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Review Article

Bone grafting materials in dentoalveolar reconstruction: A comprehensive review☆

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SUMMARY

Bone deficits of the jaws are often attributed to accidents, surgical removal of benign lesions or malignant neoplasms, congenital abnormalities, periodontal inflammation, tooth abscess or extraction and finally jaw atrophy due to advanced age or general disease.

These bone defects require rehabilitation for a variety of reasons, e.g. maintaining the normal anatomic outline, eliminating empty space, aesthetic restoration and placing dental implants. Today, several techniques have been developed to eliminate these bone deformities including bone grafting, guided bone regeneration, distraction osteogenesis, use of growth factors and stem cells.

Bone grafts consist of materials of natural or synthetic origin, implanted into the bone defect site, documented to possess bone healing properties. Currently, a variety of bone restorative materials with different characteristics are available, possesing different properties.

Despite years of effort the 'perfect' bone reconstruction material has not yet been developed, a further effort is required to make this objective feasible.

The aim of this article is to provide a contemporary and comprehensive overview of the grafting materials that can be applied in dentoalveolar reconstruction, discussing their properties, advantages and disadvantages, enlightening the present and the future perspectives in the field of bone regeneration.

1. Introduction

Bone deficits of the jaws are often attributed to accidents (traffic, labor, sports, shooting), surgical removal of benign lesions (cysts, dental tumors) or malignant neoplasms, congenital abnormalities such as clefts or visceral skull bones hypoplasia, periodontal inflammation, tooth abscess or extraction and finally jaw atrophy due to advanced age or general disease [1].

With the advancements in the field of dentoalveolar reconstruction, these jaw bone defects are capable of rehabilitation for a variety of reasons, e.g. maintaining the normal anatomic outline, eliminating empty space, aesthetic restoration and placing dental implants [2]. Today, several techniques have been developed to eliminate these bone deformities including bone grafting, guided bone regeneration, distraction osteogenesis, use of growth factors and stem cells [3].

Bone grafts consist of materials of natural or synthetic origin, implanted into the bone defect site, documented to possess bone healing properties. Currently, a variety of bone restorative materials with different characteristics are available, classified in various categories according to histologic architecture, embryologic origin, form and blood supply, as shown in Table 1. With regards to their source of origin bone grafts are divided into the following types (Table 2): 1. Autografts obtained from the patient itself, possessing no antigenic properties since the donor and the recipient are the same person; 2. Isografts derived from the same species and share the same antigenic properties (twins); 3. Allografts processed in an effort to eliminate antigenic properties since the donor and the recipient is a different person of the same species; 4. Xenografts obtained from different species to humans; 5. Synthetic bone graft substitutes developed to mimic the natural bone tissue [2,4].

Materials of various origin and composition have different bone regeneration potential associated with the following properties: 1. Osteogenesis: living osteoblasts derived from the graft contribute

Table 1
Classification of bone grafting materials by selection of different criteria.

Source	Histologic architecture	Embryologic origin	Blood supply	Form of the graft
Autologous	Cortical	Endochondral	Free graft	Bone blocks
Allografts	Cancellous	Membranous	Regional flap	Particulate bone
Xenografts	Corticocancellous			Bone slurry
Alloplasts				Bone paste

Table 2
Bone grafts classified according to their source of origin.

Graft category	Graft type	Advantages	Disadvantages	Commercially available
Autografts +Isografts	Extra-oral: Cranium, Fibula, Iliac crest, Radius, Rib, Tibia Intra-oral: Anterior maxillary sinus wall, Anterior nasal spine, Ascending ramus, Coronoid process, Incisive fossa, Mandibular symphysis, Maxillary tuberosity, Palate, Torus, Zygomatic body	Osteogenic Osteoinductive Osteoconductive No disease transmission or immunogenicity	Donor site morbidity Limited quantity Possibility of general anaesthesia and hospitalization (for extra-oral sites)	
Allografts.	Fresh and/or frozen bone Freeze dried bone Demineralized freeze dried bone	Osteoinductive Osteoconductive Relative availability	Possibility of disease transmission and immunogenicity Variability of properties depending on productive method	Allogro, DBX, DynaBlast, Dynagraft, Grafton, MTF, Opteform, OsteoSponge, Puros, Raptos
Xenografts	Bovine Porcine Equine Coralline Algae	Osteoconductive High availability Low cost	Possibility of disease transmission and immunogenicity Variability of properties depending on productive method	Algipore, Biocoral, Bio-Oss, Cerabone, Endobon, Gen-OS, Interporo 200, Lubboc, Osteograf/N, Osteobiol, Pro Osteon, THE GRAFT
Synthetic bone substitutes	Calcium phosphate Hydroxyapatite Calcium carbonate Calcium sulphate HTR polymer Bioactive glasses	Osteoconductive Availability Low cost	Variability of properties depending on productive method	Biogran, BonePlast, Calcibone, Cortoss, Eurobone, Guidor easy-graft, Hydroset, IngeniOs, Macrobone, Ostim, Perioglass, Rhakoss, Straumann, Vitoss,

