Title: What grafting materials produce greater alveolar ridge preservation after tooth extraction? A systematic review and network meta- analysis

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Abstract

A systematic review and network meta-analysis was conducted to compare different bone-substitute materials used for alveolar ridge preservation after tooth extraction. The electronic search was carried out on Embase, PubMed, Cochrane Library, Web of Science, Scopus, LILACS, and grey literature up to March 22, 2020 (registration number INPLASY202030005). Only randomized controlled trials were included to answer the following PICOS question: 'What grafting materials produce greater alveolar ridge preservation after tooth extraction?' The primary outcomes were the alveolar width resorption 1 mm below the alveolar crest and buccal height resorption in millimeters. Of the 4379 studies initially identified, 31 studies involving 1088 patients were included in the quantitative analyses. Out of 25 revised biomaterials, eight showed a statistically significant difference compared with unassisted healing in both alveolar width and height measurements (mean width differences: Apatos®, 2.27 [1.266e3.28]; Bio-Oss®, 0.88 [0.33e1.42]; Bio-Oss Coll®, 0.53 [0.04e1.01]; Bond-apatite®, 2.20 [1.30e3.11]; freeze- dried bone allograft, 1.35 [0.44e2.26]; Gen-Os®, 1.90 [0.60e3.20]; platelet-rich fibrin, 1.66 [0.66 e2.67]; and MP3®, 2.67 [1.59e3.75]). Overall, xenograft materials should be considered as among the best of the available grafting materials for alveolar preservation after tooth extraction.
Keywords: alveolar ridge preservation; grafting materials; network meta-analysis

1. Introduction

Alveolar bone remodeling is a physiological process observed after tooth extraction that may compromise the subsequent dental implant rehabilitation (Chappuis et al., 2013; Morjaria et al., 2014). Most of the alveolar bone resorption occurs during the first 3e6 months after tooth extraction, resulting in a bone width loss of 29e63% (Tan et al., 2012). Different bone-substitute materials havebeen proposed to reduce the natural collapse in the socket after tooth extraction (Canellas et al., 2019c). However, there is no grafting material that can prevent bone resorption completely (Avila-Ortiz et al., 2014; Morjaria et al., 2014; Jung et al., 2018b). Decisions regarding what types of biomaterial offer the most predictable clinical outcomes should consider the potential expected difference in alveolar bone loss between the grafting material and the natural healing, and the cost-effectiveness of each biomaterial (Canellas et al., 2019b).

Network meta-analysis is a statistical method applied to systematic reviews that allows the comparison of multiple interventions, even if these interventions were not directly comparedin the primary studies (Cipriani et al., 2013). This technique is considered a robust method for producing evidence regarding clinical questions when there is a wide variety of interventions available (Salanti, 2012).

Many grafting materials have been suggested for alveolar ridge preservation after tooth extraction (Canellas et al., 2019c). It is unlikely that individual randomized clinical trials (RCTs) and traditional pairwise meta-analyses can provide evidence for allinterventions available, since the number of RCTs reporting direct comparisons of alveolar bone loss with more than three different grafting materials is limited. Therefore, in this context, network meta-analysis becomes a key tool for answering important clinical questions to guide decision making.

To our knowledge, no previous systematic review has analyzed each type of bone-substitute material separately, and then combined the evidence from RCTs using a frequentist-weighted, least- squares model. The objective of our systematic review was to examine the clinical performances of different grafting materials for alveolar preservation after tooth extraction, using a frequentist network meta-analysis. This approach combines direct and indirect evidence from RCTs to obtain more precise pooled estimates of the treatment differences. The focused question addressed was: What grafting materials produce greater alveolar ridge preservation after tooth extraction?

2. Materials and methods

2.1. PICOS strategy and eligibility criteria

This systematic review was presented according to the PRISMA statement (Preferred Reporting Items for Systematic Review and Meta-Analyses) (Moher et al., 2009). The PICOS strategy (Patient, Intervention, Comparison, Outcome, and Study) was used to pro- duce a well-formulated question. The protocol for this systematic review was registered prospectively in the Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY), registration number INPLASY202030005 (Canellas et al., 2020c).

The primary outcomes were the alveolar width resorption 1 mm below the alveolar crest and buccal height resorption in millimeters. Width resorption was defined as the difference between alveolar width at baseline (immediately after tooth extraction) and after 3e6 months. The alveolar widths were assessed 1 mm below the crest based on radiographic images (cone-beam computed tomography or fan-beam computed tomography scans), three-dimensional virtual models, or using clinical methods such as ridge calipers, custom-made stents, and periodontal probes. The height of the alveolar bone was defined at the buccal surface using the same radiographic or clinical methods described for width analysis. Height resorption was measured by the difference be- tween alveolar height at baseline and 3 months after extraction. Bone resorption was expressed using negative values to represent the amount of bone loss in millimeters. The secondary outcomes were alveolar width resorption 3 mm below the alveolar crest, and alveolar width resorption 5 mm below the alveolar crest. The included studies were randomized clinical trials in which the out- comes were measured between 3 and 6 months after tooth extraction.

The included patients were all adults (>18 years). Studies comparing only membrane barriers, or studies using membrane barriers in the control group (no grafting) were excluded. Studies without width measurement, without focus on alveolar bone preservation, and those with incomplete data identified from the grey literature were also excluded. Only studies that reported alveolar bone changes measured 3e6 months after tooth extraction were included.

2.2 Electronic sources and search strategy

A comprehensive electronic search was conducted on EMBASE, MEDLINE/PubMed, Cochrane Library, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database (LI- LACS), and grey literature up to March 22, 2020. Medical subject heading terms (MeSH) and free-text words were used in the electronic database searches. The search strategy is presented in Electronic Supplementary Material Table 1. There were no re- strictions regarding year of publication or language of the identified studies. The grey literature search was carried out at the ClinicalTrials.gov registry platform (www.clinicaltrials.gov) to identify potential unpublished studies. Additionally, the reference lists of the included studies were cross-checked to identify relevant studies. A comprehensive manual search was conducted in the following relevant journals: International Journal of Oral and Maxillofacial Surgery, Journal of Oral and Maxillofacial Surgery, Journal of Cranio-Maxillofacial Surgery, British Journal of Oral and Maxillofacial Surgery, Oral Surgery Oral Medicine Oral Pathology Oral Radiology, Journal of Clinical Periodontology, Journal of Dental Research, Clinical Oral Implant Research, Clinical Implant Dentistry and Related Research, and International Journal of Oral and Maxillofacial Implants. Subsequently, the articles were imported into Endnote X9 software (Thompson Reuters, Philadelphia, PA, USA), where duplicates were removed.

2.3 Study selection

Two reviewers (JVC and BNS) independently screened the retrieved studies for inclusion, based on the titles and abstracts. Relevant research articles were assessed in full for eligibility ac- cording to selection criteria. The reliability of the selection of studies between the two reviewers was assessed using the kappa coefficient. A kappa coefficient equal to or greater than 0.75 suggests excellent agreement, whereas a kappa coefficient between 0.40 and 0.59, and between 0.60 and 0.74 indicate fair and good reliability, respectively (Orwin, 1994). Any discrepancies between the reviewers were discussed and resolved by consensus.

2.4 Data extraction

The following characteristics of the selected studies were gathered: author, year of publication, country, language, method used for socket measurement, study design, sample size, number and type of interventions, alveolar region, gender, dropouts, and follow-up period. The corresponding author of the study was contacted when data on primary outcomes were missing.

2.5 Publication bias and risk of bias in individual studies

The contour-enhanced funnel plot technique was used to identify asymmetry due to publication bias or other reasons. The risk of bias and methodological quality of the included studies was assessed using the Cochrane Collaboration's risk of bias tool (Higgins et al., 2011). Two authors (JVC and BNS) assessed the risk of bias independently, and the disagreements were resolved by discussion.

