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Autogenous Osteograft in Comparison to Beta-Tricalcium Phosphate Graft in Maxillary Sinus Augmentation - A Pilot Literature Review

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Abstract

Introduction: Bone augmentation materials have been researched for decades in the hopes of discovering the optimal material for augmenting bone. Autogenous bone has long been considered the gold standard, although several other types of grafts are looking promising, especially the alloplastic Beta-tricalcium phosphate which has shown clinical evidence of successful bone regeneration in maxillary sinus elevation prior to implant treatment.

Objective: This literary review's aim was to analyse existing clinical studies comparing B-tricalcium phosphate graft to autogenous bone graft in maxillary sinus elevation and their treatment outcomes to determine if B-tricalcium phosphate can be reliably and effectively used independently in sinus floor elevations.

Methods: A literary review research protocol was developed to search, filter, select and appraise existing clinical studies and their findings, from the databases of PubMed and The Cochrane Library. A total of 25 candidate articles fit the search, 4 of which were irretrievable and 6 qualified the inclusion/exclusion criteria. Each article was appraised and

analysed separately and in conjunction with and comparison to the others.

Results: The studies analysed reported some variation in the degree and type of bone regeneration when B-tricalcium phosphate was used independently of autogenous bone graft, however the results' general consensus was that B-tricalcium phosphate exhibited satisfactory bone augmentation and treatment outcome in maxillary sinus elevation given ample healing time.

Conclusions: Analysis of the 6 articles showed that clinical evidence support B-tricalcium phosphate graft's usage in simple to moderately severe maxillary atrophy or sinus floor defects

Keywords: Autogenous bone, b-tricalcium phosphate, dental implants, sinus floor elevation, bone augmentation, bone substitute materials.

Abbreviations

AGB = Autogenous bone; AGBG = Autogenous bone graft BSM = Bone substitute material; B-TCP = Beta-tricalcium phosphate; BSFE = Bilateral sinus floor elevation; USFE = Unilateral sinus floor elevation MSE = Maxillary sinus elevation; SFE = Sinus floor elevation; BSMM = Bilateral split mouth method (BSFE and each side is grafted with a different graft); LWOP = Lateral wall onlay plasty (Cortical bone graft for horizontal sinus augmentation); TCD = Tatum's classical description (Classifications of sinus augmentation techniques); HMM = Histomorphometry and derivatives (e.g. histomorphometrically); HST = Histology and derivatives; RB = Residual/original bone (bone measurement prior to augmentation); NB = New bone (bone measurement of grafted area); BV = Bone volume

Introduction

Bone and bone biology – A unique ability

The placement of dental implants and the subsequent long-term aesthetic and functional success depend mainly on the presence of qualitatively and quantitatively sufficient jaw bone. The human body, however, is dynamic in nature and in constant state of biological change, remodeling and degradation whether it be due to natural aging, disease, trauma or developmental and acquired defects. The fact concomitantly with increasing life spans and demand for teeth, has made evident the need for alternatives for tooth replacement such as the endosseous dental implant (1-5).

Due to the aforementioned processes, the possibility of placing a

dental implant is not always present, such as in the case of maxillary sinus pneumatization and/or bone resorption due to loss of teeth and must be artificially supplied by stimulating bone regeneration to support the dental implant (1,2).

Several acceptable and reliable options for bone regeneration exist: 1) osteoinduction by bone grafts; 2) osteoconduction by bone grafts or BSMs that serve as a scaffold for bone formation; 3) transfer of stem or progenitor cells capable of osteoblast differentiation; 4) distraction osteogenesis; and 5) guided bone regeneration using barrier membranes (1,2).

In common for all these options is the innate and unique ability bone possesses of complete regeneration to the original structural and functional organisation. The vital functions bone serves in the body such as mechanical support, locomotion, support and protection of the brain, spinal cord, internal organs and teeth, storage of marrow tissue for production of hematopoietic cells and mineral balance maintenance is most likely the reason bone possesses this ability. Thus, the key is to harness this ability to formulate bone to support a dental implant where it otherwise would have been unfeasible.

The bone cells

Four bone cells are responsible for bone formation, maintenance, regeneration and repair, three of which are of the osteoblast family (mesenchymal stem cells from subsequently mineralizes. The osteocytes, positioned more peripherally in lacuna-like structures, are trapped osteoblasts which develop inter-lacunae canalicular systems for nutrition, waste and ion diffusion supporting bone homeostasis and turnover. The inactive osteoblasts, also known as bone-lining cells cover the bone surface and have a notably lower metabolism than the other cells, with a possible ability of participation in activation of bone resorption by releasing osteoclast activating factors as well as contracting to expose the bone surface to osteoclasts for attachment. The osteocyte is of monocyte-macrophage hematopoietic descent and serves the function of bone resorption by degrading bone matrix (1,2,4,5).

Bone Metabolism

Sufficient vascular supply is a prerequisite for bone metabolism (formation, maintenance, remodeling, regeneration and repair) (2,4-6), the corollary of which is ample angiogenesis is the prerequisite of bone regeneration. Bone's regenerative ability however is not unlimited and is in fact inhibited partially or completely by factors such as insufficient vascular supply, mechanical instability of the area regenerating, oversized defects and competition from tissues of high proliferative activity (e.g. epithelium). The process of bone regeneration and repair is induced by any bone lesion (fracture, defect, implant insertion, vascular interruption) by releasing and producing local growth factors and bone marrow) namely the osteoblast, osteocyte and bone-lining cell/inactive osteoblast; the fourth being the osteoclast. The osteoblast is the bone-secreting cell producing osteoid and bone matrix which it

signaling molecules, bone being of the body's densest growth factor-containing tissues (1,2).

