Bilal Al-Nawas, Eik Schiegnitz

Augmentation procedures using bone substitute materials or autogenous bone – a systematic review and meta-analysis

Bilal Al-Nawas, Prof Dr Dr

Eik Schiegnitz, Dr

Both at:
Department of Oral and Maxillofacial Surgery, Plastic Surgery, University Medical Centre of the Johannes Gutenberg-University Mainz, Germany

Correspondence to:
Eik Schiegnitz
Department of Oral and Maxillofacial Surgery, Plastic Surgery, University Medical Centre of the Johannes Gutenberg-University,
Augustusplatz 2,
55131 Mainz,
Germany
Tel: 00-49-176-20197848
Fax: 00-496-131/17-6602
Email: eik.schiegnitz@unimedizin-mainz.de

Key words *bone augmentation procedures, bone substitute materials, dental implants, meta-analysis, oral implants, survival rate*

Aims: Bone substitute materials (BSM) are described as a reasonable alternative to autologous bone (AB) to simplify the grafting procedure. In a systematic review and meta-analysis, the influence of BSM compared to AB on treatment success in augmentation procedures of the edentulous jaw was analysed.

Material and methods: Literature analysis resulted in only two studies addressing reconstruction of the totally edentulous jaw using BSM. Therefore the literature analysis was extended to partially and totally edentulous jaws. The following augmentation procedures were analysed: maxillary sinus floor augmentation (MSFA) and vertical and/or lateral alveolar ridge augmentation; guided bone regeneration (minor and contained defects) were excluded. Meta-analysis was implemented using the literature from the years 2000 to early 2014 and only studies with a mean follow-up of at least 10 months were included.

Results: After screening 843 abstracts from the electronic database, 52 studies in qualitative and 14 in quantitative synthesis were included. In studies examining MSFA, the mean implant survival rate was 98.6% ± 2.6 for BSM, 88.6 ± 4.1% for BSM mixed with AB and 97.4 ± 2.2% for AB alone. For MSFA, meta-analysis showed a trend towards a higher implant survival when using BSM compared to AB, however the difference was not statistically significant ([OR], 0.59; [CI], 0.33–1.03). No statistically significant difference in implant survival for MSFA between BSM mixed with AB and AB was seen ([OR], 0.84; [CI], 0.5–1.42). Concerning ridge augmentation, the mean implant survival rate was 97.4 ± 2.5% for BSM, 100 ± 0% for BSM mixed with AB and 98.6 ± 2.9% for AB alone. Meta-analysis revealed no statistically significant difference in implant survival for ridge augmentation using BSM or AB ([OR], 1.85; [CI], 0.38 to 8.94). For BSM mixed with AB versus AB alone, a meta-analysis was not possible due to missing data.

Conclusions: Within the limitation of the meta-analytical approach taken, implant survival seems to be independent of the biomaterial used in MSFA and alveolar ridge augmentation. Therefore, based on the current literature, there is no evidence that AB is superior to BSM. The conclusions are limited by the fact that influence of defect size, augmented volume and regenerative capacity of the defects is not well described in the respective literature.

Conflict of interest statement: *There are no commercial or other associations that might create a duality of interests in connection with the article.*

Introduction

Management of partially or totally edentulous patients with implants has been a routine treatment modality for decades, with reliable long-term successes[1-6]. The predictability of the implant survival and the maintenance of long-term stability of implants in function are directly associated with the quality and quantity of the available bone for implant placement[7]. In the case of alveolar ridges with insufficient bone volume or unfavourable vertical, horizontal or sagittal intermaxillary relationships, additional surgical procedures can be necessary to reconstruct and augment the deficiency.

The physiological properties of bone grafts and bone substitute materials (BSM) are often described by the terms osteoinductivity, osteoconductivity and osteogenicity. Osteoinductivity is the capability of a graft to actively promote bone formation[8,9]. Osteoconductivity is a characteristic of the scaffold that facilitates the colonisation and ingrowth of new bone cells and sprouting capillaries by reason of its three-dimensional structure. Osteoconduction is by definition a passive process and primarily destined by the porosity properties of the scaffold and in a lower degree by its chemical and physical properties that stimulate adhesion and cell growth[10]. Osteogenicity is referred to the presence of bone-forming cells within the bone graft[11].

Autogenous bone (AB), with its osteogenic, osteoinductive and osteoconductive characteristics, is often considered as the gold standard in bone regeneration procedures[2,12]. It contains osteoblasts, osteoclast precursor cells, undifferentiated mesenchymal cells and monocytes, which promote the remodelling and formation of new bone[13,14]. However, donor site morbidity, limited quantities available, unpredictable graft resorption and the need to include additional surgical sites are unavoidable disadvantages that have encouraged the search for BSM as convenient alternatives[15,16].

There are a variety of BSM available with different biological and mechanical properties. They can be categorised in the following three groups: (1) allogenic, from another individual within the same species; (2) xenogenic, from another species; and (3) alloplastic, synthetically produced (Jensen, 2009). Chemical compositions range from biological apatites, monophasic calcium phosphates (tricalcium phosphates, hydroxyapatites [HAs]) and silicates to bi- and more-phasic mixed ceramics[13]. To date, there is no BSM commercially available that is equal to AB regarding its osteoinductive characteristics. In fact, BSM primarily serves as filling and scaffold building substances, mostly providing osteoconduction for the bone healing process[12,17,18]. However, there is strong clinical evidence that BSM can still be used successfully in augmentation procedures[2,12,19].

A multiplicity of augmentation procedures, depending on location and size of defect, are used to provide the osseous support necessary to allow placement of implants. In continuation of the study of Klein et al[12], the following classification of augmentation procedures was applied in the present review: (1) maxillary sinus floor augmentation (MSFA), including the lateral window technique and the transalveolar approach ('external' or 'internal' sinus lift); and (2) vertical and/or lateral alveolar ridge augmentation of different dimensions, including peri-implant defects in the form of dehiscence-type defects and fenestration-type defects.

The aim of the present systematic review and meta-analysis was to assess the clinical outcome of different graft materials used in augmentation procedures of the edentulous jaw.

Material and methods

Protocol development

The study protocol was designed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement as described before[20-22]. In the context of the consensus conference 'Patient centered rehabilitation of edentulism with an optimal number of implants' (Foundation for Oral Rehabilitation (F O R) at the University of Mainz, 2014), the original objective of this study was to evaluate the clinical outcome of augmentation procedures using bone substitute materials or autogenous bone in totally edentulous patients. The initial search for primary literature showed that only very few studies have been published on this specific topic[23,24]. Therefore, the literature search was expanded on augmentation procedures in partially

edentulous patients. With reference to the PICO format (Patient, Intervention, Comparison and Outcome), the following focused question was developed[25]: 'In partially and totally edentulous patients treated with dental implants and augmentation procedures, are there any differences in terms of implant survival between BSM compared to AB?' Bone augmentation procedures were classified into MSFA and vertical and/or lateral alveolar ridge augmentation as described before[12]. Minor augmentation procedures of contained defects ('guided bone regeneration') were excluded.

Literature research and meta-analysis

The current review was based on a study by Klein et al[12] that had already revised the literature on the present topic for the years from 2000 to 2010. This study was built upon by performing an extensive electronic search in the electronic databases of the National Library of Medicine for articles published between January 2010 and January 2014 to identify literature presenting implant survival data in augmentation procedures using BSM or AB. In addition, the reference lists of related review articles and publications were systematically screened. The search was completed with an additional hand search of selected journals and reviews. However, to improve the quality of this study, a meta-analysis was performed using the literature of the years 2000 to 2014. For the meta-analysis, only studies with a mean follow-up of at least 10 months were included.

Search terms

The search strategy included the following key words: 'bone substitute materials'; 'dental/oral implants'; 'augmentation'; 'implant survival', 'sinus floor elevation'; 'vertical ridge augmentation'; 'horizontal ridge augmentation'. The literature research was completed using the following MeSH Terms (Medical Subject Heading): ('dental implants' [Mesh] OR 'dental implantation' [Mesh] OR 'oral implants' [Mesh]) AND ('augmentation' [Mesh] OR 'vertical ridge augmentation' [Mesh] OR 'horizontal ridge augmentation' [Mesh] OR 'sinus floor elevation' [Mesh]) AND ('clinical outcome' [Mesh] OR 'implant survival' [Mesh]).

Inclusion criteria

All studies retrieved from the above search were screened on the basis of titles and abstracts. Screening and selection of studies for inclusion were carried out according to the following inclusion criteria:

1. Randomised controlled clinical trials (RCT), controlled clinical trials (CCT), prospective studies (PS) and retrospective studies (RS) on the topic of extended augmentation procedures with BSM or autogenous bone in partially and totally edentulous patients.
2. Use of a BSM or AB.
3. Inclusion of ≥ 10 subjects.
4. Published in English.
5. Documentation of the implant survival rate after a defined period of time.

Only solid, granular BSM of alloplastic, xenogenic or phycogenic origin were included. As growth factors and platelet rich plasma were not part of the objectives of this study, all studies including those substances were excluded.

Study selection

The abstracts derived from this extensive search were independently screened by the two authors based on the inclusion criteria. For all abstracts meeting the inclusion criteria, full texts were requested for in-depth evaluation and further data extraction. Any disagreement on study selection was resolved by discussion. Data was extracted using structured data extraction forms. The PRISMA flow diagram shows the flow of information through the different phases of the literature research (Fig 1). Concerning the quality of the selected studies, no prospective randomised studies were found on the defined PICO question. Therefore, in the present study the best available external evidence was collected as described above in the inclusion criteria. The authors are aware that the risk of bias is higher compared with other reviews that include only randomised studies.

