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Review Article

Bone Grafting with Coralline Hydroxyapatite

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Abstract

Hydroxyapatites (HA) are used as graft compounds to aid bone healing. They have found wide use and acceptance in orthopaedics and maxillo-facial surgery. HA has a scaffold structure permeated by large pores. Biological activity is influenced by pore size and surface chemistry. Coralline HA (cHA) from renewable corals is very similar in structure to native bone. cHA has excellent *in vitro* and clinical results although study sizes tend to be small. HA and cHA are being studied as a carrier for many other compounds. These include growth factors and anti-infectives. HA itself has some inherent anti-infective activity. cHA can perform better clinically than standard synthetic HA, but not as well as autograft. Although clinical results can vary with the application and precise material used. More studies are needed to clarify the mechanism of action and clinical benefits of cHA.

Keywords: *Allograft; Bone; Coralline; Graft; Hydroxyapatite*

Introduction

Bone grafts are materials used to repair defects of bone with frequent use in orthopaedic and maxillofacial surgeries. Hydroxyapatite (HA) is the major mineral component of bone and teeth [1]. HA as a graft belongs to the class of bone grafts called Ceramics. HA is a natural polymer of Calcium Phosphate, either purified from natural bone or derived from natural materials, for example coral. As such it is a renewable resource that can be produced in modified form for many different uses.

A bone graft acts as a natural hollow scaffold (Figure 1), that will fill a void in the bone where repair is required. During the healing process stem cells and vasculature migrate into the graft space where they begin the process of new bone growth. The rate of growth and properties of the new bone are determined in part by the properties of the graft material.

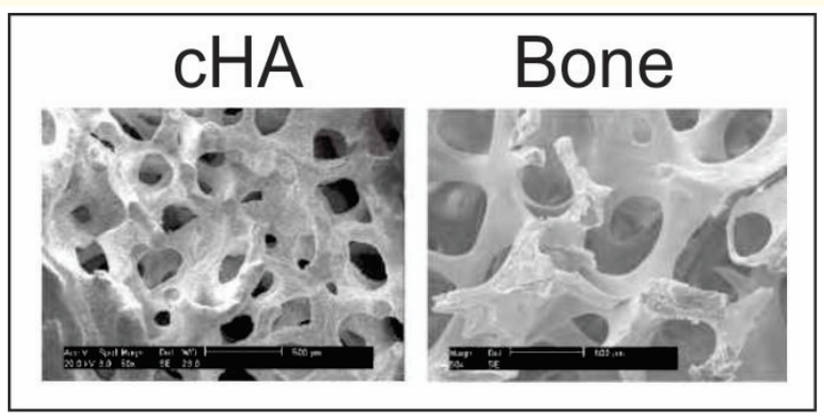

Figure 1: *Scanning electron microscope images of cHA (left) and endogenous bone (right). Images supplied by Beijing YHJ Ltd, Beijing, China.*

Bone grafts can be categorised with 3 main properties (Table 1), osteoinductive, osteogenic or osteoconductive. A fourth category, osteostimulative, has appeared recently. However, this term appears more frequently in marketing, rather than scientific, literature. At a very minimum, all bone grafts should be osteoconductive.

Property	Characteristics	Example
Osteoinductive	The graft directly stimulates differentiation of host mesenchymal stem cells to form new bone cells that make new bone	Growth factors (BMP, PDGF), autograft
Osteogenic	The graft produces new bone cells directly	Autograft, stem cells
Osteoconductive	The graft forms a scaffold to allow infiltration of cells and vasculature which aid healing	Ceramics (e.g. HA), autograft, xenograft, allograft
Osteostimulative/Osteopromotive	The graft enhances osteoinduction but is not osteoinductive itself	Ceramics, Xenograft

Table 1: *Bone graft general properties.*

Each major category of graft has advantages and disadvantages (Table 2). It is not the object of this review to examine other graft types in depth, so we have only summarised here.

Class	Advantages	Disadvantages
Autograft - from the patient's own body.	Good bone growth, no rejection	Donor site morbidity, pain, availability
Allograft - from same species but different individual.	Cost compared to autograft, availability, customisable	Potential infection, possible rejection, can be low mechanical strength, beneficial properties removed by stringent processing
Xenograft - from a different species	Cost compared to autograft	Potential infection, requires stringent processing, variable initial strength
Growth Factors	Slightly faster bone growth	Cost, is usually combined with ceramic
Ceramics	Cost, ease of use, renewable, integration	Variable initial strength, variable resorption

Table 2: *Major classes of bone graft.*

Why HA?

Many bone graft materials have been trialled over a long period of time, we refer the reader to Siddiqui., *et al.* [1] for an excellent historical synopsis. In the last two decades much improvement has been made in clinical results with bone graft. HA comprises about 50% of human bone and 70 to 80% of dentin and enamel by weight and thus is an excellent candidate for use in bone repair.

