Dear author,

Please note that changes made in the online proofing system will be added to the article before publication but are not reflected in this PDF.

We also ask that this file not be used for submitting corrections.

Int. J. Oral Maxillofac. Surg. 2019; xxx: xxx–xxx
https://doi.org/10.1016/j.ijom.2019.05.004, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Meta-Analysis
Pre-Implant Surgery

Do osteoconductive bone substitutes result in similar bone regeneration for maxillary sinus augmentation when compared to osteogenic and osteoinductive bone grafts? A systematic review and frequentist network meta-analysis

Q7

E. A. Al-Moraissi[1], A. S. Alkhutari[1], B. Abotaleb[2], N. H. Altairi[1], M. Del Fabbro[3,4] Q8

[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Thamar University, Thamar, Yemen; [2]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Ibb University, Ibb, Yemen; [3]Department of Biomedical, Surgical and Dental Sciences, Università degli Studi di Milano, Milan, Italy; [4]IRCCS Orthopaedic Institute Galeazzi, Milan, Italy Q9 Q10

E.A. Al-Moraissi, A.S. Alkhutari, B. Abotaleb, N.H. Altairi, M. Del Fabbro: Do osteoconductive bone substitutes result in similar bone regeneration for maxillary sinus augmentation when compared to osteogenic and osteoinductive bone grafts? A systematic review and frequentist network meta-analysis. Int. J. Oral Maxillofac. Surg. 2019; xxx: xxx–xxx.

Abstract. The purpose of this network meta-analysis was to identify the most effective biomaterials producing higher new bone formation (NBF) and lower residual graft (RG) and connective tissue (CT) following maxillary sinus augmentation (MSA), and to generate a ranking based on their performance. The MEDLINE, Embase, and CENTRAL databases were searched to identify randomized controlled trials (RCTs) published until March 2018, evaluating histomorphometric outcomes after MSA. Predictor variables were autogenous bone (AB), allografts (AG), xenografts (XG), alloplastic bone (AP), AB + XG, AB + AP, AG + XG, XG + AP, and grafts combined with autologous platelet concentrates/recombinant growth factors, mesenchymal stem cells (MSCs), or recombinant bone morphogenetic proteins (BMPs). Outcome variables were NBF%, RG%, and CT%. Healing time was considered. The weighted mean difference (WMD) with 95%

0901-5027/000001+020

confidence interval (CI) was calculated via frequentist network meta-analysis using Stata software. Fifty-two RCTs (1483 biopsies) were included. At a healing time <6 Q11 months, AB was superior to AP (WMD − 10.66%, 95% CI − 16.38% to −4.94%) Q12 and XG (WMD − 7.93%, 95% CI − 15.11% to −0.75%) for NBF. Regarding CT, AB was superior to XG + AP, AP, MSCs, and XG. At a healing time ≥6 months, NBF was higher for AB than AP (WMD − 7.06%, 95% CI − 12.59% to −1.52%). Q13 RG was lower in AB than AP (WMD 12.03%, 95% CI 3.04% to 21.03%), XG (WMD 14.62%, 95% CI 4.25% to 24.98%), and growth factors (WMD 12.32%, 95% CI 0.04% to 24.60%). The three highest ranked biomaterials for increasing NBF were AG + XG (95%, very low quality evidence), growth factors (69.9%, low quality evidence), and AB alone (69.8%, moderate quality evidence). The three highest ranked biomaterials for decreasing RG were BMPs (88.8%, very low quality evidence), AB alone (81.5%, moderate quality evidence), and AB + AP (58.9%, very low quality evidence). Finally, XG + AP (84.7%, low quality evidence), AP Q14 alone (77.7%, moderate quality evidence), and MSCs (76.1%, low quality evidence), were the three highest ranked biomaterials for decreasing the amount of CT. Network meta-analysis provided moderate quality evidence that AB alone is probably the best option to obtain greater NBF after MSA in the first 6 months after surgery. Additionally, the results of this network meta-analysis support the hypothesis that osteoconductive bone substitute materials should be combined with osteogenic or osteoinductive grafts for superior histomorphometric outcomes in MSA.

Key words: Sinus lift; Histomorphometric analysis; Frequentist network meta-analysis; Biomaterials; Osteoconductive bone substitutes.

Accepted for publication 13 May 2019

Maxillary sinus augmentation (MSA) Q15 through Schneiderian membrane elevation is one of the most predictable surgical procedures to reconstruct the atrophic posterior maxillary alveolar ridge. The successful placement of dental implant(s) in the jaws requires an adequate bone quantity (in vertical and horizontal dimension) and quality to ensure a high implant survival rate and to avoid surgical and aesthetic problems. MSA can be performed through two main approaches, namely lateral sinus lift and transalveolar sinus lift. In both approaches, the bone grafts are usually placed in a space created under the elevated maxillary sinus membrane. Ideally, bone grafting materials should provide or promote the three main features needed for a successful graft healing: osteoconduction to maintain space for new bone ingrowth, osteogenesis to recruit bone-forming cells, and osteoinduction to induce the differentiation of undifferentiated cells during bone regeneration or repair[1,2]. However, no bone grafting material has all such features, except autogenous bone.

Different bone grafts have been used in MSA, each of them having their own advantages and drawbacks, and achieving different degrees of newly formed bone, residual particles, and soft tissue. These bone grafts include autogenous bone (AB), allografts (AG), xenografts (XG), alloplastic materials (AP), and composite grafts. Additionally, alternative adjuncts to bone grafting materials have recently been used in MSA, either alone or in combination with these bone grafts, such as autogenous platelet concentrates, recombinant growth factors (GFs), mesenchymal stem cells (MSCs), and recombinant bone morphogenetic protein 2 (BMP-2).

The evaluation of augmented maxillary grafted sinuses is performed by histomorphometric analysis of bone biopsies, which can determine the percentage of newly formed bone (NBF), residual graft (RG) particles, and connective tissue (CT) components of the whole field of view (biopsy) at the grafted site during the healing period[3,4]. These parameters are clinically very important to assess the success of the sinus augmentation procedure: a greater NBF and lesser RG indicate a successful integration of the bone graft, which ultimately enhances implant survival[5].

Many clinical studies and systematic reviews have investigated the success of the various bone grafting materials following MSA[3,6–9]. However, it is still unclear which bone grafting material, if any, provides the most predictable histomorphometric outcome in terms of new bone formation.

A systematic review with meta-analysis of comparative studies may help synthesize the evidence related to the debate on the most predictable grafting material. Previous systematic reviews and meta-analyses on histomorphometric outcomes of different graft materials used in sinus augmentation have suggested that autogenous bone alone can induce the highest amount of new bone formation compared to the other materials, especially in the short term (≤6 months)[4,5]. Nevertheless, a combination of autogenous bone and xenografts, as well as xenografts alone and mixtures of tricalcium phosphate and hydroxyapatite may represent valid alternatives to autogenous bone when donor site morbidity is a concern[10].

Traditionally, a direct meta-analysis only allows the comparison and pooling of data from head-to-head separate but similar studies. Thus, comparisons are limited to such clinical trials. Hence, one of the main limitations of previous meta-analyses is that the effect of some bone graft materials could only be evaluated if they were compared directly with specific control materials and if there were multiple studies in which the same comparison was performed. So, in the absence of direct comparisons, the potential benefit of a given material remains unknown.

The network meta-analysis (NMA) has emerged as a suitable tool for comparing two interventions that have not been compared directly in a head-to-head clinical trial and also offers the chance to run a collective assessment of variable interventions in a single study[11]. Thus, on comparison of NMA to conventional meta-analysis, the former offers the following advantages: it produces an estimate of effect among all compared groups, enhances the precision of effect estimates,

ranks different treatments, and improves generalizability[12–14].

Statistically, a NMA can be conducted using either a frequentist or Bayesian approach[15–17]. The frequentist NMA is what researchers will commonly encounter in single randomized controlled trials (RCTs) and conventional direct meta-analyses. The results of the frequentist NMA are presented as a point estimate (effect measure such as the odds ratio, risk ratio, mean difference, or standardized mean difference) with the 95% confidence interval (CI), whereas the results of the Bayesian NMA are reported as the point estimate with a 95% credibility interval (CrI)[16].

There are currently no published RCTs comparing the following different bone grafts with regard to histomorphometric outcomes of the different bone grafting materials after MSA: (1) AB alone and the combination of XG and AP, AG and XG and BMP-2; (2) XG and the combination of AB with AP and AG with XG; (3) AP to AB in combination of AP with AG or XG or BMP-2 alone; (4) AG to a mixture of XG with AP, AB with AP, AB with XG or GFs; (5) AB in combination with AP or XG in combination with AG versus XG mixed with AP or AG. Thus, a NMA of RCTs was conducted to make comparisons among the different bone grafting materials and to rank the ideal bone grafting materials according to their histomorphometric performance.

The following hypotheses were postulated: (1) there is no difference in histomorphometric outcomes between the different bone grafting materials after MSA; (2) the alternative hypothesis, i.e. that with respect to autogenous bone alone, the use of acellular osteoconductive bone substitute materials will result in lower NBF and higher RG and CT when compared to the combination of osteoconductive bone substitute materials plus osteogenic and/or osteoinductive bone grafts; (3) autogenous bone shows the fastest healing time and the highest NBF at any given time, among the grafting materials investigated.

The specific aims of this NMA were to challenge these hypotheses and to identify the best bone grafting material, providing the greatest NBF and lowest RG and CT following MSA.

Materials and methods

Protocol and registration

A NMA of RCTs was conducted according to the PRISMA Extension Statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions (Supplementary Material File 1 shows the PRISMA-NMA checklist)[18]. The protocol is registered in the PROSPERO database (systematic review registration CRD42018089357)[19].

Search strategy

Relevant RCTs, in any language and with any publication date, were retrieved by systematic search of MEDLINE, Embase, and the Cochrane Central Registry of Controlled Trials (CENTRAL) from the date of inception of each database (Supplementary Material File 2).

Eligibility criteria

Inclusion criteria

The following inclusion criteria were adopted based on the PICOTS process: patients (P) were those with an atrophic posterior maxilla that required augmentation of the maxillary sinus using different biomaterials, with immediate or delayed dental implant placement; the intervention (I) was MSA using one of the following bone grafting materials: allograft (AG), xenograft (XG), alloplastic graft (AP), autogenous bone and allograft (AB + AG), autogenous bone and xenograft (AB + XG), autogenous bone and alloplastic graft (AB + AP), allograft and xenograft (AG + XG), any bone graft associated with GFs, any graft associated with recombinant BMP-2, any graft associated with MSCs; the comparator (C) was autogenous bone (AB); the primary outcomes (O) were histomorphometric outcomes, namely the percentage NBF, RG particles, and CT in the whole field of view; the time (T) was all healing times, including 3, 4, 6, and 9 months and more than 1 year (short to intermediate term defined as <6 months and long term defined as ≥6 months); the study design (S) was RCTs, including split-mouth and parallel studies, that reported the outcomes of interest.

Exclusion criteria

The following exclusion criteria were applied: (1) studies with none of the basic data required to perform a meta-analysis, such as the mean percentage of NB, RG, and CT, standard deviation, and number of biopsies; (2) non-randomized clinical studies, case series, retrospective studies, and cohort studies; (3) review articles; (4) animal or in vitro studies; (5) publications using duplicated data.

Data extraction

Data were extracted from the included studies according to a predetermined datasheet. Two reviewers (A.A. and B.A.) independently tested the datasheet using two randomly chosen studies, to ensure the consistency of the data extraction process. After adjustment of the extraction form, the data were extracted independently in duplicate. In the case of disagreement, a third reviewer (E.A.) was consulted. The following information was extracted from each study: main features of the study and participants (authors, study design, patients' age and sex), type of grafting material, membranes used (if any), number and characteristics of biopsy samples, timing of biopsy, timing of implant surgery, histomorphometric outcomes assessed.

Assessment of the risk of bias

Two authors (B.A and N.A.) independently evaluated the risk of bias of each included study using a modified version of the Cochrane tool for risk of bias assessment[20,21]. The domain regarding blinding of participants and personnel (performance bias) was not considered, because in MSA, neither the surgeon nor the patient can be efficiently masked to the bone graft material used, especially if it is autogenous bone.

Data synthesis

Network geometry

The geometry of the network was represented by a spider web-like plot to show the connections between the different studies using different graft materials. Before undertaking the NMA, potential effect modifiers were identified, such as the duration of follow-up and the risk of bias. Hence, distinct network plots were created, in which the potential effect modifiers were highlighted in different colours, in order to guarantee the balance across the comparisons[22].

Measures of treatment effect

In the meta-analysis, the weighted mean difference (WMD) was calculated for continuous outcomes. The results of the NMA for each possible pair of graft materials were reported as a summary of the relative effect sizes. In split-mouth studies, the statistical unit of analysis was the augmented sinus, while it was the patient in parallel studies.

Please cite this article in press as: Al-Moraissi EA, et al. Do osteoconductive bone substitutes result in similar bone regeneration for maxillary sinus augmentation . . . , *Int J Oral Maxillofac Surg* (2019), https://doi.org/10.1016/j.ijom.2019.05.004

Assessment of transitivity across comparisons

In order to assess the transitivity across graft materials, the distribution of the following potential effect modifiers was evaluated: age, sex, and type of core biopsy (crestal or lateral core biopsy).