Quality assessment

According to the study of Proskin et al[26], six quality categories were used to analyse the quality of

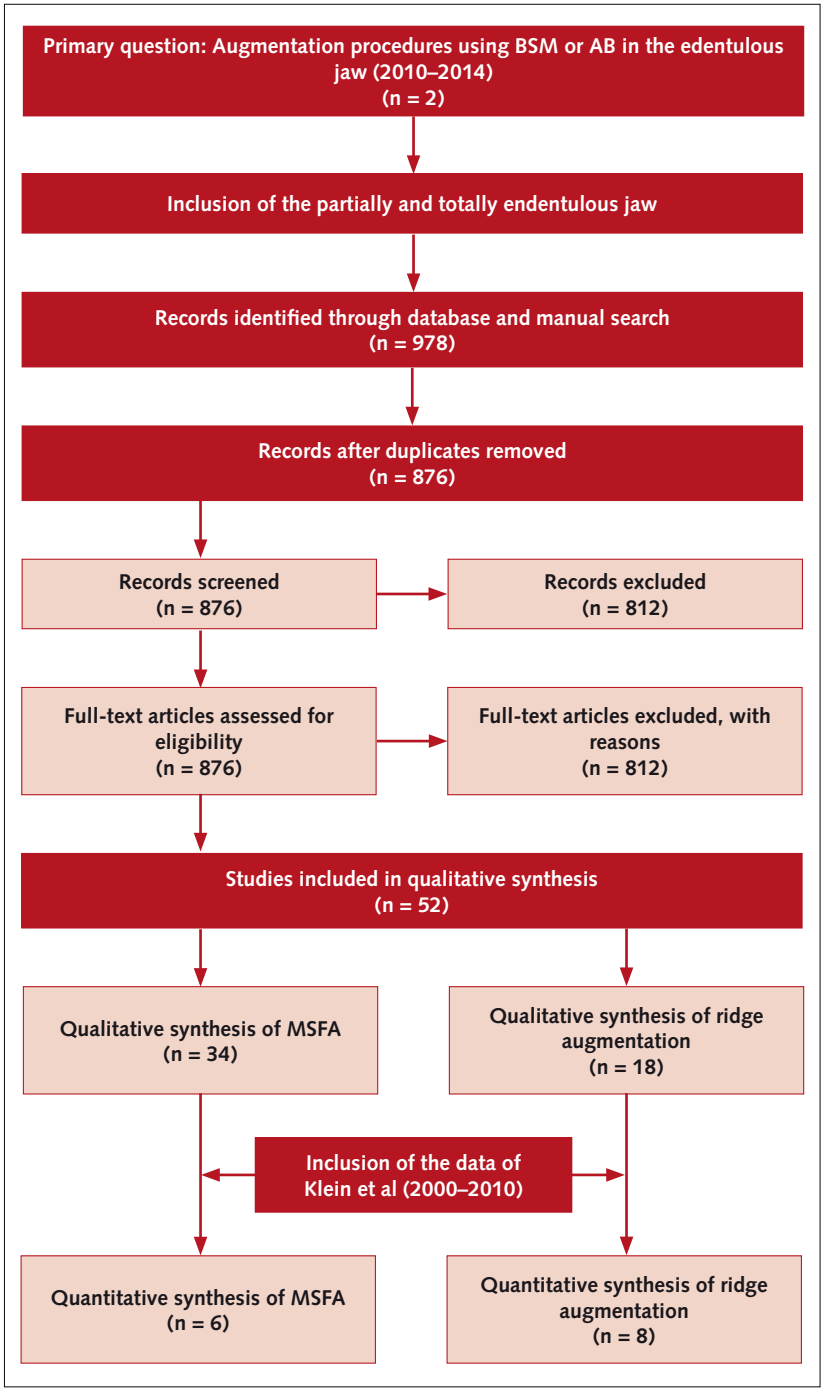

Fig 1 PRISMA flow diagram.

each selected study according to its design: 'fair' for a retrospective study; 'average' for a prospective case study; 'good' for a prospective study with historical controls; 'better' for a prospective study with concurrent controls; 'best' for a double-blind randomised controlled trial (RCT); and 'unknown' when the study design could not be ascertained or fit none of the definitions.

Statistical analysis

The overall estimated effect was considered significant if P was <0.05. Meta-analysis was conducted using the statistical software package RevMan (Review Manager (RevMan) [Computer program]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) to collect the data, calculate the overall estimated effects and to produce the forest plots.

Results

Study selection

The electronic search of the databases and the manual search resulted in the identification of 978 abstracts (Fig 1). Sixty-four of these 978 abstracts were considered potentially relevant and complete texts of these studies were sampled and reviewed. Further reference cross-checks generated four additional publications for a full text analysis. Finally, 52 methodologically acceptable publications with relevant data on implant survival in augmentation procedures were selected to be included for interpretation and statistical analysis. These articles were further subdivided into two categories according to the augmentation procedures: 34 articles reporting on MSFA (category I) and 18 articles reporting on vertical and/or lateral alveolar ridge augmentation (category II) were provided. Hereof, six studies were used for meta-analysis on implant survival in MSFA and eight studies used for meta-analysis on implant survival in ridge augmentation procedures.

Quality assessment of selected studies

Fifteen of the included studies were RCTs and were rated as 'best'. Three studies were classified as 'better'. Seventeen studies were categorised as 'average', as they were prospective case studies without historical or concurrent controls. The remaining 17 studies were retrospective and were classified as 'fair'. In general, both quality and level of evidence of the investigated articles were limited. Most of the studies were categorised as 'average' and 'fair'. However, this review includes 15 RCTs with best

Study or subgroup	Experimental		Control			Odds Ratio	Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hallmann et al, 2002	2	43	6	33	21.7%	0.22 [0.04, 1.17]	
Merli et al, 2013	2	32	0	27	1.7%	4.51 [0.21, 98.07]	
Sbordone et al, 2011	0	146	6	136	22.5%	0.07 [0.00, 1.23]	
Velich et al, 2004	29	309	12	108	54.1%	0.83 [0.41, 1.69]	
Total (95% CI)		**530**		**304**	**100.0%**	**0.59 [0.33, 1.03]**	
Total events	33		24				

Heterogeneity: Chi² = 6.04, df = 3 (*P* = 0.11); I² = 50%
Test for overall effect: Z = 1.84 (*P* = 0.07)

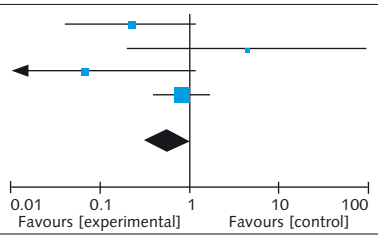

Fig 2 Forest plot of implant survival in maxillary sinus lift procedures using BSM (experimental) versus AB (control).

quality level. Allocation concealment at a high risk of bias, lack of reporting characteristics of drop-out, missing blind examiners to assess clinical outcomes and lack of CONSORT adherence suggests being cautious with data interpretation and drawing general conclusions derived from these studies.

Results for MSFA using BSM or AB

A summary of all studies examining the implant survival rate in patients receiving MSFA is shown in Table 1. Altogether, in the investigated studies 1816 patients received a total of 4687 implants. The numbers of patients ranged between 10 and 461 and the age of patients between 21 and 83 years. Sinus membrane perforation occurred in 19.2 ± 10.8% of the cases. Sinusitis was reported in four studies. Mean healing periods were 5.5 ± 1.9 months for BSM, 5.4 ± 1.3 for BSM mixed with AB and 4.33 ± 0.57 for AB.

The mean follow-up was 39.7 ± 34.6 months (a range of 4 to 170 months). The mean implant survival rate of all examined studies (2010 to January 2014) was 98.6% ± 2.6 for BSM, 88.6 ± 4.1% for BSM mixed with AB and 97.4 ± 2.2% for AB alone. Implant success was described in eight studies and ranged from 91.7% to 100%.

This study aimed at performing a meta-analysis on the implant survival of augmentation procedures using BSM or AB. In the literature of the past 14 years (2000 to 2014), four studies comparing implant survival after MSFA using BSM or AB were found (Table 2). Meta-analysis showed a trend towards a higher implant survival when using BSM compared to AB, however the difference was not statistically significant (odds ratio [OR], 0.59; confidence interval [CI], 0.33–1.03; Fig 2). Begg and Mazumdar's funnel plot indicated a low risk for publication bias for this meta-analysis (Fig 3). In addition, four studies comparing implant survival after MSFA using BSM mixed with AB or using AB alone were found. Meta-analysis of these studies revealed no statistically significant difference in implant survival between the two groups ([OR], 0.84; [CI], 0.5–1.42; Fig 4). Begg and Mazumdar's funnel plot for this meta- analysis is shown in Fig 5.

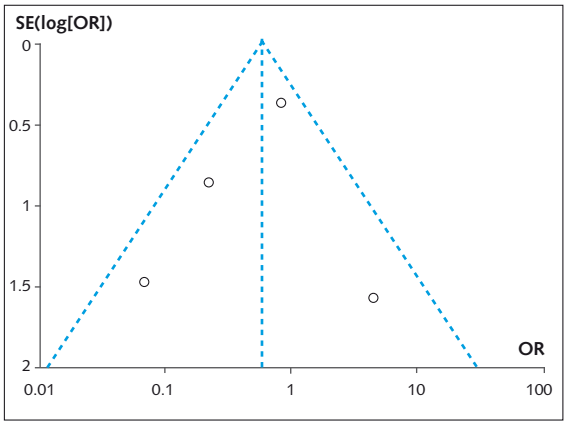

Fig 3 Funnel plot calculated for selected studies reporting on implant survival in maxillary sinus lift procedures using BSM versus AB.

