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A Meta-Analysis of Histomorphometric Results and Graft Healing Time of Various Biomaterials Compared to Autologous Bone Used as Sinus Floor Augmentation Material in Humans

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Background: To date, no studies have been published in which histomorphometric data from a large group of patients comparing various biomaterials for sinus floor augmentation procedures were evaluated.
Materials and Methods: A meta-analysis of the English literature from January 1993 till April 2009 was carried out. Out of 147 titles, according to our criteria, 64 articles were selected for analysis describing the use of autologous bone and their alternatives, such as allogenic, xenogenic, and alloplastic materials.
Results: On the basis of autologous bone grafting, a reference value for total bone volume (TBV) of 63% was found. Particulation of the bone graft resulted in a general reduction of −18% in TBV. Delayed implant placement reduced the TBV with −7%. Overall TBV was 8% or 6% higher if a biopsy was, respectively, taken before 4.5 months or after 9.0 months after initial sinus augmentation surgery. Allogenic, xenogenic, alloplastic, or combinations of graft materials all resulted in a significant lower amount of TBV compared to autologous bone grafting ranging from −7% to −26%. Inventorying the effect of "biopsy time" for autologous bone, the TBV was significantly higher before 4.5 and after 9.0 months of healing time compared to period in between. Surprisingly, no significant differences in TBV with respect to "biopsy time" for bone substitutes were found.
Conclusions: On the basis of the aspect of TBV autologous bone still has to be considered to be the gold standard in sinus augmentation surgery. However, the consequence of the TBV for implant survival is still unraveled yet.

Introduction

Sinus floor augmentation surgery has become a routine procedure to generate primary implant placement and stability in the lateral part of the maxilla, resulting in an implant survival rate of 90% for 3 to 5 years.[1–7] Autologous bone is the most commonly used graft material and, as such, still considered to be the gold standard.[8,9] Unfortunately, harvesting an autologous bone graft is associated with several disadvantages. Donor-site surgery requires prolonged operating time and may cause morbidity.[10–14] To avoid serious advents of taking iliac crest bone transplants, such as hypersensitivity,[15] pelvic instability, infection,[14,16] and paraesthesia,[17] the mandibular symphysis has been advocated as an alternative donor site[13,18–20]; however, grafting chin bone may induce complications as well, such as paraesthesia[21] and apical root damage.[12,22] In contrast to intraoral donor sites, a relative larger amount of bone is available in the iliac crest that can be harvested in multiple forms (particles, strips, and blocks).

To overcome the disadvantages of autologous bone grafting in sinus augmentation surgery, various allogenic, xenogenic, and alloplastic graft materials or combination of these materials have been tested, followed by variable results.[23] Demineralized freeze-dried bone allograft (DFDBA) and also mineralized freeze-dried bone allograft (MFDBA) are obtained from cadaver bone that is cleaned and chemically treated.[24] Both have been proven to be biocompatible and osteoconductive[25] and are harvested in the same matter, with the only difference that the DFDBA material undergoes the additional step of decalcification. This also accounts for anorganic deproteinized bovine bone,[26] which is a xenogenic bone graft from which all organic components have been removed,[27] although still small amounts of proteins may be present, including growth factors such as transforming growth factor-β and bone morphogenetic protein (BMP)-2.[28] Further alloplastic materials have been investigated. As such, promising results for bioactive glass (BG) composites were reported.[29] Their bioactivity stimulates the reparative process,[30] resulting

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in a relatively fast bone ingrowth compared to for example hydroxyapatite (HA).[31] HA, either hydrothermally converted from coral or synthetically manufactured, shows a crystalline spatial structure close to that of cortical bone matrix[32] and it is considered to be osteoconductive.[27,33] The degradation of HA is relatively slow and is related to the amount of porosity of the material; it may dissolute at the surface or resorb by the activity of macrophages and multinucleated giant cells.[34,35] Pure-phase beta-tricalcium phosphate (β-TCP), as a derivate of HA, has been shown to be completely resorbable and, in addition, is simultaneously replaced by new bone formation.[36,37] For the sake of completeness, also calcium sulfate, calcium carbonate, hydrogels, biodegradable polymers, and tissue-engineered constructs, either combined with growth factors or cultured cells, are described in the literature as graft material in human sinus floor augmentation. Except for the selected biomaterial, other variables may also influence the final outcome.[38] For example, some authors advise to apply a resorbable or nonresorbable barrier membrane over the sinus graft osteotomy site,[39–42] or propagate immediate or delayed placement of dental implants. Others recommend a prolonged graft healing time.[7]

It is reported that a higher percentage of bone volume results in a higher implant–bone contact, thereby resulting in a higher implant survival.[38] Further, the percentage of total bone volume (TBV) formed is an important parameter of the performance of a bone graft or bone replacement graft in an augmented sinus.[24,43–45] Till now, no studies have been published that evaluated histological and histomorphometric data related to different biomaterials and their variables from a large group of patients. Therefore, to answer which graft material results in the highest TBV in human sinus floor augmentation surgery and which graft healing time is the most optimal, a meta-analysis was conducted.

Materials and Methods

Search protocol and selection of articles

An online and manual search was conducted of the Medline database from January 1993 till April 2009 using the PubMed search machine entering the following search terms: "(maxillary) sinus augmentation or (maxillary) sinus lift" and "human or clinical or patient" and "histology or histomorphometry or histomorphometric." A hand search was performed in the following journals: *Clinical Oral Implant Research*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Periodontics and Restorative Dentistry*, and *The Journal of Periodontology*. As well, the references of the retrieved articles were searched. The results were limited to humans and to articles published in the English literature. Articles were only regarded eligible if they included lateral sinus augmentation surgery in which an autogenic, allogenic, xenogenic, or alloplastic graft material, solely or in combination, was placed. Further, histomorphometric data about TBV needed to be present. Effects elucidated by a graft mixture with >90% volume of one biomaterial were fully accounted to that specific biomaterial, except if platelet-rich plasma (PRP) was added. Each retrieved citation was reviewed by two independently working reviewers. Most articles were excluded on the basis of information provided by the title or abstract. If the citation could not be excluded unequivocally, any disagreement was resolved by consensus. To ensure consistency of the results for the included studies, clear definitions of outcome were defined. For example, TBV was based on histomorphometric data as a percentage of the whole field of view. Subsequently, the included studies were carefully analyzed concerning data on "graft material," "biopsy time," "block grafting technique," "particulated grafting technique," the usage of a "(non)-resorbable membrane" over the lateral window, "immediate or delayed" implant placement, and TBV. Where adequate data were available, subgroups of similar interventions were identified. At least five subgroups, including at least two sinus floor augmentations per group, describing a graft material or combination of graft materials, had to be reported in the literature to include their data in this analysis.