Methods for direct treatment comparisons

A traditional pairwise meta-analysis (PMA) of all possible direct comparisons was also undertaken[23]. A random-effects model was chosen, using the software Comprehensive Meta-Analysis version 2 (Biostat, Inc., Englewood, NJ, USA).

Methods for mixed and network comparisons

The comparisons were performed through the tool ''Network meta-analysis'' in Stata Statistical Software Release 14, 2011 (StataCorp., College Station, TX, USA)[24,25]. The ''mvmeta'' command was used (White, 2012)[26], together with self-programmed Stata routines (available at http://www.mtm.uoi.gr).

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity: In the traditional PMA, distinct heterogeneity variances were assessed for any pairwise comparison. Conversely, a single, common estimate of the heterogeneity variance across all individual comparisons was assumed in the NMA[27].

Assessment of statistical inconsistency

Local approaches for assessing inconsistency: The loop-specific approach was used to assess the presence of inconsistency locally in each closed loop of the network. The difference between direct and indirect estimates was assessed for any specific comparison in the loop (inconsistency factor). Hence, the size of the inconsistency factors and the 95% CI were used to estimate the inconsistency at the level of each loop. Moreover, a common heterogeneity estimate was assumed within each loop[28]. A forest plot was created with the ''ifplot'' command in Stata to summarize the results of this approach.

Global approaches for evaluating inconsistency: To verify the assumption of consistency in the overall network, the 'design-by treatment' model with the ''mvmeta'' command in Stata was used, as described by Higgins et al.[28–30].

Relative treatment ranking

The ranking probabilities were estimated for all of the grafting materials at each possible rank associated with any material. Then, the hierarchy of grafting materials was calculated using the 'surface under the cumulative ranking' (SUCRA) curve, as well as the mean ranks[31]. The SUCRA may also be evaluated as the probability of a given treatment to be ranked first without uncertainty. The rank-heat plot was done to visualize and show the grafting material hierarchy across the multiple outcomes of interest[32].

Subgroup and meta-regression analysis

This was done in order to identify the possible sources of inconsistency. All biopsies were divided according to the duration of the healing period into the following subgroups: (1) <6 months, and (2) ≥6 months. Hence, subgroup analysis based on the healing time was undertaken for all outcomes.

In order to investigate whether the healing time had an effect on NBF, meta-regression analysis was done considering the overall mean percentage of NBF (for 52 RCTs) and the healing times at which core biopsies were harvested for all of the studies. Additionally, meta-regression analysis was done based on subgroup analysis for those groups that included a larger number of RCTs for the outcome of NBF.

Sensitivity analysis

In order to make certain that the assumptions made in the analysis do not represent a bias for the NMA outcomes, and to ensure that a sufficient number of studies was found, the NMA was repeated after the exclusion of (1) studies in which fewer than 10 core biopsies were analyzed; (2) groups consisting of fewer than five studies, namely allografts combined with xenografts (only one RCT) and xenografts combined with alloplastic grafts (three RCTs); and (3) studies with a high risk of bias.

Assessment of publication bias

In order to assess the network-wide publication bias and the effect of small-sized studies for outcomes with at least 10 studies in the network, a comparison-adjusted funnel plot was constructed[33]. Grafting materials were ordered chronologically from the oldest to the newest studies[34].

Results

Study selection

Fig. 1 shows a flow diagram of the article screening process for inclusion in the review and in the NMA. The electronic search strategy yielded a total of 350 studies from all databases. Fifteen additional studies were identified from other sources (hand-search). Of the 365 articles, 102 were duplicates and were removed. Based on the titles and abstracts, a further 100 articles were excluded. The full-text articles of the remaining 163 eligible studies were evaluated by two reviewers (N.A. and B.A.) for inclusion. After full-text analysis, 111 studies were excluded because they did not meet the inclusion criteria. Finally, a total of 52 RCTs met the inclusion criteria and were submitted to review[35–86].

Presentation of network geometry

A network diagram of all eligible comparisons for the primary outcome is presented in Fig. 2. Eleven interventions were in-

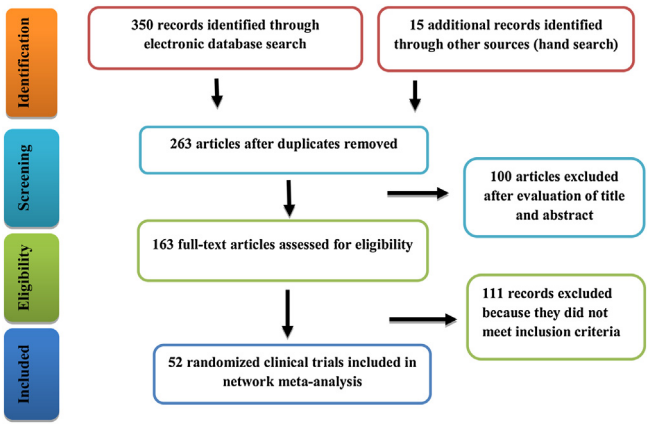

Fig. 1. PRISMA flow diagram of the screening and selection process. Q1

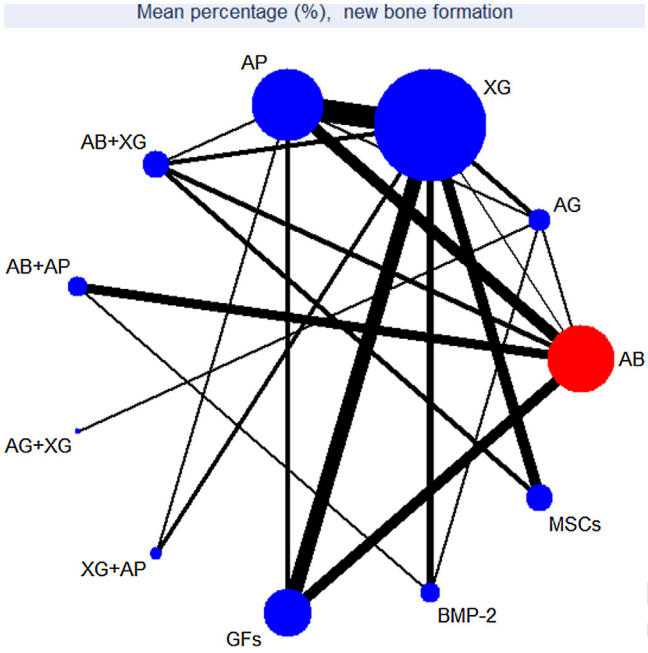

Fig. 2. Network geometry for the outcome 'new bone formation'.

cluded in the network diagram (AB, AG, XG, AP, AB + XG, AB + AP, AG + XG, XG + AP, GFs, BMP-2, and MSCs). Ten comparisons between the different bone grafting materials and AB were considered.

Summary of network geometry

For the outcome of overall NBF, the total sample consisted of 1483 biopsies in 52 RCTs on MSA[35–86]. The grafting materials were AB alone ($n = 16$ trials; 215 biopsies)[37,39,41,43,44,52,54,58,65,68,71,73,76,80,81,83], AG alone ($n = 6$ trials; 78 biopsies)[47,49,57,73,74,83], XG alone ($n = 27$ trials; 365 biopsies)[36,38,42,43,45,46,48–51,53,55,56,59,60,62–64,66,67,73,75,77–79,82,85], AP alone ($n = 19$ trials, 263 biopsies)[35,38,40,42,44,48,51,57,59–61,67,73,75–77,80,84,86], AB + XG ($n = 7$ trials, 113 biopsies)[36,39,52,66,69,70,86], AB + AP ($n = 4$ trials, 51 biopsies)[58,65,72,81], AG + XG ($n = 1$ trial, 17 biopsies)[74], XG + AP ($n = 3$ trials, 40 biopsies)[35,45,46], GFs ($n = 12$ trials, 145 biopsies)[37,40,41,50,54,61,62,68,71,78,79,85], BMP-2 ($n = 5$ trials, 116 biopsies)[47,53,55,56,72], and MSCs ($n = 5$ trials, 80 biopsies)[63,64,69,70,82]. AB alone was used as the comparator arm.

Study characteristics

The characteristics of the RCTs, patients, and biomaterials are summarized in Table 1.

Risk of bias within included studies

Twenty RCTs had a low risk of bias, 28 RCTs had an unclear risk of bias, and four RCTs showed a high risk of bias. More details are shown in Supplementary Material File 3.

Results of individual studies

A summary of individual data for all outcomes of interest (NBF, RG, and CT), including mean percentages, standard deviations, and the number of core biopsies for all groups, is presented in Supplementary Material File 4.

Synthesis of results

New bone formation (NBF)

With regard to the overall mean percentage of NBF (over a duration of 3–15 months), a total of 1483 core biopsies in 52 RCTs consisting of 11 groups were included[35–86]. There was a statistically significant difference between AP and AB (WMD = −8.04%, 95% CI − 12.11 to −3.97) and between XG and AB (WMD = −4.49%, 95% CI − 8.91% to 0.08%), in favour of AB (Fig. 3).

For the mean percentage NBF with a healing time <6 months (range 3–5 months), a total of 645 biopsies in 19 RCTs consisting of 10 groups were included[35,37,39,45,46,50,55,56,58,64,66,68–73,81,82]. NBF was significantly higher in AB compared to AP alone (WMD = −10.66%, 95% CI − 16.38% to −4.94%) and XG alone (WMD = −7.93%, 95% CI − 15.11% to −0.75%).

There was no statistically significant difference between AB alone and AB + AP (WMD = 0.42%, 95% CI − 5.41% to 6.24%), AG alone (WMD = −7.93%, 95% CI − 17.39% to 1.53%), MSCs (WMD = −8.17%, 95% CI − 16.38% to 0.04%), AB + XG (WMD = −7.62%, 95% CI − 15.35% to 0.10%), BMP-2 (WMD = −1.48%, 95% CI − 9.78% to 6.81%), XG + AP (WMD − 3.05%, 95% CI − 11.24% to 5.13%), or GFs (WMD = 1.69%, 95% CI − 3.38% to 6.76%) (Fig. 4).

Sensitivity analysis based on subgroup analysis showed no significant increase in the amount of NBF at augmented sites when GFs were added to AB. However, there was a significant increase in NBF when using GFs in conjunction with XG ($P = 0.001$). These findings were derived from seven direct RCTs[50,61,62,70,78,79,85].

For the mean percentage NBF with a healing time of ≥6 months, a total of 872 biopsies were included in 37 RCTs consisting of 10 groups. These RCTs compared different bone grafting materials and investigated the amount of new bone after at least 6 months following MSA[36,38,40–44,47–54,57,59–65,67,74–86]. There was statistically significant superiority of AB with respect to AP alone (WMD = −7.06%, 95% CI − 12.59% to −1.52%). There was no significant difference between AB and all other groups (Fig. 5). Q16

Residual graft particles (RG)

With regard to the overall mean percentage RG (over a duration of 3–15 months), a total of 1159 biopsies in 38 RCTs consisting of 11 groups were included[35,36,40,42,44–53,55–57,59–64,66,67,69,70,72–76,81–86]. There was a statistically significant difference between AB and XG (WMD = 9.62%, 95% CI 0.40% to 18.84%), but not with respect to the other groups (Fig. 6).

For the mean percentage RG with a healing time of <6 months (range 3–5 months), a total of 509 biopsies in 15 RCTs involving 10 groups were included[35,36,45–47,55,56,64,66,69,70,72,73,81,82]. There was no statistically significant difference between AB and any of the other nine groups (Fig. 7).

For the mean percentage RG with a healing time of ≥6 months, a total of 616 biopsies in 27 RCTs involving 10 groups were included[40,42,44,47–53,57,59–64,67,74–76,81–86]. There was a statistically

YJOM 4196 1–20

Q6 *Table 1.* Characteristics of all included studies, including patients and biomaterials.