Vertical and/or lateral alveolar ridge augmentation using BSM or AB

Concerning vertical and/or lateral alveolar ridge augmentation, Table 3 shows a summary of all studies found in the electronic search. In these studies, 417 patients received a total of 1216 implants. The number of patients varied between 11 and 50 and the age of patients between 17 and 84 years. Mean healing periods were 4.7 ± 1.1 months for BSM, 5.25 ± 1.9 months for BSM mixed with AB and 5.1 ± 1.4 months for AB alone. The mean follow-up was 30.6 ± 27.1 months (a range of 4 to 120 months). A mean implant survival rate of 97.4 ± 2.5% for BSM, 100 ± 0% for BSM mixed with AB and 98.6 ± 2.9% for AB alone was seen. Implant success was indicated in five studies and ranged from 90.3% to 100% (from 2010 to Jan 2014).

Table 1 Summary of studies on implant survival in sinus lift with BSM or AB.

Study	Study type	Indication	No. of patients	No. of implants	BSM	Healing period	Complications	Mean follow-up (months)	ISR BSM	Success BSM
Bae et al, 2010[40]	PS	SL	16 (52.3; 36–68)	32	70% HA + 30% b-TCP	Simultan and 4 months	6 perforations of sinus membrane (37.5%), 2 cases of sinusitis	15 (12–30)	96.9% (1 of 32)	96.9% (1 of 32)
Calvo-Guirado et al, 2010[60]	PS	Transalveolar	30 (53.6; 36–63)	60	Porcine HA	Simultan	ND	36	96.6% (2 of 60)	96.6% (2 of 60)
Cho-Lee et al, 2010[36]	RS	SL	119 (50.02;	272 1) 123 2) 149	1) AB + DBBM 2) AB	Simultan and delayed	17 perforations of sinus membrane (9.6%), 6 cases of sinusitis (3.7%)	60.7 ± 36.5	1) 93.5% 2) 94%	ND
Covani et al, 2011[61]	PS	SL	15 (61.5 ± 8.9)	40	HA + b-TCP	6 months	ND	14.9 ± 3.1	92.5% (3 of 40)	ND
Esposito et al, 2010[62]	RCT	SL	10 (50; 35–60)	24	DBBM	6 months	1 perforation of sinus membrane	12	100% (0 of 24)	ND
Garlini et al, 2010[63]	RS	SL	26 (58)	47	HA	Simultan	ND	72	100% (0 of 47)	ND
Lambert et al, 2010[64]	RS	SL	40 (56.5; 38–79)	120	DBBM	Simultan	9 perforations of sinus membrane (18%), 2 subantral artery lesion (4%)	45 (32–74)	98% (2 of 102)	ND
Scarano et al, 2010[65]	RS	SL	121 (54; 51–63)	279	Porcine HA	4–6 months	20 perforations of sinus membrane	60	92% (21 of 279)	ND
Tetsch et al, 2010[66]	RS	1) SL 2) SL	1) 461 (65.1)	1207 1) 1085 2) 131	1) DBBM 2) b-TCP	ND	148 perforations of sinus membrane (13.4%)	1) 170 months 2) 91 months	1) 95.5% 2) 94.1%	ND
Uckan et al, 2010[41]	RS	SL	62	121	b-TCP	Simultan	ND	29.8	99.17% (1of 121)	ND
Urban et al, 2010[67]	PS	SL	79 (52.4; 30–80)	245	DBBM + AB	7 months	10 perforations of sinus membrane (10 %)	60 months	99.6% (1 of 245)	96.5%
Viscioni et al, 2011[68]	RS	SL	12 (50.4; 40–61)	84	Homologous fresh frozen bones, cryopreserved homologue grafts	Simultan	ND	14 months	96.4% (3 of 84)	ND
Sbordone et al, 2011[29]	RS	SL	93 (51.9; 37–83)	282 1) 146 2) 136	1) DBBM 2) AB (iliac, chin)	3–5 months	ND	24	1) 100% (0 of 146) 2) 95.6% (6 of 136)	ND
Sakka and Krenkel, 2011[69]	RS	SL	17 (62)	77	AB (parietal)	Simultan	ND	12	94.8% (4 of 77)	ND
Lee et al, 2011[70]	PS	SL	12 (61.2; 41–86)	12	DBBM	9 months		37.2	100%	100%
Kim et al, 2011[71]	PS	SL	27 (54.09 ± 11.25)	61	Allogenic + xenogenic	Simultan	22 perforations of sinus membrane (36%)	12.56 ± 5.95	98.4% (1 of 61)	ND
Hansen et al, 2011[72]	RS	SL	ND (14 augmented regions)	58	AB, DBBM	6.5 months (3–14)	1 sinusitis	12	91% (5 of 58)	ND
Barone et al, 2011[16]	PS	SL	41 (53.6)	201	AB + porcine HA	6 months	ND	55.5	86.1% (28 of 201	ND

Caubet et al, 2011[73]	RS	SL	34 (53; 35–74)	65	AB + DBBM	4 months	9 perforations of sinus membrane (22.5%)	60	96.9% (2 of 65)	ND
Sivolella et al, 2011[74]	RS	SL	14 (53.7; 34–67)	31	DBBM	simultan	3 cases of mucosal laceration	43.2 (11.4–41.6)	100% (0 of 31)	93.3% (2 of 31)
Wagner et al, 2011[75]	RCT	SL	98 (52.5; 22.7–82.6)	1) 172 2) 66	1) Biphasic micro- and macroporous calcium phosphate combined with fibrin sealant (MBCP-FS) 2) DBBM + AB	6 months	Minor perforations of sinus membrane	12	1) 95.7% (7 of 163) 2) 94.9% (3 of 59)	1) 94.7% (8 of 150) 2) 94% (3 of 50)
Pieri et al, 2012[23]	PS	SL	20 (54.6; 47–69)	90	DBBM + AB	4–5 months	ND	12	97.7% (2 of 90)	ND
Lindgren et al, 2012[76]	RCT	SL	11 (67; 50–79)	48 1) 25 2) 23	1) HA + b-TCP 2) DBBM	8 months	ND	36	1) 95.8% (1 of 25) 2) 95.7% (1 of 23)	1) 91.7% (2 of 25) 2) 95.7% (1 of 23)
Cha et al, 2012[77]	PS	SL	161	462	DBBM	Simultan	35 perforations of sinus membrane (16.13%)	57.1 ± 15.6 (36–98)	98.91% (5 of 462)	96.54% (16 of 462)
Canullo et al, 2012[78]	PS	SL	30 (58.3)	67	HA	Simultan	4 perforations of sinus membrane	24	97% (2 of 67)	
Felice et al, 2012[101]	RCT	SL	20 (58.5; 45–75)	37	Porcine HA	4 months	5 perforations of sinus membrane	4 months post-loading	(0 of 31)	
Schmitt et al, 2012[79]	RS	SL	25 (64.4; 35-84)	127	AB	4 months	ND	120 months	95.45% (1 of 22)	
Espostio et al, 2012[80]	RCT	SL	20 (57.6; 45–80)	44	Porcine HA	3 months	4 perforations of sinus membrane	5 months post-loading	100% (0 of 44)	
Si et al, 2013[81]	RCT	Transalveolar	21	21	DBBM + AB	Simultan	ND	36	95.2% (1 of 21)	
Sbordone et al, 2013[82]	RS	SL	27 (50.3; 35–64)	30	AB	5 months	ND	60	93.3% (2 of 30)	
Merli et al, 2013[94]	RCT	SL	40 1) 20 (49.8; 38–62) 2) 20 (51.5; 38–66)	59 1) 32 2) 27	1) DBBM 2) AB	Simultan	1) 1 complication 2) 2 complications	15	1) (2 of 32) 2) (0 of 27)	
Cannizzaro et al, 2013[83]	RCT	SL	20 (53.3; 30–72)	44	AB + DBBM	Simultan	2 perforations of sinus membrane, 1 sinusitis, 1 abscess	60	5 of 44	
Cannizzaro et al, 2013[83]	RCT	Transalveolar	20 (47.5; 21–70)	38	AB	Simultan	None	60	1 of 38	
Felice et al, 2013[84]	RCT	SL	60 (ND)	135 1) 66 one-stage approach 2) 69 two-stage approach	DBBM	1) Simultan 2) 4 months	3 complications	4 months post-loading	1) (3 of 66) 2) (1 of 69)	

Max = maxilla; Man = mandible; ND = no data available or data cannot be separated; PS = prospective study; RS = retrospective study; RCT = randomised controlled trial; CSS = cross sectional study; ISR = implant survival rate; BSM = bone substitute material; AB = autogenous bone; DBBM = deproteinised bovine bone mineral; DFDBA = demineralised freeze-dried bone allograft; HA = hydroxyapatite; b-TCP = b-tricalcium phosphate; CM = collagen barrier membranes; ACS = absorbable collagen sponge carrier (ACS).

Table 2 Summary of studies on sinus lift for meta-analysis.