2.6 Statistical analysis

A frequentist network meta-analysis was carried out to compare the different types of grafting material, even if they were not directly compared in the primary studies. The pooled mean differences between the interventions were calculated using a random-effect network meta-analysis model. A forest plot was used to identify which were the effective grafting materials compared with natural healing. The differences between active interventions were measured by head-to-head analysis. Mean differences for treatment estimates in which the value '0' was included in the 95% confidence interval were considered not statistically significant. The SUCRA value (surface under the cumulative ranking) was used to identify which intervention had the highest probability of obtaining greater alveolar bone preservation. The frequentist network meta-analysis was performed using R software version 3.6.2 with the net meta package for Mac OS X. This package is available from the Comprehensive R Archive Network (CRAN) at https://CRAN.R-project.org. Inconsistency was assessed by comparing direct and indirect evidence. A net heat plot was performed to show the contribution of each design to the network estimate and the extent of inconsistency due to each design.

3 Results

The flow diagram of the identified, screened, and included studies is presented in Fig. 1. Initially, 8955 potential studies were identified. Of these, 4379 studies were retained after excluding duplicated papers. The titles and abstracts were then screened, and 4186 studies did not meet the eligibility criteria and were excluded, resulting in 183 studies included for full-text reading. The agree- ment for the inclusion of studies was considered excellent ¼(kappa coefficient 0.77). After full-text reading, 32 RCTs (Iasella et al., 2003; Aimetti et al., 2009; Festa et al., 2013; Jung et al., 2013, 2018a, 2018c; Das et al., 2016; Mayer et al., 2016; Sadeghi et al., 2016; Temmerman et al., 2016; Barone et al., 2017; Iorio-Siciliano et al., 2017, 2020; Lim et al., 2017, 2019; Nart et al., 2017; Serrano Mendez et al., 2017; Walker et al., 2017; Clark et al., 2018; Leeet al., 2018, 2020; Nunes et al., 2018; Tomasi et al., 2018; Kollatiet al., 2019; Llanos et al., 2019; Machtei et al., 2019; Santana et al., 2019; Sapata et al., 2020; Sun et al., 2019; Avila-Ortiz et al., 2020; Canellas et al., 2020a; Flores Fraile et al., 2020) fulfilled the inclu- sion criteria and were subjected to qualitative analysis.

The network meta-analysis included data from 31 studies comparing 25 different bone-substitute materials (Iasella et al., 2003; Aimetti et al., 2009; Festa et al., 2013; Jung et al., 2013, 2018a, 2018c; Mayer et al., 2016; Sadeghi et al., 2016; Temmermanet al., 2016; Barone et al., 2017; Iorio-Siciliano et al., 2017, 2020; Lim et al., 2017, 2019; Nart et al., 2017; Serrano Mendez et al., 2017; Walker et al., 2017; Clark et al., 2018; Lee et al., 2018, 2020; Nunes et al., 2018; Tomasi et al., 2018; Kollati et al., 2019; Llanos et al., 2019; Machtei et al., 2019; Santana et al., 2019; Sapata et al., 2020; Sun et al., 2019; Avila-Ortiz et al., 2020; Canellas et al., 2020a; Flores Fraile et al., 2020). Eight trials were considered at low risk of bias in all domains. Another 19 trials were judged as having an unclear risk of bias because one or more domains were considered to be at unclear risk of bias. The remaining five trials were assessed as being at high risk of bias because high risk of bias was identified in one or more of the seven domains (Electronic Supplementary Material Fig. 1).

The network plots are presented in Fig. 2. In total, 25 grafting materials were included in the network meta-analysis for alveolar width resorption, and 24 grafting materials were included in the network meta-analysis for alveolar height resorption. The charac- teristics of the selected studies are presented in Electronic Supplementary Material Table 2. Ten grafting materials, namely Apatos®, Bio-Oss®, Bio-Oss Coll®, Bond-apatite®, Cerabone® PRF, FDBA, Gen-Os®, leukocyte- and platelet-rich fibrin (L-PRF), MP3®, and tooth-derived dentin, were more effec- tive in preventing width resorption than natural healing (Fig. 3). Eleven grafting materials, namely advanced platelet-rich fibrin (A- PRF), A-PRF AlloOss®, Apatos®, Bio-Oss®, Bio-Oss Coll®, Bond- apatite®, enCore®, FDBA, Gen-Os®, L-PRF, and MP3®, were more effective than natural healing in preventing height resorption (Fig. 4). The predicted intervals for width and height resorption were [0.22; 2.05] and [0.32; 1.45], respectively (Figs. 3 and 4). A summary of findings is presented in Electronic Supplementary Material Table 3.

Head-to-head comparisons between the different grafting material modalities are shown in Fig. 5. There were statistically significant differences between some of them, even between bone grafts of the same type. In these head-to-head comparisons, twoxenograft materials d MP3® and Gen-Os® d had the highest number of significant differences for width and height preservation, respectively. The ranking of interventions by cumulative probability, according to SUCRA values, is presented in Electronic Supplementary Material Tables 4 and 5 Three xenograft materials showed greater efficacy in preventing width resorption: MP3 ®, Apatos®, and Gen-Os®. One synthetic biomaterial (Bond-apatite®) and one platelet concentrate (L-PRF) showed greater efficacy in preventing width resorption. The five grafting materials with greatest efficacy in preventing height resorption were three xenograft materials (Gen-Os®, Apatos®, and MP3®), one platelet concentrate (A-PRF), and the combination of A-PRF allograftmaterial (AlloOss®). The lowest ranking positions were assigned tothe no grafting group and the tetracycline allograft group for width and height resorption, respectively.

The evidence in the network appeared to be consistent when the random effect model was applied. The Q statistic showed no significant inconsistency (p ¼ 0.202) in bone width measurements. In contrast, significant inconsistency was found in bone height measurements (p ¼ 0.003). For visual inspection and a detailed inconsistency assessment, two net heat maps are provided in Electronic Supplementary Material Figs. 2 and 3. The area of grey squares is proportional to the contribution from direct comparison in each column with the network estimates in the row. If the largest grey square is on the diagonal, it means that the direct evidence is the greatest source of information. Grafting comparisons are omitted when there is only one source of evidence. The three-arm design is represented by '_' in the net heat maps. The colors relate tothe change in inconsistency between indirect and direct evidence. Warm colors indicate an increase in inconsistency and blue colors a decrease.

Finally, the p-values for the linear regression tests of funnel plot asymmetry were 0.869 and 0.265 for width and height resorption, respectively. These results confirmed no publication bias in our network meta-analysis.

4 Discussion

In this systematic review, 25 bone-substitute materials (4Bone-Bondbone®, A-PRF, A-PRF AlloOss®, AlloGraft®, AlloOss®, Apa- tos®, Bio-Oss®, Bio-Oss Coll®, Bio-Oss Coll EMD®, Bond- apatite®, Cerabone® PRF, Colla-Oss®, enCore®, FDBA, L-PRF, MP3®, Gen-Os®, ReproBone®, Sil-Oss®, Surgiplaster®,Tetracycline FDBA, THE Graft®, tooth derived-dentin, tooth derived-dentin BMP2, and B-TCP) were assessed by network meta-analysis using a frequentist model. Our study focused on the bone changes measured 3e6 months after tooth extraction. Our results suggested that no grafting material can completely prevent post-extraction resorption, and some quantity of bone loss might be expected. Similar results have been reported in previous systematic reviews on this topic.(Avila-Ortiz et al., 2014; Morjaria et al., 2014). These review papers included traditional meta- analyses to compare grafting materials with natural healing. However, our findings showed that the amount of bone resorption may vary according to the type of bone-material substitute used in the socket after tooth extraction. Therefore, pairwise comparisons grouping all biomaterials in the same arm may not be the most appropriate approach to synthesizing the information.