Author	Study design	Age (years) M/F ratio	Number of sinuses/ patients	Type of biopsy	Biomaterials	Membrane	Implant placement	Healing time (months)	Residual bone height	Assessed outcomes
Ahmet et al., 2016[35]	RCT	(53.8) 10/6	G4: 15	Crestal bone core biopsy	G4: biphasic calcium sulphate + alloplastic Histomorphometric + volumetric	Resorbable collagen barrier membrane	Delayed	5	<5 mm	
			G7: 12		G7: biphasic calcium sulphate + deproteinized bovine bone					
Alayan et al., 2016[36]	RCT	(57.70) 0.43	G5: 20	Crestal bone core biopsy	G5: anorganic bovine bone + autogenous bone	Porcine collagen membrane	Delayed	5	≤5 mm and ≥1 mm	Histomorphometric
		(54.60) 0.33	G3: 20		G3: collagen-stabilized anorganic bovine bone					
Badr et al., 2016[37]	RCT	(36) 8/14	G1: 9	Crestal bone core	G1: autogenous	No	Delayed	3–4	NM	Histomorphometric
			G9: 13		G9: autologous bone + PRP					
Rodriguez y Baena et al., 2017[38]	RCT	(56 ± 13) NM	G4: 4	Crestal bone core biopsy	G4: poly(lactic-co-glycolic acid/ hydroxyapatite)	Collagen membrane	Delayed	6	<4 mm	Histomorphometric
			G3: 6		G3: deproteinized bovine bone					
Barone et al., 2005[39]	RCT	(46.7) 6/12	G1: 18	Lateral bone core biopsy	G1: autogenous	Collagen membrane	Delayed	6	<3 mm	Histomorphometric
			G5: 19		G5: autogenous bone and corticocancellous pig bone					
Comert Kiliç et al., 2017[40]	RCT	(31.51 ± 8.52)	G4: 9	Bone core biopsy	G4: β-TCP	Resorbable collagen membrane	Delayed	6	<7 mm	Histomorphometric
		(34.01 ± 9.59) 17/9	G8: 9		G8: β-TCP + PRP					
Consolo et al., 2007[41]	RCT	(NM) 5/11	G1: 16	Crestal bone core	G1: autologous bone	NM	Delayed	6–8	NM	Histomorphometric
			G8: 16		G8: autologous bone + PRP			6–8		
Cordaro et al., 2008[42]	RCT	(18–70) NM	G4: 14	Crestal bone core biopsy	G4: Straumann Bone Ceramic	Collagen membrane	Delayed	180–240 days	≥3 mm and <8 mm	Histomorphometric
			G3: 18		G3: anorganic bovine bone					
Correia et al., 2014[43]	RCT	(42–64) NM	G1: 6	Bone core biopsy	G1: autogenous	Collagen membrane	Delayed	6	2–4.6 mm	Histomorphometric
			G3: 6		G3: xenograft					
Danesh-Sani et al., 2016[44]	RCT - split-mouth	(25–72) NM	G1: 10	Lateral bone core	G1: autogenous	Resorbable collagen membrane, in case of perforation	Delayed	6–8	<5 mm	Histomorphometric
			G4: 10		G4: BCP (60% hydroxyapatite and 40% β-TCP)					

Dogan et al., 2017[45]	RCT	(33–69) 5/8	G3: 13 G8: 13	Bone core biopsy	G3: collagenated heterologous bone graft G8: hyaluronic matrix and collagenated heterologous bone graft	Collagen membrane	Delayed	4	≤4 mm	Histomorphometric
Dursun et al., 2016[46]	RCT	(45.06 ± 14.5) 8/7	G3: 15 G7: 15	Crestal bone core biopsy	G3: xenograft Histomorphometric + volumetric G7: xenograft + porous titanium granules	Resorbable collagen membrane	Delayed	8.4	NM	
Froum et al., 2006[49]	RCT	(59) NM	G2: 10 G3: 9	Lateral core biopsy	G2: mineralized cancellous bone allograft G3: anorganic bovine bone	Synthetic bioabsorbable collagen membrane	Delayed	26–32 weeks	<5 mm	Histomorphometric
Froum et al., 2008[48]	RCT - pilot study	(NM) NM	G3:11 G4:10	Lateral bone core biopsy	G3: xenografts G4: alloplast	Resorbable collagen membrane, in case of perforation	Delayed	6–8	<5 mm	Histomorphometric
Froum et al., 2013[47]	RCT	(NM) NM	G2: 11 G10: 10	Lateral bone core biopsy	G2: allograft G10: bone grafts + bioactive protein	Resorbable collagen membrane, in case of perforation	Delayed	6–9	4–5 mm	Histomorphometric
Froum et al., 2013[50]	RCT	(61.2) 14/10	G3: 12 G9: 12	Lateral bone core biopsy	G3: xenograft G9: xenograft with PDGF	Resorbable collagen membrane	Delayed	4–5 7–9	4–5 mm	Histomorphometric
Garlini et al., 2014[51]	RCT	(57) 2/3	G3: 5 G4: 5	Lateral bone core	G3: Bio-Oss G4: Algipore	Resorbable membrane (Bio-Gide)	Delayed	6–8	<5 mm	Histomorphometric
Hallman et al., 2002[52]	RCT	(54) 7/14	G1: 11 G5: 11	Lateral micro-implants with the surrounding bone	G1: autogenous G5: autogenous + xenograft	Resorbable collagen membrane, in one group	Delayed	12–15	<5 mm	Histomorphometric
Kao et al., 2012[53]	RCT	(50.8) 13/9	G9: 10 G3: 10	Lateral bone core	G9: Bio-Oss + rhBMP-2/ACS G3: Bio-Oss	NM	Not clear It seems to be immediate	6	<5 mm	Histomorphometric
Khairy et al., 2013[54]	RCT	(38) NM	G1: 5 G8: 5	Bone core	G1: autologous bone G8: autologous bone + PRP	Resorbable collagen membrane	Delayed	6 4 and 6	≤5 mm	Histomorphometric
Kim et al., 2015[56]	RCT	(52.37) 22/19	G3: 20 G10: 21	Crestal bone core	G3: xenografts G10: rhBMP-2 + microporous BCP	Resorbable collagen membrane, in case of perforation	Delayed	6	<3 mm	Histomorphometric and volumetric

Please cite this article in press as: Al-Moraissi EA, et al. Do osteoconductive bone substitutes result in similar bone regeneration for maxillary sinus augmentation . . . , *Int J Oral Maxillofac Surg* (2019), https://doi.org/10.1016/j.ijom.2019.05.004

YIJOM 4196 1–20

Table 1 (*Continued*)

Author	Study design	Age (years) M/F ratio	Number of sinuses/ patients	Type of biopsy	Biomaterials	Membrane	Implant placement	Healing time (months)	Residual bone height	Assessed outcomes
Kim et al., 2015[55]	RCT	G3: (53.91)	G3:62	Lateral bone core	G3: xenografts	NM	Delayed	3	NM	Histomorphometric and volumetric
		G10: (53.15) 93/34	G10: 65		G10: rhBMP-2 + hydroxyapatite					
Kolerman et al., 2017[57]	RCT	(58) 6/7	G4: 13	Crestal bone core biopsy	G4: BCP	Bioabsorbable porcine collagen barrier membrane	Delayed	9	<5 mm	Histomorphometric
			G2: 13		G2: freeze-dried bone allograft					
Kühl et al., 2013[58]	RCT	(54) 17/13	G1: 6	Trephine bone core biopsy	G1: autogenous	No	Delayed	5	NM	Volumetric
			G6: 8		G6: autogenous + alloplast					
Kurkcu et al., 2012[59]	RCT	(48.65) 12/11	G3: 13	Crestal bone core biopsy	G3: xenograft	No	Delayed	Average of 6.5	<5 mm	Histomorphometric
			G4: 10		G4: alloplast					
Lindgren et al., 2012[60]	RCT	(67) NM	G3: 5	Crestal bone core with micro-implants	G3: deproteinized bovine bone	Resorbable collagen membrane	Delayed	36	<5 mm	Histomorphometric
			G4: 5		G4: BCP					
Meimandi et al., 2017[61]	RCT - split-mouth	(30–60) 4/6	G4: 10	Crestal bone core biopsy	G4: alloplast	Resorbable collagen membrane	Delayed	6	2–4 mm	Histomorphometric
			G9: 10		G9: bone grafts + growth factors					
Nizam et al., 2018[62]	RCT	(49.92 ± 10.37) 9/4	G8: 13	Crestal bone core biopsy	G8: deproteinized bovine bone + leukocyte and PRF Histomorphometric + volumetric	Resorbable membrane (Bio-Gide)	Delayed	6	<5 mm	
			G3: 13		G3: deproteinized bovine bone					
Pasquali et al., 2015[63]	RCT	(55.4 ± 9.2) NM	G3: 8	Crestal bone core	G3: Bio-Oss	Collagen membrane	Delayed	6	≤4 mm	Histomorphometric
			G10: 8		G10: Bio-Oss + bone marrow aspirate concentrate					
Payer et al., 2014[64]	RCT	(58.2) 3/3	G10: 6	Crestal bone core	G10: Bio-Oss + autotransplanted tibial bone marrow aspirates	Collagen membrane	Delayed	3–6	<3 mm	Histomorphometric
			G3: 6		G3: Bio-Oss					
Pereira et al., 2017[65]	RCT	(NM) NM	G1: 10	Crestal bone core biopsy	G1: autogenous	No	Delayed	6	<5 mm	Histomorphometric
			G6: 10		G6: autogenous + alloplast					
Pikdöken et al., 2011[66]	RCT	G3: (59.83) G5: (57.92) 15/9	G3: 12 G5:12	Lateral bone core biopsy	G3: xenografts G5: autogenous xenograft	Resorbable collagen membrane	Delayed	4	<5 mm	Histomorphometric

Portelli et al., 2017[67]	RCT	(56) NM	G3: 6 G4: 4	Crestal bone core biopsy	G3: xenografts G4: alloplast	Resorbable collagen membrane	Delayed	274 days 293 days	4–5 mm	Histomorphometric
Raghoebar et al., 2005[68]	RCT	(58.4 ± 1.9) 2/3	G1: 5 G8: 5	Crestal bone core	G1: autogenous G8: autogenous + PRP	No	Delayed	3	<5 mm	Histomorphometric
Rickert et al., 2011[69]	RCT	(60.8 ± 5.9) NM	G5: 11 G10: 12	Crestal bone core	G5: bovine bone mineral + autogenous bone G10: bovine bone mineral + autogenous stem cells	Collagen membrane	Delayed	13–16 weeks	1–3 mm	Histomorphometric
Sauerbier et al., 2011[70]	RCT	(56.6) 8/18	G5: 11 G11: 34	Trephine bone core biopsy	G5: autogenous + xenograft G11: bone grafts + mesenchymal cells	Resorbable collagen membrane	Delayed	3–4 (mean 3.46 ± 0.43)	2–3 mm	Histomorphometric and volumetric
Schaaf et al., 2008[71]	RCT	(NM) NM	G1: 34 G9: 34	Bone core	G1: autologous bone G9: autologous bone + PRP	NM	Delayed	4	NM	Histomorphometric
Stavropoulos et al., 2011[72]	RCT	(53.8) 15/15	G6: 10 G10: 10	Crestal bone core biopsy	G6: autogenous + alloplast G10: bone grafts + growth factors	Resorbable collagen membrane, in case of perforation	Delayed	3 4	<5 mm	Histomorphometric
Schmitt et al., 2013[73]	RCT	(38–79) 13/17	G1: 12 G2: 12 G3: 12 G4: 14	Crestal bone core biopsy	G1: autologous bone G2: mineralized cancellous bone allograft G3: anorganic bovine bone G4: BCP	Collagen membrane	Delayed	5	≤4 mm	Histomorphometric
Sehn et al., 2015[74]	RCT	(51.32 ± 6.44) 8/21	G2: 17 G7: 17	Lateral bone core	G2: fresh-frozen bone allograft G7: bovine bone mineral + fresh-frozen bone allograft	Resorbable collagen membranes	Delayed	6	≤5 mm	Histomorphometric
Stacchi et al., 2017[75]	RCT	(60.1 ± 10.7) 18/10	G4: 26 G3: 26	Crestal bone core biopsy	G4: nanohydroxyapatite G3: anorganic bovine bone	Resorbable bovine collagen membrane	Delayed	6	0.5–3 mm	Histomorphometric
Szabo et al., 2005[76]	RCT	(52) 9/11	G1: 20 G4: 20	Crestal bone core biopsy	G1: autogenous G4: alloplast	No	Delayed	6	<5 mm	Histomorphometric and volumetric
Taschieri, et al., 2015[77]	RCT - split-mouth	NM 4/1	G3: 10 G4: 10	Lateral bone core	G3: xenografts G4: alloplastic	No	Delayed	6	<4 mm	Histomorphometric
Taschieri et al., 2018[78]	RCT	(49–69) 8/12	G3: 5 G8: 5	Bone core	G3: deproteinized bovine bone G8: BCP + PRP	NM	Delayed	6	<4 mm	Histomorphometric

Please cite this article in press as: Al-Moraissi EA, et al. Do osteoconductive bone substitutes result in similar bone regeneration for maxillary sinus augmentation . . . , *Int J Oral Maxillofac Surg* (2019), https://doi.org/10.1016/j.ijom.2019.05.004

YIJOM 4196 1–20

Table 1 (*Continued*)