Study	Study type	No. of patients	No. of implants	BSM	Preoperative alveolar crest height	Mean follow-up (months)	Implant survival rate BSM	Implant survival rate BSM + AB	Implant survival rate AB
Hallman et al, 2002[27]	RCT	21	36	DBBM	ND	12	96% (2 of 43)	94.4% (2 of 35)	82.4% (6 of 33)
Velich et al, 2004[30]		624	1482	HTR Polymer, Algipore, Biocoral Gel, Cerasorb	2–6 mm	>12	HTR Polymer: 89.9% (19 of 188) Algipore: 88.5% (2 of 16) Biocoral Ge 93.4% (1 of 15) Cerasorb 92.2% (7 of 90) Total: 29 of 309	HTR Polymer: 87.7% (29 of 235) Algipore: 97.3% (1 of 37) Biocoral Ge 83.3% (2 of 12) Cerasorb 92.6% (6 of 81) Total: 38 of 365	88% (12 of 108)
Diserens et al, 2005[35]	RS	33	44	DBBM	5.78 ± 1.4	15	ND	100%	100%
Cho-Lee et al, 2010[36]	RS	119	272	DBBM	6.59 ± 2.11	60.7 ± 36.5	ND	93.5% (8 of 123)	94% (9 of 149)
Sbordone et al, 2011[29]	RS	119	282	DBBM	ND	24	100% (0 of 146)	ND	95.6% (6 of 136)
Merli et al, 2013[28]	RCT	40	59	DBBM	1) 2.0 ± 0.8 2) 2.3 ± 0.9	15	(2 of 32)	ND	(0 of 27)

Max = maxilla; Man = mandible; ND = no data available or data cannot be separated; PS = prospective study; RS = retrospective study; CSS = cross sectional study; ISR = implant survival rate; BSM = bone substitute material; AB = autogenous bone.

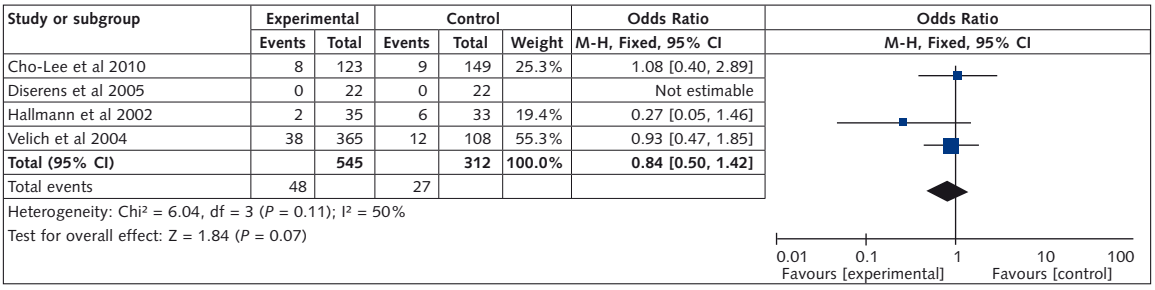

Fig 4 Forest plot of implant survival in maxillary sinus lift procedures using BSM mixed with AB versus AB alone.

Five studies compared the clinical outcome of ridge augmentation procedures using BSM or AB (from 2000 to Jan 2014; Table 4). Meta-analysis of these studies showed no statistically significant difference between BSM and AB ([OR], 1.85; [CI], 0.38 to 8.94; Fig 6).

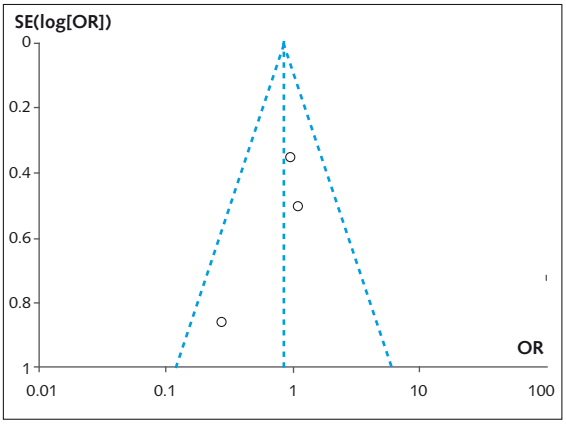

Fig 5 Funnel plot calculated for selected studies reporting on implant survival in maxillary sinus lift procedures using BSM mixed with AB versus AB alone.

Fig 7 shows Begg and Mazumdar's funnel plot for this meta-analysis. Three studies comparing implant survival after ridge augmentation using BSM mixed with AB or AB alone were identified. As all of these studies showed in both the experimental as well as in the control group, with an implant survival of 100%, a meta-analysis of these data was not possible (Fig 8).

■ Discussion

The wide range of graft materials available has provided numerous alternatives to AB. Therefore, it was the aim of this study to analyse the literature of the years 2000 to 2014 to identify graft materials that provide the best reconstructed osseous ridge for successful implant placement and long-term function.

Study or subgroup	Experimental		Control			Odds Ratio	Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Dottore et al, 2012	1	22	1	22	40.4%	1.00 [0.06, 17.07]	
Felice et al, 2009	1	19	1	19	40.1%	1.00 [0.06, 17.25]	
Lopez-Cedrun, 2011	0	32	0	33		Not estimated	
Meijndert et al, 2008	2	31	0	31	19.5%	5.34 [0.25, 115.89]	
Simion et al, 2001	0	26	0	82		Not estimated	
Total (95% CI)		**130**		**187**	**100.0%**	**1.85 [0.38, 8.94]**	
Total events	4		2				

Heterogeneity: Chi² = 0.81, df = 2 (*P* = 0.67); I² = 0%
Test for overall effect: Z = 0.76 (*P* = 0.45)

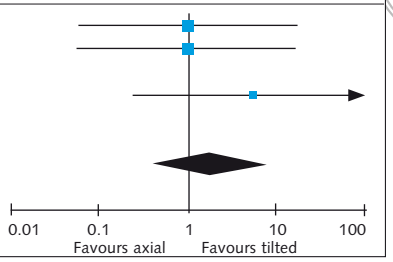

Fig 6 Forest plot of implant survival in ridge augmentation procedures using BSM versus AB.

Maxillary sinus floor augmentation (MSFA)

In the examined period, four studies regarding implant survival after MSFA using BSM or AB were published[27-30]. All of them showed no significant difference in implant survival between BSM and AB. Our meta-analysis of these combined studies confirmed the individual findings, as no significant difference in implant survival was seen. In a systematic review examining animal studies on this subject, the initial osseointegration of implants seemed independent of the biomaterial used in grafting procedures[31]. For human histomorphometric data, Klein et al showed a sufficient formation of at least 20% to 30% new vital bony tissue both for BSM and AB[12]. In addition, several current literature reviews indicated that the success of MSFA is independent of the used graft material[2,3,12,32,33]. For example, Jensen et al in their review observed the same implant survival rate in sinuses augmented with BSM alone (96.1%) versus augmentation protocols including AB (95.8%)[32]. In contrast, one review by Pjetursson et al[34] showed significantly lower annual failure rates for AB, compared to BSM in MSFA. However, all types of grafting materials had high survival rates ranging from between 96.3% and 99.8% after 3 years in this review. Further, it must be noted that a constant annual event rate was assumed throughout the follow-up time after placement of the reconstruction, which limits the validity of this review.

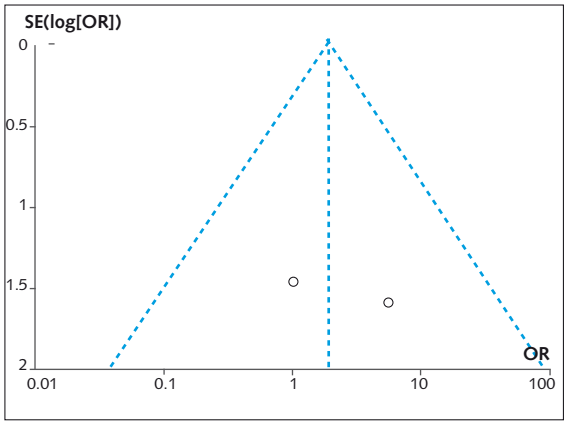

Fig 7 Funnel plot calculated for selected studies reporting on implant survival ridge augmentation procedures using BSM versus AB.

Regarding the origin of the BSM, the use of deproteinised bovine bone mineral (DBBM) for MSFA is particularly well documented in the literature[27-29,35-39]. Besides DBBM, there are several studies with a favourable clinical outcome for synthetic porous beta-tricalcium phosphate (beta-TCP)[40-42]. From a biological aspect, it might be advantageous to mix BSM with AB due to the osteoinductive properties of AB[38]. However, two recently published systematic reviews concluded that the amount of new bone formation was comparable when DBBM or DBBM mixed with AB were used as graft material for MSFA[43]. The hypothesis that there are no differences between DBBM or DBBM mixed with AB as graft for MSFA could neither be confirmed nor rejected[38]. Moreover, four clinical studies showed no

Study or subgroup	Experimental		Control			Odds Ratio	Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cordaro et al 2010	0	12	0	37		Not estimable	
Cordaro et al 2011	0	28	0	27		Not estimable	
Urban et al 2011	0	43	0	15		Not estimable	
Total (95% CI)		**83**		**79**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

Fig 8 Forest plot of implant survival in ridge augmentation procedures using BSM with AB versus AB alone.

Table 3 Summary of studies on implant survival in vertical or/and horizontal ridge augmentation with BSM or AB.

