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Alveolar ridge preservation techniques: a systematic review and meta-analysis of histological and histomorphometrical data

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Abstract

Aim: The aim of this article was to systematically review histological and histomorphometrical data from literature that provide information regarding the effect of alveolar ridge preservation procedures on healing after tooth extraction in humans.

Materials and methods: The MEDLINE-PubMed and the Cochrane CENTRAL databases were searched up to September 2012; 38 papers were selected from 646 founded. A meta-analysis was performed regarding the variations in the mean percentage of Bone, Connective Tissue and Residual Graft Material between three different types of Procedures.

Results: The highest value regarding bone percentages is produced at 3 months by Procedures with Allografts (54.4%), while the lowest is obtained, at 5 months, by those using Xenografts (23.6%). Referring to connective tissue, the highest and lowest values are shown at 7 months, with Allografts (67%) and Alloplasts (27.1%), respectively. Regarding residual graft material, the lowest rates are displayed by Procedures with Allografts (12.4–21.11%), while those using Xenografts and Alloplasts showed the best results at 7 months (37.14 and 37.23%). No statistical difference was found.

Conclusions: With the limitations due to the features of the selected papers, no major histological and histomorphometrical differences arose among different procedures or when compared to spontaneous healing. Thus, it might be argued that in preserved sites it is unnecessary to wait over 3 to 4 months prior to implant insertion.

After tooth extractions, either single or multiple, a consequent loss in height and width of the alveolar process always takes place. The amount of the horizontal bone loss is generally the greatest and occurs mainly on the buccal plate as opposed to the lingual/palatal aspect of the ridge, meanwhile a subsequent reduction of vertical ridge height is slighter and more pronounced on the facial side as well (Araujo & Lindhe 2005; Van der Weijden et al. 2009; Tan et al. 2012). This double resorption process of extraction sites results in narrower and thinner ridges with a reduced vertical height (Pinho et al. 2006) and a lingual/palatal shifting of their long axis. Many studies have shown that resorption of the buccal plate may have devastating functional and esthetical consequences as insufficient vertical and horizontal volume of alveolar bone might eventually be present

at the extraction sites, impairing the execution of both traditional and implant supported dentures (Bartee 2001a,b; Cardaropoli et al. 2003; Araujo & Lindhe 2005; Pinho et al. 2006). Thus, over the past 20 years, various surgical procedures, with different nomenclatures, have been introduced aiming both to maintain an ideal ridge profile in aesthetic sites, and to prevent alveolar ridge collapse, preserving adequate dimensions of bone in order to facilitate correct implant placement (Darby et al. 2008). In fact, in many clinical studies, several methods have already been looked into, such as socket grafting with autogenous bone grafts (Becker et al. 1994), demineralized freeze-dried bone allografts (DFDBA) (Becker et al. 1994, 1996; Froum et al. 2002), deproteinized bovine-bone mineral (DBBM) (Artzi et al. 2000), other xenografts, alloplasts (Serino et al. 2003), and bone morphogenic pro-

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teins (BMP) (Fiorellini et al. 2005). Furthermore, guided bone regeneration (GBR) procedures with or without bone grafts, with reabsorbable or non-reabsorbable barriers, have also been evaluated (Lekovic et al. 1997, 1998; Iasella et al. 2003; Barone et al. 2008; Mardas et al. 2010, 2011). Consequently, among clinicians, an increasing interest has arisen regarding the concept called "alveolar ridge preservation" (ARP), which was defined as "any procedure undertaken at the time of or following an extraction that is designed to minimize external resorption of the ridge and maximize bone formation within the socket" (Horvath et al. 2013). Hence, since 2009 various systematic reviews have been published on this topic, confirming the efficacy of different "ARPs" in preventing post-extraction dimensional changes of alveolar ridges (Ten Heggeler et al. 2010; Vignoletti et al. 2012; Horvath et al. 2013; Vittorini Orgeas et al. 2013). The last consensus "Osteology Consensus Report" (Hammerle et al. 2012) stated the indications for "ARPs" as follows:

- Maintenance of the existing soft and hard tissue envelope.
- Maintenance of a stable ridge volume for optimizing functional and esthetic outcomes.
- Simplification of treatment procedures subsequent to the ridge preservation.

