein. There is increasingly widespread refusal of animal-derived products as a result of religious beliefs [6] and lifestyle choices such as veganism.

The use of synthetic graft materials is growing in popularity. These materials are finding increasing favour as more peer-reviewed research is emerging to support their performance in a range of dental indications [7-10]. Because these materials can be manufactured to tightly controlled parameters, the biological response on implantation is consistent and predictable, and they are widely available in a range of physical forms (granules, setting pastes and putties). However, there is great variation in the composition of synthetic graft materials available (see Table 1), with some claiming enhanced bone healing responses over the expected osteoconductive behaviour [11-14].

In the United States, the use of human-derived tissues such as irradiated cancellous bone and deminer-

Table 1
Various dental bone graft materials in comparison.

Product, manufacturer	Chemical composition	Origin
Biocoral, Biocoral France	Calcium carbonate	Coral
Biogran, Biomet 3i	SiO_2 bioactive glass	Synthetic
Bio-Oss, Geistlich Pharma AG	Hydroxyapatite	Bovine
Bioresorb Macropore, Sybron Implant Solutions GmbH	β-tricalcium phosphate	Synthetic
Bone Ceramic, Straumann	β-tricalcium phosphate/hydroxyapatite	Synthetic
Bonit Matrix, DOT	Hydroxyapatite/SiO2 bioactive glass/ β-tricalcium phosphate	Synthetic
BondBone, Augma	Calcium sulphate	Synthetic
Calc-i-oss, Degradable Solutions AG	β-tricalcium phosphate	Synthetic
Cerasorb-M, Curasan AG	β-tricalcium phosphate	Synthetic
Cerabone, Botiss Dental GmbH	Hydroxyapatite	Bovine
Ceros, Mathys AG	β-tricalcium phosphate	Synthetic
Easy-Graft, Degradable Solutions AG	Polymer/β-tricalcium phosphate	Synthetic
Easy Graft Crystal, Degradable Solutions AG	Polymer/β-tricalcium phosphate/hydroxyapatite	Synthetic
Fortoss Cema, Biocomposites UK	Calcium sulphate	Synthetic
Fortoss Perma, Biocomposites UK	Hydroxyapatite	Synthetic
Fortoss Resorb, Biocomposites UK	β-tricalcium phosphate	Synthetic
Fortoss Vital, Biocomposites UK	β-tricalcium phosphate/calcium sulphate	Synthetic
Frios Algipore, Friadent GmbH	Hydroxyapatite	Plant-derived (seaweed)
Maxgraft, Botiss Dental GmbH	Bone tissue	Human allograft
Maxresorb, Botiss Dental GmbH	β-tricalcium phosphate/hydroxyapatite	Synthetic
Nanobone, Artoss Gmbh	Hydroxyapatite/SiO_2 bioactive glass	Synthetic
Novabone Perioglas, Novabone US	SiO_2 bioactive glass	Synthetic
OsteoBiol Apatos, Tecnoss Dental s.r.l.	Hydroxyapatite	Porcine
OsteoGraf, Friadent GmbH	Hydroxyapatite	Bovine
Pepgen P15, Friadent GmbH	Peptide/hydroxyapatite	Bovine
PerOssal, Botiss Dental GmbH	Hydroxyapatite/calcium sulphate	Synthetic
Puros, Zimmer Dental GmbH	Bone tissue	Human allograft
RTR Syringe, Septodont France	β-tricalcium phosphate	Synthetic
Tigran Porous Titanium Granules (PTG), Tigran Technologies AB, Sweden	Titanium granules	Synthetic

alized bone matrix has found greater uptake amongst dental surgeons. These materials are also widely used in orthopaedic procedures. The harvesting of these allograft tissues is guided by regulations [15] to minimize the risk of disease transmission between donor and host, particularly for non-irradiated materials such demineralized bone. Despite these guidelines, problems are well documented [16-20] where tainted tissue has been implanted during surgical procedures.

A means by which to understand the effect of bone graft composition on clinical behaviour is to consider the resorption profile on implantation. Whilst almost all commercially available bone graft materials claim an appropriate resorption profile, some confusion is inevitable considering the wide range of resorption rates presented by different products.