to the production of new bone; 2. Osteoinduction: stimulation of osteoprogenitor cells that differentiate into osteoblasts, usually influenced by a bone morphogenetic protein (BMP) released from the graft; 3. Osteoconduction: grafts provide a 'skeleton' aiding capillaries and precursor bone cells to develop, thus creating a scaffold which bone can be created in and around [5].

The ideal material for bone rehabilitation should possess the following characteristics: 1. Osteogenic, osteoinductive and osteoconductive properties; 2. Stimulation of neo-angiogenesis; 3. Lack of antigenic, teratogenic or carcinogenic reactions; 4. Supply in sufficient quantities; 5. Satisfactory support and stability; 6. Minimum to zero morbidity — complications; 7. Hydrophilic nature; 8. Easy handling; 9. Low cost [6].

Despite years of effort the 'perfect' bone reconstruction material has not yet been developed, a further effort is required to make this objective feasible.

The aim of this article is to provide a contemporary and comprehensive overview of the grafting materials that can be applied for bone reconstruction in dentoalveolar reconstruction, discussing their properties, advantages and disadvantages, enlightening the present and the future perspectives in the field of bone regeneration.

2. Bone grafting physiology

Bone is a specialized, mineralized tissue providing structural support and participating in calcium metabolism homeostasis of the organism. It consists of inorganic minerals and organic components, incorporating cells that produce and absorb bone constantly, in the context of bone remodeling.

Integration of the graft into the recipient site is a procedure that includes the following stages: inflammation, revascularization, osteoinduction, osteoconduction and finally remodeling. To achieve bone regeneration, bone grafts should exhibit three fundamental elements: 1. Osteoprogenitor mesenchymal cells or even living osteoblasts; 2. Growth factors that are beneficial for the regenerative process; and 3. A 'skeleton' capable of mechanically supporting adhesion of cells, further leading to their growth and proliferation [7].
M
esenchymal cells further differentiating or even mature osteoblasts are likely to be present within the bone graft structure as in the case of osteogenic materials.

Growth factors represent a variety of molecules that stimulate mesenchymal cells recruitment, proliferation and differentiation from the surrounding environment into the bone deficit. Bone tissue is a rich source of growth factors, including BMPs, platelet-derived growth factor, insulin-like growth factor-1, vascular endothelial growth factor and fibroblast growth factor. The BMP family is considered to be the most important group of molecules of this category including members like BMP-2, 4, 6, 7 that exhibit satisfactory bone growth [8]. Bone grafts possessing such molecules are characterized as osteoinductive.

Finally, the skeleton — scaffold is represented by the bone graft, regardless of its biological origin. Its function is to recreate a three-dimensional mechanical structure that hosts and supports cells and extra-cellular matrix. Porous elements are essential for the

formation of the scaffold, allowing migration and proliferation of osteoblasts, mesenchymal cells and neo-vascularization while they accelerate biodegradation of the material by increasing contact with body fluids [9]. Osteoblasts are thought to perform greater migration, adhesion, and proliferation in the presence of pores with a diameter of 200–400 mm, while when greater than 300 mm, more intense vascular formation occurs. Generally, researchers suggest a porosity of more than 50% by volume and pore sizes between 200 and 800 mm as optimal for the development of bone tissue [10,11]. Apart from pore size, other parameters like pore morphology, pore percentage and pore interconnectivity seem to be important [12]. These grafting properties are defined as osteoconductive, as described above.