Furthermore, the authors suggest the following clinical recommendations:

- Raising of a flap and placement of biomaterials (biomaterial for ridge contouring and/or barrier membrane).
- Primary wound closure.
- Materials with a low resorption and replacement rate.
- Raising of flaps and placement of a device/devices for contouring the ridge profile.

However, a systematic assessment of the nature and quality of the newly formed tissue, with proper evaluation of histomorphometric data, has not been carried out.

The aim of this paper was to systematically review the literature, including RCTs, CTs, and Case Series, searching for histological data that provide informations on the effect of different ARPs in patients requiring tooth extractions in terms of residual graft, bone, and connective tissues percentages as compared with physiological healing processes in untreated sites.

Materials and methods

Focused question

Considering patients treated by means of ARPs after tooth extraction and prior to implant insertion, are there differences in the mean histomorphometrical values of bone, connective tissue and graft material, if used, among the different techniques and in comparison with spontaneous healing, over a 3–7 months period?

Search strategy

Up to September 2012, The National Library of Medicine, Washington, DC (MEDLINE-PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched, using the following free-text terms: (fresh extraction socket OR alveolar socket) AND (socket preservation OR alveolar ridge preservation OR biomaterial OR graft OR membrane OR barrier OR flap OR flap-less OR immediate implant placement OR immediate implant). Then, the terms: NOT (trauma OR tumour OR injuries OR cancer OR cleft lip and palate) were added to exclude any off topic studies. This research was supplemented by cross-checking the reference list of selected studies and review articles, looking for additional papers that could meet the eligibility criteria fixed for the study. Also, the so-called "grey literature" was investigated by means of direct contacts with authors and companies.

The inclusion criteria were as follows:

- human studies
- publications in English
- Randomized Controlled Clinical Trials, Controlled Clinical Trials, prospective/retrospective clinical trials or case series with a minimum of four biopsy cores analyzed per group
- studies describing the use of biomaterials and/or barriers
- histomorphometrical evaluation of hard tissues over a period of 3–7 months.

The exclusion criteria were as follows:

- animal studies
- publications reporting the same data of later publications by the same authors
- studies describing immediate implant placement in fresh extraction sockets
- letters, narrative or historical review.

Screening process

First, two reviewers (V.D.R., M.C.) screened the titles and abstracts independently and did the primary search. Subsequently, the

studies appearing to meet the inclusion criteria, or those with insufficient data in the title and abstract to make a clear decision, were selected for evaluation of the full manuscript, which was carried out independently by the same two reviewers who determined their eligibility. Any disagreement was resolved by discussion with a third reviewer (G.V.O.). To prevent selection bias, the reviewers were blind to the name of the authors, institutions and journal titles. All studies that met the inclusion criteria underwent a validity assessment. The reasons for rejecting studies at this or at subsequent stages were recorded. Special attention was paid to duplicate publications to avoid the likely stronger impact of the same data on the overall result. All reference lists of selected studies, relevant reviews, and studies from the "grey literature" were screened for additional papers that might have met the eligibility criteria of this systematic review (Fig. 1).

Assessment of heterogeneity

In order to evaluate the heterogeneity of the primary outcomes between the selected studies, the following factors were recorded (Table 1):

- study design and setting
- duration of follow-up
- mean age (range), number and gender of subjects
- smoking status
- surgical procedures and pharmacological treatments
- histomorphometrical outcomes.