Bone augmentation materials – Classification

Bone augmentation materials may be divided into two general categories: the first is bone grafts and bone graft substitutes; and the second growth and differentiation factors; of which the latter functions by inducing and/or improving osteoinduction, osteoconduction and osteogenesis separately or in conjunction with bone graft materials (see table 1 below for classification of bone augmentation materials).

Bone augmentation materials – Application

The applications of bone grafts and bone graft substitutes span replacing missing (congenital diseases) or lost bone tissue (acquired diseases/defects/trauma), induction of bone regeneration and repair, bone augmentation, facilitation of bone defect repair by osteoconduction, mechanical membrane support, facilitation of bone healing by blood clot stabilisation, as well as delivery of growth/differentiation factors. Such vast applicability and usage necessitates an array of material requirements and ideally the proposed requirements are: safe of use and nontoxicity, biocompatibility, possibility of vascular maintenance and angiogenesis, provision of mechanical support and osteoconductive scaffolding, osseointegration or resorptive ability, clinical ease of use and cost-effectiveness (1,2).

	Autografts	**Allografts**	**Xenografts**	**Alloplasts**
Definition	Graft from the same individual	Graft from another individual within the same species	Graft from another species	Synthetic graft
Subtypes	Cortical bone	Fresh-frozen bone (FFB)	Derived from bone mineral	Calcium Phosphates
	Cancellous/spongious bone	Freeze-dried bone allograft (FDBA)	Derived from calcifying corals	Polymers

	Corticocancellous bone	Demineralised Freeze-dried bone allograft (DFDBA)	Derived from calcifying algae	Bioactive glasses
Properties	Osteoinductive, osteoconductive, osteogenic	Osteoconductive, osteoinductive	Osteoconductive	Osteoconductive
	Limited	Abundant	Abundant	Unlimited

Main categories and subcategories are listed atop one another

Table 1: Legend – Bone Augmentation Materials

The bone augmentation yardsticks

There are three osseous properties by which these materials are categorised and evaluated: osteoinduction, osteoconduction and osteogenic property (1,2). Osteoinduction is the process by which proteins stimulate proliferation and differentiation of progenitor cells into osteoblast cells creating new bone, whereas osteoconduction is the process whereby a material/matrix acts as a scaffold for bone apposition and deposition. For osteoconduction to occur the scaffold must be either bioinert or bioactive as well as possess morphological characteristics facilitating tissue and bone ingrowth. Cancellous bone-like morphology is the optimum environment for this purpose. An osteogenic material is a material containing osteogenic cells, osteoblasts and their precursors, which are able to form bone given the appropriate milieu (1,2).

Autogenous bone grafts

For a notable time autogenous bone has been the gold standard bone graft material to which all others are compared, due to its osteoinductive, osteoconductive and osteogenic ability (7-12). AGBGs have been shown to produce the greatest regeneration potential and outcome (2,12). Absence of cross-infection and immunological episodes are further advantages of AGBG. AGBG is the only material with long-standing and substantial scientific data, especially in regards to its osteoinductive capacity. On the other hand however, autogenous harvesting entails a possible additional surgical exposure increasing operative time, risk, morbidity (e.g. postoperative pain, nerve and vessel injury, infection, hemorrhage), recovery time and costs. Niedhart et al (13) showed that AGBG and its sequelae require additional surgery of at least 30 minutes on the patient, possibly a second team of surgeons as well as an anaesthesiologist. Another drawback is that potentially substantial resorption of the graft may occur. Further, AGB in an individual is not unlimited in quantity nor quality and runs the risk of being insufficient or causing aesthetic or postoperative complications in the donor site (1,2,7,8,12).

Alloplasts – The alternative

This stimulates the need and demand for BSMs fulfilling the same requirements and is the cause of the surge of such materials appearing in the market today (1,2,7,8). Alloplastic materials have been shown to have similar osteoconductive properties as AGB and they have the same advantage of eliminated risk of cross-contamination and immunoreactions while being unlimited in quantity (1,2). This would make for an excellent material substitute should it retain scientific backing for widespread clinical use.

Alloplastic materials can be modified to be resorbable/non-resorbable, particular or block, porous or non-porous and are bioactive in the sense that they promote bone regeneration. They are osteoconductive in nature though not osteoinductive nor osteogenic. Another great advantage of their synthetic nature is the potential to manipulate their characteristics such as porosity, resorbability, surface properties, particle size and thereby angiogenesis, resorption and mechanical stability. In contrast however the optimal combination and selection of these characteristics and their sequelae has not yet been discovered. One clinically tested alloplast that demonstrates biodegradation and high density bone replacement is Beta-tricalcium phosphate (2,7,8,10).

Outcomes of AGB, BSMs and a combination of both have been histomorphometrically (HMM) studied to reveal that: bone volume augmentation occurred over time irrespective of graft material used, AGB alone produced faster bone formation compared to any other kind of substitute and lastly that favourable bone density for implant support required more time the higher the proportion of bone substitute to AGB used. In addition, HMM showed however that bone formation and resorption was comparable in all grafts used after 15-24 months, although these studies beyond bone volume do not illuminate the important issue of bone quality attained in the regenerated bone site (2).

their biocompatibility. [10,11] Conversely, studies investigating compomers are not available in the literature.

An interesting point to note is the fact that implant placement following maxillary sinus floor elevation without any form of simultaneous grafting has shown clinical evidence of bone formation as well as implant stability after multiple years (17). Two additional examples of studies supporting this are Lundgren et al (18) which had the purpose of investigating whether implant placement after MSE without grafts is a valid treatment modality and the study of Cricchio et al (19) who wanted to evaluate immediate implant loading following MSE without grafting materials. Lundgren et al showed a great capacity for healing and bone formation while Cricchio et al demonstrated “predictable results after 2 years of functional loading.” Considering the risks and morbidity of autogenous bone transplants as well as the costs and time demands of bone grafting materials, there is benefit in further researching and comparing the long-term outcomes of grafted versus non-grafted implant therapy in MSE.