Meta-analysis

Linear regression, a form of meta-analysis, was performed to determine the effect of the independent variables: "graft material," "biopsy time," "block grafting technique," "particulated grafting technique," the usage of a "(non)-resorbable membrane" over the lateral window, and "immediate or delayed" implant placement on the histomorphometric outcome after maxillary sinus floor augmentation. The amount of TBV was used as the dependent variable. To evaluate the general influence of "biopsy time" on the histomorphometric data outcome, all data were equally divided into three different groups of time: 0–4.5 months, 4.5–9 months, and longer than 9 months. The reference group comprised the use of an autologous bone graft with a biopsy time between 4.5 and 9 months, immediate implant placement, and no membrane use. The overall averages were controlled for study characteristics and weighted by study size.

A second linear regression was performed to correct the found TBV for each graft material or combination of graft materials, for "biopsy time." All subgroups were divided into three subgroups based on biopsy time: 0–4.5 months, 4.5–9 months, and longer than 9 months. The amount of TBV was used as the dependent variable. Independent variables were "block grafting technique," "particulated grafting technique," the usage of a "(non)-resorbable membrane" over the lateral window, and "immediate or delayed implant placement." The reference group was identical. All effects have been corrected for different parameters inside the model by linear regression and group size. The outcome, among corresponding *p*-values, had to be summed and recalculated for the groups with combined use of different graft materials in sinus augmentation surgery.

Results

The basis search provided 147 titles for consideration. As a result, 64 articles met our inclusion criteria. Describing autologous bone,[29,36,37,39,41,42,46–64] addition of PRP,[47,52,55] DFDBA,[65–69] MFDBA,[24,25,68,70–73] anorganic deproteinized bovine bone,[24,26,48,53,60,62,69,74–85] bioactive glass (BG),[29,56,86,87] synthetic HA,[53,64,81,82,88–90] coral-derived HA,[91,92] β-TCP,[36,37,54,58–60,85,93–95] and combinations of these materials.[24,42,48,49,60,62,67,69,78,87,95–98] The majority of these 64 articles were prospective controlled studies (48). Only eight randomized clinical trials met the inclusion

Table 1. Literature Overview

	n
"Sinus Augmentation" or "Sinus Lift"	428 hits
AND (human or patient or clinical)	401 hits
AND (histology or histomorphometric or histomorphometry	147 hits
Included	64 articles
Randomized clinical trails	8 articles
Prospective controlled trials	48 articles
Case series	8 articles

Table 2. Overview of Grafting Materials

Material	n *subgroups*	n *sinusses*
Autologous bone graft	47	438
PRP	7	35
MFDBA	7	96
ADBB	29	319
ADBB + autologous bone	29	261
ADBB + DFDBA	9	113
Synthetic HA	10	108
Phycogenic HA	9	52
β-TCP	8	116
β-TCP + autologous bone	7	62
Bioactive glass + autologous bone	8	72
Total $\sum$	170	1672

PRP, platelet-rich plasma; MFDBA, mineralized freeze-dried bone allograft; ADBB, anorganic deproteinized bovine bone; DFDBA, demineralized freeze-dried bone allograft; HA, hydroxyapatite; β-TCP, beta-tricalcium phosphate.

criteria, followed by eight case series (Table 1). In total, histomorphometric data were obtained from 1677 grafted sinuses divided in 172 subgroups. As a result, 11 material groups were recognized of similar bone graft or combination of bone graft materials (Table 2). A specific overview of these subgroups is provided in Tables 3–13. Graft materials were used as blocks, particulated grafts, or as combination of both. The topic of using (non)-resorbable barrier membranes over the lateral wall was addressed in 24 out of the 64 articles.

Statistical analysis

In total, 17 variables entered into the regression model as depicted in Table 14 along with their *p*-values and confidence intervals. The R^2 for the full model was 0.460; the adjusted R^2 was 0.403.

Graft material. After linear regression a reference value for TBV of 63% was calculated. Most graft materials showed significant differences in TBV compared to this reference value (Table 14) (Fig. 1). The addition of PRP to an autologous bone graft reduced the TBV with −18.0%. Usage of a xenogenic bone graft decreased the TBV with −13%, while usage of a xenogenic bone graft combined with autologous bone resulted in a less decrease of −8%. The confidence intervals showed a significant overlap, indicating that the addition of autologous bone made no statistically significant difference. Combining DFDBA with a xenogenic bone graft, however, resulted in a significant lower TBV, as a decrease of −25% compared to the reference was found. Combining BG with autologous bone resulted in a −17% decrease, and combining β-TCP with autologous bone resulted in a reduction of −9% in TBV. Sinus floor augmentation with synthetically manufactured HA or hydrothermally converted coral reduced TBV with −11% or −12% respectively. Further, almost significant, MFDBA and β-TCP resulted both in a TBV decrease of −7%. Thus, most bone substitutes, even mixed with autologous bone, resulted in a significant lower TBV compared to the reference value of 63% for autologous bone. On the other hand, taken into account that the confidence intervals of most substitutes had a significant overlap, the difference between them regarding amount of TBV was not statistically significant. This, however, did not account for DFDBA with a xenogenic bone graft.

Biopsy time. There is significant evidence that the TBV was influenced by graft healing time in general and thus the "biopsy time" of all samples. Overall TBV was 8% or 6% higher if a biopsy was, respectively, taken before 4.5 months or after 9.0 months after the sinus augmentation surgery. After performing the second linear regression (Table 15), correcting each bone graft material for "biopsy time," a summation had to be made for the combined use of graft materials with their corresponding *p*-values (Table 16).