Quality assessment

Assessment of methodological study quality was performed, as proposed by Van der Weijden et al. (Van der Weijden et al. 2009), combining the criteria of the PRISMA-Preferred Items for Reporting of Systematic Reviews and Meta-analysis (Liberati et al. 2009), of the CONSORT statement, of Moher et al. (Moher et al. 1999, 2001), of the MOOSE statement (Stroup et al. 2000), of the STROBE statement (von Elm et al. 2007), of Esposito et al. (Esposito et al. 2001) and Needleman (Needleman 1999). This combination resulted in the quality criteria mentioned in Table 2. A given study was classified as low risk of bias when the following criteria were met: (i) random allocation, (ii) defined inclusion/exclusion criteria, (iii) blinding to patient

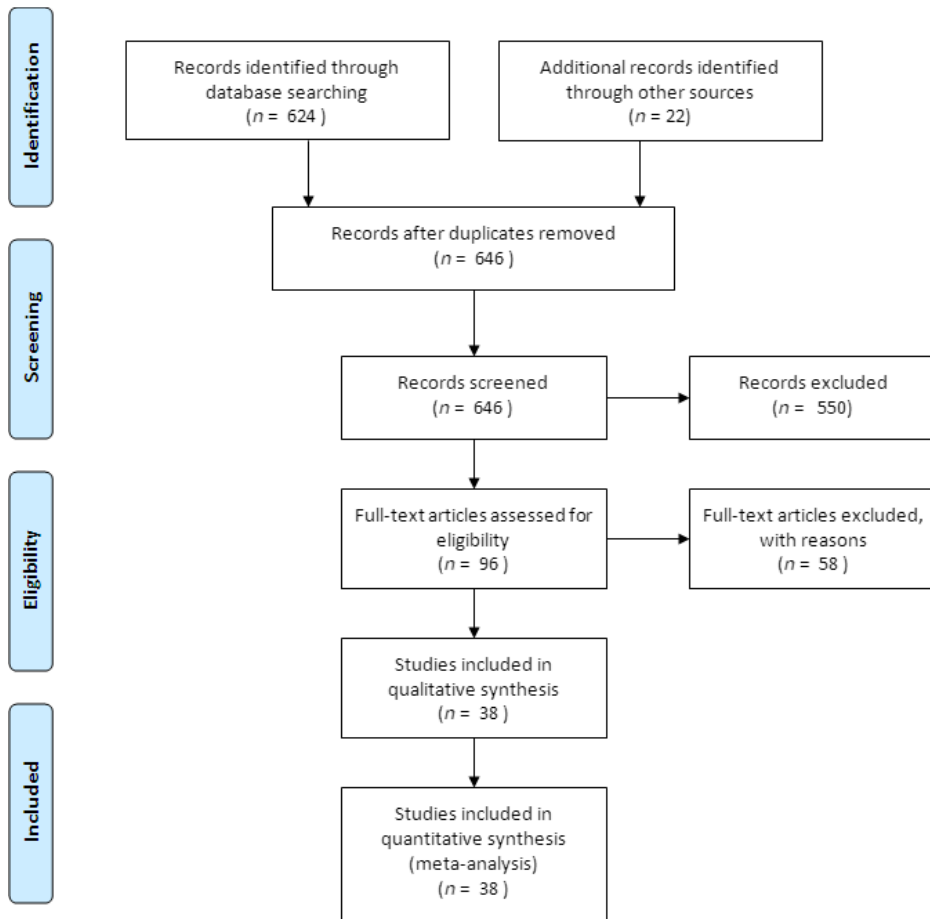


Fig. 1. The PRISMA flow-chart of search results.

and examiner, (iv) balanced experimental groups, (v) an identical treatment between groups except for intervention, and (vi) report of follow-up. When one of these six criteria was missing the study was classified as having a moderate potential risk of bias. When two or more of these criteria were missing, this resulted in a high potential risk of bias. In addition, the Centre for Evidence Based Medicine (CEBM) document for "Levels of Evidence" was used to assess the methodological quality of all included studies. The Jadad score (Jadad et al. 1996) was used to assess the quality of Randomized Controlled Clinical Trials.

Data extraction and analysis

Two authors (V.D.R. and A.M.) performed the statistical analysis according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (Liberati et al. 2009) and the Cochrane Handbook for Systematic Reviews (Higgins et al. 2008).

Data were extracted by two independent examiners (V.D.R and M.C.); any disagree-

ment on the data were resolved by a third examiner (G.V.O.). Data extracted from the selected studies were processed for the analysis. As outcome variables were selected the percentage of Bone (% B), Connective Tissue (% CT) and Residual Graft Material (% RGM), if used. Mean values and standard deviations were calculated from the statistical examiner if only raw data were reported.