Author	Study design	Age (years) M/F ratio	Number of sinuses/ patients	Type of biopsy	Biomaterials	Membrane	Implant placement	Healing time (months)	Residual bone height	Assessed outcomes
Torres et al., 2009[79]	RCT	(NM) 40/47	G3: 5	Crestal bone core	G3: anorganic bovine bone	NM	Delayed	6	<7 mm	Histomorphometric
			G8: 5		G8: anorganic bovine bone + PRP					
Tosta et al., 2013[80]	RCT	(18–70) NM	G4: 15	Crestal bone core	G4: BCP	Resorbable collagen membranes	Delayed	9	3 and 6 mm	Histomorphometric
			G1: 15		G1: autogenous					
Turunen et al., 2004[81]	RCT	(50) 1/16	G6: 17	Crestal bone core	G6: bioactive glass + autologous bone	NM	Delayed	21–34 weeks and at 49–62 weeks	NM	Histomorphometric
			G1: 14		G1: autologous bone					
Wagner et al., 2012[86]	RCT/ RCT - split-mouth	(52.5) 61/24	G4: 64	Crestal bone core	G4: alloplastic	No	Delayed	6	NM	Histomorphometric
			G5: 29		G5: autogenous + xenograft					
Wildburger et al., 2014[82]	RCT	(58) NM	G10: 7	Crestal bone core	G10: bovine bone + mesenchymal stem cells	Collagen membrane	Delayed	3	<3 mm	Histomorphometric
			G3: 7		G3: bovine bone			6 3 6		
Xavier et al., 2015[83]	RCT	(54) 8/7	G1: 15	Lateral bone core biopsy	G1: autogenous bone	Resorbable Bio-Gide collagen membrane	Delayed	6	≤3 mm	Histomorphometric
			G2: 15		G2: fresh frozen allograft					
Zerbo et al., 2004[84]	Non RCT	(52) 6/3	G4: 9	Crestal and lateral bone core	G4: tricalcium phosphate	No	Delayed	6	<4 mm	Histomorphometric
			G1: 5		G1: autologous bone					
Zhang et al., 2012[85]	RCT	G3: (43.5)	G3: 5	Crestal bone core biopsy	G3: xenografts	Resorbable collagen membrane	Delayed	6	<5 mm	Histomorphometric
		G9: (46.2) 8/2	G9: 6		G9: bone grafts + growth factors					

ACS, absorbable collagen sponge; BCP, biphasic calcium phosphate; β-TCP, beta tricalcium phosphate; F, female; G1, autogenous bone grafts alone; G2, allografts alone; G3, xenografts alone; G4, alloplastic alone; G5, autogenous with allograft; G6, autogenous with xenograft; G7, autogenous with alloplastic; G8, allografts with xenografts; G9, bone grafts plus growth factors; G10, rhBMP-2; G11, bone grafts plus mesenchymal stem cells; M, male; NM, not mentioned; PDGF, platelet-derived growth factor; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; RCT, randomized controlled trial; rhBMP-2, recombinant human bone morphogenetic protein 2.

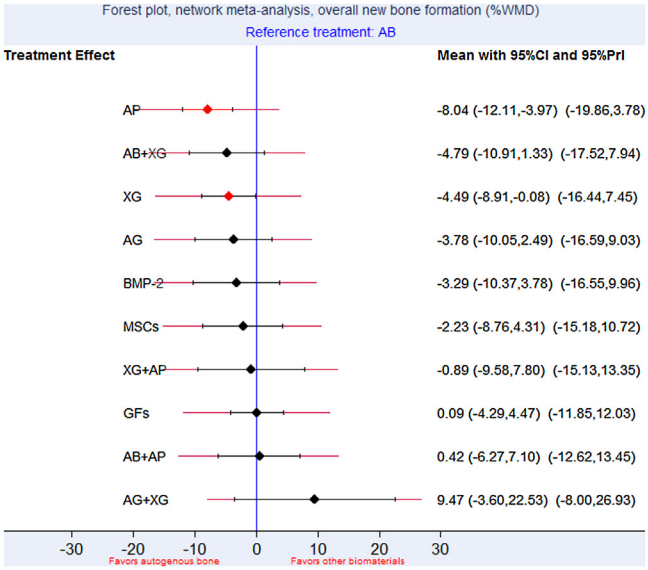

Fig. 3. Forest plot of the network meta-analysis for overall new bone formation (NBF): percentage weighted mean difference (WMD) with 95% confidence interval (CI) and 95% predictive interval (PrI).

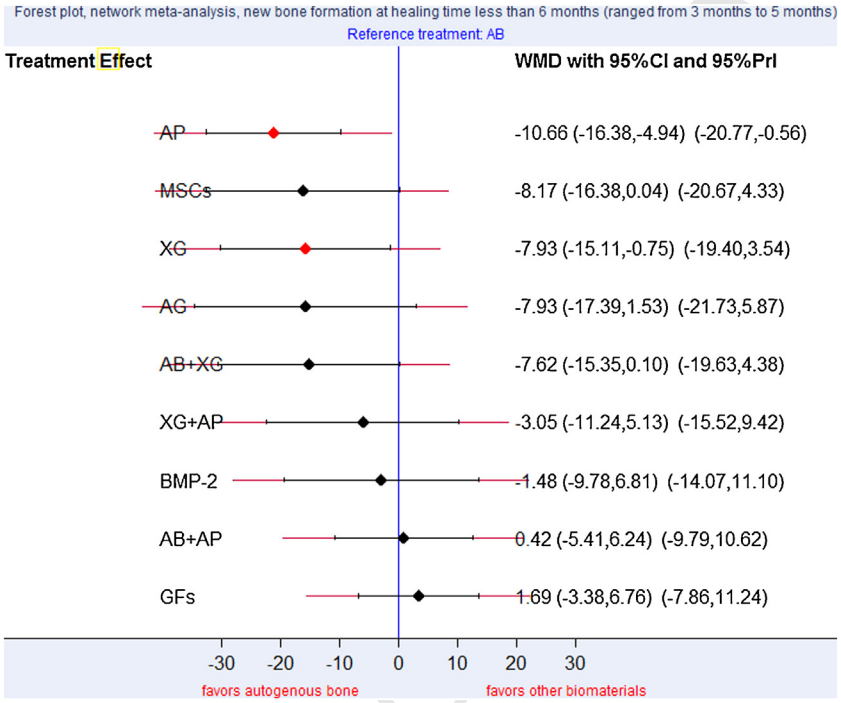

Fig. 4. Forest plot of the network meta-analysis for new bone formation (NBF) at a healing time of <6 months (range 3–5 months): percentage weighted mean difference (WMD) with 95% confidence interval (CI) and 95% predictive interval (PrI).

significant difference between AB alone and AP alone (WMD = 12.03%, 95% CI 3.04% to 21.03%), XG alone (WMD = 14.62%, 95% CI 4.25% to 24.98%), and GFs (WMD = 12.32%, 95% CI 0.04% to 24.60%). There was no statistically significant difference between AB alone and the other groups (Fig. 8).

Connective/soft tissues (CT)

With regard to the overall mean percentage (%) CT (over a duration of 3–9 months), a total of 1038 biopsies in 33 RCTs consisting of 11 groups were included[35,36,40,42–46,48–51,53,55–57,59,62–66,69,70,72–75,80,82,83,85,86].

There was a statistically significant difference between AB alone and the following: XG + AP (WMD = −14.62%, 95% CI − 27.37% to −1.87%), AP (WMD = −12.22%, 95% CI − 20.28% to −4.16%), MSCs (WMD = −12.05%, 95% CI − 22.84% to −1.26%), and XG (WMD = −11.06%, 95% CI − 19.05% to −3.08%).

There was no statistically significant difference in the amount of CT after MSA between AB alone and AB + XG (WMD = −10.71%, 95% CI − 21.51% to 0.09%), AB + AP (WMD = −1.46%, 95% CI − 17.28% to 14.35%), GFs (WMD = −8.39%, 95% CI − 19.52% to 2.73%), BMP-2 (WMD = 0.63%, 95% CI − 11.43% to 12.69%), AG alone (WMD = −1.60%, 95% CI − 11.67% to 8.47%), or AG + XG (WMD = 11.65%, 95% CI − 6.81% to 30.11%) (Fig. 9).

With regard to the mean percentage CT over a healing time of <6 months (range 3–5 months), a total of 474 biopsies in 14 RCTs involving 10 groups were included[35,36,45,46,50,55,56,64,66,69,70,72,73,82]. There was a statistically significant difference between AB alone and the following: XG + AP (WMD = −18.20%, 95% CI − 25.90% to −10.49%), AP (WMD = −17.35%, 95% CI − 32.32% to −2.37%), BMP-2 (WMD = −14.75%, 95% CI − 23.02% to −6.48%), GFs (WMD = −13.83%, 95% CI − 27.27% to −0.39%), MSCs (WMD = −11.42%, 95% CI − 19.81% to −3.02%), XG (WMD = −11.13%, 95% CI − 16.99% to −5.27%), and AB + XG (WMD = −9.54%, 95% CI − 16.88% to −2.21%). There was no statistically significant difference between AB + AP and AB alone (WMD = −16.35%, 95% CI − 40.63% to 7.93%) or between AG alone and AB alone (WMD = −7.91%, 95% CI − 23.73% to 7.92%) (Fig. 10).

For the mean percentage CT over a healing time of ≥6 months, a total of 564 biopsies in 22 RCTs involving 10 groups were included[40,42–44,48–51,53,57,59,62–65,74,75,80,82,83,85,86]. The CT% in the BMP-2 group was significantly lower than that in the AB alone group (WMD = 23.85%, 95% CI 6.42% to 41.27%). There was no significant difference between the AB alone group and all other groups (Fig. 11).

Exploration for inconsistency

Loop-specific tests did not detect any statistical inconsistency between direct and indirect evidence (local inconsistency). All confidence intervals for ratio of odds ratios (RoRs) were compatible, with zero inconsistency (RoR = 1) for all study out-

Please cite this article in press as: Al-Moraissi EA, et al. Do osteoconductive bone substitutes result in similar bone regeneration for maxillary sinus augmentation . . . , *Int J Oral Maxillofac Surg* (2019), https://doi.org/10.1016/j.ijom.2019.05.004

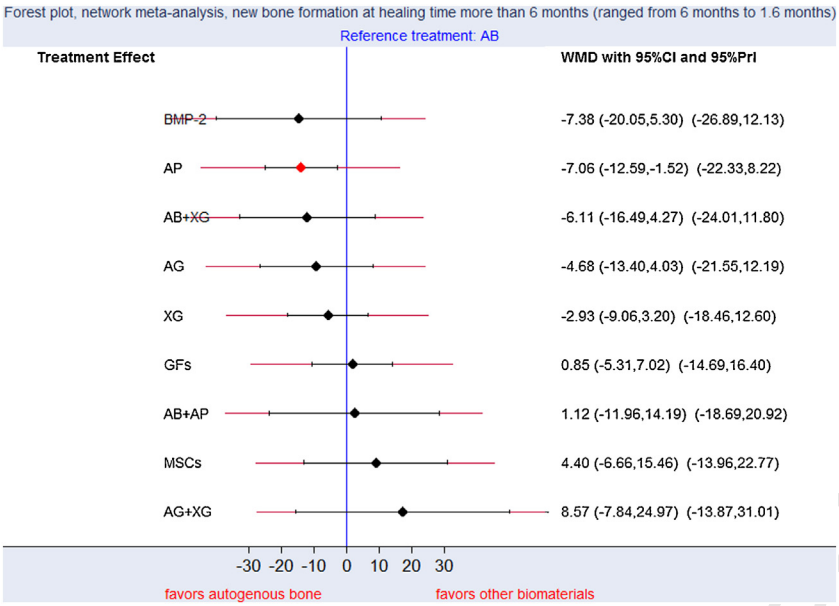

Fig. 5. Forest plot of the network meta-analysis for new bone formation (NBF) at a healing time of ≥6 months (range 6–15 months): percentage weighted mean difference (WMD) with 95% confidence interval (CI) and 95% predictive interval (PrI).

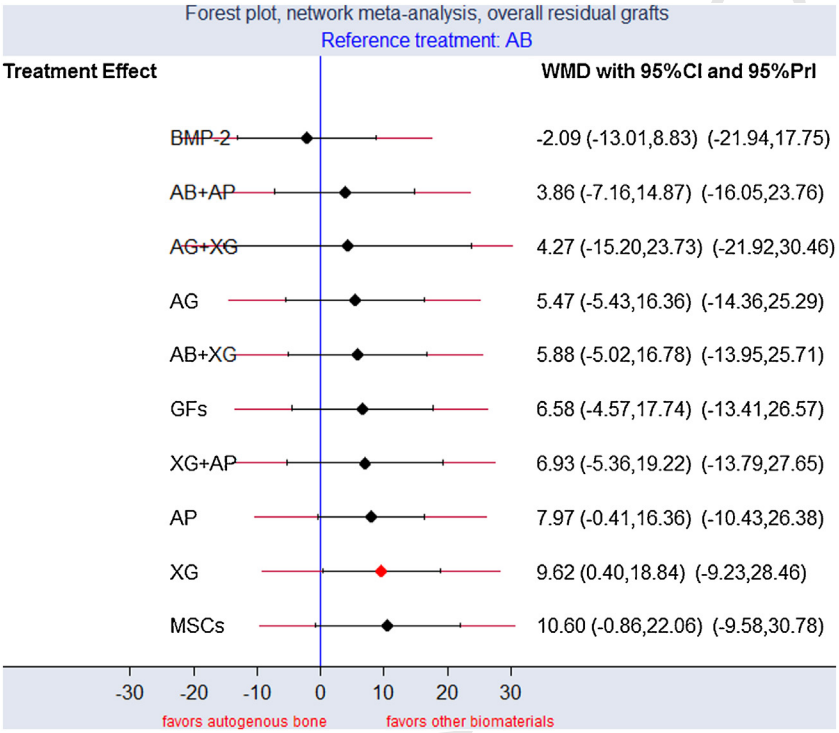

Fig. 6. Forest plot of the network meta-analysis for overall residual graft (RG) particles: percentage weighted mean difference (WMD) with 95% confidence interval (CI) and 95% predictive interval (PrI).

comes and subgroup analyses (Supplementary Material File 5).