Only in case of autologous bone grafting and the combined use of autologous bone with a xenogenic bone graft, "biopsy time" had a significant influence on the TBV: a biopsy time of <4.5 months resulted in an increase in TBV of 11% compared to a biopsy taken between 4.5 and 9.0 months. Additionally, a biopsy time of 9.0 months or longer increased the TBV with 10% compared to the centered group. Further, the combined use of autologous bone and a xenogenic bone graft started with a plus of 26% of TBV compared to the period between 4.5 and 9 months. Surprisingly, no further significant difference could be detected between the various graft materials in time.

Variables. Compared to the reference value of TBV, usage of a particulated graft significantly decreased the TBV with −18%, while usage of a block resulted in an decrease of −6% TBV, although not to a significant level. In addition, "delayed" implant placement, significantly resulted in a lower TBV of −7% compared to "immediate" implant placement. Further, no evidence was found that the use of a resorbable membrane over the lateral window had any effect, positive or negative, on the amount of TBV.

Discussion

Maxillary sinus floor augmentations are ideal test sites to histomorphometricaly assess a grafted material. Before preparing the implant bed to install dental implants, a biopsy of the reconstructed area can be easily taken, implicating no extra burden for the patient. As an additional advantage this procedure can be performed under local anesthesia. In the selected studies various bone substitutes were used, or solely or as a bone graft extender in combination with autologous bone. Till now, autologous bone grafts are considered to be the gold standard.[8,9] This postulation, however, is only based on implant survival, while bone quality in the grafted area is

Table 3. Overview of Autologous Bone Grafting

Author	*Year*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Lundgren	1996	Particulate	10	None	Delayed	0	45.00
Lundgren	1996	Block	10	None	Delayed	0	58.00
Pejrone	2002	Block	26	None	Delayed	0	59.30
Lorenzetti	1998	Block	8	None	Delayed	0	60.00
Lorenzetti	1998	Particulate	3	None	Delayed	0	65.60
Lorenzetti	1998	Block	3	None	Delayed	0	65.60
Thor	2007	Particulate	11	None	Delayed	3	11.00
Zerbo	2003	Block	5	Collagen	Delayed	3	39.38
Raghoebar	2005	Block + particulate	5	None	Delayed	3	41.10
Consolo	2007	Particulate	2	None	Delayed	4	26.00
Zerbo	2003	Block	6	Collagen	Delayed	4	39.78
Tadjoedin	2000	Particulate	3	None	Delayed	4	40.94
Lorenzetti	1998	Block	3	None	Delayed	4	62.60
Consolo	2007	Particulate	2	None	Delayed	5	29.20
Crespi	2007	Particulate	6	Collagen	Delayed	5	34.00
Tadjoedin	2000	Particulate	3	None	Delayed	5	42.24
John	2004	Particulate	2	None	Delayed	5	53.50
John	2004	Particulate	2	None	Immediate	5	53.50
Crespi	2007	Particulate	10	Collagen	Delayed	5	69.70
Barone	2005	Particulate	18	Collagen	Delayed	5	70.00
Crespi	2009	Particulate	15	None	Delayed	5	78.40
Gerressen	2009	Particulate	15	None	Delayed	5	29.35
Gerressen	2009	Particulate	15	None	Delayed	5	37.87
Thor	2007	Particulate	11	None	Delayed	6	13.00
Groeneveld	1999	Particulate	3	None	Delayed	6	26.20
Van den Bergh	2000	Particulate	3	None	Delayed	6	26.60
Consolo	2007	Particulate	2	None	Delayed	6	29.00
Szabo	2001	Particulate	4	None	Delayed	6	37.05
Szabo	2005	Particulate	20	None	Delayed	6	38.34
Lundgren	1996	Particulate	10	None	Delayed	6	40.00
Scarano	2006	Particulate	16	None	Delayed	6	40.10
Zerbo	2003	Block	3	Collagen	Delayed	6	40.90
Zerbo	2004	Particulate	5	None	Delayed	6	41.00
Zijderveld	2005	Particulate	6	None	Delayed	6	41.00
Tadjoedin	2000	Particulate	3	None	Delayed	6	43.65
Lorenzetti	1998	Particulate	8	None	Delayed	6	53.00
Pejrone	2002	Block	26	None	Delayed	6	54.10
Suba	2006	Particulate	17	None	Delayed	7	34.70
Consolo	2007	Particulate	2	None	Delayed	7	20.00
Turunen	2004	Block + particulate	17	None	Delayed	7	25.10
Simunek	2008	Particulate	8	None	Delayed	9	49.20
Le Lorc'h-Bukiet	2005	Particulate	24	None	Delayed	10	49.40
Lorenzetti	1998	Particulate	3	None	Delayed	11	69.30
Turunen	2004	Block + particulate	17	None	Delayed	12	25.10
Lundgren	1996	Particulate	10	None	Delayed	12	48.00
Pejrone	2002	Block	26	None	Delayed	12	63.90
Hallman	2002	Particulate	11	None	Delayed	13	37.30

TBV, total bone volume.

Table 4. Overview of Addition of Platelet-Rich Plasma

Author	*Year*	*Graft name*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Thor	2007	ABG + PRP	Particulate	11	None	Delayed	3.0	22.00
Raghoebar	2005	ABG + PRP	Block + particulate	5	None	Delayed	3.0	38.40
Consolo	2007	ABG + PRP	Particulate	2	None	Delayed	4.0	43.30
Consolo	2007	ABG + PRP	Particulate	2	None	Delayed	5.0	39.30
Thor	2007	ABG + PRP	Particulate	11	None	Delayed	6.0	14.00
Consolo	2007	ABG + PRP	Particulate	2	None	Delayed	6.0	29.00
Consolo	2007	ABG + PRP	Particulate	2	None	Delayed	7.0	20.00

Table 5. Overview of Mineralized Freeze-Dried Bone Allograft

Author	*Year*	*Graft name*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Choukroun	2006	FDBA	Particulate	3	None	Delayed	4.0	20.31
Stacchi	2008	FFB	Particulate	10	Collagen	Delayed	5.0	48.15
Kassolis	2005	FDBA	Particulate	10	Collagen	Delayed	5.3	26.50
Froum	2006	Puros	Particulate	13	Collagen	Delayed	6.6	28.25
Kolerman	2008	FDBA	Particulate	23	Collagen	Delayed	9.0	29.09
Noumbissi	2005	Puros	Particulate	6	None	Delayed	9.0	40.33
Cammack	2005	FDBA	Particulate	31	(Non)-resorbable	Delayed	11.2	41.07

often left out of consideration.[7,27] Further, implant survival and bone quality may be confounded by factors other than the graft material.[7,38] The aim of this study was to give a powerful estimate of the true effect of the various variables: "graft material," "biopsy time," "block grafting technique," "particulated grafting technique," the usage of a "(non)-resorbable membrane" over the lateral window, and "immediate or delayed" implant placement, on the histomorphometric outcome after sinus floor augmentation surgery. Because of the general absence or differences of other histomorphometric indices in the studies, TBV was solely used as dependent variable.

