

The Application Of Hydroxyapatite In Socket Preservation: A Review Of The Past And Current Advancement

ABSTRACT

Alveolar ridge dimensional loss is a physiologic consequence of tooth extraction. Often, this event causes compromised feasibility of implant placement, prosthetic rehabilitation and esthetic outcome. As an attempt to minimize the shrinkage of the alveolar bone, socket preservation was introduced to intervene with the natural process by providing a scaffold with antibacterial and regenerative properties that aid in the healing process. For past decades, hydroxyapatites (HA) are one of the biomaterials used in socket preservation procedure and was thought to be biocompatible, long-term resorbable or non-resorbable and osteoconductive. Several improvements have been made to enhance the properties of hydroxyapatites that acted in providing a framework during the healing process to provide better outcomes. Here, we summarize the past and current advancements in the use of hydroxyapatite in socket preservation and its future direction.

Key words: tooth extraction, socket preservation, hydroxyapatite, alloplast

INTRODUCTION

Maintenance and improvement of natural dentition to achieve optimum health, comfort, and function is an ultimate goal in periodontal therapy[1]. However, under certain circumstances based on the clinician's opinion on prognosis, dental extraction is preferable, indicating that the tooth cannot be successfully treated[2]. Following extraction, a local inflammatory response occurs, with a subsequent variable degree of alveolar ridge atrophy, characterized by a degree of bone resorption[3]–[5]. Depending on individual local and systemic factors, the alveolar ridge showed the mean reduction in the width of 3.87 mm and 1.21 mm clinically and radiographically[6]. This physiologic resorption may complicate implant placement, prosthetic rehabilitation and esthetic outcome[7]. Numerous studies have addressed socket preservation after tooth extraction as an effective treatment approach in compensating alveolar bone resorption, hence reduces the need for bone augmentation[8]–[11].

During the early stage of the healing process, the implantation of graft materials into the fresh extraction socket helps stabilize the coagulum and act as a scaffold that probably sustains in the socket until the formation of mineralized tissue is completed. It was reported that some graft materials have the potential to directly modulate the gene expression of osteoblastic cells, promoting increased production of the protein of the extracellular matrix[6]. Ideal bone grafts should enhance 1) osseointegration: provide direct attachment of the graft without fibrous tissue interference [12], [13] 2) osteoconduction: provide a framework for ingrowth of blood vessels, mesenchymal cells and osteoblasts 3) osteoinduction: recruitment of mesenchymal cells to differentiate into osteoblastic cells and 4) osteogenesis: provide osteoblast and stem cells for new bone formation[13]. They should have the capacity to be resorbed whilst being replaced by new bone and sustain mechanical force at the grafted site[14]. Various osseous graft materials are available, including autografts (harvested from the host), allografts (derived from a cadaver), xenografts (derived from other species) and alloplasts (synthetic materials obtained from natural and synthetic sources). Previously, autografts were considered as the 'gold standard' graft material[15], [16]. However, they are often associated with the risk of morbidity at the donor site, such as nerve damage, infection due to graft contamination, and loss of function[17]. Allografts have issues with tissue integration and revascularization, the potential of disease transmission, and often, patients refuse to have cadaver's bone implanted in their oral cavity [18], [19]. Xenografts have shown long term adverse effects, including the high risk of host immune response, displacement of graft materials, cystic formation and chronic inflammation[20]. These issues emphasize the interest in the exploration of new bone substitutes that mimic the properties of bone to overcome the weaknesses of currently available graft materials.

Hydroxyapatite

Hydroxyapatite (HA) is one of the important classes of substitute materials belonging to the calcium phosphate ceramic group that has been extensively used in bone regeneration surgery. Bone is made up of 69 wt% mineral apatite, 22 wt% organic component (matrix proteins, lipid and osteogenic factors) and 9 wt% water. The mineral components of the bone were idealized as calcium hydroxyapatite, which contains irregularly shaped particles of various sizes ranges 30-45 nm length and width and an average of about 5nm thickness. HA with the general formula $(Ca_{10}(PO_4)_6(OH)_2)$ contains a calcium phosphate ratio of 1.67, similar to the mineral components of the bone. HA is one of the most stable calcium phosphate-based materials, which is less soluble. Since it contains only calcium and phosphate, it does not cause any tissue inflammation, and can be considered biocompatible[21]. HA properties depend on manufacturing methods, particle size, crystallinity, porosity, and specific surface area[22]. The commercially available HA includes HA cement, injectable form, porous and non-porous HA, nanocrystalline HA and implant coatings.