Study	Study type	Indication	No. of patients	No. of implants	Jaw region	BSM	Healing augmentation	Complications	Mean follow-up (months)	Bone gain	Implant survival rate	Implant success rate
Beitlitum et al, 2010[91]	PS	Vertical and/or horizontal ridge deficiencies	50 1) 27 2) 23	106	Max, Man	1) FDBA 2) FDPA + AB	4–6 months	Membrane exposure: 24%	5–7 months	1) 3.47 ± 1.25 vertical and 5 ± 1.25 horizontal 2) 3.5 ± 1.2 vertical and 3.6 ± 1. 72 horizontal	1) 100% 2) 100%	ND
Canullo et Sisti, 2010[78]	PS	Vertical ridge augmentation	20 (59; 30–72)	42	Max, Man	HA	3 months	Membrane exposure: 2%	24 months	5.6 ± 1.4	100%	ND
Le et al, 2010[93]	PS	Vertical ridge augmentation	15 (50.06; 22–69)	32	Max, Man	Allograft	4–5 months	2-stage grafting n = 5; partial wound dehiscence n = 2, screw head exposure n = 3	16.8 months (4–38)	ND	100%	ND
Merli et al, 2010[94]	RCT	Vertical ridge augmentation	22	77	Man	AB	Simultan	None	36	ND	100%	ND
Boronat et al, 2010[95]	RS	Vertical ridge augmentation	37 (48.9; 25–68)	73 bone grafts: 39	Max, Man	AB (chin, retromolar area, maxillary tuberosity	Simultan	Graft failure: 5.1% (2 of 39)	12	ND	ND	95.9% (3 of 73)
Cordaro et al, 2010[88]	PS	Inlay–onlay grafting	16 (51)	49 1) 12 2) 37	Max	1) AB + DBBM 2) AB	4 months	1 case of wound dehiscence	40 (32–48)	2.1 ± 0.3 mm vertical and 4.3 ± 1.1 mm horizontal	1) 100% 2) 100%	1) 100% 2) 100%
Pelo et al, 2010[96]	PS	Two-step osteotomy	19 (58.8; 48–68)	141 1) 73 2) 68	Man	1) AB (symphyseal area) 2) AB (molar area)	4 months	3 cases with small sequestrum	48	11 ± 1	1) 96% (3 of 73) 2) 91% (6 of 68)	ND
Lopez-Cendrun, 2011[85]	RS	Sandwich osteotomy	23	65 1) 24 segments 2) 6 segments	Man	1) DFDBA 2) AB (iliac crest)	5–6 months	4 cases of minor dehiscence	(12–93)	5.3 mm (2–10)	1) 100% 2) 100%	ND
Urban et al, 2011[90]	PS	Horizontal ridge augmentation	22 (50)	58 1) 43 2) 15	Max, Man	1) AB + DBBM 2) AB	8.12 ± 2.32	None	45.88 ± 12.43	5.56 ± 1.45	1) 100% 2) 100%	ND

Cordaro et al, 2011[89]	RCT	Horizontal ridge augmentation	17 (42; 19–66)	55 1) 28 2) 27	Man	1) AB + DBBM 2) AB	4 months	1) Partial dehiscence (n = 3) 2) Partial dehiscence (n = 1)	24	1) 4.18 ± 1.17 2) 4.56 ± 1.38	1) 100% 2) 100%	1) 100% 2) 100%
Nissan et al, 2011a[97]	PS		31 (32; 17–70)	63	Max	Allograft	6 months	Soft tissue breakdown and graft exposure n = 13 (28%)	34 (6–59)	5 ± 0.5 mm horizontally, and 2 ± 0.5 mm vertically	98% (1 of 19)	ND
Nissan et al, 2011b[98]	PS	Vertical ridge augmentation	21 (55; 40–65)	85	Man	Allograft	6 months	Graft failure: 6	37 (6–60)	Mean horizontal and vertical bone gains were 5.6 and 4.3 mm	95.2%	ND
Esposito et al, 2011[99]	RCT	Vertical ridge augmentation	30 (55; 43–67)	61	Man	DBBM	5 months	Graft failure: 2 of 28; other complications: 22 of 61	36 months	ND	95.1% (3 of 61)	ND
Chiapasco et al, 2012[100]	PS	Vertical ridge augmentation	18	60	Max, Man	AB 1) Calvarium 2) Ramus	4–7 months		19 months (12–36 months)	ND	1) 100% 2) 100%	1) 90.3% 2) 93.1%
Esposito et al, 2012[80]	RCT	Vertical ridge augmentation	20 (54.1; 42–70)	47	Man	Equine HA, porcine HA	3 months	Graft failure: 15% 7 temporary lower lip paraesthesia	5 months post-loading	ND	93.6% (3 of 47)	ND
Schmitt et al, 2012[79]	RS	Onlay augmentation	25 (64.4; 35–84)	127	Max	AB (iliac crest)	4 months	ND	120 months	ND	95% (2 of 40)	ND
Dottore et al, 2012[54]	PS	Sandwich osteotomy	11 (54.2)	44 1) 22 2) 22	Man	1) HA 2) AB	6 months	None	12	1) 7.0 ± 2.6 vertical 2) 6.5 ± 1.6 vertical	1) 95.5% (1 of 22) 2) 95.5% (1 of 22)	1) 90.9% (2 of 22) 2) 90.9% (2 of 22)
Felice et al, 2012[101]	RCT	Vertical ridge augmentation	20 (52.8; 42–70)	31	Man	bovine HA	4 months	Transient paraesthesia n = 14	4 months post-loading	ND	96.8% (1 of 31)	ND

Max = maxilla; Man = mandible; ND = no data available or data cannot be separated; PS = prospective study; RS = retrospective study; RCT = randomised controlled trial; CSS = cross sectional study; ISR = implant survival rate; BSM = bone substitute material; AB = autogenous bone; DBBM = deproteinised bovine bone mineral; DFDBA = demineralised freeze-dried bone allograft; HA = hydroxyapatite; b-TCP = b-tricalcium phosphate; CM = collagen barrier membranes; ACS = absorbable collagen sponge carrier (ACS).

Table 4 Summary of studies on ridge augmentation for meta-analysis.

Study	Study type	No. of patients	No. of implants	BSM	Mean follow-up (months)	Implant survival rate BSM	Implant survival rate BSM + AB	Implant survival rate AB	Bone gain (mm)
Simion et al, 2001[87]	RS	49	108	DFDBA (allograft)	AL: 39.3; AU: 30.4	100% (0 of 26)	ND	100% (0 of 82)	ND
Felice et al, 2009[52]	RCT	10	38	DBBM	12	1 of 19	ND	1 of 19	ND
Meijndert et al, 2008[50]	RCT	49	93	DBBM	ND	93.5% (2 of 31)	ND	100% (0 of 31)	ND
Cordaro et al, 2010[88]	PS	16	49	DBBM	40	ND	100% (0 of 12)	100% (0 of 37)	lateral: 4.3 ± 1.1 vertical: 2.1 ± 0.3
Lopez-Cedrun, 2011[85]	RS	23	65	DFDBA	12–93	100%	ND	100%	5.3
Urban et al, 2011[90]	PS	22	58	DBBM	45.88	ND	100% (0 of 43)	100% (0 of 15)	5.56 ± 1.45
Cordaro et al, 2011[89]	RCT	17	55	DBBM, CM	24	ND	100% (0 of 28)	100% (0 of 27)	1) 4.18 ± 1.17 2) 4.56 ± 1.38
Dottore et al, 2012[54]	PS	11	44	ncHA	4	95.5% (1 of 22)	ND	95.5% (1 of 22)	1) 6.5 ± 1.6 2) 7.0 ± 2.6

Max = maxilla; Man = mandible; ND = no data available or data cannot be separated; PS = prospective study; RS = retrospective study; CSS = cross sectional study; ISR = implant survival rate; BSM = bone substitute material; AB = autogenous bone.

significant difference in the clinical outcome for BSM in combination with AB or AB alone[27,30,35,36]. The results of meta-analysis affirmed these conclusions, as no significant differences in implant survival after MSFA using BSM mixed with AB or using AB alone were found. Potentially, if the ideal mix of AB and BSM will be found in the future, those results might change as currently there is no common understanding on the best makeup of this combination.

A common technical challenge in MSFA is the sinus membrane perforation. The results showed that in 19.2 ± 10.8% of the cases a perforation occurred. This is in accordance with the study of Pjetursson et al, which indicated a value of 19.5% (a range of 0% to 58.3%)[34]. Karabuda et al stated that sinus membrane perforation does not compromise the osseointegration process or the survival rate[44]. Additionally, a relation between sinus membrane perforation and extended postoperative sinusitis or implant loss could not be described[45]. Nkenke et al demonstrated in their review that the event of sinusitis, partial, or total graft loss is independent of the used graft material[2]. Consequently, applying AB instead of BSM in MSFA will not protect patients from developing sinusitis or graft loss.

Vertical and horizontal ridge augmentation

For ridge augmentation, there are techniques available to effectively and predictably increase the width (horizontal) and the height (vertical) of the alveolar ridge[12,46,47]. Generally, survival rates of implants placed in ridge augmentation are high[46-48]. Long-term analysis by van Steenberghe et al over 10 years for simultaneous placement of autogenous bone grafts and implants showed high success rates of 95%[49]. Five studies comparing implant survival after ridge augmentation using BSM or AB were published between 2000 and 2014[50-54]. None showed any significant difference in implant survival. Our meta-analysis of these studies confirmed these results, indicating no statistically significant difference in implant survival for ridge augmentation using BSM or AB. In a Cochrane systematic review on this topic, three randomised controlled clinical trials (RCC) comparing BSM and AB were described[46]. These studies showed heterogeneous results. Felice et al[52] investigated whether DBBM could replace AB harvested from the iliac crest for vertical augmentation of atrophic posterior mandibles. No statistical differences for clinical outcomes were described in this study, however, statistically significant more patients preferred the augmentation procedure with the BSM. The split-mouth pilot study by Fontana et al[55], including only five patients, showed significantly more vertically augmented bone for the BSM compared to AB. In contrast, the study of Meijndert et al[56] indicated that implants placed in bone augmented with DBBM showed increased healing time and failure rates, although all failed implants could be successfully replaced without the need for additional augmentation.