Network meta-analysis is a statistical technique that combines direct and indirect information to generate precise evidence oftreatment differences when comparing multiple interventions (Cipriani et al., 2013). This method can provide less biased estimates than traditional meta-analysis, and can inform decision making more effectively than pairwise meta-analysis (Song et al., 2008). Our study used a frequentist-weighted least-squares method to identify what grafting materials produce greater alveolar ridge preservation after tooth extraction. Indirect comparisonsconnect treatments via a common comparator to establish differences between grafting materials that have not been compared in randomized controlled trials. Moreover, the indirect estimates are free of optimism or sponsorship bias that can compromise thequality of evidence in pairwise comparisons (Salanti, 2012).

To our knowledge, no frequentist network meta-analysis has been published comparing the efficacy of different bone-substitute materials in reducing bone resorption after tooth extraction. Only one previous Bayesian network meta-analysis (Iocca et al., 2017), including six studies with a total sample of 181 patients, is avail- able. However, Iocca et al. grouped the grafting materials accordingto their sources, and yet our results demonstrated that grafting materials derived from the same source (e.g. xenograft) for use in alveolar preservation can differ significantly regarding the amountof alveolar bone preservation after tooth extraction. Moreover, a recent systematic review showed that bone formation differed among commercially available xenograft materials used in maxillary sinus floor elevation surgery (Canellas et al., 2021). It is likely that the differences in clinical outcome between them were relatedto the manufacturing process (do Desterro Fde et al., 2014). Therefore, the most appropriate method for comparing grafting materials is to group them by trademark. To the best of our knowledge, our study is the most comprehensive systematic re- view of evidence on the use of different grafting materials to pre- serve alveolar ridge after tooth extraction, including 31 studies and1088 patients.

Our network meta-analysis differed from the previous systematic reviews because it specifically compared the biomaterials by trademark using a network approach free of sponsorship bias. Basing the treatment arm assignment on trademark provided a head-to-head comparison between biomaterials derived from the same biological group, supporting the selection of adequate bone- substitute materials for alveolar ridge preservation. Moreover, it potentially reduced clinical heterogeneity and increased the consistency of the results.

In total, eight bone-substitute materials showed greater maintenance of alveolar width and height after tooth extraction (Apatos®, Bio-Oss®, Bio-Oss Coll®, Bond-apatite®, FDBA, Gen-Os®, L- PRF, MP3®) when compared with natural healing. Among these materials, five grafting materials were xenografts (Apatos®, Bio-Oss®, Bio-Oss Coll®, Gen-Os®, and MP3®), one was a synthetic biomaterial (biphasic calcium sulfate with hydroxyapatite d Bond-apatite®), one was an allograft (freeze-dried bone allograft d FDBA), and one was an autologous fibrin (leukocyte and platelet- rich fibrin d L-PRF). A recent systematic review (Canellas et al., 2019c) did not find statistical differences in histomorphometric performance among different bone-substitute materials used for alveolar ridge preservation. However, the authors emphasized thattheir study did not attempt to evaluate dimensional alveolar changes. Our network meta-analysis detected important differences in alveolar width and height resorption among the investigated grafting materials.

The most studied grafting materials were Bio-Oss® and Bio-Oss Coll®, which were assessed in 10 studies (191 patients) and 12 studies (185 patients), respectively. They were evaluated in more than half of the included studies. Due to the large amount of in- formation, these biomaterials appeared to be a reliable option, once the results revealed a statistically significant effect on alveolar preservation compared with natural healing. Similarly, Bio-Oss® seems to be very useful for lateral ridge augmentation surgery, according to recent findings (Aludden et al., 2017). Only one study included Apatos®, Bond-apatite®, MP3®, or Gen-Os®. Further studies are needed to enhance the understanding on the effec- tiveness of these biomaterials on alveolar preservation. Studiescomparing Bio-Oss® with Bond-apatite®, MP3®, or Gen-Os® are needed to improve the quality of direct evidence regarding these biomaterials.

Cost-effectiveness is an important aspect when choosing the bone-material substitute. Leukocyte and platelet-rich fibrin (L-PRF)is a second-generation platelet concentrate produced using autol- ogous blood and applying a specific centrifugation protocol ¼(2700 RPM for 12 min, relative centrifugal force, RCF-clot 408 g, using an IntraSpin centrifugation device) (Miron et al., 2019). L-PRF has been recommended in several surgical procedures, showing promising results in bone healing (Canellas et al., 2017, 2020b; Hartlev et al., 2019; Ritto et al., 2019). Our results support the use ofL-PRF as a biomaterial for alveolar ridge preservation. The head-to-head comparison between L-PRF and unassisted healing showed that L-PRF reduced width and height bone loss significantly after tooth extraction. This result was similar to other recent systematic reviews.(Miron et al., 2017; Canellas et al., 2019a). Although some grafting materials have shown greater alveolar ridge preservation in the rankogram, the head-to-head comparisons did not identify any statistically significant differences between L-PRF and the otherthree best biomaterials. Due to the low cost of preparation, L-PRF becomes an attractive option for alveolar preservation.

The main purpose of alveolar preservation is to avoid natural alveolar collapse, eliminating or reducing further bone augmentation procedures during implant surgery, but evidence to support the clinical benefit of alveolar preservation is limited (Horvath et al., 2013). Our systematic review provides resources to support the selection of a bone-substitute material aimed at preservingalveolar bone dimensions after tooth extraction, which will assist the decision-making process in the clinical scenario. The surgeon, however, should take into account several other factors when choosing the most appropriate bone-substitute for each individual case. Our study did not investigate which grafting materials pro- mote better bone healing, or provide better results in terms of primary implant stability or long-term implant success. This would have required a different methodology. The osteoconductive po- tential, size, shape, and microporous structure of the particles contained in each biomaterial can influence the biological and clinical response (do Desterro Fde et al., 2014). Future RCTs assessing whether alveolar preservation can reduce additional bone augmentation and improve implant performance are desirable.

Some limitations of our study should be acknowledged. First, there was a small number of RCTs analyzing a large number of in- terventions. Therefore, further RCTs are needed to improve the quality of the results. Second, the quality of the included RCTs was uncertain, once an unclear or high risk of bias was detected in 24 ofthe 32 studies included. However, when direct evidence has methodological inadequacies, indirect evidence can be used to obtain a better estimate. Third, some heterogeneity and inconsis- tency among studies was observed, mainly in height measurement. As previously described (Avila-Ortiz et al., 2014), there are several factors that can influence bone resorption after tooth extraction, such as socket morphology, periodontal biotype, smoking status, differences in surgical technique, and the number of neighboring teeth extracted. Thus, some of the expected heterogeneity and inconsistency cannot be explored without individual patient data. Finally, some of the studies analyzed included molar and non-molar teeth in their samples, and the patterns of alveolar resorption could have been different between the anterior and posterior regions.

5 Conclusion

Our systematic review provides updated information on theefficacy of different bone-material substitutes for alveolar preser- vation after tooth extraction. In general, bone-substitute materials are effective in reducing alveolar changes after tooth extraction. Xenograft materials should be considered as among the best of the available grafting materials for alveolar preservation after tooth extraction.

References

Aimetti, M., Romano, F., Griga, F.B., Godio, L., 2009. Clinical and histologic healing of human extraction sockets filled with calcium sulfate. Int. J. Oral Maxillofac. Implants 24, 902e909.

Aludden, H.C., Mordenfeld, A., Hallman, M., Dahlin, C., Jensen, T., 2017. Lateral ridgeaugmentation with Bio-Oss alone or Bio-Oss mixed with particulate autogenous bone graft: a systematic review. Int. J. Oral Maxillofac. Surg. 46, 1030e1038.

Avila-Ortiz, G., Elangovan, S., Kramer, K.W., Blanchette, D., Dawson, D.V., 2014. Effect of alveolar ridge preservation after tooth extraction: a systematic review and meta-analysis. J. Dent. Res. 93, 950e958.