Based on the design-by-treatment interaction model, no significant inconsistency between direct and indirect evidence was identified within the evidence network as a whole (global inconsistency) ($P > 0.05$).

Treatment ranking

NBF

According to the SUCRA ranking, the most effective bone grafting material that increased NBF after MSA at a healing time ranging from 3 months to 15 months was AG + XG (95%, very low quality evidence), followed by GFs (69.9%, low quality evidence), AB alone (69.8%, moderate quality evidence), AB + AP (68.3%, low quality evidence), XG + AP (59.1%, very low quality evidence), MSCs (50.8%, low quality evidence), BMP-2 (40.3%, low quality evidence), AG alone (35.9%, low quality evidence), XG alone (28.8%, moderate quality evidence), AB + XG (28.1%, low quality evidence), and AP alone (4.3%, moderate quality evidence) (Fig. 12; Supplementary Material File 6).

RG

According to the SUCRA ranking, the most effective bone grafting material that decreased RG after MSA at a healing time ranging from 3 months to 15 months was BMPs (88.8%, very low quality evidence), followed by AB alone (81.5%, moderate quality evidence), AB + AP (58.9%, very low quality evidence), AG + XG (55.9%, very low quality evidence), AG alone (51.2%, low quality evidence), AB + XG (50.1%, low quality evidence), GFs (45.1%, very low quality evidence), XG + AP (42.3%, very low quality evidence), AP alone (34.7%, moderate quality evidence), XG alone (22%, moderate quality evidence), and MSCs (19.8%, low quality evidence) (Fig. 12; Supplementary Material File 6).

CT

According to the SUCRA ranking, the most effective bone grafting material that decreased CT after MSA at a healing time ranging from 3 months to 9 months was XG + AP (84.7%, low quality evidence), followed by AP alone (77.7%, moderate quality evidence), MSCs (76.1%, low quality evidence), XG alone (71.1%, moderate quality evidence), AB + XG (68.6%, low quality evidence), GFs (56.8%, very low quality evidence), AB + AP (33.1%, low quality evidence), AG alone (30.1%, low quality evidence), AB alone (23.6%, low quality evidence), BMP-2 (23.1%, low quality evidence), and AG + XG (5.1%, very low quality evidence) (Fig. 12; Supplementary Material File 6).

According to the SUCRA ranking, the bone grafting materials with the highest probability of achieving the highest NBF %, the lowest RG%, and the lowest CT% up to 6 months after MSA were, respectively, AG + XG (95% probability), BMP-2 (88.8%), and XG + AP (84.7%) (Fig. 12; Supplementary Material File 6).

Please cite this article in press as: Al-Moraissi EA, et al. Do osteoconductive bone substitutes result in similar bone regeneration for maxillary sinus augmentation . . . , *Int J Oral Maxillofac Surg* (2019), https://doi.org/10.1016/j.ijom.2019.05.004

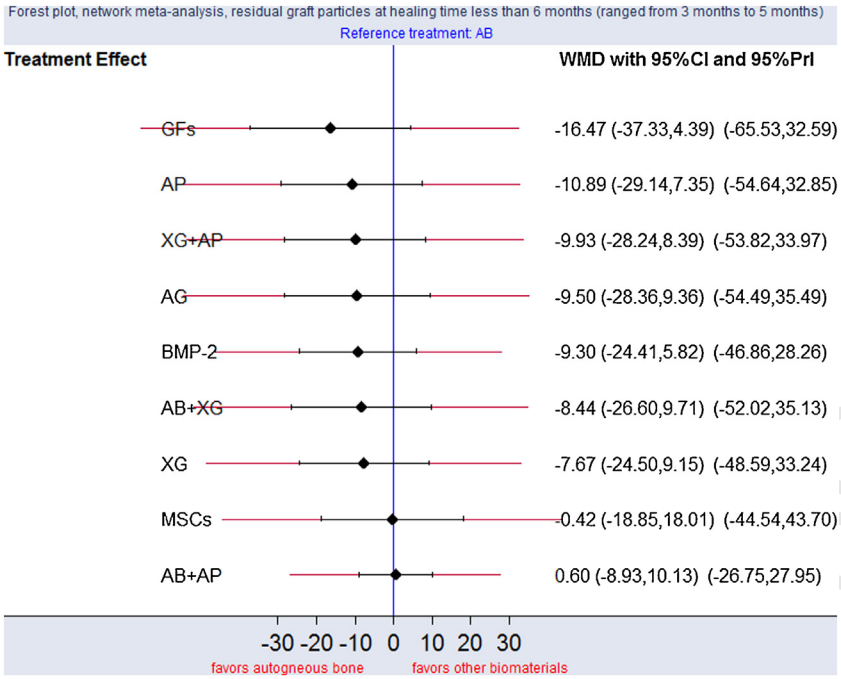

Fig. 7. Forest plot of the network meta-analysis for residual graft (RG) particles at a healing time of <6 months (range 3–5 months): percentage weighted mean difference (WMD) with 95% confidence interval (CI) and 95% predictive interval (PrI).

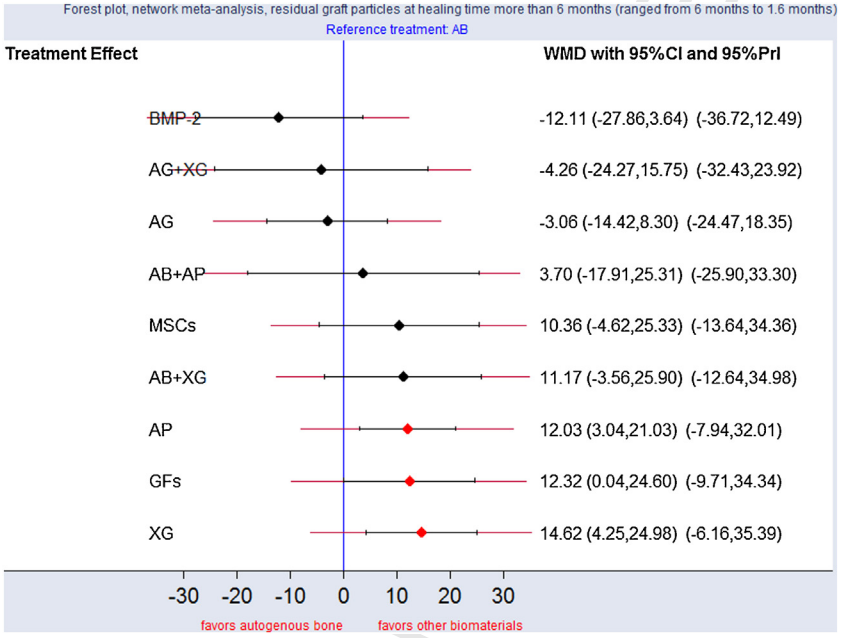

Fig. 8. Forest plot of the network meta-analysis for residual graft (RG) particles at a healing time of ≥6 months (range 6–15 months): percentage weighted mean difference (WMD) with
Q3 95% confidence interval (CI) and 95% predictive interval (PrI).

Meta-regression analysis

Meta-regression analysis showed that there was a negative and insignificant relationship between the overall mean percentage of NBF (52 RCTs) and healing time ($r = -0.35$, 95% CI − 1.2 to 0.54; $P = 0.342$). Meta-regression analysis based on subgroup analysis revealed that there was a negative and statistically insignificant association following AB ($r = -0.75$, 95% CI − 3.1 to 1.66; $P = 0.515$), AG ($r = -0.61$, 95% CI − 10.6 to 9.4; $P = 0.874$), and GFs ($r = -1.3$, 95% CI − 4.8 to 2.1; $P = 0.405$). However, there was a positive and statistically insignificant association following XG ($r = 0.031$, 95% CI − 2.2 to 2.2; $P = 0.977$), AP ($r = 0.91$, 95% CI − 2.6 to 4.4; $P = 0.590$), BMP-2 ($r = 0.64$, 95% CI − 3.9 to 5.2; $P = 0.689$), MSC ($r = 5.9$, 95% CI − 9.9 to 21.7; $P = 0.358$), and AG+XG ($r = 1.3$, 95% CI − 3.9 to 6.7; $P = 0.531$).

Confidence of evidence

For all outcomes (NBF, RG, and CT), the quality of evidence of NMA estimates for all comparisons ranged from moderate to very low. For various comparisons, the evidence was downgraded because of study limitations, imprecision, or incoherence. Overall confidence of evidence for outcomes of interest was as follows: moderate quality of evidence for NBF and low quality for outcomes of RG and CT. More details about quality of evidence for all outcomes based on the GRADE system are summarized in Supplementary Material File 7.

Funnel plot and publication bias

The funnel plot for the outcome of NBF is shown in Fig. 13. Scatters in the funnel plot were almost symmetrical, indicating the absence of a small size effect and publication bias.

Sensitivity analysis

After excluding studies consisting of fewer than 10 core biopsies, comparisons consisting of fewer than five RCTs (AG + XG, one RCT; XG + AP, three RCTs; AB + AP, four RCTs), and studies with a high risk of bias[36,40,44,50], the overall evidence did not change.

Discussion

There is still no consensus regarding the best grafting materials in dental implantology, particularly for the MSA procedure. NMA allows a comparison of the results of treatments from RCTs with both indirect and direct comparisons, in contrast to the traditional meta-analysis, which is only based on the latter. The purpose of the current NMA, based on RCTs on MSA, was to assess the difference in histomorphometric outcomes with the use of different bone grafting biomaterials. The alternative hypothesis of a better performance of AB as compared to other materials, regarding NBF, was confirmed only for a healing time shorter

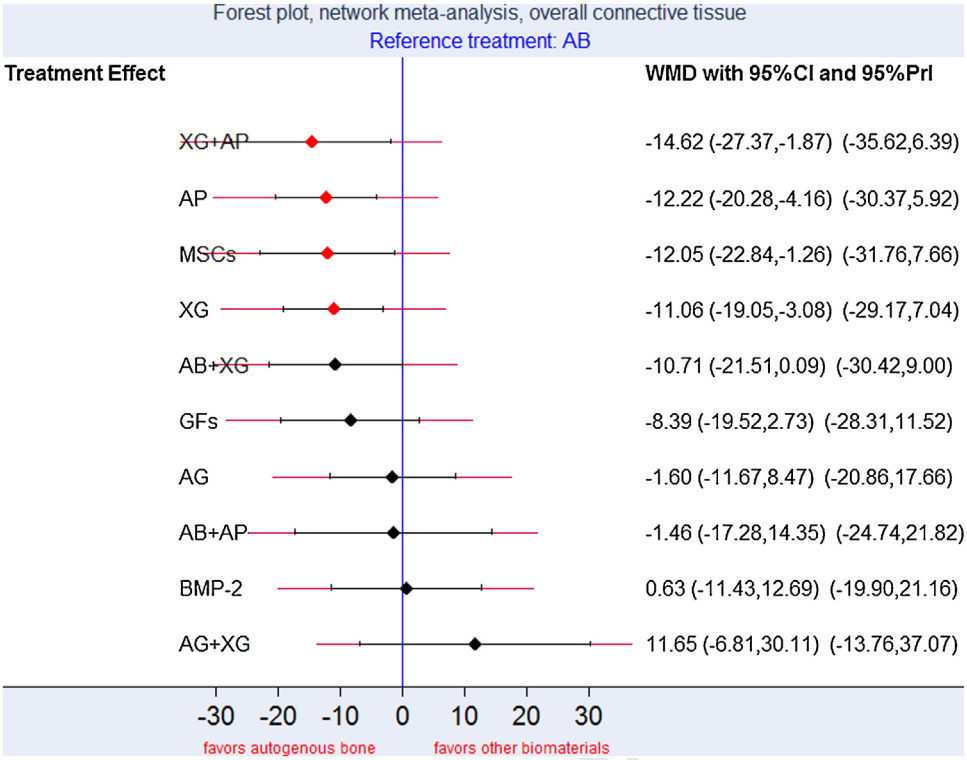

Fig. 9. Forest plot of the network meta-analysis for overall connective tissue (CT): percentage weighted mean difference (WMD) with 95% confidence interval (CI) and 95% predictive interval (PrI).