All of these results should be interpreted with caution, because they are mostly related to small initial defects and these conclusions might not be applicable to large defects. Furthermore, patient numbers in these studies were relatively small. Altogether, the use of BSM or AB in ridge augmentation procedures indicated similar clinical outcomes. However, as the quantity of initially available bone before the augmentation procedure was seldom specified, it is difficult to determine whether the clinical outcome of implants relied on the augmented tissue or on the residual native bone. Consequently, there is insufficient evidence to suggest if applying BSM or AB in ridge augmentation is preferable.

The ability to shorten treatment length with AB in augmentation procedures is another matter of scientific discussion. With the transplantation of AB, osteoinductive factors are applied to the augmented site[8,9]. For BSM, this is not the case. Therefore, it may be assumed that the ingrowth of newly formed bone is delayed with BSM compared to AB, and that implant insertion and loading in two-stage procedures will have to be postponed. A recently published review analysing the total bone volume after MSFA based on histomorphometric analysis demonstrated a significantly higher portion of mineralised bone during the early healing phase for AB, compared to various BSM[43]. Interestingly, the different total bone volumes equalled out over time, and after 9 months no statistically significant difference was detected between the various grafting materials. Our review showed contradictory results for healing periods. In MSFA studies, healing periods were shorter, and in ridge augmentation procedures longer for BSM, compared to AB. The review of Jensen et al described almost identical healing periods in MSFA for BSM and AB[32]. Hence, a clear conclusion cannot be drawn on this topic. When using graft materials, the aspect of cost cannot be ignored. A data analysis on this topic was unfortunately not possible due to missing information in the examined studies. For AB, the harvesting procedure lengthens operating time, which is especially problematic in the case of extraoral donor sites surgery, as it is often performed under general anaesthesia[57,58]. Consequently, higher costs for a longer operating time and general anaesthesia could surpass the expenses for BSM[2]. In this context, cost-effectiveness analyses are required to clarify this aspect.

In general, literature-based systematic reviews of implant prognosis and survival pose a multitude of problems[59], which were also apparent in this study. Many of the included studies failed to report the original residual bone height at the site of presumptive implant placement. There was also a lack of RCTs with sufficient statistical information for the comparison of various grafting materials. In addition, comparisons were complicated due to relevant differences in number of patients, number of implants and the type of implant surface. Furthermore, the publication bias has to be kept in mind. This means that some authors reported mainly from good results and bad or unwanted results were neglected and not published. Therefore, even the results of this meta-analysis, although representing the highest grade of evidence, indicate presumably slightly too optimistic survival rates.

Conclusions

A large but heterogeneous body of literature was available regarding BSM in augmentation procedures, including all levels of clinical evidence. Within the limits of this meta-analytic approach to the literature, we showed a comparable implant survival in MSFA and ridge augmentation between BSM, BSM mixed with AB and AB. Therefore, depending on the size of the defect, BSM might be as effective as AB for augmentation procedures. Considering the side-effects accompanying AB procedures, BSM should be seen as a valuable alternative. However, in order to improve decision-making on the type of bone graft to be used for treating large defects properly, more standardised studies are required to better understand the clinical efficacy and limitations of these grafts. Future studies should define defect size, augmented volume and regenerative capacity of the defects.

References

1. Becktor JP, Isaksson S, Sennerby L. Survival analysis of endosseous implants in grafted and nongrafted edentulous maxillae. Int J Oral Maxillofac Implants 2004 Jan-Feb;19:107–115.
2. Nkenke E, Stelzle F. Clinical outcomes of sinus floor augmentation for implant placement using autogenous bone or bone substitutes: a systematic review. Clin Oral Implants Res 2009;20:124–133.
3. Chiapasco M, Casentini P, Zaniboni M. Bone augmentation procedures in implant dentistry. Int J Oral Maxillofac Implants 2009;24:237–259.

4. Al-Nawas B, Kammerer PW, Morbach T, Ophoven F, Wagner W. Retrospective clinical evaluation of an internal tube-in-tube dental implant after 4 years, with special emphasis on peri-implant bone resorption. Int J Oral Maxillofac Implants 2011;26:1309–1316.
5. Al-Nawas B, Brägger U, Meijer HJ, Naert I, Persson R, Perucchi A, Quirynen M, Raghoebar GM, Reichert TE, Romeo E, Santing HJ, Schimmel M, Storelli S, ten Bruggenkate C, Vandekerckhove B, Wagner W, Wismeijer D, Müller F. A double-blind randomized controlled trial (RCT) of Titanium-13Zirconium versus Titanium Grade IV small-diameter bone level implants in edentulous mandibles--results from a 1-year observation period. Clin Implant Dent Relat Res 2012;14:896–904.
6. Al-Nawas B, Kammerer PW, Morbach T, Ladwein C, Wegener J, Wagner W. Ten-year retrospective follow-up study of the TiOblast dental implant. Clin Implant Dent Relat Res 2012;14:127–134.
7. Aghaloo TL, Moy PK. Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement? Int J Oral Maxillofac Implants 2007;22:49–70.
8. Calori GM, Mazza E, Colombo M, Ripamonti C. The use of bone-graft substitutes in large bone defects: any specific needs? Injury 2011;42 Suppl 2:S56–63.
9. Urist MR. Bone: formation by autoinduction. Science 1965;12;150:893–899.
10. LeGeros RZ. Properties of osteoconductive biomaterials: calcium phosphates. Clin Orthop Relat Res 2002;(395):81–98.
11. Giannoudis PV, Dinopoulos H, Tsiridis E. Bone substitutes: an update. Injury 2005 Nov;36 Suppl 3:S20–27.
12. Klein MO, Al-Nawas B. For which clinical indications in dental implantology is the use of bone substitute materials scientifically substantiated? Eur J Oral Implantol 2011;4:11–29.
13. Hallman M, Thor A. Bone substitutes and growth factors as an alternative/complement to autogenous bone for grafting in implant dentistry. Periodontol 2000 2008;47:172–192.
14. Rickert D, Slater JJ, Meijer HJ, Vissink A, Raghoebar GM. Maxillary sinus lift with solely autogenous bone compared to a combination of autogenous bone and growth factors or (solely) bone substitutes. A systematic review. Int J Oral Maxillofac Surg 2012;41:160–167.
15. Nkenke E, Weisbach V, Winckler E, Kessler P, Schultze-Mosgau S, Wiltfang J, Neukam FW. Morbidity of harvesting of bone grafts from the iliac crest for preprosthetic augmentation procedures: a prospective study. Int J Oral Maxillofac Surg 2004;33:157–163.
16. Barone A, Ricci M, Mangano F, Covani U. Morbidity associated with iliac crest harvesting in the treatment of maxillary and mandibular atrophies: a 10-year analysis. J Oral Maxillofac Surg 2011;69:2298–2304.
17. Horch HH, Sader R, Pautke C, Neff A, Deppe H, Kolk A. Synthetic, pure-phase beta-tricalcium phosphate ceramic granules (Cerasorb) for bone regeneration in the reconstructive surgery of the jaws. Int J Oral Maxillofac Surg 2006;35:708–713.
18. Kämmerer PW, Schiegnitz E, Alshihri A, Draenert FG, Wagner W. Modification of xenogenic bone substitute materials – effects on the early healing cascade in vitro. Clin Oral Implants Res 2013 Mar 31.
19. Kolk A, Handschel J, Drescher W, Rothamel D, Kloss F, Blessmann M, Heiland M, Wolff KD, Smeets R. Current trends and future perspectives of bone substitute materials - from space holders to innovative biomaterials. J Craniomaxillofac Surg 2012;40:706–718.
20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–1012.
22. Schiegnitz E, Al-Nawas B, Kammerer PW, Grotz KA. Oral rehabilitation with dental implants in irradiated patients: a meta-analysis on implant survival. Clin Oral Investig 2014; 18:687–698.
23. Pieri F, Aldini NN, Fini M, Marchetti C, Corinaldesi G. Immediate fixed implant rehabilitation of the atrophic edentulous maxilla after bilateral sinus floor augmentation: a 12-month pilot study. Clin Implant Dent Relat Res 2012;14:67–82.
24. Schmitt C, Karasholi T, Lutz R, Wiltfang J, Neukam FW, Schlegel KA. Long-term changes in graft height after maxillary sinus augmentation, onlay bone grafting, and combination of both techniques: a long-term retrospective cohort study. Clin Oral Implants Res 2014;25:38–46.
25. Miller SA, Forrest JL. Enhancing your practice through evidence-based decision making: PICO, learning how to ask good questions. J Evid Based Dent Pract 2001;1:136–141.
26. Proskin HM, Jeffcoat RL, Catlin A, Campbell J, Jeffcoat MK. A meta-analytic approach to determine the state of the science on implant dentistry. Int J Oral Maxillofac Implants 2007;22:11–18.
27. Hallman M, Sennerby L, Lundgren S. A clinical and histologic evaluation of implant integration in the posterior maxilla after sinus floor augmentation with autogenous bone, bovine hydroxyapatite, or a 20:80 mixture. Int J Oral Maxillofac Implants 2002;17:635–643.
28. Merli M, Moscatelli M, Mariotti G, Rotundo R, Nieri M. Autogenous bone versus deproteinised bovine bone matrix in 1-stage lateral sinus floor elevation in the severely atrophied maxilla: a randomised controlled trial. Eur J Oral Implantol 2013;6:27–37.
29. Sbordone L, Levin L, Guidetti F, Sbordone C, Glikman A, Schwartz-Arad D. Apical and marginal bone alterations around implants in maxillary sinus augmentation grafted with autogenous bone or bovine bone material and simultaneous or delayed dental implant positioning. Clin Oral Implants Res 2011;22:485–491.
30. Velich N, Nemeth Z, Tóth C, Szabó G. Long-term results with different bone substitutes used for sinus floor elevation. J Craniofac Surg 2004;15:38–41.
31. Browaeys H, Bouvry P, De Bruyn H. A literature review on biomaterials in sinus augmentation procedures. Clin Implant Dent Relat Res 2007;9:166–177.
32. Jensen SS, Terheyden H. Bone augmentation procedures in localized defects in the alveolar ridge: clinical results with different bone grafts and bone-substitute materials. Int J Oral Maxillofac Implants 2009;24:218–236.
33. Esposito M, Grusovin MG, Coulthard P, Worthington HV. The efficacy of various bone augmentation procedures for dental implants: a Cochrane systematic review of randomized controlled clinical trials. Int J Oral Maxillofac Implants 2006;2:696–710.
34. Pjetursson BE, Tan WC, Zwahlen M, Lang NP. A systematic review of the success of sinus floor elevation and survival of implants inserted in combination with sinus floor elevation. J Clin Periodontol 2008;35:216–240.
35. Diserens V, Mericske E, Mericske-Stern R. Radiographic analysis of the transcrestal sinus floor elevation: short-term observations. Clin Implant Dent Relat Res 2005;7:70–78.
36. Cho-Lee GY, Naval-Gias L, Castrejon-Castrejon S, Capote-Moreno AL, Gonzalez-Garcia R, Sastre-Perez J, Munoz-Guerra MF. A 12-year retrospective analytic study of the implant survival rate in 177 consecutive maxillary sinus augmentation procedures. Int J Oral Maxillofac Implants 2010;25:1019–1027.
37. Bornstein MM, Chappuis V, von Arx T, Buser D. Performance of dental implants after staged sinus floor elevation procedures: 5-year results of a prospective study in partially edentulous patients. Clin Oral Implants Res 2008;19:1034–1043.