Concerning CT and RCT, proportion meta-analysis of both B, CT and RGM were performed: pooled weighted means with respective confidence interval at 95% (CI95%) were reported.

Moreover, for each time interval, forest plots were computed.

The Cochran χ^2 (Cochran Q) test was used to evaluate the between-study heterogeneity in the different groups. If $\chi^2 < 0.05$, heterogeneity was not found and fixed-effect model is shown. On the contrary, the random-effect model is reported. The level of significance was set at $P < 0.05$.

In addition, for each outcome variable, a description of percentage variations during

time was represented by a linear diagram and Spearman's Coefficient was reported to estimate direct or indirect correlation.

The meta-analysis was conducted using StatsDirect statistical software version 2.7.8 (Stats Direct Ltd, Cheshire, UK).

Results

Search results

The databases search resulted in 624 papers. After title screening, 446 publications were excluded for incorrect topic or language. Subsequently, abstract screening resulted in 178 papers to analyze. After abstract analysis 104 articles were excluded on the basis of the inclusion criteria; most of them were concerned with socket preservation conducted with immediate implant placement or did not demonstrate histological measurements as outcomes. From the reference lists and "grey literature", other 22 papers were selected for abstract screening. A total of 96 full-text papers were analyzed and 38 papers fulfilling the inclusion criteria were processed for data extraction (Fig. 1) (Artzi et al. 2000; Froum et al. 2002, 2004; Carmagnola et al. 2003; Fugazzotto 2003a,b; Iasella et al. 2003; Norton et al. 2003; Serino et al. 2003, 2008; Guarnieri et al. 2004; Vance et al. 2004; Luczyszyn et al. 2005; Barone et al. 2008; Cardaropoli & Cardaropoli 2008; Molly et al. 2008; Neiva et al. 2008; Wang & Tsao 2008; Aimetti et al. 2009; Crespi et al. 2009, 2011a,b; Fotek et al. 2009; Lee et al. 2009; Beck & Mealey 2010; Kesmas et al. 2010; Park et al. 2010; Pelegrine et al. 2010; Checchi et al. 2011; Heberer et al. 2011; Nam et al. 2011; Nevins et al. 2011; Ruga et al. 2011; Brkovic et al. 2012; Cardaropoli et al. 2012; Clozza et al. 2012a,b; Hoang & Mealey 2012; Perelman-Karmon et al. 2012; Wood & Mealey 2012).

Assessment of heterogeneity

The selected studies showed a considerable heterogeneity and these characteristics are presented in Table 1.

Study design and follow-up

Of the selected studies, 17 were Randomized Clinical Trials (# 2-5, 7-9, 12, 13, 17, 19, 24, 26, 29, 30, 35, 37), 18 are Clinical Trials (# 1, 6, 10, 11, 14-16, 18, 20-23, 27, 28, 32-34, 36). Moreover study # 25, 31 and 38 are Case Series or Individual Cohort Clinical Trial. Two studies have a Parallel design (# 33, 36) and six have a Split-Mouth design (# 6, 8, 11, 22, 28, 34). Follow-up periods ranged between 3