Objectives and Hypothesis

Very few clinical studies exist testing two different materials in the same patient in bilateral sinus elevation (BSE) (7). Except for two very short-term (<1 year) studies from Johansson et al 1998 (9) and Ozyuvaci et al in 2003 (20), there has only been a few long-term studies

Maxillary sinus elevation

Autogenous bone graftsAccording to Kao et al. (2007), a material is considered to be biocompatible when there are no manifestations of any toxic, irritating, inflammatory, or allergic events after its placement in the oral cavity [9]. Among the GICs commercially available, the release of ions, e.g., triethylene glycol dimethacrylate (TEGDMA), urethane dimethacrylate (UDMA), 2-hydroxyethyl methacrylate (HEMA), bisphenol A-glycidyl dimethacrylate (Bis-GMA), and methyl methacrylate (MMA), and their diffusion in the oral tissues, have been associated with cytotoxic and genotoxic effects, compromising

published of radiographic changes in bone height after MSE (Geurs et al 2001 (21), Hallman et al 2002 (22), Reinert et al 2003 (23), Hatano et al 2004 (24), Velich et al 2004 (25)); further these differed in method of assessment (panoramic x-ray, tomographic Scanora or CT-scanning) as well as grafting materials used (9).

Hence, the research question formulated in this present study is “Is there satisfactory clinical evidence supporting B-tricalcium phosphate’s usage independently in maxillary sinus elevation while yielding similar and reliable results to autogenous bone grafts?”

The aims of this study are several. In light of the absence of an overview study of all present works concerning the aforementioned research question and none but the presence of one systematic review of autogenous grafts versus bone substitute material grafts (12), the author of the present study intended to conduct a pilot literature review to: summarise and quantify the findings of the contemporary literature to improve reliability and applicability of the usage of the alloplastic B-tricalcium phosphate graft independently of autogenous bone grafts; -and report on treatment outcomes of 1, 3 and 5 year follow-ups.

Autogenous bone grafts show an initial superior bone formation to B-tricalcium phosphate, whereas B- TCP demonstrates excellent biodegradation and bone volume change as well as osteoconduction. Resorption rate and

degree are slightly higher as well as more unreliable in autogenous bone grafts whilst they may theoretically be modified in the alloplastic B-TCP (1,2). The aforementioned factors taken into consideration, the present author would like to present a hypothesis as follows: analysis of the articles selected will demonstrate that bone regeneration in regards to quality and quantity as well as implant treatment outcome are comparable for both grafting materials, with autogenous bone having the slightly shorter recovery time before implants may be used. Nevertheless B-TCP will demonstrate a clear capacity for usage by itself in indicated and applicable cases.

Materials and Methods

Since one of the aims of this study is to summarise and overview the pre-existing body of information an as immaculate a literature search and selection as possible was deemed essential, prompting the development of the following research protocol in the aims of achieving this goal by recruiting the guidance of Wright et al's (26) research protocol manual.

Literature retrieval

After formulating the research question the search and retrieval of literature was performed in the online databases PubMed and The Cochrane Library against predetermined combinations of key words and MeSH terms (see table 3 and 4).

Background research in the subject matter was performed and obtained primarily from recent and up- to-date textbooks (1-5) and articles secondarily.

The research served as the background knowledge which the research question was examined against within this review.

Search key words	Last search date	Pubmed database results	The Cochrane Library results
"autogenous" AND "graft" AND "tricalcium	20140210	120	**19**
"autogenous" AND "graft" AND "tricalcium" AND "combination"	20140210	14	**2**
"autogenous" AND "graft" AND "tricalcium" AND "comparison"	20140210	5	**5**
"autogenous" AND "graft" AND "implant"	20140210	717	**126**
"autogenous" AND "graft" AND "implant" AND "combination"	20140210	78	**20**
"autogenous" AND "graft" AND "implant" AND "comparison	20140210	34	**27**
"autogenous" AND "graft" AND "tricalcium" AND "combination" AND "implant"	20140210	11	**0**
"autogenous" AND "graft" AND "tricalcium" AND "comparison" AND "implant"	**20140210**	**3**	**3**

All searches conducted between 20130921 and 20140210.

Key word combinations used in both databases.

Table 2: Legend – Search key words

MeSH term	1 "Bone Regen-eration"	2 "Bone substitutes"	3 "Tri-calcium phosphate"	4 "Sinus Floor Augmen-tation"	5 "Dental Implants"
Combin-ation searched	1 + 2 + 3	1 + 2 + 4	1 + 4 +5	3 + 4 + 5	
Results	72	19	35	0	
Last search date	20140210	20140210	20140210	20140210	

MeSH terms selected are shown in the first row. Combinations used for search in PubMed are shown in the second row and their results in the rows below together with the last search date.

Table 3: Legend – MeSH terms

Screening method and inclusion/exclusion criteria

The search results obtained using the aforementioned methods were screened by title and abstract as a first-stage screening to filter search results; and against specific inclusion/exclusion criteria as a second-stage screening for selection of the articles analysed.

First-stage filtration:

The article title must pertain to the present review's research question directly, i.e. must pertain to autogenous osteografts and/or tricalcium phosphate and/or dental implants and/or comparisons of these modalities.

Second-stage filtration – Inclusion/exclusion criteria:

(i) The study must be in vivo trials/studies on humans (in order that the present review's benefits may be applicable clinically and directly on humans)

(ii) The study must either be a randomised control trial or control trial to be included in those articles whose results will be analysed; otherwise they may only be included in the introduction and background build-up or for discussional purposes

(iii) The study must not predate the year 2000 to maintain up-to-date research

(iv) The study must be available in English/Swedish for full text retrieval online

Further, each included article that passed the second-stage screening will have their bibliographies examined for additional articles to be reviewed, outlined as "Third-stage filtration" below.