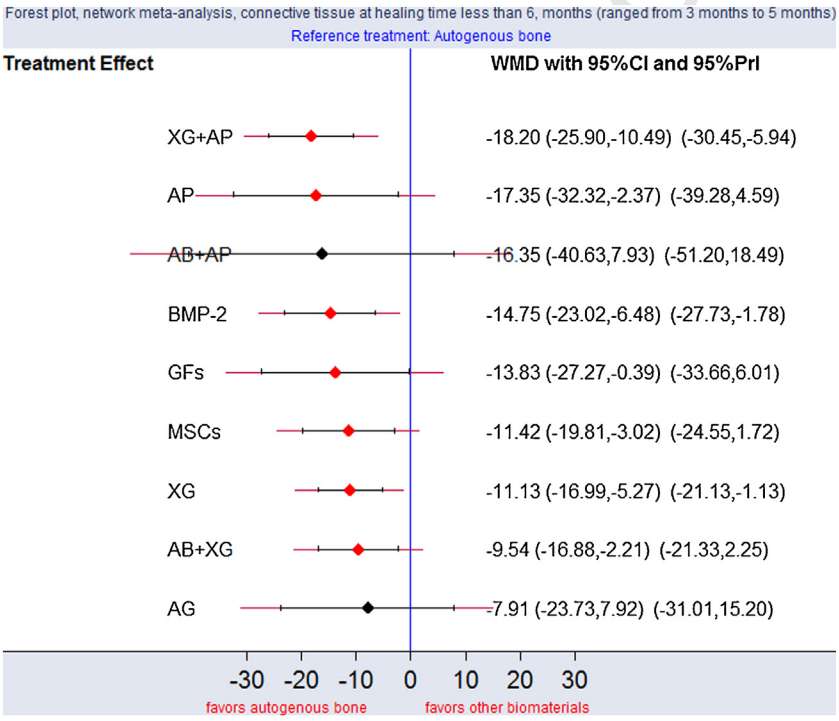

Fig. 10. Forest plot of the network meta-analysis for connective tissue (CT) at a healing time of <6 months (range 3–5 months): percentage weighted mean difference (WMD) with 95% confidence interval (CI) and 95% predictive interval (PrI).

than 6 months. For a healing time of 6 months or longer, the null hypothesis could generally be accepted for all histomorphometric parameters considered.

From the biological perspective of bone grafting materials, the present study revealed moderate quality evidence suggesting that the application of acellular osteoconductive scaffold bone grafts alone, such as XG or AP, resulted in the lowest NBF and highest RG and CT in MSA, when compared to osteogenic and/or osteoinductive bone grafts.

Autogenous bone vs. Allografts

When comparing each graft material to autogenous bone, some considerations can be made. For autogenous bone vs. allografts, the absence of a significant difference in NBF (moderate quality evidence) is compatible with some previous studies[59] and differs from others[58,72]. NMA showed no significant difference in RG% between AG and AB (low quality evidence), in agreement with other studies and indicating similar resorption rates for the two materials[5,83].

Please cite this article in press as: Al-Moraissi EA, et al. Do osteoconductive bone substitutes result in similar bone regeneration for maxillary sinus augmentation . . . , *Int J Oral Maxillofac Surg* (2019), https://doi.org/10.1016/j.ijom.2019.05.004

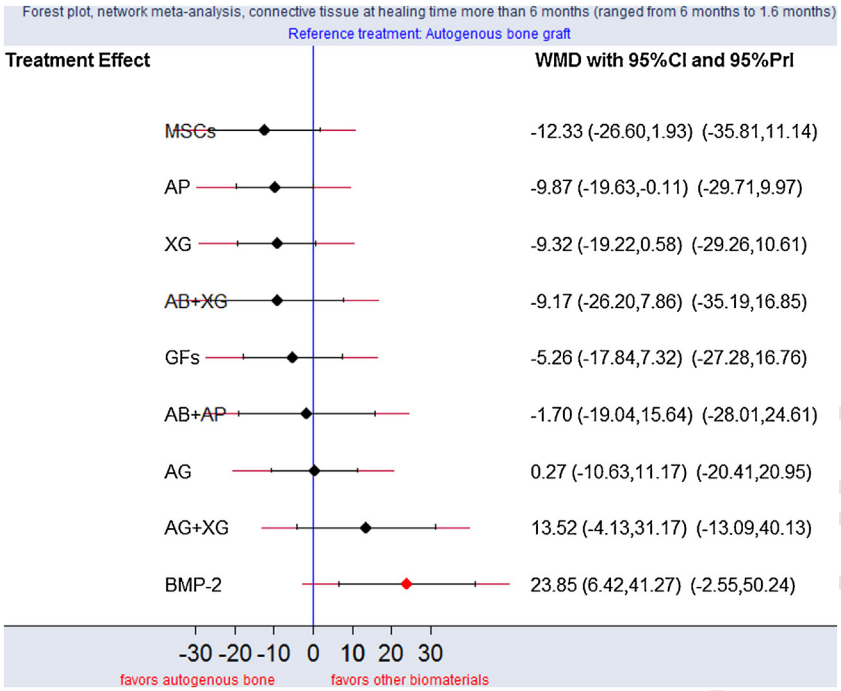

Fig. 11. Forest plot of the network meta-analysis for connective tissue (CT) at a healing time of ≥6 months (range 6–9 months): percentage weighted mean difference (WMD) with 95% confidence interval (CI) and 95% predictive interval (PrI).

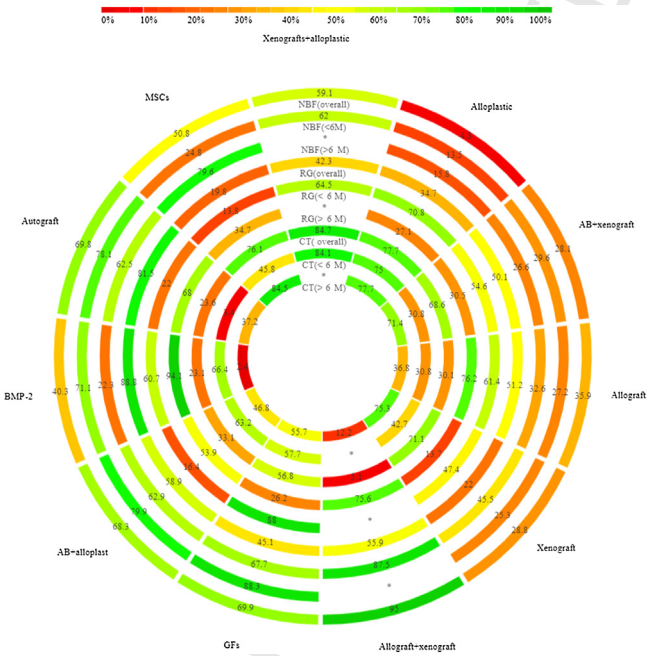

Fig. 12. Rank-heat plot identifying the hierarchy of multiple treatments for all outcomes, for the healing time overall and for subgroups of healing times.

Autogenous bone vs. Xenografts

Autogenous bone showed higher NBF than xenografts at a healing time <6 months[43,52,73]. However, when the healing time was ≥6 months, no statistically significant difference was found, in spite of a weak trend in favour of AB (moderate quality evidence). This would suggest that graft healing proceeds faster with AB, but with time the total NBF tends to be similar. Recently published systematic reviews with meta-analyses have reported a similar finding[5,10,73]. Notably, NMA showed that XG at different healing times resulted in a significantly greater RG% and lower CT% than AB alone, up to 6 months, indicating a slower resorption rate than for AB.

Autogenous bone vs. Alloplastic materials

The performance of AP biomaterials was found to be inferior to that of AB at any healing time (moderate quality evidence). Previous reports are in agreement with the present study[5,44,84]. AP biomaterials are the least effective biomaterial in terms of increasing NBF following MSA. It may be hypothesized that the very low NBF when using AP as compared to AB, at different healing times, depends on the higher resorption rate of AP. This has been suggested for combinations of hydroxyapatite with tricalcium phosphate, due to osteoclast recruitment induced by tricalcium phosphate[87].

Autogenous bone vs. Combination of AB with XG

Based on the results derived from PMA and NMA (low quality evidence), a combination of AB and XG has no benefits with regard to the amount of NBF when compared to AB alone. A recent study reported the same result[5]. Any reduction in NBF following the use of a mixture of AB and XG might be explained by the different proportions of XG or AB used, the different donor sites of AB used, and by a difference in bone resorption rate between AB and XG. Consequently, all of these factors could lead to a decrease in percentage of NBF. Similarly, the results of the present study showed no advantage in terms of NBF when AB is combined with AP as compared to AB alone, in contrast to the findings of another systematic review[5].

Autogenous bone vs. Combination of XG with AG

There were no RCTs directly comparing AB alone and the combination of XG and AG. Although the amount of NBF in the maxillary sinuses augmented using a mixture of XG and AG was higher than that for AB at the healing time of 6 months, the difference was not statistically significant (due to large variability and low sample size) and the quality of evidence was very low. This composite graft was ranked as the first (95%) biomaterial likely to increase NBF formation at 6 months, but

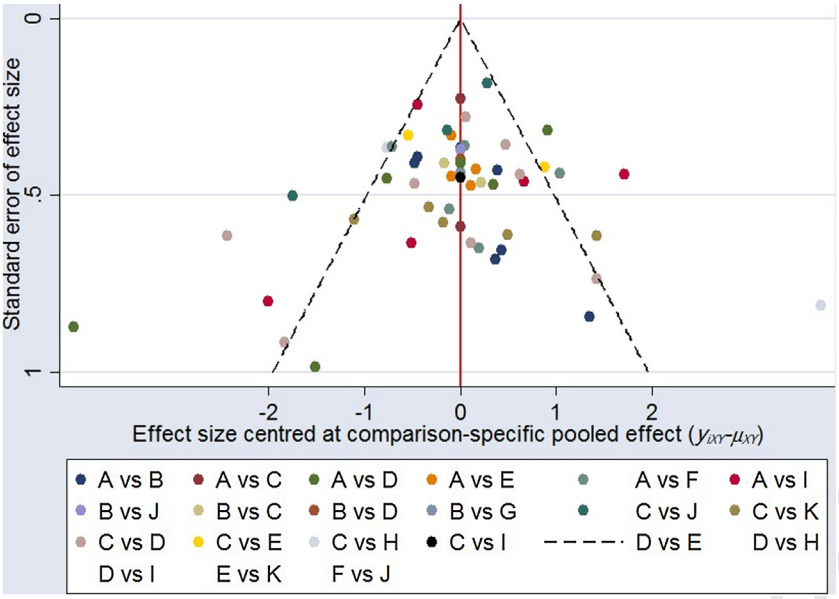

Fig. 13. Funnel plot for publications bias—new bone formation. A = autogenous bone, B = allografts, C = xenografts, D = alloplastic bone, E = AB + XG, F = AB + AP, G = AG + XG, I = XG + AP, J = grafts combined with autogenous platelet concentrates or recombinant growth factors (GFs), H = mesenchymal stem cells (MSCs), or K = recombinant bone morphogenetic protein 2 (BMP-2).

only one RCT was included in the NMA[74]. So, more RCTs are needed to assess histomorphometric outcomes using a mixture of XG + AG vs. AB or any biomaterials before drawing conclusions.

Autogenous bone vs. Mixture of xenografts and alloplastic materials

No RCTs directly compared AB to XG combined with AP biomaterials. Very low quality of evidence through indirect evidence showed that there was some advantage when combining XG to AP biomaterials at a healing time of 4–5 months. Two RCTs investigated XG alone vs. XG with AP[19,45]. There was a significant increase in NBF for composite bone graft (XG and AP) vs. XG alone (P = 0.001).

Autogenous bone vs. Different bone grafts plus GFs

Five RCTs directly compared AB alone with combinations of different grafting biomaterials plus GFs (including platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and recombinant platelet-derived growth factor (PDGF)) at a healing time ranging from 4 to 8 months[37,41,54,68,71]. No statistically significant difference was found by either PMA (P = 0.84) or NMA (low quality of evidence). This result is consistent with several published reports[10,68,71,88]. Autologous PRP, PRF, or rhPDGF has been applied in regenerative medicine as an adjunct to osteoconductive materials such as AB, XG, and AP biomaterials. Thus, it is clinically relevant to assess which biomaterials combined with GFs may enhance NB formation. Interestingly, the combination of GFs with different bone grafts showed the greatest probability of producing the highest NBF (88.3%, low quality evidence) and the lowest RG (88%, very low quality evidence) after MSA at a healing time of <6 months.

Autogenous bone vs. BMP-2/different bone grafts plus MSCs

There is a lack of RCTs directly comparing AB vs. BMPs as well as directly investigating the effect of the adjunctive use of MSCs with autogenous grafts. Three RCTs directly assessed NBF comparing XG and BMPs[53–55], and another three RCTs directly compared XG to XG plus MSCs, with follow-up shorter than 6 months[63,64,82]. In both cases, PMA and NMA (low quality of evidence) found no statistically significant difference. Such results are in agreement with those of previous studies[63,64,82,89,90]. Nevertheless, the application of MSCs in combination with any osteoconductive biomaterials (xenografts or autograft with xenografts) resulted in a greater amount of NBF when the healing time was more than 6 months, suggesting that remodelling may require a longer time when using these materials, in spite of the association with MSCs.

Meta-regression analysis showed that there was a negative and insignificant relationship between NBF and healing time. Again, this is further evidence supporting the assumption of consistency and absence of transitivity in the present study.

Interestingly, meta-regression analysis for those subgroups that included a larger number of RCTs revealed that there was a negative and statistically insignificant association following grafting with AB. Conversely, a positive but statistically insignificant association was found after grafting with XG and AP. Similar results using a simple correlation analysis within a PMA were reported previously by Handschel et al. in 2009[4]. In spite of a negative correlation, AB maintains a higher NBF than other materials at any given time, thus a variation in healing time would not affect the percentage of NBF. This finding would suggest that new bone is formed early with AB and is slowly resorbed. In contrast, XG and AP showed a positive relationship between NBF and healing time, suggesting that for these bone grafts, new bone deposition proceeds slowly and with a delay as compared to AB.