Graft material

Autologous bone. Compared to autologous bone, for each biomaterial or combination of graft materials in sinus augmentation surgery a significant lower TBV was found. Evidently, autologous bone grafting resulted in the highest percentage of mineralized bone. It should, however, be emphasized that when evaluating biopsies from autologous-bone-grafted areas, not only the new bone formation but also the transplanted bone volume is scored. This in contrast to examining biopsies from sites reconstructed with bone substitutes, from which only the newly formed bone can be measured.

Table 6. Overview of Anorganic Deproteinized Bovine Bone (ADBB) Grafting

Author	*Year*	*Graft name*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Wheeler	1996	Interpore 200	Particulate	4	None	Delayed	4.00	12.02
Orsini	2006	Cortical pig bone	Particulate	10	Collagen	Delayed	5.00	36.00
John	2004	Bio Oss	Particulate	7	None	Delayed	5.50	29.52
John	2004	Bio Oss	Particulate	14	None	Immediate	5.50	29.52
Yildirim	2000	Bio Oss	Particulate	3	Collagen	Delayed	6.00	13.15
Lee	2006	Bio Oss	Particulate	14	Collagen	Delayed	6.00	18.30
Valentini	2000	Bio Oss	Particulate	20	None	Delayed	6.00	21.08
Mangano	2007	Bio Oss	Particulate	20	None	Immediate	6.00	36.20
Scarano	2006	PepGen P-15	Particulate	16	None	Delayed	6.00	37.00
Scarano	2006	Bio Oss	Particulate	16	None	Delayed	6.00	39.00
Yildirim	2000	Bio Oss	Particulate	2	Collagen	Delayed	6.50	19.15
Froum	2006	Bio Oss	Particulate	13	Collagen	Delayed	6.60	12.44
Cordaro	2008	Bio Oss	Particulate	23	Collagen	Delayed	6.70	19.80
Yildirim	2000	Bio Oss	Particulate	2	Collagen	Delayed	7.00	10.85
Ozyuvaci	2003	Bio Oss	Particulate	20	None	Immediate	7.00	47.50
Froum	2008	Bio Oss	Particulate	11	Collagen	Delayed	7.17	22.30
Froum	1998	Osteograft/n	Particulate	5	None	Delayed	7.50	8.50
Yildirim	2000	Bio Oss	Particulate	2	Collagen	Delayed	7.50	15.25
Froum	1998	Osteograft/n	Particulate	10	None	Delayed	7.50	17.00
Springer	2006	Bio Oss	Particulate	5	None	Delayed	8.00	25.00
Yildirim	2000	Bio Oss	Particulate	2	Collagen	Delayed	9.00	16.50
Simunek	2008	Bio Oss	Particulate	10	None	Delayed	9.00	34.20
Wheeler	1996	Interpore 200	Particulate	2	None	Delayed	10.00	25.10
Lee	2006	Bio Oss	Particulate	14	Collagen	Delayed	12.00	26.60
Valentini	2000	Bio Oss	Particulate	20	None	Delayed	12.00	27.55
Artzi	2002	Bio Oss	Block	10	Collagen	Immediate	12.00	34.20
Artzi	2001	Bio Oss	Particulate	4	Collagen	Delayed	12.00	42.10
Artzi	2001	Bio Oss	Particulate	16	Collagen	Immediate	12.00	42.10
Hallman	2002	Bio Oss	Particulate	14	Collagen	Delayed	14.50	41.70
Traini	2008	Bio Oss	Particulate	10	None	Delayed	20.00	38.00

Table 7. Overview of ADBB Grafting and Autologous Bone

Author	*Year*	*Graft name*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Tadjoedin	2003	Bio Oss + ABG 1:5	Particulate	2	None	Delayed	5.0	37.30
Barone	2005	Osteobiol + ABG 1:1	Particulate	18	Collagen	Delayed	5.0	67.00
John	2004	Bio Oss + ABG 66:33	Particulate	7	None	Delayed	5.5	32.23
John	2004	Bio Oss + ABG 66:33	Particulate	6	None	Immediate	5.5	32.23
Wheeler	1996	Interpore 200 + ABG	Particulate	2	None	Delayed	6.0	4.72
Yildirim	2001	Bio Oss + ABG	Particulate	2	Collagen	Delayed	6.0	15.17
Yildirim	2001	Bio Oss + ABG	Particulate	2	Collagen	Delayed	6.0	15.67
Wheeler	1996	Interpore 200 + ABG	Particulate	2	None	Delayed	6.0	23.00
Galindo-Moreno	2008	Bio Oss + ABG 1:1	Particulate	5	Collagen	Delayed	6.0	31.02
Yildirim	2001	Bio Oss + ABG	Particulate	2	Collagen	Delayed	6.5	18.27
Yildirim	2001	Bio Oss + ABG	Particulate	2	Collagen	Delayed	6.5	20.62
Hallman	2001	Bio Oss + ABG 18:82	Particulate	20	None	Delayed	6.7	31.40
Hallman	2001	Bio Oss + ABG 18:82	Particulate	20	None	Delayed	6.7	31.40
Wheeler	1996	Interpore 200 + ABG	Particulate	3	None	Delayed	7.0	14.82
Wheeler	1996	Interpore 200 + ABG	Particulate	2	None	Delayed	7.0	15.60
Froum	1998	Osteograft/n + ABG	Particulate	7	None	Delayed	7.5	18.50
Froum	1998	Osteograft/n + ABG	Particulate	31	None	Delayed	7.5	29.00
Wallace	2005	Bio Oss + ABG 5:1	Particulate	6	None	Delayed	8.0	12.10
Wallace	2005	Bio Oss + ABG 5:1	Particulate	21	e-PTFE	Delayed	8.0	16.90
Wallace	2005	Bio Oss + ABG 5:1	Particulate	37	Collagen	Delayed	8.0	17.60
Moy	1993	Interpore 200 + ABG 1:1	Block + particulate	4	None	Delayed	8.0	44.40
Wheeler	1996	Interpore 200 + ABG	Particulate	2	None	Delayed	9.0	12.60
Yildirim	2001	Bio Oss + ABG	Particulate	2	Collagen	Delayed	9.0	18.88
Simunek	2008	Bio Oss + ABG 85:15	Particulate	10	None	Delayed	9.0	24.40
Lorenzetti	1998	Interpore 200 + ABG 1:1	Particulate	3	None	Delayed	12.0	43.60
Artzi	2005	Bio Oss + ABG	Particulate	2	Collagen	Delayed	12.0	45.60
Artzi	2005	Bio Oss + ABG	Particulate	10	Collagen	Immediate	12.0	45.60
Hallman	2002	ABG + Bio Oss 1:4	Particulate	11	None	Delayed	12.5	39.90
Hallman	2001	ABG + Bio Oss 18:82	Particulate	20	None	Delayed	36.0	51.50