Bovine-derived hydroxyapatite, when presented in a granular form, has a slow to inexistent resorption profile [21,22], with data indicating no overt signs of resorption at twelve months [23] and persistence at the implantation site up to nine years post operatively [24]. As a result, it has been referred to as behaving as a permanent implant [25].

In contrast, human allograft resorption is variable. Research suggests that resorption is dependent upon the volume implanted, with small amounts of cancellous allograft in humans usually being remodelled completely, and larger allografts becoming incorporated by limited surface intramembranous bone formation [26]. Indeed, when mineralized block allografts are used, graft incorporation into host bone can be observed at twelve months, but resorption ranges from none to "slight" [27].

With synthetic graft materials, in-vivo resorption rates can be adjusted by controlling the material composition and physical characteristics. Complete characterization of different synthetic materials has been reviewed in depth [28-31] and is beyond the scope of this article. However, some broad statements can be made regarding the inherent resorption capacity of synthetic grafts.

Hydroxyapatite materials (formula $Ca_{10}(PO_4)_6(OH)_2$) are commonly brittle and undergo a slow resorption. As such, implants of this material can become a focus of mechanical stress [28]. Tricalcium phosphate (formula $Ca_3(PO_4)_2$, alternative name: Whitlockite) is also a commonly used material. It is available in two phases, alpha and beta, the alpha phase having greater solubility.

In contrast to hydroxyapatite, the surface of tricalcium phosphate ceramic materials has been shown to enhance bonding with adjacent host bone, thus stimulating osteoclastic resorption and osteoblastic bone formation on the surface of and within the resorbed implant [28].

It is important to note that both hydroxyapatite and tricalcium phosphate can be referred to as "calcium phosphate" or CaP. This does not adequately describe their composition as these materials have markedly different in-vivo behaviour. It is therefore important to have some understanding of graft material composition in order to anticipate the resorption characteristics.

Calcium sulphate (formula $CaSO_4 \cdot 2\ H_2O$, alternative name: gypsum) has a relatively fast resorption profile of the synthetic graft materials commonly used, with complete resorption reported within four to twelve weeks depending on the defect size [30]. Despite what is generally regarded as a relatively rapid resorption rate, it is still reported as appropriate for use as an effective osteoconductive graft material with applications in dental indications [32].

Particle size

The question of appropriate particle size is often considered in relation to the planned surgical procedure. A number of manufacturers claim to produce granular products of "optimal" particle size, and it is therefore important to determine on what basis such a claim can be made. A review of literature was undertaken in order to clarify the current level of scientific data in relation to preferred granular dimensions for bone regeneration. In-vitro and in-vivo research was reviewed to consider cell response and biological responses to a range of graft materials in varied granular dimensions.

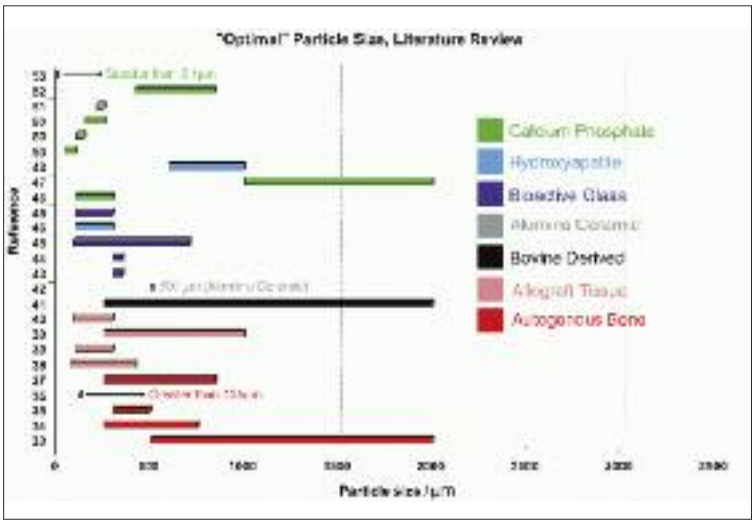


Fig. 1 "Optimal" particle size, literature review.

In order to obtain a balanced view, research was reviewed relating to autogenous bone, human derived materials, animal derived materials (xenogeneic), and synthetic biomaterials.