Avila-Ortiz, G., Gubler, M., Romero-Bustillos, M., Nicholas, C.L., Zimmerman, M.B., Barwacz, C.A., 2020. Efficacy of alveolar ridge preservation: a randomized controlled trial. J. Dent. Res. 99, 402e409.

Barone, A., Toti, P., Quaranta, A., Alfonsi, F., Cucchi, A., Negri, B., Di Felice, R., Marchionni, S., Calvo-Guirado, J.L., Covani, U., Nannmark, U., 2017. Clinical and histological changes after ridge preservation with two xenografts: preliminary results from a multicentre randomized controlled clinical trial. J. Clin. Perio- dontol. 44, 204e214.

Canellas, J.V.D.S., Grugos, L., Ritto, F.G., Fischer, R.G., Medeiros, P.J.D., 2021. Xenograft materials in maxillary sinus floor elevation surgery: a systematic review with network meta-analyses. Br. J. Oral Maxillofac. Surg. https://doi.org/10.1016/ j.bjoms.2021.02.009.

Canellas, J.V.D.S., da Costa, R.C., Breves, R.C., de Oliveira, G.P., Figueredo, C., Fischer, R.G., Thole, A.A., Medeiros, P.J.D., Ritto, F.G., 2020a. Tomographic and histomorphometric evaluation of socket healing after tooth extraction using leukocyte- and platelet-rich fibrin: a randomized, single-blind, controlled clinical trial. J. Cranio-Maxillo-Fac. Surg. 48 (24e32).

Canellas, J.V.D.S., Fraga, S.R.G., Santoro, M.F., Netto, J.N.S., Tinoco, E.M.B., 2020b. Intrasocket interventions to prevent alveolar osteitis after mandibular third molar surgery: a systematic review and network meta-analysis. J. Cranio- Maxillo-Fac. Surg9 48, 902e913.

Canellas, J.V.D.S., Medeiros, P.J.D., Figueredo, C., Fischer, R.G., Ritto, F.G., 2019a. Platelet-rich fibrin in oral surgical procedures: a systematic review and meta- analysis. Int. J. Oral Maxillofac. Surg. 48, 395e414.

Canellas, J.V.D.S., Medeiros, P.J.D., Figueredo, C., Fischer, R.G., Ritto, F.G., 2019b. Which is the best choice after tooth extraction, immediate implant placement or delayed placement with alveolar ridge preservation? A systematic review and meta-analysis. J. Cranio-Maxillo-Fac. Surg. 47, 1793e1802.

Canellas, J.V.D.S., Ritto, F.G., Figueredo, C., Fischer, R.G., de Oliveira, G.P., Thole, A.A., Medeiros, P.J.D., 2019c. Histomorphometric evaluation of different grafting materials used for alveolar ridge preservation: a systematic review and network meta-analysis. Int. J. Oral Maxillofac. Surg. 49, 797e810.

Canellas, J.V.D.S., Ritto, F.G., Medeiros, P.J.D., 2017. Evaluation of postoperative complications after mandibular third molar surgery with the use of platelet-rich fibrin: a systematic review and meta-analysis. Int. J. Oral Maxillofac. Surg. 46, 1138e1146.

Canellas, J.V.D.S., Soares, B., Ritto, F.G., Fischer, R.G., Vidigal, G.M., Vettore, M.V., Medeiros, P.J.D., 2020c. What is the best biomaterial for alveolar ridge preser- vation after tooth extraction? A systematic review and network meta-analysis protocol. Inplasy Protocol. https://doi.org/10.37766/inplasy2020.3.0005, 202030005.

Chappuis, V., Engel, O., Reyes, M., Shahim, K., Nolte, L.P., Buser, D., 2013. Ridge al- terations post-extraction in the esthetic zone: a 3D analysis with CBCT. J. Dent. Res. 92, 195Se201S.

Cipriani, A., Higgins, J.P., Geddes, J.R., Salanti, G., 2013. Conceptual and technical challenges in network meta-analysis. Ann. Intern. Med. 159, 130e137.

Clark, D., Rajendran, Y., Paydar, S., Ho, S., Cox, D., Ryder, M., Dollard, J., Kao, R.T., 2018. Advanced platelet-rich fibrin and freeze-dried bone allograft for ridge preservation: a randomized controlled clinical trial. J. Periodontol. 89, 379e387.

Das, S., Jhingran, R., Bains, V.K., Madan, R., Srivastava, R., Rizvi, I., 2016. Socket preservation by beta-tri-calcium phosphate with collagen compared to platelet-rich fibrin: a clinico-radiographic study. Eur. J. Dermatol. 10, 264e276.

do Desterro Fde, P., Sader, M.S., Soares, G.D., Vidigal Jr., G.M., 2014. Can inorganic bovine bone grafts present distinct properties? Braz. Dent. J. 25, 282e288.

Festa, V.M., Addabbo, F., Laino, L., Femiano, F., Rullo, R., 2013. Porcine-derived xenograft combined with a soft cortical membrane versus extraction alone for implant site development: a clinical study in humans. Clin. Implant Dent. Relat. Res. 15, 707e713.

Flores Fraile, J., Lopez-Valverde, N., Garcia de Castro Andews, A., Santos Marino, J.A., Ramirez, J.M., Gomez de Diego, R., Montero, J., Lopez-Valverde, A., Blanco Antona, L.A., 2020. Safety and efficacy of a new synthetic material based on monetite, silica gel, ps-wallastonite, and a hydroxyapatite calcium deficient: a randomized comparative clinic trial. Med (Kaunas) 56 (2), 46.

Hartlev, J., Spin-Neto, R., Schou, S., Isidor, F., Norholt, S.E., 2019. Cone beam computed tomography evaluation of staged lateral ridge augmentation using platelet-rich fibrin or resorbable collagen membranes in a randomized controlled clinical trial. Clin. Oral Implants Res. 30, 277e284.

Higgins, J.P., Altman, D.G., Gotzsche, P.C., Juni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne, J.A., 2011. Cochrane bias methods G, Cochrane statistical methods G: the Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343, d5928.

Horvath, A., Mardas, N., Mezzomo, L.A., Needleman, I.G., Donos, N., 2013. Alveolar ridge preservation. A systematic review. Clin. Oral Invest. 17, 341e363.

Iasella, J.M., Greenwell, H., Miller, R.L., Hill, M., Drisko, C., Bohra, A.A., Scheetz, J.P., 2003. Ridge preservation with freeze-dried bone allograft and a collagen membrane compared to extraction alone for implant site development: a clinical and histologic study in humans. J. Periodontol. 74, 990e999.

Iocca, O., Farcomeni, A., Pardinas Lopez, S., Talib, H.S., 2017. Alveolar ridge preser- vation after tooth extraction: a Bayesian network meta-analysis of grafting materials efficacy on prevention of bone height and width reduction. J. Clin. Periodontol. 44, 104e114.

Iorio-Siciliano, V., Blasi, A., Nicolo, M., Iorio-Siciliano, A., Riccitiello, F., Ramaglia, L., 2017. Clinical outcomes of socket preservation using bovine-derived xenograft collagen and collagen membrane post-tooth extraction: a 6-month randomized controlled clinical trial. Int. J. Periodontics Restor. Dent. 37 e290ee296.

Iorio-Siciliano, V., Ramaglia, L., Blasi, A., Bucci, P., Nuzzolo, P., Riccitiello, F., Nicolo, M., 2020. Dimensional changes following alveolar ridge preservation in the posterior area using bovine-derived xenografts and collagen membrane compared to spontaneous healing: a 6-month randomized controlled clinical trial. Clin. Oral Invest. 24, 1013e1023.

Jung, G.U., Jeon, T.H., Kang, M.H., Um, I.W., Song, I.S., Ryu, J.J., Jun, S.H., 2018a.Volumetric, radiographic, and histologic analyses of demineralized dentin matrix combined with recombinant human bone morphogenetic protein-2 for ridge preservation: a prospective randomized controlled trial in comparison with xenograft. Appl. Sci. 8 (8).