Limitations and strengths of the systematic review

This systematic review has several limitations: (1) both PMA and NMA were performed according to the study level data, because the studies included did not report individual patient data. This is a common limitation encountered when performing systematic reviews and meta-analyses. (2) Included studies contained some confounding factors that may have affected the results, such as (a) possible inaccuracies in differentiating between the amount of NBF and RG particles in the AB group because of biological similarities between them; (b) differences in the technique for taking core biopsies, volume of the core (diameter and height), and sites of the biopsy (apical, central, or crestal). All of these factors could have had an impact on histomorphometric outcomes. (3) Variation or omission in reporting the preoperative residual bone height in the included studies, which could represent a co-variable affecting the amount of NBF, as a residual bone ridge with thicker cortical and cancellous layers would provide a better nourishment wall to the grafted sinus than thin ridges. (4) The amount of vestibular–palatine distance, because the greater it is, the higher the percentage

of connective tissue, which in turn could cause a decrease in the amount of NBF[91]. (5) Including and pooling different subtypes of each main biomaterial category (AG, XG, and AP) in separate groups regardless of their processing method and composition, which might have influenced the histomorphometric performance evaluation. (6) Using different sources of AB (e.g. intraoral and extraoral) and different proportions of biomaterials in the case of composite grafts (AG + AP, AG + XG, AG + AP, and AG + XG). (7) Variations in healing time among the included studies. To partially overcome this confounding factor, a subgroup analysis was conducted based on the healing time. Additionally, meta-regression analysis was performed to identify whether healing time influenced the outcomes of interest. (8) Several of the included studies used a barrier membrane over the lateral window osteotomy, to cover the graft, while others did not use a membrane or did not report whether they used a membrane or not. (9) In this study it was assumed that the lower the CT% the higher the fraction of graft able to provide support (either new bone or residual graft). However, the definition of CT% is generic in most studies, as the detailed composition of this fraction is rarely provided. Typically, connective tissue is mostly composed of collagen type I fibrils; these may become mineralized and turn into mature bone tissue with time, leading to an increase in the total bone volume in the graft[92,93]. However, there is the possibility that this fraction is composed of other types of fibrous tissue, or adipose tissue or other tissues, that may limit the capability of the graft to provide greater support in the future. An additional potential limitation of this study is that very few RCTs were found for some groups, such as AG + XG (one RCT) and XG + AP (two RCTs). So, even though the healing process occurs independently of the type of study in which the patient is involved, the present results regarding the relative performance of these composite grafts are not conclusive and should be interpreted with great caution.

Strengths of this study are (1) the novel performance of an NMA of RCTs with a clinical research question concerning the most effective biomaterials in term of histomorphometric outcomes after MSA. (2) This systematic review included the application of new NMA methods, which simultaneously pooled direct and indirect evidence from RCTs. (3) This study included a high number of RCTs due to a comprehensive literature search. (4) To assess the certainty of confidence derived from the results of this study, the GRADE rating system was used, which allows the identification of inconsistency. (5) A sensitivity analysis was performed after excluding studies comparing fewer than 10 biopsies, studies with a high risk of bias, and co-interventions including fewer than five RCTs. (6) Meta-regression analysis was conducted to assess the effect of healing time (effect modifier) on the amount of NBF.

Conclusions

In conclusion, most of the results of this NMA are in agreement with those of other systematic reviews that have addressed some of the specific comparisons and aspects separately. For example, the healing time has a prominent effect on new bone formation, especially when using biomaterial characterized by a slow resorption rate such as xenografts, which need longer healing times to achieve a high NBF compared to materials with a faster resorption rate. In fact, autogenous bone showed the best performance only when the healing time was shorter than 6 months, while for a longer healing time the majority of materials achieved similar histomorphometric results. The clinical implication of this finding is that grafting with autogenous bone is recommended when implant rehabilitation is planned within 6 months of the grafting procedure. Also, the addition of autogenous bone, GFs, or MSCs to any biomaterial may increase the healing rate. The combination of alloplastic materials and autogenous bone represents a satisfactory alternative to autogenous bone alone to achieve high NBF in combination with reduced morbidity. If harvesting site morbidity is a concern, many alternative graft materials can be used as they may achieve results similar to AB, but healing times longer than 6 months are advised.

NMA therefore represents a powerful tool able to overcome some of the limitations of standard PMA, in particular the need for head-to-head RCTs, in order to draw conclusions on the relative efficacy of alternative treatments.

Funding

None.

Competing interests

There is no conflict of interest to declare.

Ethical approval

Not required.

Patient consent

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijom.2019.05.004.

References

1. Block MS, Kent JN. Sinus augmentation for dental implants: the use of autogenous bone. *J Oral Maxillofac Surg* 1997;**55**:1281–6.
2. Schlegel KA, Fichtner G, Schultze-Mosgau S, Wiltfang J. Histologic findings in sinus augmentation with autogenous bone chips versus a bovine bone substitute. *Int J Oral Maxillofac Implants* 2003;**18**:53–8.
3. Corbella S, Taschieri S, Weinstein R, Del Fabbro M. Histomorphometric outcomes after lateral sinus floor elevation procedure: a systematic review of the literature and meta-analysis. 2016: 27: 1106–1122.
4. Handschel J, Simonowska M, Naujoks C, Depprich RA, Ommerborn MA, Meyer U, Kubler NR. A histomorphometric meta-analysis of sinus elevation with various grafting materials. *Head Face Med* 2009;**5**:12.
5. Danesh-Sani SA, Engebretson SP, Janal MN. Histomorphometric results of different grafting materials and effect of healing time on bone maturation after sinus floor augmentation: a systematic review and meta-analysis. *J Periodontal Res* 2017;**52**:301–12.
6. Al-Nawas B, Schiegnitz E. Augmentation procedures using bone substitute materials or autogenous bone—a systematic review and meta-analysis. *Eur J Oral Implantol* 2014;**7**(Suppl. 2):S219–34.
7. Del Fabbro M, Testori T, Francetti L, Weinstein R. Systematic review of survival rates for implants placed in the grafted maxillary sinus. *Int J Periodontics Restorative Dent* 2004;**24**:565–77.
8. 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**(Suppl. 4):124–33.
9. Starch-Jensen T, Jensen JD. Maxillary sinus floor augmentation: a review of selected treatment modalities. *J Oral Maxillofac Res* 2017;**8**:e3.
10. Corbella S, Taschieri S, Weinstein R, Del Fabbro M. Histomorphometric outcomes after lateral sinus floor elevation procedure: a systematic review of the literature and meta-

analysis. *Clin Oral Implants Res* 2016;**27**: 1106–22.
11. Kanters S, Ford N, Druyts E, Thorlund K, Mills EJ, Bansback N. Use of network meta-analysis in clinical guidelines. *Bull World Health Organ* 2016;**94**:782–4.
12. Faltinsen EG, Storebø OJ, Jakobsen JC, Boesen K, Lange T, Gluud C. Network meta-analysis: the highest level of medical evidence? 2018: 23: 56–59.
13. Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, Boersma C, Thompson D, Larholt KM, Diaz M, Barrett A. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health* 2011;**14**: 429–37.
14. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;**3**:80–97.
15. Madden LV, Piepho HP, Paul PA. Statistical models and methods for network meta-analysis. *Phytopathology* 2016;**106**:792–806.
16. Greco T, Edefonti V, Biondi-Zoccai G, Decarli A, Gasparini M, Zangrillo A, Landoni G. A multilevel approach to network meta-analysis within a frequentist framework. *Contemp Clin Trials* 2015;**42**:51–9.
17. Al Khalifah R, Florez ID, Guyatt G, Thabane L. Network meta-analysis: users' guide for pediatricians. *BMC Pediatr* 2018;**18**:180.
18. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catala-Lopez F, Gotzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA Extension Statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;**162**:777–84.
19. Al-Moraissi E, Abotalab B, Al-tairi N. What is the best bone graft in maxillary sinus augmentations has a positive histomorphometric and volumetric outcomes? PROSPERO 2018: CRD42018089357.
20. Higgins J, Green S. *Cochrane handbook for systematic reviews of interventions version 5.1.0*. The Cochrane Collaboration; 2011.
21. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–6.
22. Salanti G, Kavvoura FK, Ioannidis JP. Exploring the geometry of treatment networks. *Ann Intern Med* 2008;**148**:544–53.
23. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med* 2017;**12**:103–11.
24. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol* 2009;**62**:857–64.
25. StataCorp. *Stata Statistical Software: release 13*. College Station, TX: StataCorp.; 2013.
26. White IR. Network meta-analysis. *Stata J* 2015;**15**:951–85.
27. Harbord RM, Higgins JPT. Meta-regression in Stata. *Stata J* 2008;**8**:493–519.
28. Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. *Stat Med* 1996;**15**:2733–49.
29. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;**3**:98–110.
30. White IR, Barrett JK, Jackson D, Higgins J. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;**3**:111–25.
31. Salanti G, Ades A, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;**64**:163–71.
32. Veroniki AA, Straus SE, Fyraridis A, Tricco AC. The rank-heat plot is a novel way to present the results from a network meta-analysis including multiple outcomes. *J Clin Epidemiol* 2016;**76**:193–9.
33. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med* 2001;**20**: 641–54.
34. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in Stata. *PLoS One* 2013;**8**:e76654.
35. Ahmet S, Alper Gultekin B, Karabuda ZC, Olgac V. Two composite bone graft substitutes for maxillary sinus floor augmentation: histological, histomorphometric, and radiographic analyses. *Implant Dent* 2016;**25**: 313–21.
36. Alayan J, Vaquette C, Farah C, Ivanovski S. A histomorphometric assessment of collagen-stabilized anorganic bovine bone mineral in maxillary sinus augmentation—a prospective clinical trial. *Clin Oral Implants Res* 2016;**27**:850–8.
37. Badr M, Oliver R, Pemberton P, Coulthard P. Platelet-rich plasma in grafted maxillae: growth factor quantification and dynamic histomorphometric evaluation. *Implant Dent* 2016;**25**:492–8.
38. Rodriguez y Baena R, Pastorino R, Gherlone EF, Perillo L, Lupi SM, Lucchese A. Histomorphometric evaluation of two different bone substitutes in sinus augmentation procedures: a randomized controlled trial in humans. *Int J Oral Maxillofac Implants* 2017;**32**:188–94.
39. Barone A, Crespi R, Aldini NN, Fini M, Giardino R, Covani U. Maxillary sinus augmentation: histologic and histomorphometric analysis. *Int J Oral Maxillofac Implants* 2005;**20**:519–25.
40. Comert Kiliç S, Gungormus M, Parlak SN. Histologic and histomorphometric assessment of sinus-floor augmentation with beta-tricalcium phosphate alone or in combination with pure-platelet-rich plasma or platelet-rich fibrin: a randomized clinical trial. *Clin Implant Dent Relat Res* 2017;**19**: 959–67.
41. Consolo U, Zaffe D, Bertoldi C, Ceccherelli G. Platelet-rich plasma activity on maxillary sinus floor augmentation by autologous bone. *Clin Oral Implants Res* 2007;**18**: 252–62.
42. Cordaro L, Bosshardt DD, Palattella P, Rao W, Serino G, Chiapasco M. Maxillary sinus grafting with Bio-Oss or Straumann Bone Ceramic: histomorphometric results from a randomized controlled multicenter clinical trial. *Clin Oral Implants Res* 2008;**19**:796–803.
43. Correia F, Pozza D, Gouveia S. Sinus lift with two different grafts – histological and radiological findings – preliminary reports. *Clin Oral Implants Res* 2014;**25**(Suppl 10):444.
44. Danesh-Sani SA, Wallace SS, Movahed A, El Chaar ES, Cho SC, Khouly I, Testori T. Maxillary sinus grafting with biphasic bone ceramic or autogenous bone: clinical, histologic, and histomorphometric results from a randomized controlled clinical trial. *Implant Dent* 2016;**25**:588–93.
45. Dogan E, Dursun E, Tosun E, Bilgic E, Akman AC, Orhan K, Celik HH, Korkusuz P, Caglayan F. Evaluation of hyaluronic matrix efficacy in sinus augmentation: a randomized-controlled histomorphometric and micro-computed tomography analysis. *Int J Oral Maxillofac Surg* 2017;**46**:931–7.
46. Dursun CK, Dursun E, Eratalay K, Orhan K, Tatar I, Baris E, Tozum TF. Effect of porous titanium granules on bone regeneration and primary stability in maxillary sinus: a human clinical, histomorphometric, and microcomputed tomography analyses. *J Craniofac Surg* 2016;**27**:391–7.
47. Froum SJ, Wallace S, Cho SC, Khouly I, Rosenberg E, Corby P, Froum S, Bromage T, Schoor R, Norman R, Tarnow DP. Histomorphometric comparison of different concentrations of recombinant human bone morphogenetic protein with allogeneic bone compared to the use of 100% mineralized cancellous bone allograft in maxillary sinus grafting. *Int J Periodontics Restorative Dent* 2013;**33**:721–30.
48. Froum SJ, Wallace SS, Cho SC, Elian N, Tarnow DP. Histomorphometric comparison of a biphasic bone ceramic to anorganic bovine bone for sinus augmentation: 6- to 8-month postsurgical assessment of vital bone formation. A pilot study. *Int J Periodontics Restorative Dent* 2008;**28**:273–81.
49. Froum SJ, Wallace SS, Elian N, Cho SC, Tarnow DP. Comparison of mineralized can-