Initially HA has low structural strength, its major drawback [2]. However, on integration the graft has a strength similar to endogenous bone [2]. HA forms a strong bond to new bone through an epitaxal layer. After healing HA can be indistinguishable to autologous graft [3]. While non-porous HA in block form is very slow to degrade and form new bone, porous granular HA is more rapid.

Pore size is a major determinant of graft properties [4]. Optimal bone growth occurs around the pore size of bone, which HA, in particular from coral, has.

HA as a natural structure has low immunogenicity with low inflammatory response. There is also low risk of infection compared to allograft and xenograft (Table 2).

HA properties

HA is a porous scaffold remarkably similar to endogenous bone. HA pores facilitate cell migration and development [5]. The well structured scaffold facilitates cell migration and stability and vascular development. After only 5 weeks in situ, a granular HA with more porosity enhances cell viability in situ, although after this short time period there was no influence on mechanical strength [6].

Less widely appreciated is that the surface chemistry of the HA scaffold is very important in new bone development [7]. Minor substitution with different ions has a significant effect on the structure and biocompatibility of HA. As the ability of cells to migrate over the surface is critical to new bone growth, this intuitively makes sense. External cellular proteins essential for migration interact with HA and HA may also be a reservoir for external growth factors [8].

HA polymers are an active area of research. Because of the innate compatibility and safety profile of HA they are being investigated for a wide range of purposes. HA has been combined with many compounds [9], including graphenes for strength [10] and peptides for growth [11]. Of particular clinical relevance are efforts to minimise post-operative infection by combination with silver ions [12] and antibiotics [13].

Particle Size has some effect on the efficacy of HA granules. A rule of thumb in the clinic is smaller granules are for smaller voids, where they can pack closer. Larger granules are generally recommended for larger voids. Granule size does affect biological activity but not as dramatically as other factors [14]. Nano-hydroxyapatite is HA that has less than 100 nm diameter particle size. It is small enough to enter cells and so has a different mechanism to "microscale" HA and is not considered in this review.

Coralline HA (cHA)

Biomimetics is the design and implementation of artificial structures that mimic natural structure. Much research effort is expended on design of new biomimetic scaffolds for bone repair. A natural biomimetic for bone exists in the form of corallineHA (cHA).

cHA is prepared by heat treatment of Calcium Carbonate from naturally abundant *porite spp* corals [15]. Heat treatment occurs in the presence of ammonium phosphate [16]. The *porites* are preferred as they have a structure and composition close to human bone (Figure 1). At least one commercial form is a partial heat treatment, containing both carbonate and a low conversion to HA [15]. This review focuses on HA with little residual carbonate as the untransformed coral lacks structural strength. cHA has been used for many years in dental applications, for example in sinus floor augmentation [17]. cHA mimics natural bone structure better than artificial granular HA's [17]. cHA initially is slow to incorporate, like other HA compounds, but once incorporated is almost as strong as natural bone [18].

When compared to non-coralline HA, cHA enhances vascular growth [19]. And cHA was comparable to the "silver standard" ceramic, biphasic calcium phosphate, in new bone formation and vascularisation [20]. cHA performs better than human allograft in an vertebral model [21]. cHA enhances cell attachment, outperforming other materials such as freeze dried allograft [22].

cHA did not induce an inflammatory reaction in a goat intra-articular model, when compared to "gold standard" autograft [23]. There was significantly less inflammation for cHA than for 3 different allograft products [24]. When given sufficient time, cHA is well integrated with no abnormal reactions [25], like most HA's. In oncologic bone repair, cHA is tolerated well with good bone repair and no reaction [26].

Pountos and Gionnoudis [15] have summarised 16 clinical trials with cHA. The data set is not large but cHA generally performs well, sometimes comparable to "gold standard" autograft (2 studies) and better than freeze dried bone (1 study). Performance was good even in difficult procedures such as lumbar spine fusion where failure rates are typically high [27]. However cHA alone is not recommended for

spine fusion as autograft performed better [28] although cHA use was associated with a faster procedure and less donor site morbidity. A mixture of autograft or allograft with cHA has been recommended for spine fusion [27].

We have summarised comparative studies of cHA in table 3. Autograft is superior to cHA (Table 3), but cHA does not have the issues of co-mobidity, infection risk and expense. In some cases, but not all, cHA gives better clinical results to standard granular HA (Table 3). This reinforces the concept that for bone grafting, each clinical procedure should be evaluated based on the available data. In certain circumstances autograft may be superior, others cHA and still others another form of HA or other graft type.