Jung, R.E., Ioannidis, A., Hammerle, C.H.F., Thoma, D.S., 2018b. Alveolar ridge pres- ervation in the esthetic zone. Periodontol. 2000 77, 165e175.

Jung, R.E., Philipp, A., Annen, B.M., Signorelli, L., Thoma, D.S., Hammerle, C.H., Attin, T., Schmidlin, P., 2013. Radiographic evaluation of different techniques for ridge preservation after tooth extraction: a randomized controlled clinical trial.J. Clin. Periodontol. 40, 90e98.

Jung, R.E., Sapata, V.M., Hammerle, C.H.F., Wu, H., Hu, X.L., Lin, Y., 2018c. Combined use of xenogeneic bone substitute material covered with a native bilayer collagen membrane for alveolar ridge preservation: a randomized controlled clinical trial. Clin. Oral Implants Res. 29, 522e529.

Kollati, P., Koneru, S., Dwarakanath, C.D., Gottumukkala, S.N.V.S., 2019. Effectiveness of naturally derived bovine hydroxyapatite (Cerabone™) combined with platelet-rich fibrin matrix in socket preservation: a randomized controlled clinical trial. J. Indian Soc. Periodontol. 23, 145e151.

Lee, J.H., Kim, D.H., Jeong, S.N., 2020. Comparative assessment of anterior maxillary alveolar ridge preservation with and without adjunctive use of enamel matrix derivative: a randomized clinical trial. Clin. Oral Implants Res. 31 (1e9).

Lee, J.S., Cha, J.K., Kim, C.S., 2018. Alveolar ridge regeneration of damaged extraction sockets using deproteinized porcine versus bovine bone minerals: a randomized clinical trial. Clin. Implant Dent. Relat. Res. 20, 729e737.

Lim, H.C., Jung, U.W., You, H., Lee, J.S., 2017. Randomized clinical trial of ridge preservation using porcine bone/cross-linked collagen vs. bovine bone/non- cross-linked collagen: cone beam computed tomographic analysis. Clin. Oral Implants Res. 28, 1492e1500.

Lim, H.C., Shin, H.S., Cho, I.W., Koo, K.T., Park, J.C., 2019. Ridge preservation in molar extraction sites with an open healing approach: a randomized controlled clinical trial. J. Clin. Periodontol. 46, 1144e1154.

Llanos, A.H., Sapata, V.M., Jung, R.E., Hammerle, C.H., Thoma, D.S., Cesar Neto, J.B., Pannuti, C.M., Romito, G.A., 2019. Comparison between two bone substitutes for alveolar ridge preservation after tooth extraction: cone-beam computed tomography results of a non-inferiority randomized controlled trial. J. Clin. Periodontol. 46, 373e381.

Machtei, E.E., Mayer, Y., Horwitz, J., Zigdon-Giladi, H., 2019. Prospective randomized controlled clinical trial to compare hard tissue changes following socket pres- ervation using alloplasts, xenografts vs no grafting: clinical and histological findings. Clin. Implant Dent. Relat. Res. 21 (14e20).

Mayer, Y., Zigdon-Giladi, H., Machtei, E.E., 2016. Ridge preservation using composite alloplastic materials: a randomized control clinical and histological study in humans. Clin. Implant Dent. Relat. Res. 18, 1163e1170.

Miron, R.J., Pinto, N.R., Quirynen, M., Ghanaati, S., 2019. Standardization of relative centrifugal forces in studies related to platelet-rich fibrin. J. Periodontol. 90, 817e820.

Miron, R.J., Zucchelli, G., Pikos, M.A., Salama, M., Lee, S., Guillemette, V., Fujioka- Kobayashi, M., Bishara, M., Zhang, Y., Wang, H.L., Chandad, F., Nacopoulos, C., Simonpieri, A., Aalam, A.A., Felice, P., Sammartino, G., Ghanaati, S., Hernandez, M.A., Choukroun, J., 2017. Use of platelet-rich fibrin in regenerative dentistry: a systematic review. Clin. Oral Invest. 21, 1913e1927.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339, b2535.

Morjaria, K.R., Wilson, R., Palmer, R.M., 2014. Bone healing after tooth extraction with or without an intervention: a systematic review of randomized controlled trials. Clin. Implant Dent. Relat. Res. 16 (1e20).

Nart, J., Barallat, L., Jimenez, D., Mestres, J., Gomez, A., Carrasco, M.A., Violant, D., Ruiz-Magaz, V., 2017. Radiographic and histological evaluation of deproteinized bovine bone mineral vs. deproteinized bovine bone mineral with 10% collagen in ridge preservation. A randomized controlled clinical trial. Clin. Oral Implants Res. 28, 840e848.

Nunes, F.A.S., Pignaton, T.B., Novaes Jr., A.B., Taba Jr., M., Messora, M.R., Palioto, D.B., Spin-Neto, R., de Souza, S.L.S., 2018. Evaluation of a bone substitute covered with a collagen membrane for ridge preservation after tooth extraction. Clinical and tomographic randomized controlled study in humans. Clin. Oral Implants Res. 29, 424e433.

Orwin, R.G., 1994. Evaluating coding decision. In: Cooper, H., Hedges, L.V. (Eds.), The Handbook of Research Synthesis. Russell Sage Foundation, New York (NY).

Ritto, F.G., Pimentel, T., Canellas, J.V.S., Junger, B., Cruz, M., Medeiros, P.J., 2019. Randomized double-blind clinical trial evaluation of bone healing after third molar surgery with the use of leukocyte- and platelet-rich fibrin. Int. J. Oral Maxillofac. Surg. 48, 1088e1093.

Sadeghi, R., Babaei, M., Miremadi, S.A., Abbas, F.M., 2016. A randomized controlled evaluation of alveolar ridge preservation following tooth extraction using deproteinized bovine bone mineral and demineralized freeze-dried bone allo- graft. Dent. Res. J. 13, 151e159.

Salanti, G., 2012. 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 3 (80e97).

Santana, R., Gyurko, R., Kanasi, E., Xu, W.P., Dibart, S., 2019. Synthetic polymeric barrier membrane associated with blood coagulum, human allograft, or bovine bone substitute for ridge preservation: a randomized, controlled, clinical and histological trial. Int. J. Oral Maxillofac. Surg. 48, 675e683.

Sapata, V.M., Llanos, A.H., Cesar Neto, J.B., Jung Re, R.E., Thoma, D.S., Hammerle, Ch CHF., Pannuti, C.M., Romito, G.A., 2020. Deproteinized bovine bone mineral is non-inferior to deproteinized bovine bone mineral with 10% collagen in maintaining the soft tissue contour post-extraction: a randomised trial. Clin. Oral Implants Res. 31 (3), 294e301.

Serrano Mendez, C.A., Lang, N.P., Caneva, M., Ramirez Lemus, G., Mora Solano, G., Botticelli, D., 2017. Comparison of allografts and xenografts used for alveolar ridge preservation. A clinical and histomorphometric RCT in humans. Clin. Implant Dent. Relat. Res. 19, 608e615.

Song, F., Harvey, I., Lilford, R., 2008. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical in- terventions. J. Clin. Epidemiol. 61, 455e463.