Table 1. Main clinical characteristics of selected studies

| ID # | Author | Title | Design/ setting | Follow-up time (months) | Mean age ± SD, number of subjects and gender | Smokers (control/ test) | Groups | Pharmacological treatment (Days) | Outcomes | Biopsy core number per group, dimension (length × diameter × thickness), and treatment | Histomorphometrical analysis | Flap raised/ releasing incisions/closure |
|------|-------------------------------|---|--------------------------|-------------------------------|---|-------------------------------|--|---|---|---|--|--|
| # 1 | Ciozza et al. (2012a,b) | Healing of Fresh Extraction Sockets Filled with Bioactive Glass Particles: Histological Findings in Humans | CT/ University | 6 | 55 ± 10 years (range 41–76) 13 (3 m/10f) | 0 (0/0) | Test: Sockets filled with active bioglass (BioRestore-Ion Oy) A: Socket filled with DBBM (Bio-Oss, Geistlich Pharma) B: Socket filled with DBBM (Bio-Oss, Geistlich Pharma) covered by a collagen membrane (Bio-Gide, Geistlich Pharma) and a mucoperiosteal flap | AID (an) CHX(14) | % of bone % of provisional matrix % of residual graft material % of bone | Test: 22 10 mm × 2 mm × 5 µm Fixed in 10% formalin and embedded in paraffin. Stained with hematoxylin–eosin A: 13 B: 10 8 mm × 2.5 mm × 5 µm Fixed in 10% neutral buffered formalin, decalcified with 5% formic acid and embedded in paraffin. Stained with hematoxylin–eosin Test: 24 Control: 24 7 mm × 2 mm × 7 µm Fixed in 10% neutral buffered formalin, dehydrated in ethanol and embedded in methyl methacrylate resin. Stained with Azure II and pararosaniline and with fast green and acid fuchsin A: 16 B: 16 8 mm × 2 mm × 4 µm Fixed in 10% neutral buffered formalin, decalcified and embedded in paraffin. Stained with Harris's hematoxylin and eosin | Single trained calibrated examiner Light microscope Single trained calibrated examiner Point – counting procedure with a microscope and a 64-square graticule Optical microscope and an image analysis software Image analysis softwares to create layers and pixel counting (Photoshop Elements 7 + Image J) | ? ? No Yes Yes No |
| # 2 | Perelman-Karmon et al. (2012) | Socket Site Preservation Using Bovine Bone Mineral With and Without a Bioresorbable Collagen Membrane | RCT/ University | 9 | ? ± 7 years (range 26–68) 23 (7 m/16f) | 0 (0/0) | Test: Sockets filled with DBBM (Bio-Oss, Geistlich Pharma) and porcine collagen (Bio-Oss Collagen, Geistlich Pharma) covered by a collagen membrane (Bio-Gide, Geistlich Pharma) Control: Any treatment | AID (14) CHX (14) | % of vital bone % of mineralized fraction % of residual graft material % connective tissue + bone marrow | Control: 24 7 mm × 2 mm × 7 µm Fixed in 10% neutral buffered formalin, dehydrated in ethanol and embedded in methyl methacrylate resin. Stained with Azure II and pararosaniline and with fast green and acid fuchsin A: 16 B: 16 8 mm × 2 mm × 4 µm Fixed in 10% neutral buffered formalin, decalcified and embedded in paraffin. Stained with Harris's hematoxylin and eosin | Single trained calibrated examiner Point – counting procedure with a microscope and a 64-square graticule Optical microscope and an image analysis software Image analysis softwares to create layers and pixel counting (Photoshop Elements 7 + Image J) | Yes Yes No Yes No |
| # 3 | Cardaropoli et al. (2012) | Socket Preservation Using Bovine Bone Mineral and Collagen Membrane: A Randomized Controlled Clinical With Histological Analysis | RCT/ Private Practice | 4 | 47.2 ± 12.9 years (range 24–71) 41 (24 m/17f) | 0 (0/0) | Test: Sockets filled with DBBM (Bio-Oss Collagen, Geistlich Pharma) covered by a collagen membrane (Bio-Gide, Geistlich Pharma) Control: Any treatment | ABD (6) AID (3) CHX (7) Hyaluronic acid and amino acids gel (3) | % of vital bone % of mineralized fraction % of residual graft material % connective tissue + bone marrow | Control: 24 7 mm × 2 mm × 7 µm Fixed in 10% neutral buffered formalin, dehydrated in ethanol and embedded in methyl methacrylate resin. Stained with Azure II and pararosaniline and with fast green and acid fuchsin A: 16 B: 16 8 mm × 2 mm × 4 µm Fixed in 10% neutral buffered formalin, decalcified and embedded in paraffin. Stained with Harris's hematoxylin and eosin | Single blinded examiner Optical microscope and an image analysis software Image analysis softwares to create layers and pixel counting (Photoshop Elements 7 + Image J) | No No No |