Cortical and cancellous bone histology of the grafts plays a significant role in their biologic behavior that can be summarized into the following: 1. Cancellous grafts stimulate osteogenesis given the presence of osteoblasts, osteocytes and mesenchymal stem cells within its structure; 2. Stability is mainly provided by cortical grafts which are significantly deficient in osteogenic ability, exhibit extended absorption while new bone growth is very slow; 3. A combination of cortical and cancellous grafts can ensure stability and osteogenesis; 4. Differences also exist in mechanical strength that is increased in cancellous bones due to the faster deposition rate of new bone tissue, while in the cortical grafts mechanical strength decreases by 40% from the first 6 weeks to 6 months postoperatively [13]. Cortical substitutes are usually applied as onlay grafts, augmenting bone outside the anatomical boundaries of the skeleton while they can also be used for inlay bone healing. In general, onlay bone grafts exhibit a higher resorption rate since they are exposed less in the recipients' site vasculature and they accept forces from the surrounding soft tissues compared to inlay grafting. Cancellous grafts are commonly used in fracture non-union, lack initial mechanical strength but exhibit ease during intra-operative manipulations [14].

Vascularized bone grafts seem to be more reliable in cases with previous radiation therapy of the bone and intense deficiency of soft and/or bone tissues. Among their drawbacks, high cost, the need for specialized training and equipment, as well as relatively more donor site morbidity have to be considered [15].

Bone grafts exhibit different absorption during time due to material composition, particle size, crystallinity, porosity, and processing procedure. The absorption rate of the material should ideally be proportional to the formation of the new bone.

Successful integration of the graft material is the constituent of factors such as adequate revascularization, proper fixation — immobilization at the recipient site, soft tissue coverage, appropriate shaping of the grafts' surface to establish relative contact with the recipient site, application of aseptic technique by the surgeon, meticulus post-operative care, while details from patients' medical history such as prior irradiation of the area as well use of drugs that are likely to cause osteonecrosis of the jaws should be considered [16].

A comprehensive description of the various categories of bone grafting materials is following below.

2.1. Bone grafts

2.1.1. Autografts

Autografts are considered the 'gold standard' among the various available grafting materials due to their osteogenic properties, maintaining viable cells from the donor to the recipient site as well as osteoinductive characteristics since a variety of growth factors contribute to the differentiation of mesenchymal stem cells into osteoblasts. The fact that they share the same biological origin with the host organism makes the risk of an immune reaction — rejection zero, acquiring success rate >95% [17,18]. The creation of a second

trauma, sometimes affecting even the patient's systemic health and increased morbidity, especially in cases of extensive bone volume collected, counts on their drawbacks. Also, limited bone offer is described, especially when intraoral graft sites are selected, as well as possibility of chronic postoperative pain and hypersensitivity of the donor area [19].

A variety of intra- and extra-oral donor sites have been described for the repair of jaw bone deficits. Intra-oral bone harvesting possesses the following advantages over extra-oral areas: ease of surgical access, relative proximity between the donor and the recipient site, lack of permanent skin scarring and minimal postoperative morbidity [20]. In addition, membranous ossification of the maxilla and mandible appears to play an important role in their absorption rate that is lower compared to the bones of endochondral ossification as well as better integration because they contain higher concentration of growth factors and angiogenetic potential [21]. However, according to other authors, these observations are mainly attributed to the micro-architecture of the graft, in particular the ratio between cortical and cancelous bone versus their embryonic origin [7,22].

Regarding grafts derived from extra-oral regions, they are considered to provide larger graft volumes, which may affect the decision of the clinician, especially in cases of large bone deficiency repair. In such cases need for general anaesthesia, hospitalization, increased morbidity are expected in combination with clinicians' advanced training [17].

The final decision for the selection of the donor site is determined by the particularities of the bone deficit to be restored, doctor's personal experience and preferences as well as the acceptance of the therapeutic plan by the patient.

At the moment numerous autografting donor sites have been described but since their detailed description overweighs the limits of this review a concise summary of available intra- and extra-oral regions for autogenous bone harvesting is provided on Table 3 [23–38].