A wide variation in "optimal" particle size was evident from literature [33-54] (Fig. 1). Results commonly quoted an ideal size within a range of values. Less frequently, a minimum particle size value was quoted, and occasionally specific particle size was quoted as optimal.

Literature indicated a broad range when considering the influence of particle size for autologous bone grafts [33-37]. Values from 125 µm up to 2 mm were reported as preferable. A critical minimum value was reported [36] stating that particles less than 75 to 125 µm are rapidly resorbed, and do not participate in effective osteogenesis.

When considering research relating to human derived materials, results were also variable, with one paper stating that "the ideal size of bone particles used to fill bone defects is ill-defined".

Research for animal derived material also lacked definitive findings. The cellular response to a range of particles demonstrated that size did not influence the biological response [41].

Data relating to the optimal particle size for synthetic grafts was more abundant [42-54]. However, as with previous graft types, the literature indicates a

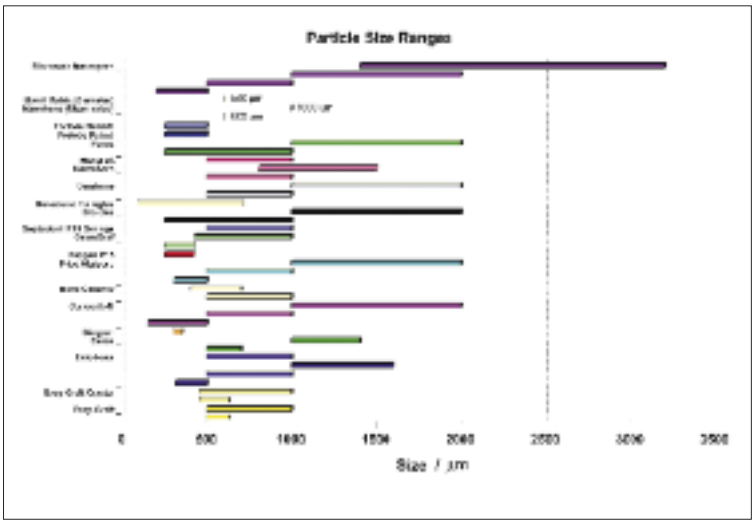


Fig. 2 Particle size ranges.

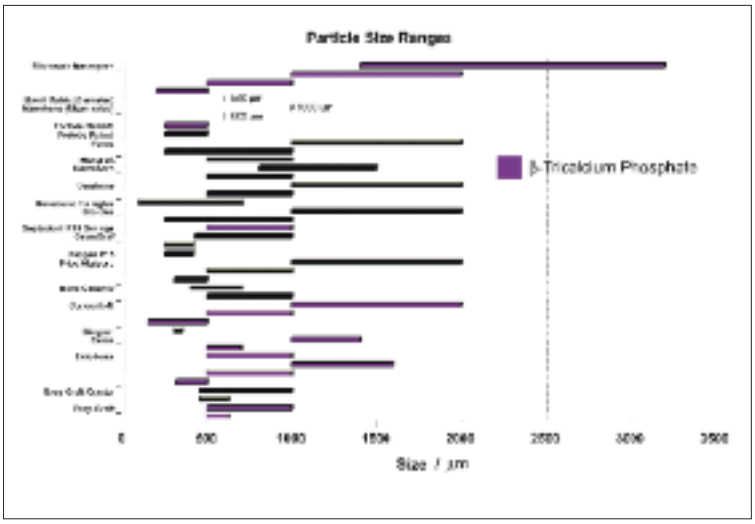


Fig. 3 Particle size ranges.

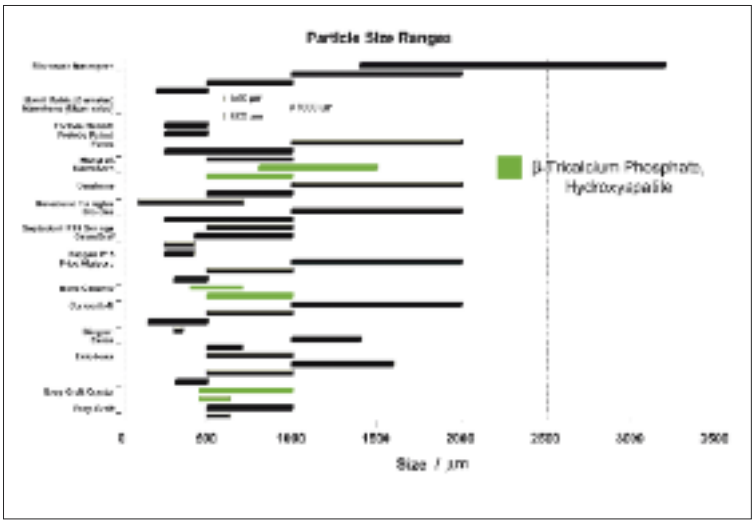


Fig. 4 Particle size ranges.