Third-stage filtration – Inclusion/exclusion criteria:

(a) Articles must meet the same requirements as for those in the "Second-stage filtration" to be selected as additional articles to be analysed, or

(b) If they meet the criteria for "First-stage filtration" they may be included for background, introduction or discussional purposes.

Data extraction

A standardized form assisted in the task of data extraction containing the following items for each article:

Reference

Objective

Study design

Population

Intervention/Control

Outcome

Discussion/Conclusions

Analysis and Quality Appraisal

When the previous steps were completed, each article was appraised in the items mentioned above, analysing them by themselves as well as against one another.

Interpretation of results, discussions and conclusions

What then followed was the author's conclusions of the results and discussions around the various findings, since the objective is to conduct an analytical review and not merely a descriptive one. The ultimate achievement is believed to have the present review re-critiqued and analysed since commentary, probing and investigation of contemporary science and research is one of the key tools in advancing the scientific community's knowledge.

Results

The results of the appraisals with a lengthier analysis of each of the selected articles (n=6) will be presented in chronological publishing order. An overview of all the analysed articles and their conclusions is mapped out in table 4 (page 40).

Zerbo et al. Histomorphometry of human sinus floor augmentation using a porous b-tricalcium phosphate: a prospective study (11)

Zerbo et al published in 2003 a prospective controlled clinical trial with the aim to analyse the pre-existing residual bone and new bone formed separately in the sinus augmented with either B-TCP or AGBG. They tested the hypothesis that augmented bone with B-TCP yields similar bone density volume to that of AGB within the same healing time of 6 months. 6 female and 3 male patients of good general health, completely or partially edentulous, between 28- 65 years of age (average 52) needing only SFE were included in the study.

MSE was performed according to Tatum's classical description (TCD) and a two-stage technique with bone biopsies taken from the augmented sites and the lateral wall for HST and HMM analysis according to Parfitt et al (27). B-TCP biopsies were difficult to remove in one piece from the trephine bur due to hardness and shattering. AGBG was mainly cortical and retrieved intra-orally for the control group while the test group received Cerasorb B-TCP with 1000-2000 micrometer particle size. No membranes were used and the healing period was 6 months. After biopsy collection, ITI Straumann full screw dental implants were placed and care was taken against premature loading (healing was on average 5 months). Residual/Original bone (RB) was responsible for primary implant stability.

6 months after grafting all patients had sufficient bone levels and primary stability for implants. No implant failures up to the completion of the study (1-3 years after biopsy retrieval) occurred. B-TCP was capable of forming bone height similar to the control group, both leading to height augmentation of 3.2-3.5mm of bone in 6 months' healing. There was however a difference in the quality of the bone. In the control group bone was mostly 80% lamellar and mature, while the test group sites had much more immature, predominately woven bone (74%) in addition to lower bone density. This indicates that the B-TCP material only acts as an osteoconductive. This process is however slow and the authors estimated from their results circa 0.5mm bone formation height per month on average. This contrasts with the control group where osteogenic cells "had dispersed throughout the entire grafted site and differentiated promoting bone deposition throughout the graft".

This osteogenesis process, occurring in the AGBG is a much faster process than osteoconduction, demonstrated by the BV (bone volume) difference between test and control groups (average 41% in AGBG, 19% bilateral or 17% for all B-TCP).

The authors also found that OV (osteoid volume) was higher in the test sites than the control sites, which the authors suggest might be explained by the fact that different ossification processes are taking place in the grafts. In control sites where osteogenesis and osteoinduction is occurring, new bone (NB) had already reached maturity which is why osteoid was laid down in a lamellar manner and more scarcely than B-TCP sites (reflected by AGBG's higher lamellar to woven bone ratio). In the B- TCP test sites, time delay occurs due to cell recruitment, migration into the osteoconductive graft and differentiation into osteoblasts prior to bone formation. Thus at 6 months' healing mainly woven bone with dense osteoid had formed while bone volume was still relatively low.

All sites reported low bone resorption indicating a slow bone remodeling which was also supported by the MAR (mineral apposition rate) values which give an indication of the mineralization speed of lamellar bone (27). MAR values did not differ between groups, and mineralization of osteoid occurred at a normal rate in both groups.

Zerbo et al compare their study with the one of Szabó et al (28) where Szabó et al's results showed no statistically significant difference between B-TCP and AGBG in bone volume, which the present study of Zerbo et al did. Also, lamellar bone was predominant in Szabó et al's study in B-TCP sites whilst the present one found woven bone. The critique launched by Zerbo et al is that Szabó et al did not specify which part of their biopsies was measured nor whether any distinction was attributed to NB versus RB, which they suggest might account for the higher lamellar bone seen.

Another important difference stated was that Szabó et al selected patients needing LWOP in combination with the SFE and that Szabó et al stated that the cortical graft was not in the biopsy. This, Zerbo et al doubt pointing to the great difficulty of taking a biopsy from a "knife-edge" wound without including cortical bone and that if the onlay bone was distinguished HST from the original bone Szabó et al did not mention it. On the other hand if the cortical plate was included in the biopsy that would influence the results favourably. Zerbo et al maintain that they selected cases needing only SFE in addition to separating the RB from the NB which they feel makes their data better reflect the biological differences between AGB and BSM.

Zerbo et al concluded that B-TCP is an adequate bone substitute by itself provided ample healing time. Also, they falsified their own hypothesis which was that Cerasorb B-TCP produces similar bone volume density as AGB after 6 months.