2.1.2. Allografts

Allografts derive from individuals of the same species but different genus, being selected, processed and preserved in bone banks where extensive donor screening, including detailed social and medical history as well as serological examinations is carried out. They originate from living donors (usually femoral head replacement) or cadaveric bone material, further processed to neutralize the immune response and transmission of infectious diseases [39]. They are available as cortical, cancellous or cortico-cancellous grafts, in various shapes and sizes.

The main types of these materials comprise: 1. Fresh frozen bone (FFB): frozen at −800 C to avoid degradation by enzymes, without further irradiation, lyophilization or demineralization process. It is acellular, possessing the highest osteoinductive and osteoconductive properties due to the presence of BMPs. Not used anymore due to disease transmission and high immune response [40]; 2. Freeze–dried bone allograft (FDBA): undergone dehydration and freezing without demineralization, leading to decreased antigenicity. It has only osteoconductive potential40; 3. Demineralized freeze–dried bone allograft (DFDBA): apart from dehydration, the inorganic part of the bone is eliminated, leaving only the organic part that contains BMPs. These materials exhibit osteoconductive and inductive features [4,41].

The advantages of allografts include availability in adequate quantities, sizes and shapes, predictable results and the elimination of an additional donor site surgery. On the other hand, disease transmission from the donor to the recipient, although extremely small, cannot be totally excluded and additional testing for HIV, Hepatitis B virus, Hepatitis C virus and Treponema serologic markers should be performed [42]. It must be also noted

Table 3
Available intra- and extra-oral sites for bone harvesting.

Graft type	Advantages	Disadvantages	Complications[*]
A. EXTRA − ORAL			
Cranium [23]	Slow resorption High stability Low donor site morbidity Large quantities harvesting Scar hidden by hair	Mainly cortical bone Need for general anaesthesia	Dural injuries Epidural hematoma Alopecia
Fibula [24]	Large quantities harvesting Corticocancellous graft	long incision Need for general anaesthesia	Partial restriction of joint motions Ankle instability Muscular weakness Long scar
Iliac crest [25]	Large quantities harvesting Ideal for onlay grafting	12%–60% resorption rate of the initial bone graft Need for general anaesthesia	Pelvic instability Fatigue fracture Iliac hernia Fistula Uretal injury Heterotopic bone formation
Radius [26]	Corticocancelous graft No need for general anaesthesia	Limited bone quantity	DeQuervain's tenosynovitis Local soft-tissue infection Fracture Superficial radial nerve neuromas
Rib [27]	Can be splitted to double the surface area of the graft Rib donor area can regenerate Adequate bone length that can bridge large defects	Mainly cortical bone	Pneumothorax Chest wall depression Pleuritic pain
Tibia [28]	Large quantities of cancellous bone Local anaesthesia possible Minimal scar	Cancellous bone gained of inferior quality compared to iliac crest	Gait disturbance Entrance into joint space Edema Paresthesia Tibial fracture
B. INTRA − ORAL			
Anterior maxillary sinus wall [29]	Recipient site in proximity Low resorption	Mainly cortical bone	Perforation of Schneiderian membrane
Anterior nasal spine [30]	Easy bone harvesting Low morbidity	Limited bone quantity	Basement membrane perforation Aesthetic alterations
Ascending ramus [31]	Preferred by patients compared to symphysis	Mainly cortical bone Limited graft size and shape	Damage of inferior alveolar or/and lingual nerve Trismus Hematoma Fracture
Coronoid process [32]	No scarring Easy bone harvesting Low morbidity	Requires hospitalization	Trismus Damage of buccal branch of trigeminal nerve
Incisive fossa [33]	Easy bone harvesting Corticocancellous graft Presence of osteoprogenitor cells	Type IV bone	Tooth injury
Mandibular symphysis [34]	Easy bone harvesting Corticocancelous bone, mainly cancellous Lower morbidity compared with ramus	Several post-operative complications Small – medium size defects	Damaged submental and sublingual arteries Damage to mandibular tooth roots Mental nerve paresthesia – altered lower lip sensation Alteration of facial contour
Maxillary tuberosity [35]	Low morbidity Easy bone harvesting Corticicancellous bone Presence of osteoprogenitor cells	Poor quality and quantity of bone	Oroantral fistula Hematoma
Palate [36]	Low morbidity	Limited bone quantity Difficult access	Tooth injury Nasal floor perforation
Torus [37]	Easy bone harvesting Low morbidity	Mainly cortical bone	Lingual nerve injury Vascular injury of the floor of the mouth
Zygomatic body [38]	Easy bone harvesting Corticocancellous bone	Limited bone quantity	Ocular complications