broad range of "ideal" particle sizes. Studies of hydroxyapatite granules also concluded that there was a lack of consensus in the literature toward the most suitable granule size for bone substitution [54].

In an attempt to find a more definitive answer regarding particle size, material composition was cross referenced with granular dimensions. No obvious correlation was noted.

By means of comparison, the range of particle sizes available for commercial graft materials was reviewed (Fig. 2) and compared with those identified as "optimal" in peer-reviewed literature (see Fig. 1).

The results showed an obvious difference in commercial particle sizes and those studied in the literature. Most commercial products were available in a number of particle size ranges, with some similarity noted between products, as the majority have particles available within the set range of 500 to 1000 µm. A number of the products considered were composed of β-tricalcium phosphate, or were of a "biphasic" composition (β-tricalcium phosphate and hydroxyapatite). Once again, cross referencing material compositions with granular dimensions indicated no obvious correlation with the particle sizes available (Figs. 3 and 4).

The set size ranges in which granular products are available coupled with a lack of correlation with the scientific literature indicates the influence of other factors on commercial particle size. Handling characteristics of granular bone grafts may be a major influence, as larger particles (500-1000 µm) are easier to manipulate. In addition, manufacturing processes may also determine the uniform granule size ranges.

To provide granules within set size ranges for laboratory testing, particulates are passed through sieves of standardised mesh size [55,56]. Thus, by passing particles through sieves of progressively smaller mesh size, particles of clearly defined particle size ranges can be obtained. This methodology is commonplace in large-scale ceramic manufacture and is likely to be applied to the manufacture of granular bone graft materials.

Pore size, porosity and surface area

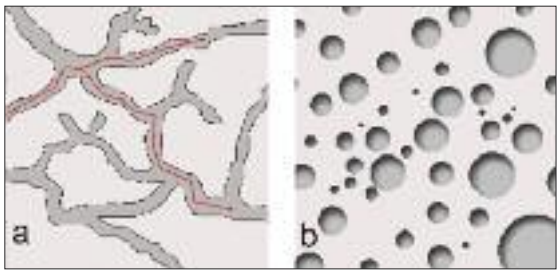
Measures relating to the pore characteristics are considered fundamental to the ability of a graft material to support new bone growth, and it is important to have a clear understanding of these and related terms when discussing their interactions at the implant site.

Porosity can be defined as ratio of the volume of void spaces in a material to the total volume of its bulk. This fraction of the volume of voids over the total volume is normally expressed as a percentage.

When discussing pore size, we are referring to the dimensions of the pores in the material. This is normally expressed in terms of units of size, such as µm. This is an important distinction, as a material can have high porosity but a small pore size, such that the pores inhibit cellular infiltration and revascularisation, processes essential to support bony ingrowth.

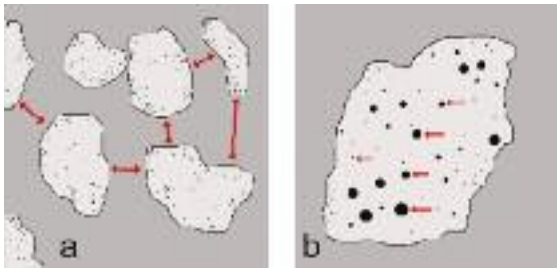
Other important definitions relate to the nature of a material's porosity. Effective porosity (open porosity) refers to the fraction of the total volume in which fluid flow is able to effectively take place. This includes caternary and dead-end pores but excludes isolated pores (or non-connected cavities). For a graft material, this is important for effective infiltration by extracellular matrix and cells (Fig. 5a).