38. Jensen T, Schou S, Stavropoulos A, Terheyden H, Holmstrup P. Maxillary sinus floor augmentation with Bio-Oss or Bio-Oss mixed with autogenous bone as graft: a systematic review. Clin Oral Implants Res 2012;23:263–273.
39. Ferreira CE, Novaes AB, Haraszthy VI, Bittencourt M, Martinelli CB, Luczyszyn SM. A clinical study of 406 sinus augmentations with 100% anorganic bovine bone. J Periodontol 2009;80:1920–1927.
40. Bae JH, Kim YK, Kim SG, Yun PY, Kim JS. Sinus bone graft using new alloplastic bone graft material (Osteon)-II: clinical evaluation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:14–20.
41. Uckan S, Deniz K, Dayangac E, Araz K, Ozdemir BH. Early implant survival in posterior maxilla with or without beta-tricalcium phosphate sinus floor graft. J Oral Maxillofac Surg 2010;68:1642–1645.
42. Aguirre Zorzano LA, Rodriguez Tojo MJ, Aguirre Urizar JM. Maxillary sinus lift with intraoral autologous bone and B--tricalcium phosphate: histological and histomorphometric clinical study. Med Oral Patol Oral Cir Bucal 2007; 12:E532–536.
43. Handschel J, Simonowska M, Naujoks C, Depprich RA, Ommerborn MA, Meyer U, Kübler NR. A histomorphometric meta-analysis of sinus elevation with various grafting materials. Head Face Med 2009;5:12.
44. Karabuda C, Arisan V, Özyuvaci H. Effects of sinus membrane perforations on the success of dental implants placed in the augmented sinus. J Periodontol 2006;77:1991–1997.
45. Kaptein ML, de Putter C, de Lange GL, Blijdorp PA. Survival of cylindrical implants in composite grafted maxillary sinuses. J Oral Maxillofac Surg 1998;56:1376–1380; discussion 1380–1381.
46. Esposito M, Grusovin MG, Felice P, Karatzopoulos G, Worthington HV, Coulthard P. The efficacy of horizontal and vertical bone augmentation procedures for dental implants - a Cochrane systematic review. E ur J Oral Implantol 2009;2:167–184.
47. Chen ST, Beagle J, Jensen SS, Chiapasco M, Darby I. Consensus statements and recommended clinical procedures regarding surgical techniques. Int J Oral Maxillofac Implants 2009;24:272–278.
48. Molly L, Quirynen M, Michiels K, van Steenberghe D. Comparison between jaw bone augmentation by means of a stiff occlusive titanium membrane or an autologous hip graft: a retrospective clinical assessment. Clin Oral Implants Res 2006;17:481–487.
49. van Steenberghe D, Naert I, Bossuyt M, De Mars G, Calberson L, Ghyselen J, Brånemark PI. The rehabilitation of the severely resorbed maxilla by simultaneous placement of autogenous bone grafts and implants: a 10-year evaluation. Clin Oral Investig 1997;1:102–108.
50. Meijndert L, Raghoebar GM, Meijer HJ, Vissink A. Clinical and radiographic characteristics of single-tooth replacements preceded by local ridge augmentation: a prospective randomized clinical trial. Clin Oral Implants Res 2008; 19:1295–1303.
51. Simion M, Jovanovic SA, Tinti C, Benfenati SP. Long-term evaluation of osseointegrated implants inserted at the time or after vertical ridge augmentation. A retrospective study on 123 implants with 1-5 year follow-up. Clin Oral Implants Res 2001;12:35-45.
52. Felice P, Marchetti C, Iezzi G, Piattelli A, Worthington H, Pellegrino G, Esposito M. Vertical ridge augmentation of the atrophic posterior mandible with interpositional bloc grafts: bone from the iliac crest vs. bovine anorganic bone. Clinical and histological results up to one year after loading from a randomized-controlled clinical trial. Clin Oral Implants Res 2009;20:1386–1393.
53. Lopez-Cedrun JL. Implant rehabilitation of the edentulous posterior atrophic mandible: the sandwich osteotomy revisited. Int J Oral Maxillofac Implants 2011;26:195–202.
54. Dottore AM, Kawakami PY, Bechara K, Rodrigues JA, Cassoni A, Figueiredo LC, Piattelli A, Shibli JA. Stability of Implants Placed in Augmented Posterior Mandible after Alveolar Osteotomy Using Resorbable Nonceramic Hydroxyapatite or Intraoral Autogenous Bone: 12-Month Follow-Up. Clin Implant Dent Relat Res 2012;Nov 13.
55. Fontana F, Santoro F, Maiorana C, Iezzi G, Piattelli A, Simion M. Clinical and histologic evaluation of allogeneic bone matrix versus autogenous bone chips associated with titanium-reinforced e-PTFE membrane for vertical ridge augmentation: a prospective pilot study. Int J Oral Maxillofac Implants 2008;23:1003–1012.
56. Meijndert L, Meijer HJ, Stellingsma K, Stegenga B, Raghoebar GM. Evaluation of aesthetics of implant-supported single-tooth replacements using different bone augmentation procedures: a prospective randomized clinical study. Clin Oral Implants Res 2007;18:715–719.
57. Peleg M, Garg AK, Misch CM, Mazor Z. Maxillary sinus and ridge augmentations using a surface-derived autogenous bone graft. J Oral Maxillofac Surg 2004;62:1535–1544.
58. Iturriaga MT, Ruiz CC. Maxillary sinus reconstruction with calvarium bone grafts and endosseous implants. J Oral Maxillofac Surg 2004;62:344–347.
59. Altman DG. Systematic reviews of evaluations of prognostic variables. BMJ 2001;323:224–248.
60. Calvo-Guirado JL, Gómez-Moreno G, López-Marí L, Ortiz-Ruiz AJ, Guardia-Muñoz J. Atraumatic maxillary sinus elevation using threaded bone dilators for immediate implants. A three-year clinical study. Med Oral Patol Oral Cir Bucal 2010;15:e366–370.
61. Covani U, Orlando B, Giacomelli L, Cornelini R, Barone A. Implant survival after sinus elevation with Straumanns BoneCeramic in clinical practice: ad-interim results of a prospective study at a 15-month follow-up. Clin Oral Implants Res 2011;22:481–484. doi: 10.1111/j.1600-0501.2010.02042.x
62. Esposito M, Piattelli M, Pistilii R, Pellegrino G, Felice P. Sinus lift with guided bone regeneration or argonic bovine bone: 1-year post-loading results of a pilot randomised clinical trial. Eur J Oral Implantol 2010;3:297–305.
63. Garlini G, Redemagni M, Donini M, Maiorana C. Maxillary Sinus Elevation With an Alloplastic Material and Implants: 11 Years of Clinical and Radiologic Follow-Up. J Oral Maxillofac Surg 2010;68:1152–1157.
64. Lambert F, Lecloux G, Rompen E. One-step approach for implant placement and aubantral bone regeneration using bovine hydroxyapatite: a 2- to 6-year follow-up study. Int J Oral Maxillofac Implants 2010;25:598–606.
65. Scarano A, Piattelli A, Assenza B, Quaranta A, Perrotti V, Piattelli M, Iezzi G. Porcine Bone Used in Sinus Augmentation Procedures: A 5-Year Retrospective Clinical Evaluation. J Oral Maxillofac Surg 2010;68:1869–1873.
66. Tetsch J, Tetsch P, Lysek D. Long-term results after lateral and osteotome technique sinus floor elevation: a retrospective analysis of 2190 implants over a time period of 15 years. Clin Oral Implants Res 2010;21:497–503.
67. Urban I, Lozada J. A prospective Study of Implant Placed in Augmented Sinuses with Minimal and Moderate Residual Crestal Bone: Results after 1 to 5 years. Int J Oral Maxillofac Implants 2010; 25:1023–1212.
68. Viscioni A, Franco M, Paolin A, Cogliati E, Callegari M, Zollino I, Sollazzo V, Carinci F. Effectiveness of fresh frozen and cryopreserved homologue iliac crest grafts used in sinus lifting: a comparative study. Cell Tissue Bank 2011;12: 263–271.
69. Sakka S, Krenkel C. Simultaneous maxillary sinus lifting and implant placement with autogenous parietal bone graft: Outcome of 17 cases. J Craniomaxillofac Surg 2011;39:187–191.
70. Lee DZ, Chen ST, Darby IB. Maxillary sinus floor elevation and grafting with deproteinized bovine bone mineral: a clinical and histomorphometric study. Clin Oral Implants Res 2012;23:918–924.