Study	Comparison	Results	Citation
Thoracic vertebrae in rabbits	cHA versus autologous iliac bone graft versus human xenograft	cHA bone formation better than human xenograft but less than autograft.	[21]
Interproximal periodontal defects in humans	cHA versus freeze dried allograft	cHA induced statistically significant greater fill than allograft.	[78]
Tibial plateau fractures in humans	cHA versus cancellous autograft	No significant differences in bone growth.	[79]
Posterolateral lumbar and lumbosacral fusion in humans	cHA with marrow or bone chips versus autologous iliac bone graft	cHA inferior to iliac bone autograft only when bone contact surface area is low. But cHA faster procedure with no donor site morbidity or pain.	[27]
Posterolateral lumbar fusion in humans	cHA versus demineralised bone matrix allograft, both with autologous bone	cHA equivalent to allograft	[80]
Femoral trochlea in goats	cHA versus autograft	cHA slower to grow new bone than autograft but acceptable replacement.	[23]
Orbital implants in humans	cHA versus HA	cHA more rapid vascularisation than HA.	[19]
Periodontal ligament (PDL) cell adhesion *in vitro*	cHA versus freeze dried allograft versus freeze-dried dentin (DFDD) versus cementum	cHA provides significantly greater long term cell adhesion.	[22]
Full-thickness skull defects in rabbits	HA versus bovineHA xenograft versus autologous bone dust	HA and bovineHA xenograft equivalent bone formation results, both inferior to autologous bone dust.	[59]
Sinus implants in dogs	HA versus human freeze dried bone versus bovineHA xenograft	HA and bovineHA xenograft bone formation equivalent, both superior to human freeze dried bone.	[62]
Sinus floor augmentation in humans	HA versus bovineHA versus freeze dried bone powder	Freeze dried bone better than bovineHA better than HA	[60]

Table 3: *Comparative clinical trials of cHA and selected HA trials versus bovineHA xenograft.*

Growth factors, primarily platelet derived growth factor, are gaining clinical acceptance in combination with ceramic scaffolds [29]. Animal studies of PDGF yield variable results [30] and clinical trials in humans yield either significant or no improvement depending on the application [31]. Serum studies suggest the effect is local as systemic growth factor levels do not change on application of growth factor to a site [32]. We suggest that a good area for future research is development of other factors in combination with cHA.

The observations above collectively are part of the "osteostimulative" effect of cHA alluded to above (Table 1). cHA is not only osteoconductive, but also inherently aids formation of new bone structure. Clinical results from one of the authors' demonstrate rapid healing with cHA (Figure 2).

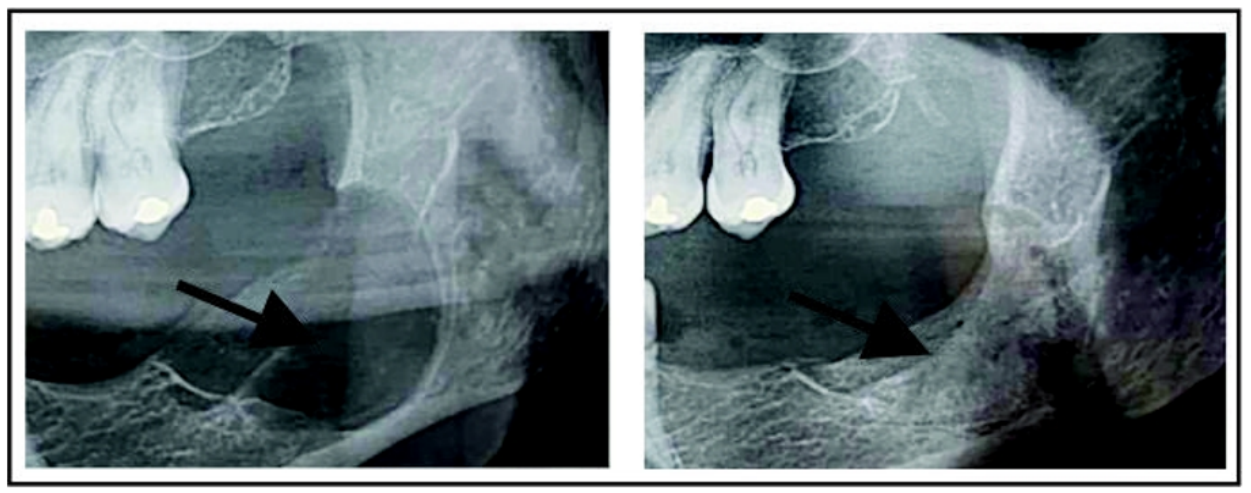

Figure 2: *X-ray images of patient with mandibular cyst (arrow) before (left) and after 90 days with cHA graft (right). Images from a case at the clinic of one of the authors (PJV), used with informed consent.*

HA as a coating material

HA is a safe and biocompatible material, therefore coating other less biocompatible materials with HA may aid acceptance by the body. In general this appears to be the case.