Ineffective porosity (closed porosity) refers to the fraction of the total volume in which fluid flow cannot effectively take place. A closed pore system is effectively inaccessible to infiltration by cells and possibly extracellular matrix (Fig. 5b).



Figs. 5a and b (a) Effective (open) porosity, (b) ineffective (closed) porosity.

When considering granular materials, it is also important to define to what a porosity value is referring. Intergranular porosity/pore space refers to the space between the granules when placed in the implant site (Fig. 6a). Intragranular porosity/pore space refers to the pores within an individual granule (Fig. 6b).



Figs. 6a and b (a) Intergranular porosity, (b) intragranular porosity.

Both of these definitions can also be further classified as open or closed porosity, in keeping with the previous definition.

Surface area is also a parameter often quoted in relation to a material's porosity, and is reported in terms of m^2/g. The inference is that a superior graft material has a greater surface area, as it takes into account the external and internal surfaces due to porosity. However, this value can have limited meaning when considering the size of the pores. The contribution of surface area from porosity is often measured using standard techniques of nitrogen adsorption (BET Method). The extent to which nitrogen gas can infiltrate a porous graft material is much greater than any cell would be able to. Therefore, although a graft may have a value for surface area, it is not necessarily the available surface area for osteoconduction. Similarly, using nitrogen gas to determine surface area is inappropriate due to the atomic scale of nitrogen gas. All surfaces are highly corrugated at the atomic scale, which can give higher than expected surface areas.

With these definitions in mind, a review of literature sought to establish definitive data regarding the optimal pore size for bone ingrowth [29,35,50,57-74]. Once again, in-vitro and in-vivo research was reviewed to consider cell response and biological responses to a range of graft materials with varied pore sizes (Fig. 7). A common message from the range of literature considered was the need for effective, interconnected porosity in a graft material. However, there is little consensus in scientific research findings as to which pore dimensions are optimal for supporting bone ingrowth. Some research makes attempts to clarify the difference in porosity required for bone ingrowth and revascularisation [29,57,70], but the majority of research considered did not draw this distinction.

It should be appreciated that the porosity and pore size within a graft bed may change post-implantation as a result of material resorption. These resorption rates are predominantly determined by the composition of the implant material. Therefore, as hydroxyapatite-based materials would tend to exhibit a static porosity as a result of their slow to non-resorbing nature, materials composed of calcium sulphate or β-tricalcium phosphate exhibit a dynamic porosity as a result of resorption through dissolution and cell mediated processes respectively. This resorption will effect changes in both inter- and intragranular porosity and may be of clinical significance.

As discussed above, it is important to clearly define the parameters used to discuss the porous nature of material. However, these characteristics are often misunderstood. As a result, the majority of commercial graft materials continue to state porosity values as percentage (Fig. 8), many without qualifying this measure in terms of pore size or pore nature. Wide variation in the material porosity values is evident, and without further information relating to pore size and the nature of porosity, these values are without meaning.