e-PTFE, expanded polytetrafluoroethylene.

Platelet-rich plasma. Platelets are a natural source of growth factors. Some authors state that the combined use of growth factors and graft material will introduce osteogenesis and improve bone healing,[99] whereas others reject the adjunctive use PRP in sinus augmentation because of disappointing results.[100,101] In this study, the addition of PRP to a autologous bone graft generally resulted in a significant lower TBV. In the literature, the regenerative potential of PRP seemed to be restricted to shorter treatment times.[47] However, in this meta-analysis, no significance evidence was found that PRP has a positive effect on TBV during graft healing time. To date, none of the studies, describing the use of growth factors, for example, BMP-2, BMP-7, or transforming growth factor-β, fulfilled the inclusion criteria.

Allogeneic bone. DFDBA was always used in combination with a xenogenic bone graft and resulted in the lowest TBV as compared to autologous bone and all other materials. Grafting with MFDBA has a tendency to result in a slightly lower TBV compared to autologous bone, but not to a significant level. Also in case of MFDBA, it must be noted that particles of nonresorbed MFDBA are described to be difficult to distinguish as graft material from new vital bone in the calculation of TBV.[24]

Xenogenetic bone. The addition of autologous bone to a xenograft resulted in a slight increase in TBV compared to its single use, but not to a significant level. This increase in TBV ranged between 15% till 50%.[42,60] As the ratio of xenogenic

Table 8. Overview of ADBB and Demineralized Freeze-Dried Bone Allograft Graft

Author	*Year*	*Graft name*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Hanisch	1999	Osteograft/n + DFDBA 1:1	Particulate	20	None	Delayed	6.0	8.10
Froum	1998	Osteograft/n + DFDBA	Particulate	8	None	Delayed	7.5	14.00
Froum	1998	Osteograft/n + DFDBA	Particulate	14	None	Delayed	7.5	23.00
Moy	1993	Interpore + DBP 200 7:1	Block + particulate	2	None	Delayed	8.0	4.60
Hanisch	1999	Osteograft/n + DFDBA 1:1	Particulate	20	None	Delayed	8.0	9.00
Noumbissi	2005	Bio Oss + DFDBA 1:1	Particulate	4	None	Delayed	9.0	38.75
Hanisch	1999	Osteograft/n + DFDBA 1:1	Particulate	20	None	Delayed	10.0	11.80
Landi	2000	Osteograft/n + DFDBA 1:1	Particulate	5	None	Delayed	10.3	27.92
Hanisch	1999	Osteograft/n + DFDBA 1:1	Particulate	20	None	Delayed	12.0	20.70

Table 9. Synthetic Hydroxyapatite

Author	*Year*	*Graft name*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Canullo	2009	Nanobone	Particulate	8	None	Delayed	3.0	8.00
Crespi	2009	SINTlife	Particulate	15	None	Delayed	5.0	29.65
Scarano	2006	Fin granule HA	Particulate	16	None	Delayed	6.0	32.00
Mangano	2007	Porous synthetic HA	Particulate	20	None	Immediate	6.0	34.70
Mangano	2006	Engipore	Block + particulate	11	None	Delayed	6.0	38.50
Canullo	2009	Nanobone	Particulate	8	None	Delayed	6.0	48.00
Artzi	2003	Osteogen	Particulate	2	Collagen	Delayed	12.0	28.10
Artzi	2003	Osteogen	Particulate	8	Collagen	Immediate	12.0	28.10
Artzi	2001	Osteogen	Particulate	4	Collagen	Delayed	12.0	32.20
Artzi	2001	Osteogen	Particulate	16	Collagen	Immediate	12.0	32.20

Table 10. Overview of Coral-Derived Hydroxyapatite

Author	*Year*	*Graft name*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Simunek	2005	Algipore	Particulate	3	None	Delayed	6.0	10.90
Simunek	2005	Algipore	Particulate	3	None	Immediate	6.0	20.10
Ewers	2005	Algipore	Particulate	29	Various	Delayed	7.1	28.95
Simunek	2005	Algipore	Particulate	3	None	Delayed	9.0	25.00
Simunek	2005	Algipore	Particulate	3	None	Immediate	9.0	31.70
Simunek	2005	Algipore	Particulate	2	None	Delayed	12.0	33.50
Simunek	2005	Algipore	Particulate	3	None	Immediate	12.0	34.80
Simunek	2005	Algipore	Particulate	3	None	Delayed	15.0	30.20
Simunek	2005	Algipore	Particulate	3	None	Immediate	15.0	51.10

Table 11. Overview of Beta-Tricalcium Phosphate

Author	*Year*	*Graft name*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Zerbo	2004	Cerasorb	Particulate	9	None	Delayed	6.0	17.00
Zijderveld	2005	Cerasorb	Particulate	10	None	Delayed	6.0	17.00
Szabo	2001	Cerasorb	Particulate	8	None	Delayed	6.0	29.37
Szabo	2005	Cerasorb	Particulate	40	None	Delayed	6.0	36.47
Suba	2006	Cerasorb	Particulate	17	None	Delayed	6.5	32.38
Ozyuvaci	2003	β-TCP	Particulate	20	None	Immediate	7.0	52.50
Zerbo	2001	Cerasorb	Particulate	2	None	Delayed	8.0	20.00
Simunek	2008	Cerasorb	Particulate	10	None	Delayed	9.0	21.40

bone mineral versus autologous bone graft increases, resorption of the bone additive decreases exponentially, because less osteoclasts can be recruited from the autogenous bone.[27,102] A reduced resorption may have negative consequences on the mechanical properties of the augmented bone and its capacity to support an implant, since the augmented bone will be a composite rather than a homogenous bone structure.[27,103] Obviously, this is the case for all bone substitutes.