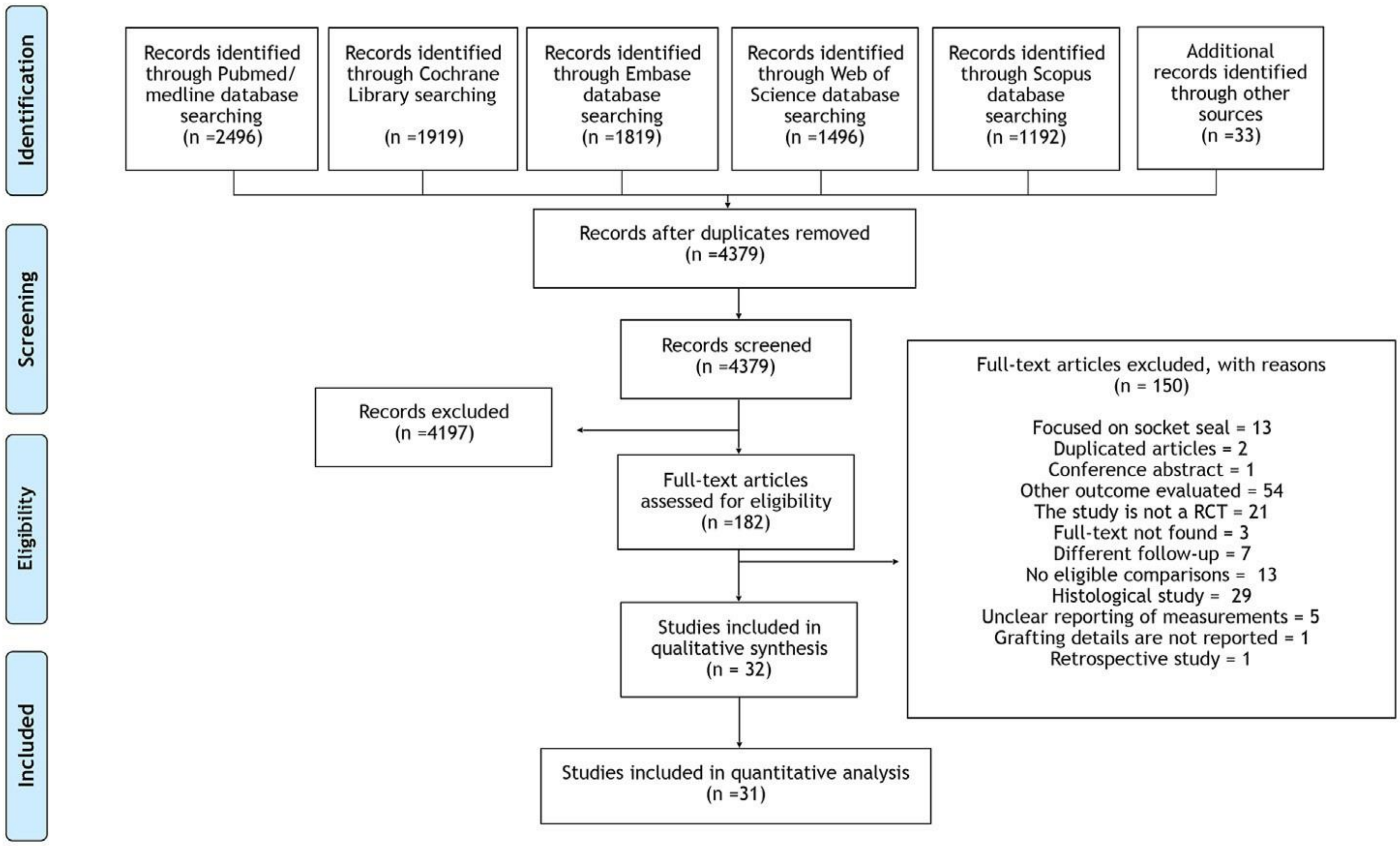
Sun, D.J., Lim, H.C., Lee, D.W., 2019. Alveolar ridge preservation using an open membrane approach for sockets with bone deficiency: a randomized controlled clinical trial. Clin. Implant Dent. Relat. Res. 21, 175e182.

Tan, W.L., Wong, T.L., Wong, M.C., Lang, N.P., 2012. A systematic review of post- extractional alveolar hard and soft tissue dimensional changes in humans. Clin. Oral Implants Res 23 (Suppl. 5), 1e21.

Temmerman, A., Vandessel, J., Castro, A., Jacobs, R., Teughels, W., Pinto, N., Quirynen, M., 2016. The use of leucocyte and platelet-rich fibrin in socket management and ridge preservation: a split-mouth, randomized, controlled clinical trial. J. Clin. Periodontol. 43, 990e999.

Tomasi, C., Donati, M., Cecchinato, D., Szathvary, I., Corrà, E., Lindhe, J., 2018. Effect of socket grafting with deproteinized bone mineral: an RCT on dimensional al- terations after 6 months. Clin. Oral Implants Res. 29, 435e442.

Walker, C.J., Prihoda, T.J., Mealey, B.L., Lasho, D.J., Noujeim, M., Huynh-Ba, G., 2017. Evaluation of healing at molar extraction sites with and without ridge preser- vation: a randomized controlled clinical trial. J. Periodontol. 88, 241e249.



Flow diagram (PRISMA) - screening and selection process.

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

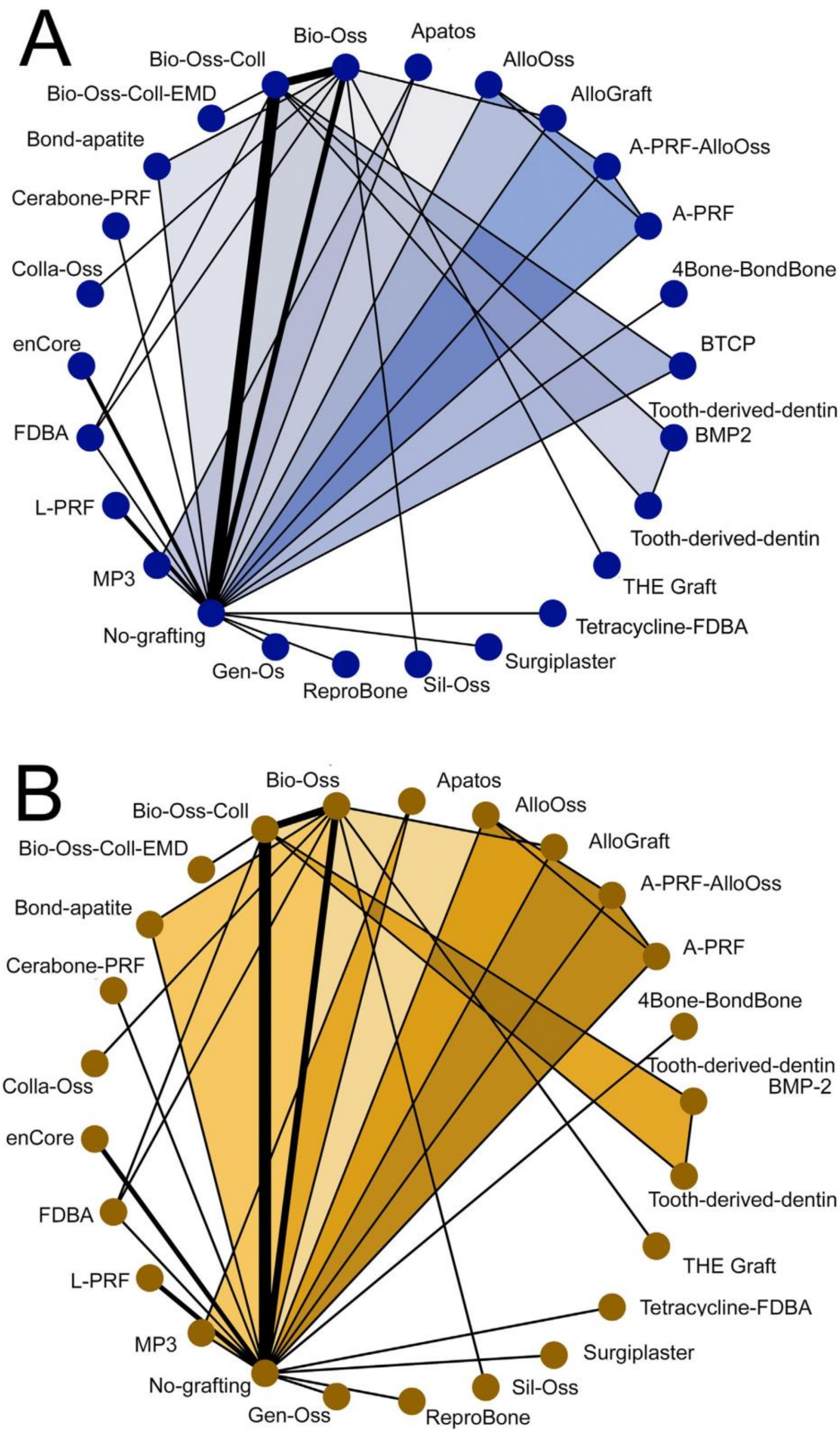


Fig. 2. Network plots for (A) width and (B) height resorption. The nodes correspond to the grafting materials. Two treatments are connected by a line when there is at least one study comparing the two grafting materials. The thickness of each line is proportional to the number of studies. The shading indicates the multi-arm studies.