HA in socket preservation - Historical context

Dennissen et al. (1979) reported the first trial in using HA as an alternative to overdenture and submerging vital root therapy in preserving the bulk of the alveolar ridge for better retention of prostheses. The study used HA in the form of solid, non-porous prepared by compression of calcium hydroxyapatite powder and sintered at 1100°C producing the desired shape dental root implants and placed in fresh root extraction[23]. Based on the fact that HA can form chemical bonds with the surrounding bone, a few other studies also demonstrated the use of pre-shaped solid HA to fit closely

into the fresh extraction socket and revealed that this biomaterial is a promising root substitute[24], [25]. However, similar complications were encountered, including exposure of root implant, mucosal erosion, migration, wound dehiscence, and implant loss, all due to negligible resorption and weak bonding at the bone-implant interface[26], [27]. James et al. found the HA root implant remains as a confined solid particle with peripheral surface surrounded by bone after two years of implantation[25]. Dennisen et al. (1989) showed that the HA root implant remains stable after eleven years of implantation with a direct attachment to the bone[28]. An animal study using dense ceramic HA in the form of granules showed that HA remained in the socket after 12 months with a trace of fibrocartilages and bone jointly interfaced with HA particles[29].

The lack of data in the literature concerning the HA degradation made this material initially believed to be non-resorbable, only applicable for the long-term preservative procedures such as augmentation of atrophic alveolar ridge and reconstruction of periodontal defects[30]–[32]. The intimate binding of HA to the bone with a lack of physiologic bone turnover raises an argument about the long term outcome of the implant placement at previously grafted sites[33]. Because of that, HA has been one of the most criticized biomaterials due to its limited ability to promote regeneration and unpredictable new bone formation. Furthermore, it does not provide any cellular elements required for osteogenesis, thus act as osteoconductive elements rather than osteoinductive [34].

The term osteoconductive refers to the ability to support tissue healing by promoting the osteogenesis on its surface and serving as a scaffold or template that guides new bone to be deposited along its surface[21], [35]. When implanted into the living tissues, HA forms interlocking between the bone with the surface irregularities and forming a neoformed layer that assures direct interaction between bone and biomaterials to prevent the interference of fibrous tissues[22]. Others described the existing calcium HA from natural bone bind to calcium phosphate biomaterial that further acts as a place holder to allow protein adsorption (from the biological environment) and further support the migration of bone cells, cytokines, and concentrates bone morphogenic proteins (BMP) that are required for production and mineralization of bone matrix[21].

The conception of nanotechnology has improved the material properties

The utilization of nanotechnology in material production has changed material properties over the last two decades and provided a greater insight into the material interaction with host tissues. The paradigm shifted from a belief that HA is biocompatible, non-resorbable and osteoconductive to the idea that HA is rather more bioactive, bioresorbable, and osteoinductive material. Nanotechnology deals with designing and the production of matter at the dimension of approximately 1-100 nm enabling material production with controlled particle morphology and porosity[36]. Nanostructured HA possess more similarity with the natural HA in terms of surface roughness, wettability and larger surface area which render more positive biological effects, improved protein adsorption, mesenchymal stem cells adhesion, enhanced differentiation and proliferation and better osteoclastic response[37], [38].

Bioactivity is the ability of biomaterials to bond directly with a newly formed bone by allowing attachment and differentiation of cells directly on their surface and stimulate osteogenesis[39]. It is well known that the bone substitute needs to possess bioactive properties by forming a carbonate apatite layer on their surface in the living tissue and bond to the bone through this layer. The properties of HA can be improved to become bioactive by modifying the key parameters of material including crystallite size, particle distribution and agglomeration[22]. Various methods have been used to manufacture nanocrystalline HA powder including wet chemical precipitation, hydrothermal methods, plasma spraying, high-temperature solid-state reactions, sol-gel methods, microemulsion techniques, and microwave-assisted synthesis method[40] that produced HA with a greater surface area and significant bioactivity compared to larger sized crystal[41]. A study by Fathi et al. investigated the bioactivity and ionic dissolution rate of microcrystalline and nanocrystalline HA (average particle size 29 nm) and found that the precipitation of bone-like apatite particles was greater on the superficial layer of nanocrystalline HA than precipitation observed on the microcrystalline HA. The bioabsorbability rate of nanocrystalline HA was higher than that of conventional HA and almost identical to natural bone apatite. The study concluded that the bioactivity and bioresorbability of nanocrystalline HA crystals could be enhanced by controlling the crystallite size. The nanocrystalline HA can be more useful for treating alveolar bone deformity than

conventional HA and could be more effective as a bone substitute material to promote bone formation[42].

Constant resorption and complementary substitution of new bone tissue are desirable for long-term bone regeneration therapy. It is evident that resorption of graft material is mediated by the action of monocytes, macrophages and osteoclasts through phagocytic activity. In vivo, HA graft is resorbed only when the particle size is suitable for phagocytosis. In-vitro, the osteoclast-like cell function was enhanced when cultured on nanophase-HA compared to larger than 100nm-sized-HA[43]. A histochemical and immunohistochemical study on human biopsies investigated the healing of nanocrystalline HA grafted in alveolar augmentation and sinus lift procedures and revealed the evidence of bone turn-over demonstrated by detection of TRAP-positive osteoclasts like cells on the graft surface and newly formed bone. An osteogenic area with bone deposition was also detected around the same graft. This postulates a possible integration of grafting materials into the physiologic bone remodeling process of the host[44].