[*] General grafting complications including wound infection, dehiscence, abscess and graft rejection are not mentioned.

that transmission of new unknown pathogens though relatively rare remains valid as they may not be eliminated by existing processing procedures. Also, higher absorption rate and immunogenic response and less revascularization and incorporation compared to autologous grafts has been reported among the disadvantages of this grafting category [43]. Finally, due to the fact that a bone allograft is not a standarised tissue since age, gender and medical status of donors may vary in combination with existing diver-

sity of processing procedures in bone banks, interprets why their properties may differ widely. All processing, maintenance and storage methods must be carefully assessed in terms of disease transmission but also their effect on biological and mechanical properties of the material. For example, although a more vigorous sterilization process can eliminate the chances of disease transmission and infection, it can also reduce osteogenic and

osteoinductive properties by destroying bone cells and denature proteins [39].

2.1.3. Xenografts

These implants derive from donors of a different species relative to the recipient, usually possess osteoconductive features with limited resorptive potential and are often combined with growth factors or bone grafts of other origin.

Several bone substitutes are included in this category, capable of mass production with a relatively affordable cost. Among their disadvantages is the fact that bone characteristics differ compared to humans while their processing procedure might affect their physico–chemical properties as in the case of allografts as well as possibility of disease transmission and stimulation of immunogenicity [43].

2.1.3.1. Bovine substitutes.
Bovine origin bone substitutes were the first xenografts applied to patients, being commercially available in a wide range of products and are considered among the most documented materials of this category. They are characterized by osteoconductive properties, being deproteinized and lyophilized, causing no immune response [14]. However, granules of these materials are considered to be subjected to poor or slow absorption, surrounded by neoplastic bone tissue rather than entering the normal bone remodeling process [44]. Processing at high temperatures to avoid immune reactions, allergies and infectious diseases such as spongiform encephalopathy is considered responsible for modifying the structure of hydroxyapatite which further leads to reduced absorption potential [45,46].

2.1.3.2. Equine substitutes.
Equine-derived bone substitutes have been described as having the ability to induce osteoblastic differentiation and angiogenesis while being absorbed by osteoclasts. In addition, the presence of neoplastic bone associated with remodeling effects was observed around the graft material 6 months postoperatively, while being described in cases of successful sinus lift [47,48].

2.1.3.3. Porcine substitutes.
Porcine-derived substitutes, recently developed, are considered to exhibit similarities regarding structure and formation compared to human bone, given the similarities of human and porcine genomes. They exhibit osteoconductive characteristics and a low risk of disease transmission [49]. However, reduced absorption capacity of these materials over time and poor development of neovascularization has been described [50]. According to others porcine bone is considered to be equally effective with bovine-derived bone implants [51]. Sinus lift procedures with porcine bone implants have also been performed, exhibiting augmentation capabilities and a high percentage of reabsorption 6 months post-operatively [52].

2.1.3.4. Algae substitutes.
Algae bone deratives lack antigenicity and inflammatory host response. This biomaterial has been combined with growth factors like BMPs and TGFβ1 [53,54]. It was documented to exhibit successful sinus augmentation via increase in cancellous bone around biomaterial particles [55]. It is resorbable, gradually substituted by newly formed bone [56].

2.1.3.5. Coral substitutes.
Madreporic corals including species Porites, Acropora, Lobophyllia, Goniopora, Polyphillia and Pocillopora have remarkable similarities to cancellous bone. Coral bone grafts have been also applied in jaw defects, presenting osteoconductive properties and functioning as carriers for growth factors, improving bone formation [57]. They exhibit initial poor mechanical strength, effectiveness related to blood supply of recipient cite and fast resorption rate. Several studies have reported the ability

to implement this material in dentoalveolar reconstruction with encouraging results [40,58].

2.1.4. Alloplastic materials

The enormous progress in the field of biomaterials science, the risk of infectious diseases transmission and finally, efforts to reduce morbidity and cost has led research into the development of a variety of synthetic origin grafts as alternatives.