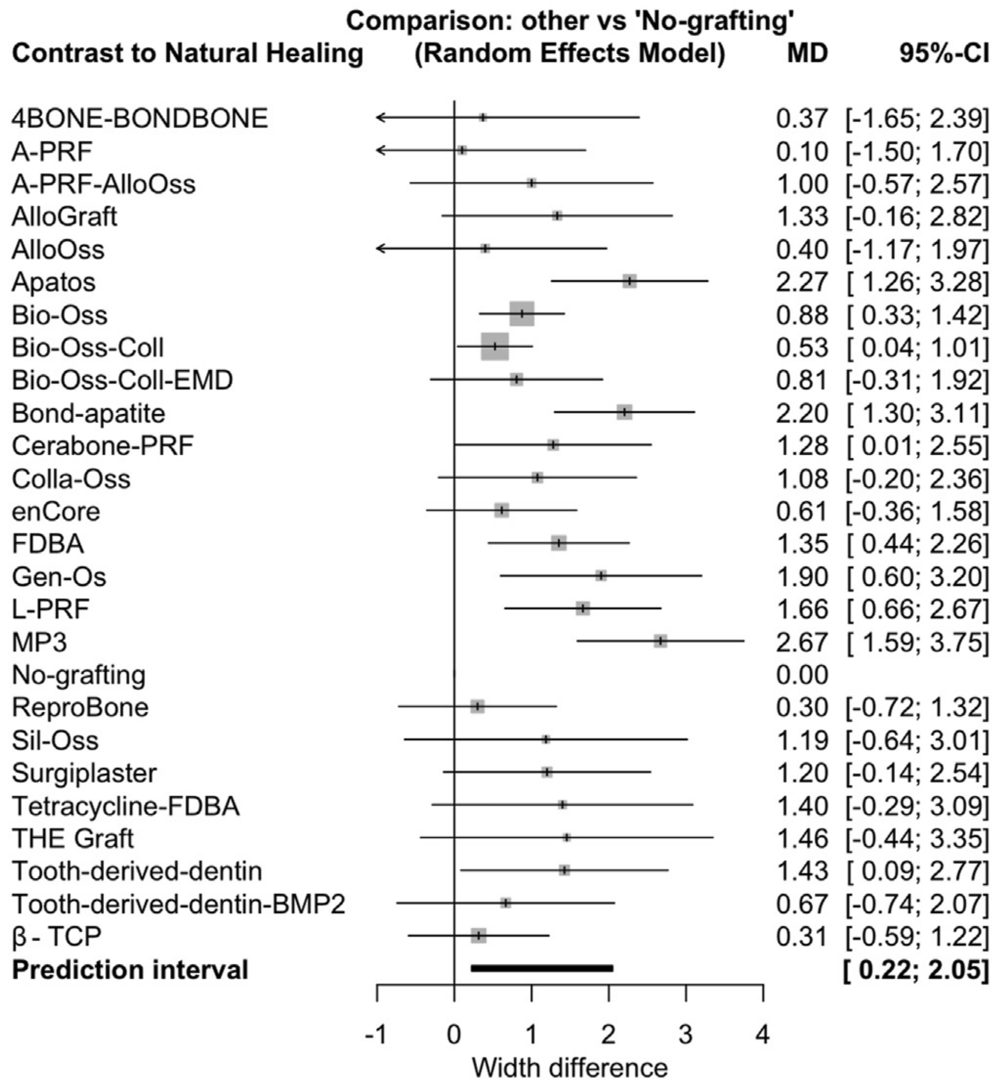


Fig. 3. Forest plot comparing width resorption between bone-material substitute and no grafting. The prediction interval represented by a black bar is the interval in which the results of a future study will fall. The changes in width resorption varied between

0.22 mm and 2.05 mm, depending on the grafting material used.

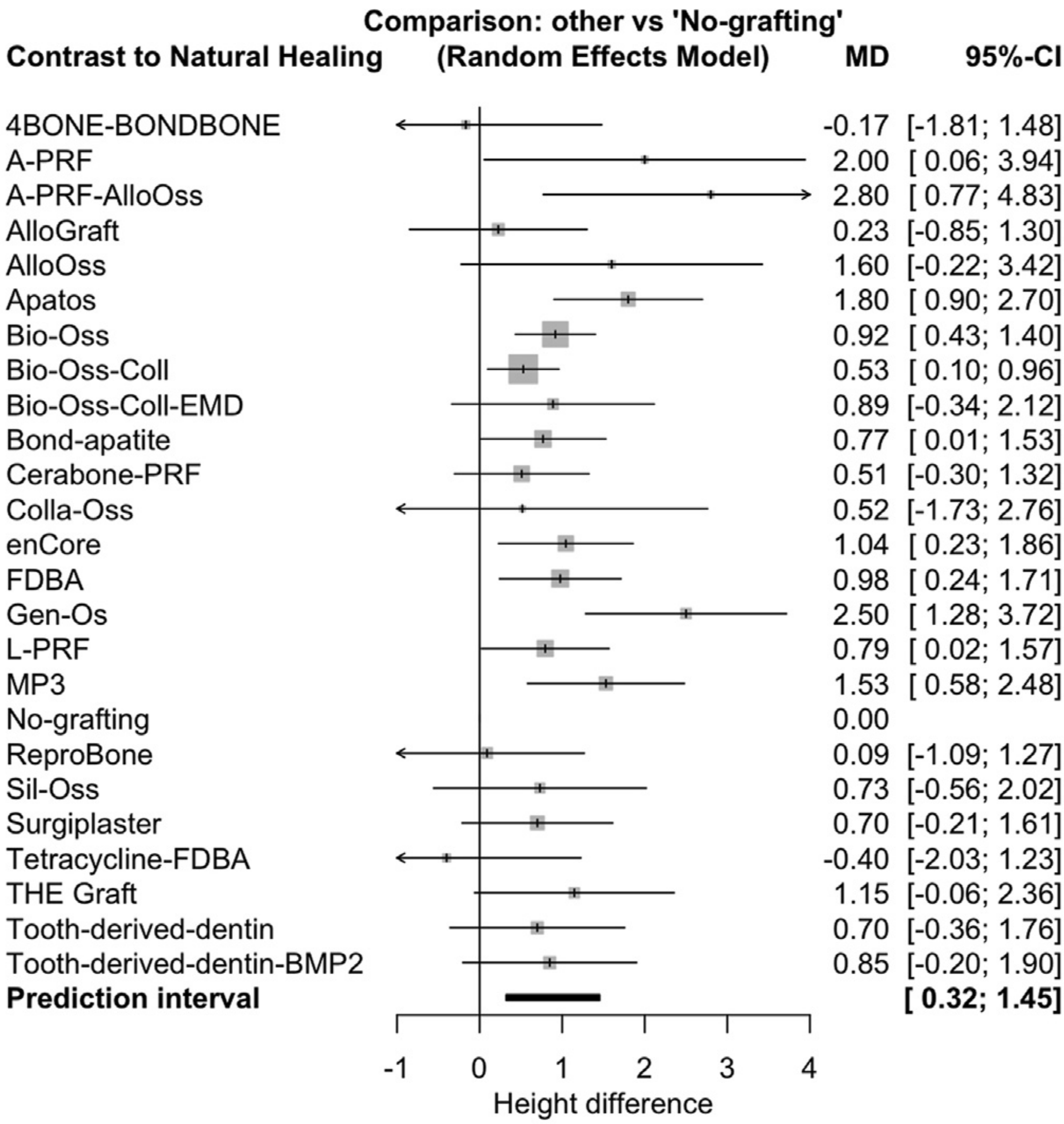


Fig. 4. Forest plot comparing height resorption between bone-material substitute and no grafting. The prediction interval represented by a black bar is the interval in which the results of a future study will fall. The changes in height resorption varied between 0.32 mm and 1.45 mm, depending on the grafting material used.