Suba et al. Maxillary sinus floor grafting with b-tricalcium phosphate in humans: density and microarchitecture of the newly formed bone (10)

Suba et al published a prospective controlled human clinical trial in 2005, which was a continuation of a previous study by Szabó et al (art 3), with a HST and HMM analysis of 17 cases according to Parfitt et al (27). The aim was to compare the effects of an alloplastic BSM, Cerasorb B-TCP, to AGBG. 17 completely edentulous individuals (10 women, 7 men) with an average age of 52 years and an average of 1.9mm residual bone height in the maxilla were included. A two-stage (delayed placement) BSMM according to TCD with either B-TCP 1.5-2g Cerasorb or AGB spongiosa from the left iliac crest was carried out.

After an average 6.5 months of healing, 68 cylindrical bone biopsies from maxilla (2 per each side on all patients) were taken and then Ankylos (Degussa, Friadent, Germany) dental implants were placed in the augmented bone.

The data obtained were analysed by the student t test with a significance level set at $P < 0.05$. On average the radiographic vertical height of the grafted sinus floor was 15mm in test side and 14.5mm in control side.

The authors discuss the possible explanations for the unilateral lower bone formation occurring in 3 cases: 2 test sites and 1 control site. In one of the test sites it was possible to explain by local inflammatory reaction and in the other case by crowding of the graft fragments. In the

control side however the authors could find no explanation.

In two cases very minor bone formation occurred bilaterally, which the authors suggest is due to in the first case it being the oldest patient of the study and in the second it being a postmenopausal woman.

The authors pose a question to be asked: whether persistence of graft material might influence or hamper the stability of the new bone. In the HMM, no statistically significant difference in bone density between the two grafts was observed. In an overwhelming majority of patients (14 out of 17) the intensity of new bone formation was similar in both groups.

Szabó et al. A prospective multicenter randomized clinical trial of autogenous bone versus b- tricalcium phosphate graft alone for bilateral sinus elevation: Histologic and Histomorphometric evaluation (7)

Szabó et al published in 2005 a multicenter RCT with the objective of determining whether donor site morbidity could be avoided by using pure-phase B-TCP (Cerasorb). The trial was conducted on 20 edentulous but healthy patients, 9 of whom were men and 11 women in the ages 38 to 67 years with a mean age of 52 years. All had less than 5mm residual sinus floor height (assessed as per Cawood and Howell classification) (7).

4 different treatment centers performed the trial, all using identical protocols for patient selection, preoperative examination, surgical procedure, implantation (of graft and dental implant), biopsy specimen retrieval, postoperative treatment and patient follow-up.

10 of the 20 patients received BSFE (according to TCD) with one side augmented with 1.5-2g Cerasorb B-TCP and the other with AGBG spongiosa from the left iliac crest. The remaining 10 patients received the same treatment in addition to a LWOP due to severe extent of alveolar resorption vertically and horizontally. The lateral augmentations were performed simultaneously with SFE, with a cortical harvest added to the spongiosa retrieved. No barrier membranes on the lateral sinus wall were used.

A 6-month healing period commenced after which implant placement (Protetim or Ankylos implants) would ensue. Prior to fixture placement cylindrical bone biopsies of the grafted areas were retrieved, 2 on each test and control side of every patient. The biopsies contained both grafted and native bone and all four centers sent the biopsies to the oral pathology unit of the Department of Oral and Maxillofacial Surgery of Semmelweis University for HMM according to the principles of Parfitt et al (27).

Statistical analysis by the Student t-test to determine statistical significance and values of $P<0.05$ were considered significant. The 10 patients who were treated with both SFE and LWOP were examined with 2D and 3D computerized tomography (CT) in addition to the panoramic x-rays. The CT assessment supplement revealed a clear superiority in surgery planning, assessment of bone quality and new bone formation using 2D CT, while 3D CT best revealed postoperative sinus graft height, new sinus floor height and the ossification process.

HST evaluation showed that the B-TCP was partially imbedded in new bone which was predominately lamellar and newly formed bone continuously replaced the BSM. The control side also contained mainly mature lamellar bone. HMM showed that there was no significant difference in mean percentage bone area between the test and control sites ($P=0.25$). For the majority of patients the new bone formation intensity was the same bilaterally and bone was sufficient bilaterally. After 12 months the B-TCP graft composition was similar to bone due to absorption and new bone formation.

1 patient got permanent sensory loss in the distribution of the lateral femoral cutaneous nerve after bone harvest, but no other donor site morbidities were reported. In the 6-month period between dental implant placement and loading 2 out of the 80 implants were lost (both Ankylos implants), one in a B- TCP site and one in a control site. Both lost implants were replaced with a 3-6 month delay

in loading.

In the authors' discussion, they state that several factors can influence bone formation in addition to the nature of the graft. In 2 patients low rate of bone formation was seen bilaterally, which they suggest might be due to general factors like old age, hormonal dysfunction, or calcium metabolism disturbance. They point out that one-sided lethargic bone formation may be explained by local factors such as blood supply disturbance or inflammatory reaction delaying bone formation; the fact that unilateral tardiness was seen both in an experimental and a control site the authors suggest supports the role of local factors.

The authors posed a question in their introduction of whether B-TCP in certain conditions could be equivalent to a patient's own spongiosa, which they in their discussion say the results suggest, and that Cerasorb in SFE is shown to be equivalent to an AGBG.

The authors imply that autogenous spongiosa in SFE mustn't necessarily still be held as the gold standard when B-TCP is shown to produce equivalent outcomes, specifically whilst AGBGs run the risk of being accompanied by donor site morbidity, relatively higher number of complications (20-30% generally), have the need for general anaesthesia as well as the high cost of hospitalisation.

In regards to barrier membranes the authors point to several studies (most notably Wallace and Froum's meta-analysis (29) and Tarnow et al's long-term study (30)) showing that their usage significantly improve outcomes in SFE which was generally accepted as fact, but chose despite of that not to utilise them. Wallace and Froum found that implant survival rates were higher when membranes were used in SFE than without. Tarnow et al found that barrier membranes tend to increase vital bone formation, have a positive effect on implant survival and that they should be considered for all SFE.