Alloplastic bone substitutes cover a wide range of bone replacement or soft tissue support applications, available in many sizes and shapes. Several techniques have been employed including surface texture, mineralized layers formation and the use of bioreactors for cells so that the final product will be able to mimic the environment in which osteoblasts naturally grow. These biomimetic materials characterized by osteoconductive, with no osteoinductive or osteogenic potential on their own, try to act as a three-dimensional scaffold to support cell growth and bone formation, increase cell adhesion and proliferation [59]. Their chemical composition, geometry, microscopic structure and mechanical properties are key factors for successful bone remodeling while in vivo absorption capacity allows for their replacement by neoplastic bone [41].

A heterogeneous group of materials, including calcium phosphate, calcium carbonate, calcium sulfate, bioactive glasses and polymers is represented in this category.

2.1.4.1. Calcium phosphate.
These materials have gained special interest due to their composition similarity with natural bone. Hydroxyapatite (HA) and tricalcium phosphate (TCP) are the most important players of this category, further classified into ceramics and cements. The former are subjected to a heat treatment called sintering, further driving to a porous and solid material. Cements are produced in the form of paste, hardening after application within the bone defect site [16].

TCP exhibits good biocompatibility and osteoconductivity, lacking osteogenic or osteoinductive properties [60]. Its' porous composition permits phagocytosis, absorption, vascularization and bone regeneration. In accordance to other calcium phosphate preparations it has been found to be brittle and weak under tension and shear, but resistant to compressive loads. Compared to HA, TCP is more quickly resorbable and less mechanically stable [61].

HA, representing the main structural inorganic component of bones and teeth has excellent biocompatibility with the human body and can therefore be used as a bone graft. HA crystals possess mainly osteoconductive properties and low resorption rate while they are brittle and fracture prone on shock loading. This bone implant has been established as an excellent carrier of osteoinductive growth factors and osteogenic cell populations [62].

Biphasic calcium phosphate (BCP) results from the mixing of TCP and HA in various concentrations in order to attain desired mechanical properties and absorption rate [63].

2.1.4.2. Calcium sulphate.
Calcium sulphate, commonly known as Paris gypsum, was first used as a bone substitute in 1892 for the filling of long bones tubular cavities [60]. It is provided in the form of cement or granules, both products exhibiting biocompatibility, bioactivity, tolerability, carrier material capability, osteoconductivity, easy handling and low cost. Rapid absorption of the material has been noted, faster that new bone formation. Efforts to combine calcium sulphate with other materials, towards the direction of delaying absorption process have been made. Also, this bone implant provides minimal structural support, not indicated in cases where increased mechanical load is expected [64]. In the field of denstistry, it has been extensively applied in periodontal, dentoalveolar and tooth extraction defects [65].

2.1.4.3. Hard tissue replacement (HTR) polymeric substitutes. The most important of the polymers used in bone augmentation is polymethyl methacrylate, a porous biomaterial exhibiting osteoconductive properties, compressive strength and elasticity similar to cortical bone, but not resorbable. The high temperature which is developed during the polymerization, depending on the exact cement composition may create thermal bone necrosis, damage of blood circulation and membrane formation between bone-cement interface [16].

2.1.4.4. Bioactive glass. Composed of active silicate-based glass, this implant exhibits significantly greater strength compared to calcium phosphates. It is capable of forming a strong bond between the glass and the host bone through hydroxyapatite crystals, a phenomenon called bioactivity. The resorption of bioactive glass is variable, based upon the relative amounts of componets like sodium oxide, calcium oxide, silicon dioxide and phosphorous present [66].

3. Conclusion

Over the past decades, extensive research has been accomplished in the field of bone regenerative materials to improve their characteristics such as mechanical strength, molecular composition, biocompatibility, and degradation capacity in order to resemble features of natural bone. With the passing of time, synthetic implants and other synchronous regenerative methods substitute use of natural bone grafts. The clinician needs to be aware of these substitutes and their properties to achieve the best possible clinical outcome for every particular patient.

Given that the ideal bone reconstruction material has not yet been acquired, a further effort is required to make this objective feasible. Development of various bone regenerative materials in the form of hybrid ingredient products that include cells, growth factors, and/or gene modifying drugs in combination with the aid of science in biochemistry, engineering and nanotechnology will further open a new horizon in the field of bone regeneration [67].

Acknowledgments and disclosure statements

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