Mean difference (Width)

AlloGraft	0.93 [-1.23; 3.10]	-0.94 [-2.74; 0.86]	0.46 [-1.02; 1.94]	0.81 [-0.71; 2.32]	-0.87 [-2.57; 0.82]	0.72 [-1.06; 2.49]	-0.02 [-1.70; 1.66]	-0.33 [-2.13; 1.47]	-1.34 [-3.18; 0.50]	1.33 [-0.16; 2.82]	-0.57 [-2.54; 1.41]	-0.09 [-2.06; 1.87]
-1.37 [-3.49; 0.74]	AlloOss	-1.87 [-3.74; -0.00]	-0.48 [-2.14; 1.19]	-0.13 [-1.77; 1.52]	-1.80 [-3.62; 0.01]	-0.21 [-2.06; 1.63]	-0.95 [-2.77; 0.86]	-1.26 [-3.13; 0.60]	-2.27 [-4.17; -0.37]	0.40 [-1.17; 1.97]	-1.50 [-3.54; 0.54]	-1.03 [-3.09; 1.04]
-1.57 [-2.97; -0.17]	-0.20 [-2.23; 1.83]	Apatos	1.39 [0.24; 2.54]	1.74 [0.62; 2.86]	0.07 [-1.29; 1.42]	1.66 [0.26; 3.06]	0.92 [-0.44; 2.28]	0.61 [-0.82; 2.03]	-0.40 [-1.48; 0.68]	2.27 [1.26; 3.28]	0.37 [-1.28; 2.02]	0.84 [-0.83; 2.52]
-0.69 [-1.77; 0.39]	0.68 [-1.20; 2.57]	0.88 [-0.14; 1.90]	Bio-Oss	0.35 [-0.14; 0.84]	-1.33 [-2.24; -0.42]	0.26 [-0.85; 1.38]	-0.48 [-1.31; 0.36]	-0.79 [-1.94; 0.36]	-1.79 [-3.00; -0.59]	0.88 [0.33; 1.42]	-1.02 [-2.44; 0.39]	-0.55 [-1.89; 0.79]
-0.30 [-1.42; 0.82]	1.07 [-0.80; 2.94]	1.27 [0.27; 2.27]	0.39 [-0.10; 0.87]	Bio-Oss-Coll	-1.68 [-2.63; -0.72]	-0.09 [-1.17; 1.00]	-0.83 [-1.69; 0.04]	-1.14 [-2.26; -0.02]	-2.14 [-3.33; -0.96]	0.53 [0.04; 1.01]	-1.37 [-2.76; 0.01]	-0.90 [-2.15; 0.35]
-0.54 [-1.81; 0.73]	0.83 [-1.14; 2.81]	1.03 [-0.15; 2.21]	0.15 [-0.60; 0.90]	-0.24 [-1.06; 0.58]	Bond-apatite	1.59 [0.26; 2.92]	0.85 [-0.35; 2.05]	0.54 [-0.82; 1.89]	-0.47 [-1.87; 0.94]	2.20 [1.30; 3.11]	0.30 [-1.28; 1.89]	0.78 [-0.79; 2.35]
-0.82 [-2.17; 0.53]	0.56 [-1.44; 2.55]	0.76 [-0.46; 1.97]	-0.13 [-1.08; 0.82]	-0.52 [-1.44; 0.41]	-0.28 [-1.39; 0.84]	enCore	-0.74 [-2.07; 0.59]	-1.05 [-2.45; 0.35]	-2.06 [-3.51; -0.61]	0.61 [-0.36; 1.58]	-1.29 [-2.91; 0.34]	-0.81 [-2.47; 0.84]
-0.75 [-1.99; 0.49]	0.62 [-1.34; 2.59]	0.82 [-0.34; 1.99]	-0.06 [-0.73; 0.62]	-0.45 [-1.17; 0.27]	-0.21 [-1.18; 0.77]	0.07 [-1.03; 1.17]	FDBA	-0.31 [-1.67; 1.05]	-1.32 [-2.73; 0.09]	1.35 [0.44; 2.26]	-0.55 [-2.14; 1.04]	-0.07 [-1.59; 1.45]
-0.57 [-1.89; 0.75]	0.81 [-1.17; 2.79]	1.01 [-0.18; 2.19]	0.12 [-0.79; 1.03]	-0.27 [-1.15; 0.62]	-0.03 [-1.11; 1.06]	0.25 [-0.87; 1.37]	0.18 [-0.88; 1.25]	L-PRF	-1.01 [-2.48; 0.47]	1.66 [0.66; 2.67]	-0.24 [-1.88; 1.41]	0.24 [-1.44; 1.92]
-1.30 [-2.74; 0.13]	0.07 [-1.99; 2.13]	0.27 [-0.76; 1.30]	-0.61 [-1.68; 0.45]	-1.00 [-2.04; 0.04]	-0.76 [-1.98; 0.46]	-0.49 [-1.74; 0.77]	-0.55 [-1.75; 0.65]	-0.74 [-1.96; 0.49]	MP3	2.67 [1.59; 3.75]	0.77 [-0.92; 2.46]	1.24 [-0.48; 2.96]
0.23 [-0.85; 1.30]	1.60 [-0.22; 3.42]	1.80 [0.90; 2.70]	0.92 [0.43; 1.40]	0.53 [0.10; 0.96]	0.77 [0.01; 1.53]	1.04 [0.23; 1.86]	0.98 [0.24; 1.71]	0.79 [0.02; 1.57]	1.53 [0.58; 2.48]	No-grafting	-1.90 [-3.20; -0.60]	-1.43 [-2.77; -0.09]
-2.27 [-3.90; -0.65]	-0.90 [-3.09; 1.29]	-0.70 [-2.21; 0.81]	-1.58 [-2.89; -0.27]	-1.97 [-3.26; -0.68]	-1.73 [-3.17; -0.30]	-1.46 [-2.92; 0.01]	-1.52 [-2.94; -0.10]	-1.71 [-3.15; -0.27]	-0.97 [-2.51; 0.57]	-2.50 [-3.72; -1.28]	Gen-Os	0.47 [-1.39; 2.34]
-0.47 [-1.95;1.01]	0.90 [-1.21; 3.01]	1.10 [-0.29; 2.49]	0.22 [-0.86; 1.30]	-0.17 [-1.13; 0.79]	0.07 [-1.19; 1.33]	0.35 [-0.99; 1.68]	0.28 [-0.93; 1.48]	0.10 [-1.21; 1.40]	0.83 [-0.59; 2.25]	-0.70 [-1.76; 0.36]	1.80 [0.19; 3.41]	Tooth-derived-dentin

Mean difference (Height)

Fig. 5. Head-to-head comparisons between interventions: mean difference (95% CI). Alveolar width resorption estimates are surrounded by green lines, and alveolar height resorption estimates are surrounded by red lines. Each rectangle represents a comparison between two bone-material substitutes in the diagonal line (grey rectangle). When the value '0' was included in the 95% confidence interval, there was deemed to be no statistically significant difference between the interventions. The blue rectangles favor the line-defined grafting material, and the orange rectangles favor the column-defined grafting material.