Zijderveld et al published a prospective controlled human clinical trial in 2005 with the objective to determine the ability of B-TCP to facilitate bone formation in comparison to AGBG in the maxillary sinus. 10 Partially or completely edentulous patients with age range of 18-72 years were included for SFE (according to TCD without membrane use). Specific inclusion criteria entailed that the remaining alveolar ridge height in the native maxilla be between 4-8mm so that the adequate original bone would provide primary implant stability and later integration. Patients needing LWOP were excluded.

Patients were divided into 2 groups, those requiring USFE (n=4) and those requiring BSFE (n=6). A healing period of 24 weeks was set for both groups. The second group got a BSMM-design with one side receiving 1.8g B-TCP and the other autogenous chin bone (control side). All cases were treated with ITI full body screw-type 4.1mm Straumann dental implants, 26 in test sites and 15 in control sites. The mean follow-up period was 1 year and 16 weeks after implant placement the referring general practitioner began prosthodontic treatment.

Biopsies were taken of the augmented bone at the time of implant placement, one biopsy from the grafted areas at the dental implant position and one lateral biopsy taken approximately 2mm below the horizontal trap door created. Six Schneiderian membranes perforated and all were covered with a resorbable demineralised freeze-dried laminar bone sheet. No lost implants occurred and all sites showed good continuity between the native maxilla and the graft.

The statistical test used was the paired student t test with a significance accepted when $P < 0.05$. HST and HMM analysis showed the following: residual and newly formed bone in control sides consisted predominantly of lamellar bone. Residual/original bone in test sites had similar architecture as the control sites and no significant difference ($P=0.19$) in bone volume percentage was recorded.

All test sides showed new bone formation (mainly woven bone), though some cases very scarcely. Greatest bone activity appeared at the adjoining area between the maxilla and B-TCP, demonstrating an osteoconductive property. Average bone volume formed on the control sides was measured at 41% and 17% for test sides, a

significant difference (P=0.5).

All patients exhibited adequate bone height clinically and histologically, vertical height obtained was measured with the panoramic x-rays. Despite the CT advantages, relying on Tronje's (31) findings that correctly taken panoramic x-rays don't significantly affect horizontal morphology, the authors opted out of CT scans for measuring vertical height to minimise patient radiation exposure.

Regarding healing time frames for B-TCP grafts, the authors shed light upon a new issue to be researched which is that unilateral sinus grafts should be studied with various healing periods to find the optimum healing time for B-TCP. They also suggest further studies in the usage of non-resorbable membranes covering the lateral maxillary wall which Froum et al (29) found significantly increased vital bone formation, and expressed interest in studying whether a resorbable membrane in combination with B-TCP enhances bone regeneration.

In contrast to Szabó et al (7,28), the authors maintain AGBG as the gold standard whilst demonstrating B-TCP's ability to be independently reliable in two-phase MSFE.

Zijderveld et al. Long-term changes in graft height after maxillary sinus floor elevation with different grafting materials: radiographic evaluation with a minimum follow-up of 4.5 years (9)

Zijderveld et al in 2008 published a long-term follow-up study of minimum 4.5 years, their aims were two-fold: first to compare long-term bone height changes in patients treated with SFE (according to TCD, without membranes) and grafts using either B-TCP or mandibular AGBG, secondly to compare the bone changes in height at three locations.

20 partially edentulous patients were included with free end situations distal to the cuspid/first bicuspid of whom 11 were women and 9 men with a mean age of 48.9 yr. The 20 cases were divided into two groups: those receiving the mandibular AGBG and those receiving the alloplastic BSM Cerosorb B- TSP. 4 of these patients needed BSFE and were thus treated using the BSMM. There was no significant difference in original bone height between the two groups.

After a median period of 5 months of healing, 4.1mm standard ITI Straumann dental implants were inserted whereupon a minimum follow-up of 4.5 years ensued with at least 5 panoramic x-rays taken: preoperatively, directly post-grafting, at implant placement, 1 year after implant placement and 5 years after placement for morphometric analysis at 3 locations (L1, L2 and L3). Each site received 2 to 3 dental implants totaling 60 ITI Straumann dental implants with 36 placed in B-TCP graft and 24 in AGBG.

To assess differences between graft groups at T0 independent t-tests were utilised and low quality x- rays were discarded. To evaluate whether vertical bone height and graft height exhibited differences over time the authors used ANOVA for repeated measures with time designated as within-subjects factor and the grafting groups as the between-subjects factor, they also examined whether these measures differed between the test groups.

ANOVA showed a statistically significant reduction over time in vertical bone height at L1 + L2 + L3; in graft height at L2 + L3. There was no statistical significant difference in reduction of vertical bone height or graft height in between groups.

Since 4 patients were in both groups due to receiving bilateral treatment, all the measurements were repeated to check whether this influenced the outcome by omitting these 4 with respect to one of the two groups (i.e. removing them from one of the groups), again yielding no statistical significant difference for the entire sample size of 20.

The authors also state that "non-resorbable graft material will not remodel and functionally adapt to surrounding bone and might be a negative mechanical factor, because it may prevent new bone from reaching the surface of the implant. Or, in other words, the graft height may be well

maintained in time, but it does not supply a bony attachment on the implant surface. A combination of the graft materials may therefore promote both osteogenesis and remodeling", favouring the resorbable B-TCP over the non-resorbable Bio-Oss (deproteinized bovine bone xenograft).