Alloplastic bone substitutes. A variety of alloplastic bone substitutes, single or in combination with autologous bone, was used in sinus augmentation surgery. In this study the effect of BG, synthetic HA, coral-derived HA, and β-TCP on the amount of TBV was investigated. Although alternative materials were described in the literature, they did not met the inclusion criteria stated for this meta-analysis. To add the osteogenic and osteoinductive components that are necessary to achieve complete bone formation, the bone substitutes were occasionally mixed with autogenous bone.[24,42,48,49,60,62,67,69,78,87,95–98] Further, in larger defects the bone additive reduces the required autologous bone needed.

BG was used in combination with autologous bone in ratios of 1:1, and 1:4. BG is a resorbable particulate synthetic bioactive glass from which the granules are supposed to function as small bone regenerative chambers.[104] Unexpectedly, after linear regression, sinus augmentation with BG resulted in the lowest TBV of all alloplastic materials.

Table 12. Overview of Beta-Tricalcium Phosphate and Autologous Bone

Author	*Year*	*Graft name*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Knabe	2008	β-TCP + ABG	Particulate	10	None	Delayed	6.0	26.70
Knabe	2008	β-TCP + ABG	Particulate	10	None	Delayed	6.0	31.70
Knabe	2008	β-TCP + ABG	Particulate	10	None	Delayed	6.0	35.50
Knabe	2008	β-TCP + ABG	Particulate	10	None	Delayed	6.0	40.30
Simunek	2008	Cerasorb + ABG	Particulate	10	None	Delayed	9.0	24.00
Artzi	2005	β-TCP + ABG	Particulate	3	Collagen	Delayed	12.0	32.00
Artzi	2005	β-TCP + ABG	Particulate	9	Collagen	Immediate	12.0	32.00

Table 13. Overview of Bioactive Glass

Author	*Year*	*Graft name*	*Graft type*	n *sinusses*	*Membrane*	*Immediate or delayed*	*Biopsy time (months)*	*TBV*
Tadjoedin	2000	BG + ABG 1:1	Particulate	3	None	Delayed	4.0	28.45
Tadjoedin	2000	BG + ABG 1:1	Particulate	3	None	Delayed	5.0	34.54
Galindo-Moreno	2008	BG + ABG 1:1	Particulate	5	Collagen	Delayed	6.0	33.08
Tadjoedin	2000	BG + ABG 1:1	Particulate	3	None	Delayed	6.0	38.07
Turunen	2004	BG S53P4 + ABG	Particulate	17	None	Delayed	7.0	25.70
Cordioli	2001	BG + ABG 4:1	Particulate	12	Collagen	Immediate	10.8	14.20
Cordioli	2001	BG + ABG 4:1	Particulate	12	Collagen	Immediate	10.8	30.60
Turunen	2004	BG S53P4 + ABG	Particulate	17	None	Delayed	12.0	28.80

Table 14. Regression Analysis 1

Model		*Unstandardized coefficients*		*Sig.*	*95% confidence interval for B*	
		B	*Std. Error*		*Lower bound*	*Upper bound*
1	(Constant)	62.66	8.28	0.00	52.77	85.48
	Particulated graft	−17.89	5.64	0.00	−29.02	−6.76
	Block graft	−5.85	4.79	0.22	−15.31	3.62
	Membrane	−13.14	8.05	0.10	−29.04	2.75
	Resorbable membrane	11.47	8.18	0.16	−4.68	27.62
	Delayed implantology	−6.46	2.91	0.03	−12.20	−0.72
	Biopsy $t < 4.5$ months	8.41	2.56	0.00	3.35	13.47
	Biopsy $t > 9.0$ months	5.57	2.13	0.01	1.35	9.78
	PRP	−17.96	6.27	0.01	−30.33	−5.59
	MFDBA	−7.30	4.52	0.11	−16.23	1.63
	ADBB	−12.74	3.02	0.00	−18.71	−6.77
	ADBB + Autologous	−8.26	3.13	0.01	−14.44	−2.09
	ADBB + DFDBA	−25.31	3.97	0.00	−33.16	−17.47
	Synthetic HA	−11.30	4.10	0.01	−19.40	−3.20
	Coral-derived HA	−11.50	5.48	0.04	−22.32	−0.67
	β-TCP	−6.53	4.04	0.11	−14.50	1.45
	β-TCP + autologous	−9.19	5.00	0.07	−19.06	0.69
	Bioactive glass + autologous	−16.82	4.79	0.00	−26.28	−7.35

Dependent variable: TBV.

Example: Calculation of expected TBV for "Particulated synthetic HA with a resorbable membrane and immediate implantology and a biopsy time of <4.5 months" = 62.66 − (17.89 − 11.3 + 11.47 + 8.41) = 53.35%.

Sinus augmentation with synthetic or coral-derived HA also resulted in a decrease of TBV. As HA was grafted without the addition of autologous bone, TBV was only influenced by new bone formation from the local sinus environment. For β-TCP with or without the addition of autologous bone, TBV differed not significantly. While others stated that along with the replacement of solely β-TCP, the TBV will consequently increase,[58] this postulation, however, could not be confirmed by this meta-analytical study. Also, the influence of adding autologous bone to β-TCP appeared to be negligible, although supplemented in 10% to 50% of the total graft volume.[60,93,95]

All bone graft substitutes, alone or in combination with an autologous bone graft, resulted in a analogous significant lower TBV compared to autologous bone grafting. On the other hand, taken into account that the confidence intervals