71. Kim YK, Kim SG, Park JY, Yi YJ, Bae JH. Comparison of clinical outcomes of sinus bone graft with simultaneous implant placement: 4-month and 6-month final prosthetic loading. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:164–169.
72. Hansen ES, Schou S, Harder F, Hjorting-Hansen E. Outcome of implant therapy involving localised lateral alveolar ridge and/or sinus floor augmentation: a clinical and radiographic retrospective 1-year study. Eur J Oral Implantol 2011:4:257–267.
73. Caubet J, Petzold C, Sáez-Torres C, Morey M, Iriarte JI, Sánchez J, Torres JJ, Ramis JM, Monjo M. Sinus Graft With Safescraper: 5-Year Results. J Oral Maxillofac Surg 2011;69:482–490.
74. Sivolella S, Bressan E, Gnocco E, Berengo M, Favero GA. Maxillary sinus augmentation with bovine and simultaneous dental implant placement in conditions of severe alveolar atrophy: A retrospective analysis of a consecutively treated case series. Quintessence Int 2011;42:851–862.
75. Wagner W, Wiltfang J, Pistner H, Yildirim M, Ploder B, Chapman M, Schiestl N, Hantak E. Bone formation with a biphasic calcium phosphate combined with fibrin sealant in maxillary sinus floor elevation for delayed dental implant. Clin Oral Implants Res 2012;23:1112–1117.
76. Lindgren C, Mordenfeld A, Johansson CB, Hallman M. A 3-year clinical follow-up of implants placed in two different biomaterials used for sinus augmentation. Int J Oral Maxillofac Implants 2012:27:1151–1162.
77. Cha HS, Kim A, Nowzari H, Chang HS, Ahn KM. Simultaneous Sinus Lift and Implant Installation: Prospective Study of Consecutive Two Hundred Seventeen Sinus Lift and Four Hundred Sixty-Two Implants. Clin Implant Dent Relat Res, 2012; Nov 15. doi: 10.1111/cid.12012. [Epub ahead of print].
78. Canullo L, Patacchia O, Sisti A, Heinemann F. Implant Restoration 3 Months after One Stage Sinus Lift Surgery in Severely Resorbed Maxillae: 2-Year Results of a Multicenter Prospective Clinical Study. Clin Implant Dent Relat Res 2012;14:412–420.
79. Schmitt C, Karasholi T, Lutz R, Wiltfang J, Neukam FW, Schlegel KA. Long-term changes in graft height after maxillary sinus augmentation, onlay bone grafting, and combination of both techniques: a long-term retrospective cohort study. Clin Oral Implants Res 2012, doi: 10.1111/clr.12045.
80. Esposito M, Cannizzaro G, Soardi E, Pistilli R, Piattelli M, Corvino V, Felice P. Posterior atrophic jaws rehabilitated with prostheses supported by 6 mm-long, 4 mm-wide implants or by longer implants in augmented bone. Preliminary results from a pilot randomised controlled trial. Eur J Oral Implantol 2012;5:19-33.
81. Si MS, Zhuang LF, Gu YX, Mo JJ, Qiao SC, Lai HC. Osteotome sinus floor elevation with or without grafting: a 3-year randomized controlled clinical trial. J Clin Periodontol 2013;40: 396–403.
82. Sbordone C, Toti P, Ramaglia L, Guidetti F, Sbordone L, Martuscelli R. A 5-year clinical and computerized tomographic implant follow-up in sinus-lifted maxillae and native bone. Clin Oral Implants Res 2013; Jul 4. doi: 10.1111/clr.12222. [Epub ahead of print].
83. Cannizzaro G, Felice P, Minciarelli AF, Leone M, Viola P, Esposito M. Early implant loading in the atrophic posterior maxilla: 1-stage lateral versus crestal sinus lift and 8mm hydroxyapatite-coated implants. A 5-year randomised controlled trial. Eur J Oral Implantol 2013:6:13–25.
84. Felice P, Pistilli R, Piatelli M, Soardi E, Pellegrino G, Corvino V, Esposito M. 1-stage versus 2-stage lateral maxillary sinus lift procedures: 4-month post-loading reuslts of a multicenter randomised controlled trial. Eur J Oral Implantol 2013:6:153–165.
85. Lopez-Cedrun JL. Implant rehabilitation of the edentulous posterior atrophic mandible: the sandwich osteotomy revisited. Int J Oral Maxillofac Implants 2011;26:195–202.
86. Meijndert L, Raghoebar GM, Meijer HJA, Vissink A. Clinical and radiographic characteristics of single-tooth replacements preceded by local ridge augmentation: a prospective randomized clinical trial. Clin Oral Implants Res 2008;19:1295–1303.
87. Simion M, Jovanovic SA, Tinti C, Benfenati SP. Long-term evaluation of osseointegrated implants inserted at the time or after vertical ridge augmentation. A retrospective Study on 123 implants with 1-5 year follow-up. Clin Oral Implants Res 2001;12;35–45.
88. Cordaro L, Torsello F, Accorsi Ribeiro C, Liberatore M, Mirisola di Torresanto V. Inlay–onlay grafting for threedimensional reconstruction of the posterior atrophic maxilla with mandibular bone. Int J Oral Maxillofac Surg 2010;39: 350–357.
89. Cordaro L, Torsello F, Morcavallo S, di Torresanto VM. Effect of bovine bone and collagen membranes on healing of mandibular bone blocks: a prospective randomized controlled study. Clin Oral Implants Res 2011;22:1145–1150.
90. Urban IA, Nagursky H, Lozada JL. Horizontal ridge augmentation with a resorbable membrane and particulated autogenous bone with or without anorganic bovine bone. derived mineral: a prospective case series in 22 patients. Int J Oral Maxillofac Implants 2011;26:404–414.
91. Beitlitum I, Artzi Z, Nemcovsky CE. Clinical evaluation of particulate allogeneic with and without autogenous bone grafts and resorbable collagen membranes for bone augmentation of atrophic alveolar ridges. Clin Oral Implants Res 2010;21:1242–1250.
92. Canullo L, Sisti A. Early implant loading after vertical ridge augmentation (VRA) using e-PTFE titanium-reinforced membrane and nano-structured hydroxyapatite: 2-year prospective study. Eur J Oral Implantol 2010;3:59–69.
93. Le B, Rohrer MD, Prassad HS. Screw "tent-pole" grafting technique for reconstruction of large vertical alveolar ridge defects using human mineralized allograft for implant site preparation. J Oral Maxillofac Surg 2010;68:428–435.
94. Merli M, Lombardini F, Esposito M. Vertical ridge augmentation with autogenous bone grafts 3 years after loading: resorbable barriers versus titanium-reinforced barriers. A randomized controlled clinical trial. Int J Oral Maxillofac Implants 2010;25:801–807
95. Boronat A, Carrilo C, Penarrocha M, Penarrocha M. Dental implants placed simultaneously with bone grafts in horizontal defects: a clinical retrospective study with 37 patients. Int J Oral Maxillofac Implants 2010;25:189–196.
96. Pelo S, Boniello R, Moro A, Gasparini G, Amoroso PF. Augmentation of the atrophic edentulous mandible by a bilateral two-step osteotomy with autogenous bone graft to place osseointegrated dental implants. Int J Oral Maxillofac Surg 2010;39:227–234.
97. Nissan J, Mardinger O, Calderon S, Romanos GE, Chaushu G. Cancellous Bone Block Allografts for the Augmentation of the Anterior Atrophic Maxilla. Clin Implant Dent Relat Res 2011a;13:2:104–111.
98. Nissan J, Ghelfan O, Mardinger O, Calderon S, Chaushu G. Efficacy of Cancellous Block Allograft Augmentation Prior to Implant Placement in the Posterior Atrophic Mandible. Clin Implant Dent Relat Res 2011b;13:4.279–285.
99. Esposito M, Cannizzaro G, Soardi E, Pellegrino G, Pistilli R, Felice P. A 3-year post-loading report of a randomised controlled trial on the rehabilitation of posterior atrophic mandibles: short implants or longer implants in vertically augmented bone? Eur J Oral Implantol 2011;4:301–311.
100. Chiapasco M, Casentini P, Zaniboni M, Corsi E. Evaluation of peri-implant bone resorption around Straumann Bone Level© implants placed in areas reconstructed with autogenous vertical onlay bone grafts. Clin Oral Implants Res 2012;23:1012–1021.
101. Felice P, Pistilli R, Piatelli M, Soardi E, Corvino V, Esposito M. Posterior atrophic jaws rehabilitated with protheses supported by 5 x 5 mm implants with a novel nanostructed calcium-incorporated titanium surface or by longer implants in augmented bone. Preliminary results from a randomised controlled trial. Eur J Oral Implantol 2012:5:149–161.