HA-coated screws are more firmly embedded [33] and have higher mechanical stability [34] indicative of increased bone formation [35]. Multiple long term studies demonstrate HA coated prosthetics have a lower failure rate with lower undesirable movement [36,37]. However the caveat is that initial stability must be provided to enable bone growth to occur into the HA [38].

HA coated dental implants have been in use many years [39]. The implants are stable with a failure rate of 2 to 18% depending on clinical use [40].

Of considerable interest are the results from external fixator pins which normally have a moderate infection rate [41]. HA coated pins used as part of external fixation have significantly lower pin loosening [42]. Use of HA coated pins can dramatically reduce infection rates [42]. However later studies in the wrist do not reproduce these results observing only a trend to better fixation and no difference in infection rate [43].

HA in dental trials

HA has been used in dental applications for many years and there are extensive reviews on its use [44]. Reflecting a common use to fill voids after tooth extraction or cyst repair, HA significantly prevents loss of bone after extraction in animal [45] and human [46] trials. There is minimal inflammation and good integration [46]. cHA induces good bone formation after 6 months and begins to be noticeably resorbed starting at 3 months with stable implantation [17].

In a statistically rigorous review of HA clinical trials Dewi and Ana [47] found that HA was not significantly different to other ceramics or xenograft (bovineHA), but inferior to autograft. However these studies were complicated by the observation that many different forms of HA were trialled and compared to many different other compounds, making analysis clouded.

Xenograft from bovine bone (bovineHA) is widely used in dental applications. Processing bovineHA with hypochlorite and high temperature [48] is required to reduce risk of infection. BovineHA performance varies depending on application, when compared to ceramics and allograft bovineHA is at times superior, equal or inferior [49-56]. BovineHA can perform as well as autograft when combined with a support membrane [57]. The major limitation of bovineHA may be its slow resorption rate [58].

In comparing HA to widely used bovineHA, there are few direct comparison studies with pure, non-derivatised, non-nano, granular HA. Dewi and Ana concluded HA and bovineHA are not statistically significantly different in sinus floor augmentation [47]. What comparative studies exist suggest bovineHA and synthetic granular HA have equivalent clinical results [59-62] (Table 3).

HA in orthopaedic trials

HA has many applications in orthopaedic surgery, reviewed elsewhere [5]. Most frequently HA is used in filling damaged voids and to aid healing [63]. Some examples are HA coating of hip replacement prostheses which promote faster osseointegration with reduced pain [64], although these results have been disputed [65].

HA is equivalent to demineralised bone allograft in lumbar fusion and tibial fracture repair [3,66]. A major benefit is that use of HA obviates the need for donor site pain experienced after autograft usage, that can persist for up to 12 months [67].

However each application is different and clinical trials need to be examined carefully to ensure exactly what form of HA was used [68] and compared exactly to what alternative. Technique may also have an influence on clinical effectiveness. Thus, each trial needs to be interpreted with careful scrutiny.

Is HA anti-infective?

Early studies of HA provided evidence that HA is anti-infective [69]. Rosen [69] suggested this was due to a structure that allows abundant vascular growth.

HA may have inherent anti-bacterial activity. Adhesion of *S. aureus* is reduced to HA compared to titanium and stainless steel, with viability on HA also reduced [70]. HA inhibits the growth of several bacterial species *in vitro* [71]. Nano-HA particles are cytotoxic to bacteria, although these particles are nano sized and can be incorporated into cells [72] a different mechanism to granular HA.

HA implants used in high-risk cranioplasty reduce the infection rate and outcome but increase epidural hematomas compared to titanium implant [73]. Cranioplasty has a high rate of infection with other materials [74]. In orthognathic (jaw) surgery, HA and calcium phosphate are associated with increased infection [75].

Rather than rely on any putative anti-bacterial activity of HA, exploration of anti-bacterial conjugates would be a better alternative [12,13].

Conclusion

HA is a clinically useful component of the surgical armamentarium. It performs as well as most alternatives except autograft and sometimes allograft, dependent on the clinical procedure and exact formulation of materials used. Each class of graft has its own disadvantages and advantages [2,76]. HA is excellent for general purpose use, has outstanding biocompatibility, is renewable and cost effective [77]. cHA is a superior form of HA that often performs better than most alternatives, depending on the clinical situation. However, the clinical data

set for cHA is not large and more studies are needed to further investigate the benefits of cHA. cHA and HA are under intense investigation as polymeric carriers of a wide range of materials. These polymers of cHA hold great promise for the future.

Conflict of Interest

Rob McPherson is an employee of Integrant which distributes graft products. Drs Slater and Vickers receive consultant fees from Integrant. This review has received no funding.

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