| # 4 | Wood & Mealey (2012) | Histological comparison of healing after tooth extraction with ridge preservation using mineralized versus demineralized freeze-dried bone allograft | RCT/ University | 5 | 56.7 ± 7 years (range 20–78) 33 (13 m/20f) | 0 (0/0) | A: Sockets filled with DFDBA (LifeNet Health) covered with a collagen membrane (Socket Repair, Collatape, Collaplug – Zimmer Dental) B: Sockets filled with FDBA (LifeNet Health) covered with a collagen membrane (Socket Repair, Collatape, Collaplug – Zimmer Dental) A: Sockets filled with DBM single-size particle (Progenics – Medtronic) covered with a collagen membrane (Collatape or Collaplug – Zimmer Dental) B: Sockets filled with DBM multiple size particle (Progenics Plus – Medtronic) covered with a collagen membrane (Collatape or Collaplug – Zimmer Dental) | ABD (7) CHX (14) | % of vital bone % of residual graft material % connective tissue | Control: 24 7 mm × 2 mm × 7 µm Fixed in 10% neutral buffered formalin, dehydrated in ethanol and embedded in methyl methacrylate resin. Stained with Azure II and pararosaniline and with fast green and acid fuchsin A: 16 B: 16 8 mm × 2 mm × 4 µm Fixed in 10% neutral buffered formalin, decalcified and embedded in paraffin. Stained with Harris's hematoxylin and eosin | Image analysis softwares to create layers and pixel counting (Photoshop Elements 7 + Image J) | No No ? |
| # 5 | Hoang & Mealey (2012) | Histological comparison of healing after ridge preservation using human demineralized bone matrix putty with one vs. two different-sized bone particles | RCT/ University | 5 | 56.1 ± 7 years (range 29–76) 30 (15 m/15f) | ? | A: Sockets filled with DBM single-size particle (Progenics – Medtronic) covered with a collagen membrane (Collatape or Collaplug – Zimmer Dental) B: Sockets filled with DBM multiple size particle (Progenics Plus – Medtronic) covered with a collagen membrane (Collatape or Collaplug – Zimmer Dental) | ABD (7) AID (an) CHX (7) | % of vital bone % of residual graft material % connective tissue | Control: 24 7 mm × 2 mm × 7 µm Fixed in 10% neutral buffered formalin, dehydrated in ethanol and embedded in methyl methacrylate resin. Stained with Azure II and pararosaniline and with fast green and acid fuchsin A: 16 B: 16 8 mm × 2 mm × 4 µm Fixed in 10% neutral buffered formalin, decalcified and embedded in paraffin. Stained with Harris's hematoxylin and eosin | Single-blinded examiner Image analysis softwares to create layers and pixel counting (Photoshop Elements 7 + Image J) | No No No |
| # 6 | Crespi et al. (2011a) | Comparison of Magnesium-Enriched Hydroxyapatite and Porcine Bone in Human Extraction Socket Healing: A Histological and Histomorphometric Evaluation | CT/ University | 4 | 53.7 ± 7 years (range 32–70) 15 (7m/7f) | 0 (0/0) | A: Sockets filled with MHA (SINLife, FinCeramica) covered with a collagen membrane (?) B: Sockets filled with CPB (Gen-Oss, Osteobiol-Tecnoss) covered with a collagen membrane (?) C: Sockets covered with a collagen membrane (?) | ABD(7) AID (7) CHX (7) | % of vital bone % of residual graft material % connective tissue | Control: 24 7 mm × 2 mm × 7 µm Fixed in 10% neutral buffered formalin, dehydrated in ethanol and embedded in methyl methacrylate resin. Stained with toluidine blue | Optical microscope and an image analysis software (Microcontrol – Alexasoft) | No No No |
| # 7 | Nevins et al. (2011) | Human Buccal Plate Extraction Socket Regeneration with Recombinant Human Platelet-Derived Growth factor BB or Enamel Matrix Derivative | RCT/ University | 5 | ? ± 7 years (range 18–70) 15 (7m/7f) | ? | A: Sockets filled with MCBS (Osteohealth) B: Sockets filled with MCBS + rPDGF-BB 0.3 mg/ml (Osteohealth) C: Sockets filled with MCBS (Osteohealth) + EMD (Straumann) D: Sockets filled with EMD (Straumann) + BCP (Bone Ceramic – Straumann) | ABD (5) CHX (14) | % of new bone | Control: 24 7 mm × 2 mm × 7 µm Fixed in 10% neutral buffered formalin, dehydrated in ethanol and embedded in methyl methacrylate resin. Stained Toluidine Blue/Pyronin G | Light microscope and an image analysis software (magic – ImageAccess) | Yes Yes ? |