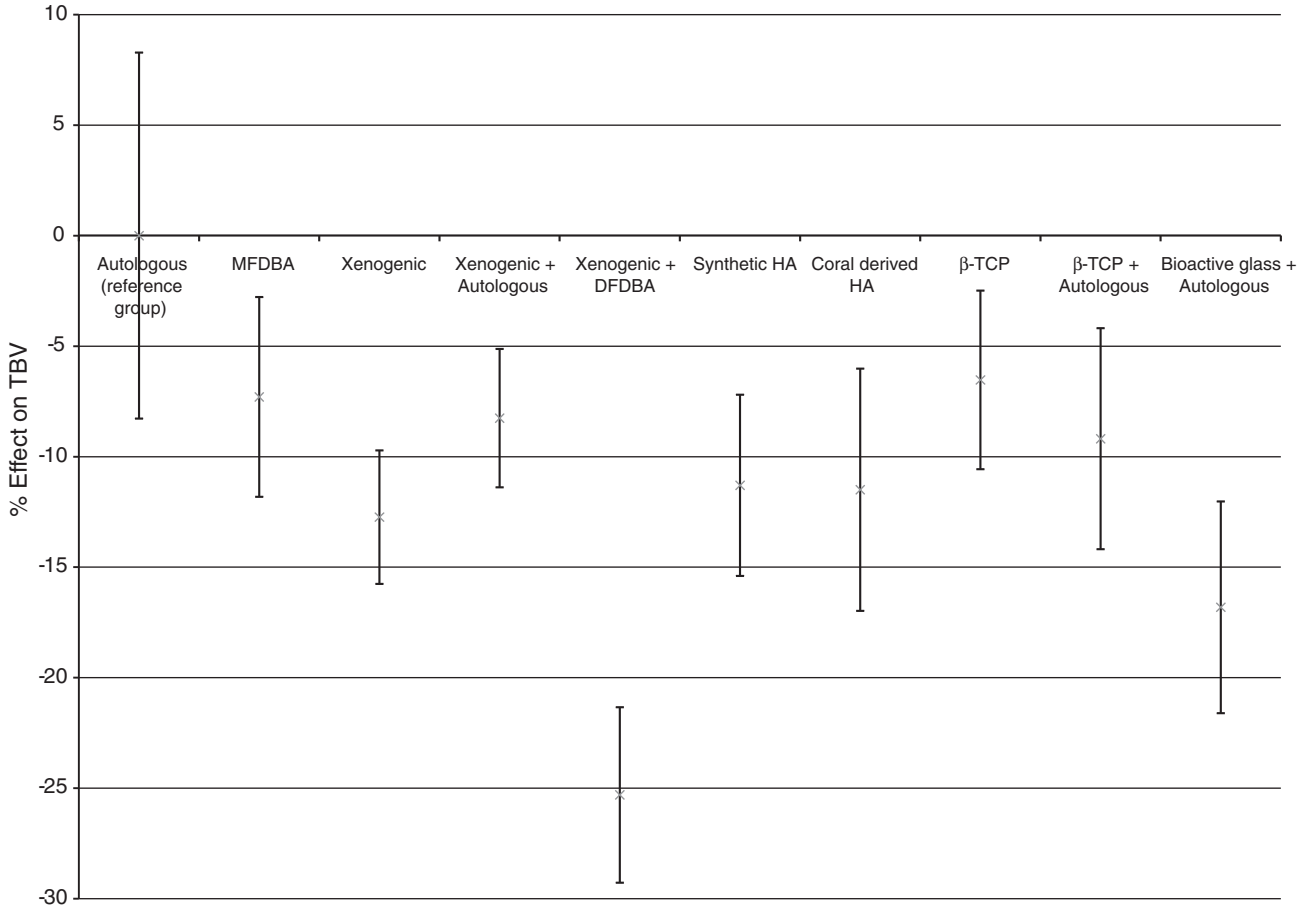

FIG. 1. Overview of the effect of type of grafting material on total bone volume compared to the reference (Table 14).

of most substitutes had a significant overlap, the differences between them regarding amount of TBV were not significant.

In a recent review by Nkenke and Stelzle, the current literature was analyzed to determine whether there are advantages of using autogenous bone over bone substitutes in sinus floor augmentation with respect to implant survival. They concluded that no evidence was present that neither supports nor refutes the superiority of autologous bone grafts over other graft materials with regard to implant survival.[7] In our study, there is a significant difference between autologous bone and their alternatives with respect to the TBV. However, the higher TBV apparently does not result in a higher implant survival.[7] Therefore, when using bone substitutes, it is still unclear what the minimal TBV is for a grafted sinus to guarantee implant survival.

Biopsy time

In literature it is reported that up to 33% of the autologous bone graft may resorb during the initial 6 months after sinus floor augmentation surgery.[47,51,105,106] This decrease in TBV affects the primary implant stability and therefore, as this effect of significant initial bone resorption may persist for years,[107–109] is a serious problem. In this meta-analysis, autologous graft resorption resulted in a significant lower TBV between 4.5 and 9.0 months. Hereafter, the TBV raised to same level of TBV, as scored in the first 4.5 months.

For the combination anorganic deproteinized bovine bone (ADBB) and autologous bone, biopsies taken in the first 4.5 months after initial surgery resulted in a significant higher TBV compared to biopsies taken at a later time point. Surprisingly, addition of autologous bone to the other bone substitutes did not result into this boost effect; the TBV did not significantly alter in time. Recently, Nkenke and Stelzle concluded in a review that implant survival seemed not to be influenced by the healing period of the graft material.[7] This is in analog with our finding that in case of using bone substitutes, the TBV is constant in time. Because of the wide variation and absence of other (cellular) histomorphometric indices in studies, no further conclusion could be drawn about resorption, bone apposition of remodeling in time in our study.