cellous bone allograft (Puros) and anorganic bovine bone matrix (Bio-Oss) for sinus augmentation: histomorphometry at 26 to 32 weeks after grafting. *Int J Periodontics Restorative Dent* 2006;**26**:543–51.
50. Froum SJ, Wallace S, Cho SC, Rosenburg E, Froum S, Schoor R, Mascarenhas P, Tarnow DP, Corby P, Elian N, Fickl S, Ricci J, Hu B, Bromage T, Khouly I. A histomorphometric comparison of Bio-Oss alone versus Bio-Oss and platelet-derived growth factor for sinus augmentation: a postsurgical assessment. *Int J Periodontics Restorative Dent* 2013;**33**: 269–79.
51. Garlini G, Redemagni M, Canciani E, Dellavia C. Maxillary sinus floor augmentation with vegetal hydroxyapatite ''versus'' demineralized bovine bone: a randomized clinical study with a split-mouth design. *J Dent Implants* 2014;**4**:118–25.
52. 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**:635–43.
53. Kao DW, Kubota A, Nevins M, Fiorellini JP. The negative effect of combining rhBMP-2 and Bio-Oss on bone formation for maxillary sinus augmentation. *Int J Periodontics Restorative Dent* 2012;**32**:61–7.
54. Khairy NM, Shendy EE, Askar NA, El-Rouby DH. Effect of platelet rich plasma on bone regeneration in maxillary sinus augmentation (randomized clinical trial). *Int J Oral Maxillofac Surg* 2013;**42**:249–55.
55. Kim HJ, Chung JH, Shin SY, Shin SI, Kye SB, Kim NK, Kwon TG, Paeng JY, Kim JW, OH Oh, Kook MS, Yang HJ, Hwang SJ. Efficacy of rhBMP-2/hydroxyapatite on sinus floor augmentation: a multicenter, randomized controlled clinical trial. *J Dent Res* 2015;**94**(9 Suppl):158s–65s.
56. Kim MS, Lee JS, Shin HK, Kim JS, Yun JH, Cho KS. Prospective randomized, controlled trial of sinus grafting using *Escherichia coli*-produced rhBMP-2 with a biphasic calcium phosphate carrier compared to deproteinized bovine bone. *Clin Oral Implants Res* 2015;**26**:1361–8.
57. Kolerman R, Nissan J, Rahmanov M, Vered H, Cohen O, Tal H. Comparison between mineralized cancellous bone allograft and an alloplast material for sinus augmentation: a split mouth histomorphometric study. *Clin Implant Dent Relat Res* 2017;**19**:812–20.
58. Kühl S, Brochhausen C, Götz H, Filippi A, Payer M, d'Hoedt B, Kreisler M. The influence of bone substitute materials on the bone volume after maxillary sinus augmentation: a microcomputerized tomography study. *Clin Oral Investig* 2013;**17**:543–51.
59. Kurkcu M, Benlidayi ME, Cam B, Sertdemir Y. Anorganic bovine-derived hydroxyapatite vs beta-tricalcium phosphate in sinus augmentation: a comparative histomorphometric study. *J Oral Implantol* 2012;**38** (Spec No):519–26.
60. 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**:1151–62.
61. Meimandi M, Moghaddam AA, Gholami GA, Abbass FM, Solati M. Histomorphometric and histologic evaluation of nano-HA with and without PRGF in bilateral sinus lift augmentation: a randomized clinical trial. *J Res Med Dent Sci* 2017;**5**:69–81.
62. Nizam N, Eren G, Akcali A, Donos N. Maxillary sinus augmentation with leukocyte and platelet-rich fibrin and deproteinized bovine bone mineral: a split-mouth histological and histomorphometric study. *Clin Oral Implants Res* 2018;**29**:67–75.
63. Pasquali PJ, Teixeira ML, de Oliveira TA, de Macedo LG, Aloise AC, Pelegrine AA. Maxillary sinus augmentation combining Bio-Oss with the bone marrow aspirate concentrate: a histomorphometric study in humans. *Int J Biomater* 2015;**2015**:121286.
64. Payer M, Lohberger B, Strunk D, Reich KM, Acham S, Jakse N. Effects of directly autotransplanted tibial bone marrow aspirates on bone regeneration and osseointegration of dental implants. *Clin Oral Implants Res* 2014;**25**:468–74.
65. Pereira RDS, Menezes JD, Bonardi JP, Griza GL, Okamoto R, Hochuli-Vieira E. Histomorphometric and immunohistochemical assessment of RUNX2 and VEGF of Biogran and autogenous bone graft in human maxillary sinus bone augmentation: a prospective and randomized study. *Clin Implant Dent Relat Res* 2017;**19**:867–75.
66. Pikdöken L, Gürbüzer B, Küçükodacı Z, Urhan M, Barış E, Tezulaş E. Scintigraphic, histologic, and histomorphometric analyses of bovine bone mineral and autogenous bone mixture in sinus floor augmentation: a randomized controlled trial—results after 4 months of healing. *J Oral Maxillofac Surg* 2011;**69**:160–9.
67. Portelli M, Cicciu M, Lauritano F, Cervino G, Manuelli M, Gherlone EF, Lucchese A. Histomorphometric evaluation of two different bone substitutes in sinus floor augmentation procedures. *J Craniofac Surg*)2017; (February 22). [Epub ahead of print].
68. Raghoebar GM, Schortinghuis J, Liem RS, Ruben JL, van der Wal JE, Vissink A. Does platelet-rich plasma promote remodeling of autologous bone grafts used for augmentation of the maxillary sinus floor? *Clin Oral Implants Res* 2005;**16**:349–56.
69. Rickert D, Sauerbier S, Nagursky H, Menne D, Vissink A, Raghoebar GM. Maxillary sinus floor elevation with bovine bone mineral combined with either autogenous bone or autogenous stem cells: a prospective randomized clinical trial. *Clin Oral Implants Res* 2011;**22**:251–8.
70. Sauerbier S, Rickert D, Gutwald R, Nagursky H, Oshima T, Xavier SP, Christmann J, Kurz P, Menne D, Vissink A, Raghoebar G, Schmelzeisen R, Wagner W, Koch FP. Bone marrow concentrate and bovine bone mineral for sinus floor augmentation: a controlled, randomized, single-blinded clinical and histological trial—per-protocol analysis. *Tissue Eng Part A* 2011;**17**:2187–97.
71. Schaaf H, Streckbein P, Lendeckel S, Heidinger K, Gortz B, Bein G, Boedeker RH, Schlegel KA, Howaldt HP. Topical use of platelet-rich plasma to influence bone volume in maxillary augmentation: a prospective randomized trial. *Vox Sang* 2008;**94**:64–9.
72. Stavropoulos A, Becker J, Capsius B, Acil Y, Wagner W, Terheyden H. Histological evaluation of maxillary sinus floor augmentation with recombinant human growth and differentiation factor-5-coated beta-tricalcium phosphate: results of a multicenter randomized clinical trial. *J Clin Periodontol* 2011;**38**:966–74.
73. Schmitt CM, Doering H, Schmidt T, Lutz R, Neukam FW, Schlegel KA. Histological results after maxillary sinus augmentation with Straumann(R) BoneCeramic, Bio-Oss (R), Puros(R), and autologous bone. A randomized controlled clinical trial. *Clin Oral Implants Res* 2013;**24**:576–85.
74. Sehn FP, Dias RR, de Santana Santos T, Silva ER, Salata LA, Chaushu G, Xavier SP. Fresh-frozen allografts combined with bovine bone mineral enhance bone formation in sinus augmentation. *J Biomater Appl* 2015;**29**:1003–13.
75. Stacchi C, Lombardi T, Oreglia F, Alberghini Maltoni A, Traini T. Histologic and histomorphometric comparison between sintered nanohydroxyapatite and anorganic bovine xenograft in maxillary sinus grafting: a split-mouth randomized controlled clinical trial. *Biomed Res Int* 2017;**2017**:9489825.
76. Szabo G, Huys L, Coulthard P, Maiorana C, Garagiola U, Barabas J, Nemeth Z, Hrabak K, Suba Z. A prospective multicenter randomized clinical trial of autogenous bone versus beta-tricalcium phosphate graft alone for bilateral sinus elevation: histologic and histomorphometric evaluation. *Int J Oral Maxillofac Implants* 2005;**20**:371–81. Q18
77. Taschieri S, Testori T, Corbella S, Weinstein R, Francetti L, Di Giancamillo A, Del Fabbro M. Platelet-rich plasma and deproteinized bovine bone matrix in maxillary sinus lift surgery: a split-mouth histomorphometric evaluation. *Implant Dent* 2015;**24**:592–7.
78. Taschieri S, Lolato A, Testori T, Francetti L, Del Fabbro M. Short dental implants as compared to maxillary sinus augmentation procedure for the rehabilitation of edentulous posterior maxilla: three-year results of a randomized clinical study. *Clin Implant Dent Relat Res* 2018;**20**:9–20.

79. Torres J, Tamimi F, Martinez PP, Alkhraisat MH, Linares R, Hernandez G, Torres-Macho J, Lopez-Cabarcos E. Effect of platelet-rich plasma on sinus lifting: a randomized-controlled clinical trial. *J Clin Periodontol* 2009;**36**:677–87.
80. Tosta M, Cortes AR, Correa L, Pinto Ddos Jr S, Tumenas I, Katchburian E. Histologic and histomorphometric evaluation of a synthetic bone substitute for maxillary sinus grafting in humans. *Clin Oral Implants Res* 2013;**24**:866–70.
81. Turunen T, Peltola J, Yli-Urpo A, Happonen RP. Bioactive glass granules as a bone adjunctive material in maxillary sinus floor augmentation. *Clin Oral Implants Res* 2004;**15**:135–41.
82. Wildburger A, Payer M, Jakse N, Strunk D, Etchard-Liechtenstein N, Sauerbier S. Impact of autogenous concentrated bone marrow aspirate on bone regeneration after sinus floor augmentation with a bovine bone substitute—a split-mouth pilot study. *Clin Oral Implants Res* 2014;**25**:1175–81.
83. Xavier SP, Dias RR, Sehn FP, Kahn A, Chaushu L, Chaushu G. Maxillary sinus grafting with autograft vs. fresh frozen allograft: a split-mouth histomorphometric study. *Clin Oral Implants Res* 2015;**26**:1080–5.
84. Zerbo IR, Zijderveld SA, de Boer A, Bronckers AL, de Lange G, ten Bruggenkate CM, Burger EH. Histomorphometry of human sinus floor augmentation using a porous beta-tricalcium phosphate: a prospective study. *Clin Oral Implants Res* 2004;**15**:724–32.
85. Zhang Y, Tangl S, Huber CD, Lin Y, Qiu L, Rausch-Fan X. Effects of Choukroun's platelet-rich fibrin on bone regeneration in combination with deproteinized bovine bone mineral in maxillary sinus augmentation: a histological and histomorphometric study. *J Craniomaxillofac Surg* 2012;**40**:321–8.
86. 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**:1112–7.
87. Davison NL, ten Harkel B, Schoenmaker T, Luo X, Yuan H, Everts V, Barrere-de Groot F, de Bruijn JD. Osteoclast resorption of beta-tricalcium phosphate controlled by surface architecture. *Biomaterials* 2014;**35**:7441–51.
88. Roffi A, Filardo G, Kon E, Marcacci M. Does PRP enhance bone integration with grafts, graft substitutes, or implants? A systematic review. *BMC Musculoskelet Disord* 2013;**14**:330.
89. Da Rosa WLO, da Silva TM, da Silva AF, Piva E. Bioactive treatments in bone grafts for implant-based rehabilitation: systematic review and meta-analysis. *Clin Implant Dent Relat Res* 2018;**20**:251–60.
90. Lin GH, Lim G, Chan HL, Giannobile WV, Wang HL. Recombinant human bone morphogenetic protein 2 outcomes for maxillary sinus floor augmentation: a systematic review and meta-analysis. *Clin Oral Implants Res* 2016;**27**:1349–59.
91. Avila-Ortiz G, Neiva R, Galindo-Moreno P, Rudek I, Benavides E, Wang HL. Analysis of the influence of residual alveolar bone height on sinus augmentation outcomes. *Clin Oral Implants Res* 2012;**23**:1082–8.
92. Bauer TW, Muschler GF. Bone graft materials. An overview of the basic science. *Clin Orthop Relat Res* 2000;**371**:10–27.
93. Wang W, Yeung KWK. Bone grafts and biomaterials substitutes for bone defect repair: a review. *Bioact Mater* 2017;**2**:224–47.

Address:
Essam Ahmed Al-Moraissi
Department of Oral and Maxillofacial Surgery
Faculty of Dentistry
Thamar University
Thamar
Yemen
Tel.: +967 777788939
E-mails: dr_essamalmoraissi@yahoo.com, dressamalmoraissi@gmail.com