Osteoinductivity is characterized by the ability of the material to induce new bone formation without the presence of osteogenic factors[21]. Generally, HA is osteoconductive; however, several synthetic HA without incorporating any osteogenic factors were reported to have osteoinductive properties whereby they were able to produce de novo bone formation when implanted at nonbony sites[45], [46]. The inductive event of some synthetic HA was associated with the composition, crystallinity, size, interconnecting macro and micro porosities and geometry³⁸. Such features were believed to allow adsorption, entrapment and concentrating the circulating BMPs, osteogenic factors and/or osteoprogenitor cells, generating osteoinductive effects of synthetic HA[21]. Certain synthetic HA showed low osteoinductive effects in animal models because BMPs were superficially adsorbed, then rapidly released and exhausted before the osteogenic effects took place[48]. Such deficiency could be enhanced by an engineered combination of osteoprogenitor cells, bone growth factors (BMPs) and other bioactive factors to intensify the bone formation[21], [47]. The characteristics of HA can further be upgraded by adding porogen (e.g., naphthalene, silicon, hydrogen peroxide)[21], [49], creating a porous structure intending to intensify angiogenesis and provide a favourable environment for the migration of cells and tissue growth [50]. Due to that, it has a faster bone regeneration capacity demonstrated by a significant increase in osteophytes compared to non-porous HA[51].

Similar to the other calcium phosphate-based materials, HA is brittle and lacks elastic deformation properties. The low mechanical strength with lack of toughness makes its application in the load-bearing area restricted[52]. As the interconnecting porosity increases, the mechanical properties drastically decrease. Porous HA has a mechanical strength of 42 MPa, less than that of cortical bone (60-110 MPa)[53]. Low mechanical properties can contribute to material disintegration under cyclic stress and result in fibrous instead of bone tissue formation[54].

The usage of nano-hydroxyapatite in socket preservation

Considering nano-HA has superior biological performance than conventional-HA, it has gained attention among clinicians to be in socket preservation procedures. Checchi et al. (2011) compared clinical-radiographic and histological outcomes of two nanostructured HA; biomimetic HA (HA enriched with magnesium ions) and nanocrystalline HA grafted in a fresh extraction socket – both showed evidence of resorption and osseointegration. The study concluded that there was no difference between both materials in the matter of new bone formation and total material resorption, in addition to the effectiveness in providing appropriate structural support during the healing period. The authors assumed that both materials could be used in the fresh extraction socket to limit the amount of alveolar ridge shrinkage[55]. Another study by Luigi et al. (2015) evaluated the effects of Mg-enriched nano-HA found that this material allowed complete tissue healing and demonstrated significant graft resorption after 12 months of the study period. The report suggested that due to this characteristic, Mg-enriched nano-HA is suitable to be grafted at postextraction sites and subsequent implant placement, reducing the possibility of failure in osseointegration due to the presence of residual graft materials[56]

Nanocrystalline HA in socket preservation procedures resulted in similar, less alveolar ridge dimensional alteration following tooth extraction compared with xenografts. A study by Gholami et al. (2011) concluded that no conclusive evidence of the superiority of one specific material was obtained from the histological and histomorphometric standpoint. The only difference was in respect to the source of the material; one material is animal derivative, and another is synthetic[57]. In contrast with the finding by Rodrigo et al. (2019), when nanostructured HA was substituted with carbonate ions, a

greater amount of new bone formation and higher biodegradation was demonstrated compared to bovine xenograft (Bio-Oss). The physicochemical structure of carbonated HA produces greater wettability, thermal stability and uniform morphology that have biological performance and bonding capacity between graft materials and bone. However, their findings should be interpreted with caution due to lack of comparison in regards to alveolar ridge dimensional alteration with and without biomaterial filling[58]. Other than that, efforts have been made to produce more ideal economic graft substitutes by utilizing eggshell-derived nano-HA, which showed desirable bone regeneration potential in the grafted than that in the ungrafted sites[59].

CONCLUSION

Since more than 3 decades, numerous studies have investigated the performance of different types of HA in socket preservation. Nanostructured HA can be considered as a promising alternative material for regenerating new bone in socket preservation procedures. The improved material properties such as osteoinduction are biodegradability, and, more importantly, mimicking extracellular bone matrix to allow undifferentiated mesenchymal cell infiltration and proliferation to produce new bone. However, most of the mentioned studies only involved a small number of subjects using different types of nano-HA with the lack of important parameters needed for comparison in alveolar ridge dimensional changes. When metal ions are substituted, the biological behaviour of the materials is altered. This warrants a larger sample with well-design studies for each material modification to provide a deeper understanding of bone regeneration patterns.

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