The authors comment on their choice to only use panoramic x-rays despite it being two-dimensional versus the 3D CT stating that since only height was investigated which panoramic x-rays are capable of measuring and not volume or homogeneity, which at any rate would be difficult since B-TCP appears very dense on CT scans, in addition to disallowance due to medicolegal reasons of CT scanning patients yearly, panoramic assessment was deemed sufficient and satisfactory. Further they report that Ozyuvaci et al (20) reported no statistical significant difference in vertical height between panoramic x-rays and tomography.

Rickert et al. Maxillary sinus lift with solely autogenous bone compared to a combination of autogenous bone and growth factors or (solely) bone substitutes. A systematic review (12)

Rickert et al performed a systematic review in 2011 in which literature regarding the outcome of MSE to create sufficient bone fraction to enable implant placement was systematically reviewed. Bone fraction and implant survival rate were assessed to determine whether grafting material or applied growth factor affected bone fraction. 12 articles passed the inclusion/exclusion process, all of which except one were RCT BSMM trials.

Rickert et al reported that B-TCP (Cerasorb) has been used as a test group in studies by Suba et al, Szabó et al, Zerbo et al and Zijderveld et al (7-12). Using AGB resulted in a significantly (P=0.036) higher bone fraction 5 to 6 months after grafting the meta-analysis of the present study showed. AGB was formed into mostly mature lamellar bone type (80%), while in the B-TCP augmentations the formed bone within the same time frames was more immature and consisted mainly of woven bone type (74%). All dental implants placed in grafts irrespective of nature (AGB alone or in combination with BSM/growth factors or BSM alone) had a similar 1-year survival rate (97% for AGB alone and 98% for the other combinations of grafts)

This systematic review reported no clinical evidence supporting the superiority of AGBG to most BSM's when it comes to SFE when allowing for a reasonably ample healing period (at least 5 months). Decreased risk of donor site morbidity and patient discomfort are a few the advantages of using BSM's in SFE instead of AGB which most commonly is retrieved from the iliac crest. The systematic meta- analysis also reported however that using AGBG alone yielded shorter healing periods of 3 to 4 months which would allow earlier implant placement.

Discussion

The discussion, with the aim of fulfilling the objective mentioned in 'Materials and Method' of analysing the articles both separately as well as to the others, will proceed with this aim in mind following the same order in which the articles were presented in 'Results': article 1 page 16, article 2 page 19, article 3 page 20, article 4 page 23, article 5 page 25 and article 6 page 27. In other words, each article will now be analysed and discussed independently as well as be compared to the other articles. Finally, the present study will be discussed as well.

One of Zerbo et al's study's (11) strong points is that they evaluated both original bone levels as well as new ones which gives a more reliable result of the actual therapeutic influence the test material possesses and allows one to assume that their findings in type and density of new bone formed are reliable to draw conclusions from. Another is that Zerbo et al tested a hypothesis stating that B-TCP would yield the same bone density as AGBG since assessing both bone quality as well as quantity is imperative when researching bone augmentation materials.

Thus, Zerbo et al's (11) critique against Szabó et al's (28) findings wasn't without merit since the fact that Szabó et

al (28) neither made a distinction between RB and NB nor were they clear surrounding their biopsies (of whether the lateral cortical grafts truly were possible to be excluded or not), which lends credit to the notion that it clouds their findings, in effect decreasing their reliability.

Zerbo et al's study (11) on the other hand also demonstrated some weaker points, first and foremost that bias realistically cannot be separated from their study because they received financial support from the Cerasorb company Curasan Pharma GmbH, as acknowledged by the authors. The author of the present review also points to a disputable hypothesis from Zerbo et al expecting B-TCP to generate bone density equal to that of AGBG when it is generally accepted that B-TCP is an osteoconductive material without osteoinductive properties. This dictates the initial formation of woven (and less dense and mature) bone before remodeling to denser lamellar bone may occur and AGBGs initially show quicker and denser bone apposition (8,12). Pre-emptively the present author would like to point out that the present review's hypothesis albeit resembling the one critiqued made that distinction in the hypothesis and in the reasoning leading up to it.

Suba et al (10) state in their study the great opportunity BSFE presents to test different graft materials' bone-regenerating effects. The author of the present study agrees with the notion in that two materials to be compared must be so under as identical circumstances as possible, in essence giving trials with BSFE with a BSMM superior evidence rank and credibility, which Suba et al had.

Suba et al (10) write "clinical observations in humans require non-invasive techniques, such as radiology and macromorphometry. However, the most effective way of evaluation of the density and stability of newly formed bone is histology and histomorphometry. An advantageous approach is the application of a two-stage technique: when the first step is the graft insertion and the second, after several months, is the implant placement in the grafted site (Lundgren et al. 1997). This second step provides an excellent possibility for taking biopsy specimens from the regenerating bone" which lends itself well to the notion that studies using the two-stage approach with biopsies analysed HST and HMM can be assumed superior to those using only radiographic or macromorphometric assessment.

The present review's author observed that Szabó et al (7) have apparent and well-merited disinclination towards AGBGs due to the increased morbidity and different types of costs associated to them. This is demonstrated by the fact that Szabó et al uphold that the AGB harvest in the LWOP group was ethically mandated due to lateral sinus augmentation requiring cortical bone, while they express ethical uncertainty over subjecting the SFE-only group to the additional surgery and morbidity of AGB harvest when they have experienced equivalent outcomes using only B-TCP. This is further illuminated by the fact that they intended to minimise the number of cases (n=20) while maintaining the necessary case sample to allow conclusions to be drawn, which they with their 80 biopsies and unambiguous findings maintain they do. The present author, though recognising the scientific and ethical intention of Szabó et al would like to suggest that a pre-existing disinclination towards AGBGs indicates possibility of bias.

Regarding the issue of Szabó et al (7) not using any membranes despite the general accepted notion of their positive influence, the present study's author opines that their aim was to avoid jeopardising their trial's findings by possibly entering a confounding variable of a proven factor, such as membranes' positive influence, into the study and thereby clouding differences of the outcomes between the experimental and control sites.