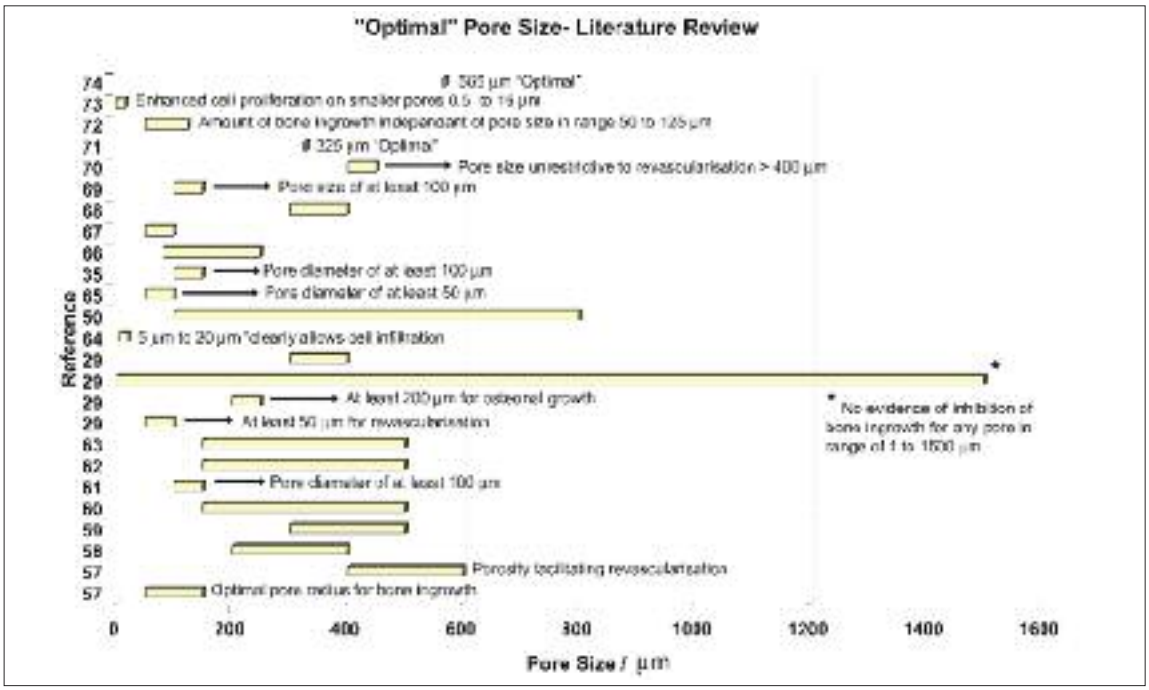


Fig. 7 "Optimal" pore size, literature review.

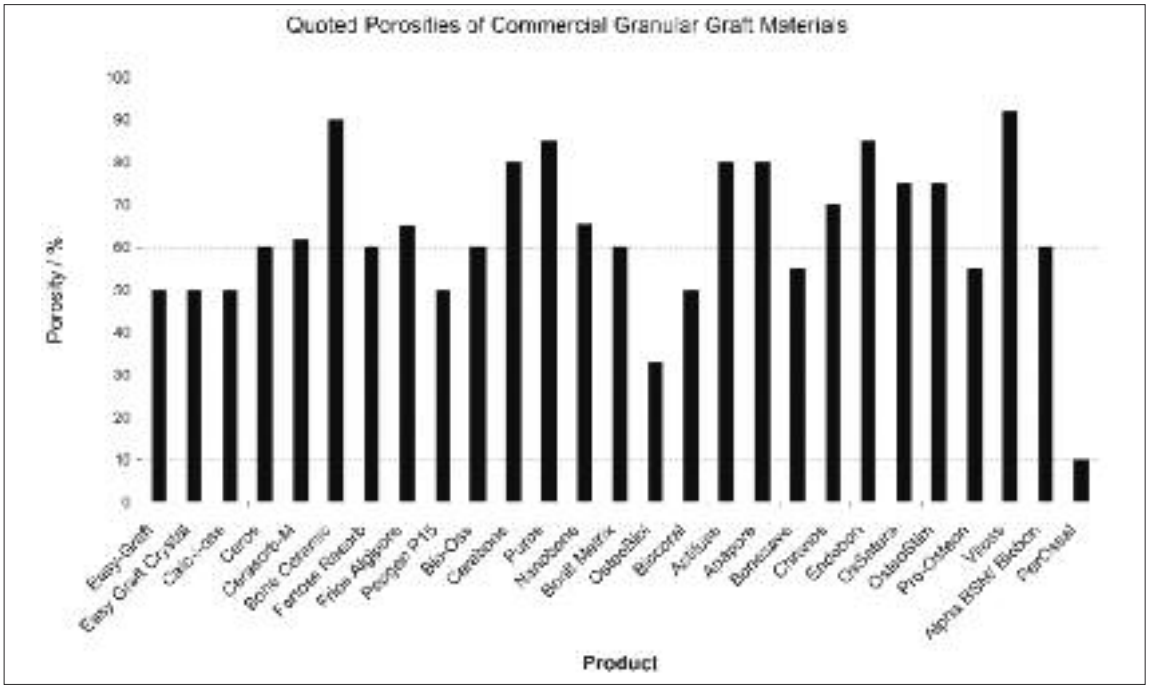


Fig. 8 Quoted porosities of commercial granular graft materials.