Table 1. Continued

| ID # | Author | Title | Design/ setting | Follow-up time (months) | Mean age ± SD, number of subjects and gender | Smokers (control/ test) | Groups | Pharmacological treatment (Days) | Outcomes | Biopsy core number per group, dimension (length × diameter × thickness), and treatment | Histomorphometrical analysis | Flap raised/ releasing incisions/closure |
|------|-----------------------|---|--------------------|-------------------------------|--|-------------------------------|---|---|---|---|--|--|
| # 8 | Crespi et al. (2011b) | Corticancellous porcine bone in the healing of human extraction sockets: combining histomorphometry with osteoblast gene expression profiles <i>in vivo</i> | RCT/ University | 4 | 53.7 ± 7 years (range 32–70) 15 (7m/7f) | 0 (0/0) | A: Sockets filled with CPB (Gen-Oss, Osteobiol-Tecross) covered with a collagen membrane (Condress – Abiogen Pharma) B: Sockets covered with a collagen membrane (Condress – Abiogen Pharma) | ? | % of vital bone % of residual graft material % connective tissue | A: 15 B: 15 7 mm × 2 mm × 10–30 µm Fixed in 4% buffered formaldehyde, dehydrated through a series of alcohols solutions and embedded in epoxy resin. Stained with toluidine blue | Optical microscope and an image analysis software (Microcontrol – Alexasoft) | ? |
| # 9 | Heberer et al. (2011) | Healing of ungrafted and grafted extraction sockets after 12 weeks: a prospective clinical study | RCT/ University | 3 | 49.9 ± 7 years (range 36–67) 25 (15 m/10f) | 0 (0/0) | Test: Sockets filled with DBBM and collagen (Bio-Oss Collagen, Geistlich Pharma) Control: Any treatment | NONE | % of vital bone % of residual graft material % connective tissue | Test: 20 Control: 19 7 mm × 2 mm × 4 µm Fixed in 4% formalin, decalcified and embedded in paraffin. Stained with hematoxylin–eosin and Masson trichrome | Single blinded examiner Digital image analysis (Axiovision 4.6, Zeiss) | No No No |
| # 10 | Ruga et al. (2011) | Clinical and histological outcomes of calcium sulfate in the treatment of post-extraction sockets | CT/ University | 3 | 47.8 ± 7 years (range 18–69) 35 (9 m/26f) | ? | Test: Sockets filled with CaS (New Plaster, Classimplant) | ABD (5) AID (3) Corticosteroids (3) CHX (10) | % of vital bone % of residual graft material % connective tissue | Test: 19 7 mm × 3 mm × 7 µm Stained with hematoxylin–eosin, silver staining and Masson trichrome | ? | Yes Yes Yes |
| # 11 | Nam et al. (2011) | Enhanced ridge preservation by bone mineral bound with collagen-binding synthetic oligopeptide: a clinical and histological study in humans | CCT/ University | 6 | ? ± 7 years (range 36–65) 42 (20 m/22f) | ? | A: Socket filled with DBBM (Bio-Oss, Geistlich Pharma) coated with synthetic oligopeptide covered by a collagen membrane (Bio-Gide, Geistlich Pharma) B: Socket filled with DBBM (Bio-Oss, Geistlich Pharma) covered by a collagen membrane (Bio-Gide, Geistlich Pharma) | ABD (7) CHX (7) | % of new bone % of residual graft material % fibrous tissue | A: 7 7 mm × 2 mm × 7 µm Fixed in 10% neutral buffered formalin, dehydrated through a series of ethanol solutions and embedded in resin. Stained with a multiple stain kit | Light microscope and an image analysis software (Tomoro Scope Eye 3.6, Techna Digital Imaging) | Yes Yes Yes |