Zijderveld et al (8) contrasted their own study which excluded patients needing LWOP as opposed to Szabó et al's study (28), which Zijderveld et al state is the reason (the absence of cortical LWOP) why Zijderveld et al could better assess clinical appearance of the tested B-TCP during the implant placement procedure than could Szabó et al. The present review's author highlights that the most effective method to assess the density and stability of newly-formed bone is HST and HMM analysis since clinical, radiographic and macroscopic methods cannot equally assess both quantity and quality

of the newly formed bone in the grafted site (8,10).

For example, if as in the case of Zijderveld et al's (8) study a set inclusion criteria of minimum ridge height is required in order to provide primary implant stability, the outcomes of the tested graft material could be clouded by the influence of the residual bone's. Therefore Zijderveld et al's reasoning that clinical appearance entails superior assessments is suggested to need revising. This suggestion is further substantiated by the fact that by their own accord Zijdervald et al state that the prerequisite of having minimally 4mm starting ridge height as an inclusion criteria clouds the quality of the B-TCP treatment outcome since original bone could account for the primary stability and integration of the dental implants.

Zijderveld et al (8) reported a process of osteoconduction slower in test sides and osteogenesis faster in control sides which they explain being due to the difference of osteoconduction rates of the grafts. Since osteoconduction is the dominant factor, the main response must come from the walls encompassing the grafts (medial wall, original denuded sinus floor and the inward rotated door) and thus they suggest that one could expect that the center of the graft be last to ossify. This is in agreement with the findings of Zerbo et al (11). They also suggest that the slow process of osteoconduction in relation to the resorption of B-TCP is too long for cases where original ridge height is less than 4mm, which is in contradiction to what Suba et al (10) and Szabó et al (7) found in their respective studies.

Zijderveld et al (8) illuminate that in contrast to several studies, Szabó et al's (7,28) included which showed complete resorption of B-TCP in time, their study revealed various amounts of graft remnants were found clinically and histologically in all patients. They also mention that in 2 patients very little resorption occurred after 6 months. They do not present however a possible explanation for the discontinued resorption, which would have been valuable to contemplate considering the opposite results the other studies have showed (7,28). The present author suggests value in further research being conducted on whether the ceased resorption and following bone replacement simply is a question of time as Zerbo et al (11) expressed or if B-TCP in vivo does exhibit irregular biodegradation patterns and how this would influence bone regeneration and long-term dental implant prognosis.

Zijderveld et al in their study (8) also suggest that the slow process of osteoconduction in relation to the resorption of B-TCP is too long for cases where original ridge height is less than 4mm. This is in direct contrast to Szabó et al (7,28) who made no such distinction and in fact all their subjects had less than 5mm residual sinus floor height sparking inquisitiveness.

Zijderveld et al's long-term follow-up study (9) included a good wide spread overview and mention of existing literature. However in their discussion focus is mainly placed on these studies instead of discussing, critiquing and hypothesizing their own.

They (9) discuss the possible explanation for their good treatment outcomes and one of them was that the procedure was a relatively simple SFE as compared to both vertical and horizontal sinus augmentation, where the healing occurs only from the floor which prompted Zijderveld et al citing von Arx et al 2001 (32) to put forward the claim that B-TCP degrades too fast to retain sufficient bone support for ideal bone formation in larger defects. This is in contrast to the explicit findings of Szabó et al's studies (7,28) who successfully used B-TCP to augment severe maxillary atrophy.

Rickert et al (12) included in their systematic review both RCT's as well as cohort studies, prospective and retrospective studies and case reports. This would demote the systematic review to a lower evidence grade making its conclusions less reliable, something the authors clearly stated.

Granted, the studies analysed reported some variation in the degree and type of bone regeneration when B-TCP was used independently of autogenous bone graft however the results' general consensus was that B-TCP exhibited satisfactory bone augmentation and treatment

outcome in maxillary sinus elevation (7-9,11); that initially bone apposition was tardier and commenced with immature woven bone formation before progressively showing evidence of maturation into lamellar bone (8,11,12); that implant stability and survival was satisfactory up to 4.5 years after installation (9,11,12); and finally that B-TCP yielded comparable treatment outcomes to AGBGs provided ample healing time (7,8,11).

The present review suffered some deficiencies as well. The literature searches yielded a total of 25 candidate articles in stage I, II and III as described in 'Materials and Methods'. 12 of these were in the stage I group and 13 in the stage III group. In stage I, 4 articles were irretrievable of which 2 would have qualified to stage II had they been available, while the other 2 were Hungarian articles with English abstracts and hence would not have qualified. Irrespective of the cause, these 4 articles could all have been valuable and benefiting to this review since they all compared B-TCP to AGBG in one way or another and their omittance decreases from this study's aim of reviewing existing clinical findings pertaining to these bone augmentation materials.

Another weak point in this study is that it was conducted by a sole author and seeing as the appraisal of the literature and research retrieved was not insubstantial the added precision of an additional researcher to further guard against possible oversights would have been beneficial to this review. Nevertheless, considering the scientific unambiguous research protocol owing to Wright et al (26) and the strict adherence to it the author maintains that the findings and conclusions of the present literature review can be assumed reliable.

Conclusions

In light of the reports above the present author suggests that clinical evidence support B-tricalcium phosphate graft's usage in simple to moderately severe maxillary atrophy or sinus floor defects. The hypothesis presented is hence suggested to be verified, however the author expresses further interest in researching literarily and clinically the issues of what the optimal healing time for B-TCP grafting prior to implant placement should be, whether B-TCP is completely resorbable in vivo or not and what sequelae this entails, or whether a combination of B-TCP and AGB can yield superior treatment outcomes than independently since these are all factors that could increase cost-effectiveness for clinicians and patients alike.

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