Variables

After statistical analysis, particulation of the graft resulted in a significant lower amount of TBV, but there was no such evidence for block grafting. Almost all grafted materials were used in a particulated structure. Occasionally, autologous bone was used as block graft, but only a few articles compared block versus particulate grafting.[26,39,49–52,56,67,88]

Placement of endosseous dental implants is done either simultaneously or after a certain time period to allow for consolidation of the grafted material. Simultaneous implant placement is less invasive and more effective.[110] Also, "delayed" implant placement resulted in a significant decrease

Table 15. Regression Analysis 2

Model		Unstandardized coefficients			95% confidence interval for B	
		B	Std. error	Sig.	Lower bound	Upper bound
1	(Constant)	62.20	8.41	0.00	52.29	85.52
	Particulated graft	−18.91	5.54	0.00	−29.86	−7.95
	Block graft	−7.52	4.73	0.11	−16.87	1.82
	Membrane	−8.16	7.96	0.31	−23.90	7.57
	Resorbable membrane	7.31	8.08	0.37	−8.65	23.27
	Delayed implantology	−6.70	2.99	0.03	−12.60	−0.80
	PRP $t < 4.5$ months	4.18	12.28	0.73	−20.09	28.46
	PRP $t = 4.5$–9.0 months	−19.79	9.22	0.03	−38.01	−1.57
	Autologous $t < 4.5$ months	10.86	3.79	0.00	3.37	18.34
	Autologous $t > 9$ months	9.52	4.31	0.03	0.99	18.05
	MFBBA $t < 4.5$ months	6.74	11.78	0.57	−16.55	30.03
	MFBBA $t = 4.5$–9.0 months	−7.49	10.11	0.46	−27.48	12.50
	MFBBA $t > 9$ months	8.07	10.39	0.44	−12.46	28.60
	ADBB $t < 4.5$ months	1.17	6.29	0.85	−11.27	13.61
	ADBB $t = 4.5$–9.0 months	−10.82	3.96	0.01	−18.65	−3.00
	ADBB $t > 9$ months	6.19	4.24	0.15	−2.19	14.57
	ADBB + autologous $t < 4.5$ months	14.83	7.55	0.05	−0.10	29.76
	ADBB + autologous $t = 4.5$–9.0 months	−11.53	4.06	0.01	−19.54	−3.51
	ADBB + autologous $t > 9$ months	5.40	6.79	0.43	−8.03	18.82
	ADBB + DFDBA $t = 4.5$–9.0 months	−24.09	5.10	0.00	−34.17	−14.00
	ADBB + DFDBA $t > 9$ months	6.77	6.45	0.30	−5.97	19.51
	Synthetic HA $t < 4.5$ months	−13.56	8.56	0.12	−30.47	3.36
	Synthetic HA $t = 4.5$–9.0 months	−0.91	5.49	0.87	−11.78	9.95
	Synthetic HA $t > 9$ months	−9.35	8.20	0.26	−25.55	6.85
	Coral-derived HA $t = 4.5$–9.0 months	−9.81	6.70	0.15	−23.05	3.42
	Coral-derived HA $t > 9$ months	4.11	10.33	0.69	−16.30	24.52
	β-TCP $t = 4.5$–9.0 months	−3.35	4.40	0.45	−12.06	5.35
	B-TCP $t > 9$ months	−11.84	11.24	0.29	−34.06	10.39
	β-TCP + autologous $t = 4.5$–9.0 months	−3.04	6.08	0.62	−15.06	8.98
	β-TCP + autologous $t > 9$ months	−16.98	10.13	0.10	−37.01	3.05
	Bioactive glass + autologous $t < 4.5$ months	−8.19	15.91	0.61	−39.65	23.26
	Bioactive glass + autologous $t = 4.5$–9.0 months	−7.76	7.38	0.29	−22.34	6.83
	Bioactive glass + autologous $t > 9$ months	−16.72	9.82	0.09	−36.13	269

Reference group is autologous bone grafting and biopsy time (t) between 4.5 and 9.0 months.

of TBV compared to "immediate" implant placement. However, residual alveolar ridge height and implant stability should be the decisive argument for the decision of staged implant placement.[111]

Another examined variable was the use of a membrane over the lateral window of the sinus. Tarnow *et al*. reported that the placement of an expanded polytetrafluoroethylene (e-PTFE) barrier membrane tends to increase vital bone formation.[112] Others suggested that this effect also can be achieved using a poly(lactic acid) membrane.[113] In a meta-analysis on the survival of endosseous dental implants, Wallace and Froum concluded that membrane utilization is a

Table 16. Summation of Regression Analysis 2

	t < 4.5 compared to t = 4.5–9.0			t > 9.0 compared to t = 4.5–9.0		
	Effect	95% CI	p-Value	Effect	95% CI	p-Value
Autologous	10.86	[2.41, 19.3]	0.02	9.52	[−0.1, 19.14]	0.05
PRP	15.04	[−13.62, 43.71]	0.27			
MFDBA	6.74	[−19.53, 33.02]	0.58	8.07	[−15.1, 31.23]	0.46
ADBB	1.17	[−12.87, 15.2]	0.86	6.19	[−3.27, 15.65]	0.18
ADBB + autologous	25.69	[6.84, 44.53]	0.01	5.40	[−9.75, 20.54]	0.45
ADBB + DFDBA				6.77	[−7.6, 21.15]	0.32
Synthetic HA	−13.56	[−32.64, 5.53]	0.14	−9.35	[−27.63, 8.93]	0.28
Phycogenic HA				4.11	[−18.92, 27.14]	0.70
β-TCP				−11.84	[−36.91, 13.24]	0.32
β-TCP + autologous				−16.98	[−39.58, 5.62]	0.12
Bioactive glass + autologous				−7.20	[−31.12, 16.72]	0.52

CI, confidence interval.

useful adjunctive therapy that results in an increased survival rate of implant in the grafted maxillary sinus.[38] This increase in implant survival could be explained by a higher percentage of bone volume.[38,112] However, our study shows no significant effect, positive or negative, of the use of a (non)-resorbable membrane over the lateral window on the amount of TBV.

Conclusions

"Particulate grafting," "immediate and delayed implant placement," and "biopsy time" were determined as general significant variables on the histomorphometric outcome of TBV after sinus floor augmentation surgery using various biomaterials. Allogenic, xenogenic, and alloplastic graft materials or combinations will result in a significant lower TBV compared to autologous bone grafting. The addition of PRP to an autologous bone graft in sinus augmentation has a negative effect on the TBV. In the second analysis, inventorying the effect of "biopsy time" for autologous bone, the TBV was significantly higher before 4.5 and after 9.0 months of healing time compared to period in between. For bone substitutes only the ADBB in combination with autologous bone performed significant higher in the first 4.5 months. Surprisingly, for all other bone substitutes no significant effect on TBV in time could be proven. On the basis of this histomorphometric meta-analysis autologous bone grafting results in the highest TBV and has still to be considered to be the gold standard. All described bone graft substitutes showed less TBV. However, it must be emphasized that the consequence of the TBV for implant survival is still unraveled yet.

Disclosure Statement

No competing financial interests exist.

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