The question of "optimal" porosity for a graft material takes on a new dimension when considering the few commercial materials offering an alternative to the many granular, membrane dependent analogues. These setting materials (Fortoss Vital, Biocomposites UK, composition: β-tricalcium phosphate and calcium sulphate; Fortoss Cema, Biocomposites UK, composition: calcium sulphate; BondBone, Augma, composition: calcium sulphate) are all presented as powder and liquid, which when combined form a mouldable paste designed to be contoured to the surgical site, prior to setting hard. When set, these materials are intended to possess an integral barrier function, preventing soft-tissue ingrowth and removing the need for an additional membrane. The setting reaction in these products is due to the calcium sulphate component. The calcium sulphate hemihydrate present in the powder reacts when combined with a volume of water.

$$CaSO_4 \cdot ½\ H_2O + 1½\ H_2O \rightarrow CaSO_4 \cdot 2\ H_2O$$

The hemihydrate (alternative name: plaster of Paris) is converted to calcium sulphate dihydrate (alternative name: gypsum) that will set hard within minutes of mixing. The application of calcium sulphate alone has been well documented as a barrier to soft-tissue infiltration [75] with the potential to aid guided tissue regeneration [76] and as a bone void filler and regenerative material [32].

As these setting products are composed of resorbable materials, an opening porosity will develop following implantation. In the case of single component products considered this will be a result of the short term dissolution of calcium sulphate. In the case of the β-tricalcium phosphate-containing matrix (Fortoss Vital), longer-term cell-mediated resorption processes will take place. These products present an increasingly porous nature to the site of implantation over time, and have the potential to perform the dual function of barrier and scaffold for bone growth. The presence of the longer-term β-tricalcium phosphate phase in the Fortoss Vital material may contribute to longer-term osteoconductive support, whilst avoiding the potential problems discussed previously when using slow to non-resorbing material such as hydroxyapatite.

Surface modification

Although this is a lesser reported parameter when considering the efficacy of a bone graft material compared to the factors discussed previously, it is not without significance.

A well-known class of materials with well-documented surface effects is that of bioactive glasses. The ability of these materials to demonstrate biocompatibility and to bond with bone has been established for many years [77]. This ability is a result of the glass developing a bone-like apatite layer on the material surface when implanted, through chemical interchange with the surrounding biological fluid. This mineral layer allows it to chemically bond with host bone, an effect often referred to as bioactivity. However, it is important to point out that bioactivity is not a property exclusive to bioactive glass, as the effect has been observed in other materials such as hydroxyapatite and β-tricalcium phosphate-based materials [78,79]. Bioactive glasses have shown great promise as a result of this bone bonding ability, although the long-term presence of the material at the implant site has been noted up to four years in the mandibular ridge [80].

The modification of the surface chemistry of synthetic graft material has also been investigated. Ionically substituted calcium phosphates have been designed to more closely mimic the mineral composition of human bone, with the incorporation of elements such as silicon, strontium, magnesium, zinc and manganese [81]. However, the use of silicon substituted materials has raised some controversy [82], and their application has been associated with acute inflammation on implantation [83].

An important parameter affecting the reactivity of bone-forming cells to an implant material is the three-dimensional morphology of the substrate [84]. Various studies [85] demonstrated that bone cells are sensitive to the gross morphology of a material but difficulty exists on interpreting the present data due to a lack of comparable studies. An important physico-chemical characteristic of a material surface is the surface charge, often expressed as the zeta potential [84]. This is a novel area of research, with a number of studies finding that bone forming cells are profoundly influenced by the property of the surface charge [86-90]. Recent research evaluated a commercial implant material manufactured with a negative zeta potential (Fortoss Vital, Biocomposites UK) and found this property to be favourable for bone regeneration and osseointegration of dental implants [91].

Conclusions

The parameters of the optimal bone graft material are yet to be defined. It is important to closely examine the claims made by manufacturers regarding the "optimal" nature of the available graft materials, and to make a judgement based upon a more complete understanding of material characteristics. It is clear from the examination of literature that there is little consensus in the scientific community regarding these individual characteristics that contribute to a graft material's biofunctionality. As research into these materials continues, our understanding should grow with respect to the variety of parameters involved in the successful bone cell interaction, material integration and clinical efficacy. Further research should encompass an approach that considers the importance and interrelation of the numerous physical and compositional parameters that can contribute to engineering an "optimal" graft material. ■

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