| # 12 | Brkovic et al. (2012) | Beta-tricalcium phosphate/type I collagen cones with or without a barrier membrane in human extraction socket healing: clinical, histological, histomorphometric, and immunohistochemical evaluation. | RCT/ University | 9 | 49/46 ± 15/13 years (range 20–55) 20 (8 m/12f) | 0 (0/0) | A: Socket filled with β-TCP/Cig cones (RTR Cone) B: Socket filled with β-TCP/Cig cones (RTR Cone) covered by a collagen membrane (Bio-Gide, Geistlich Pharma) and a mucoperiosteal flap | ABD (7) AID (7) | % of new bone % of marrow % of residual graft material % fibrous tissue | A: 8 B: 7 6 mm × 3 mm × 45 µm Fixed in 10% neutral buffered formalin, dehydrated in alcohol for 9 days. Stained with Stevenel's blue and Van Gieson's picro fuchsin. | Image analysis softwares (Photoshop + Public NIH Image program) | Yes Yes Yes |
| # 13 | Cecchi et al. (2011) | Clinical, radiographic and histological evaluation of two hydroxyapatites in human extraction sockets: a pilot study | RCT/ University | 6 | 54 ± 8 years (range 43–76) 10 (0 m/10f) | 0 (0/0) | A: Socket filled with granules of biomimetic MHA (F-BHA, SINTLife, FinCeramica hydroxyapatite putty (C-sponge (Collaplug – Zimmer Dental) B: Socket filled with nanocrystalline hydroxyapatite putty (C-NHA, Ostim, Heraeus Kulzer) covered by a collagen sponge (Collaplug – Zimmer Dental) | CHX (10) AID (n) | % of mature bone % of osteoid tissue % of residual graft material % fibrous tissue | A: 5 B: 5 8 mm × 2 mm × 6 µm Fixed in 10% neutral buffered formalin, dehydrated and embedded in methyl methacrylate. Stained with haematoxylin–eosin and Giemsa (Goldner's trichromic stain) | Two blinded examiners Light microscope | ? |
| # 14 | Park et al. (2010) | Socket preservation using deproteinized horse-derived bone mineral | CT/ University | 6 | ? ± 7 years (range ?–?) 4 (7m/7f) | ? | Test: Socket filled with EBM (OCS-H, Nibe) covered by a collagen membrane (Bio-Gide, Geistlich Pharma) | ABD (14) CHX (28) | % of vital bone % of residual graft material % connective tissue | Test: 3 7 mm × 3 mm × 7 mm Fixed in 10% neutral buffered formalin, dehydrated in ethanol and embedded in Stained with a Multiple Stain Kit | Light microscope and an image analysis software (Tomoro Scope Eye 3.6, Techna Digital Imaging) | Yes Yes Yes |

Table 1. Continued

| ID # | Author | Title | Design/ setting | Follow-up time (months) | Mean age ± SD, number of subjects and gender | Smokers (control/ test) | Groups | Pharmacological treatment (Days) | Outcomes | Biopsy core number per group, dimension (length × diameter × thickness), and treatment | Histomorphometrical analysis | Flap raised/ releasing incisions/closure |
|------|----------------------------|--|--------------------|-------------------------------|--|-------------------------------|---|-------------------------------------|--|---|--|--|
| # 15 | Beck & Mealey (2010) | Histological analysis of healing after tooth extraction with ridge preservation using mineralized human bone allograft | CT/ University | 3–6 | 57.4 ± 7 years (range 39–76) 33 (13 m/20f) | ? | A: Socket filled with hydrated particles of HBMA (Puros – Zimmer Dental) covered by a collagen membrane (Colla tape – Zimmer Dental) – 3 m healing B: Socket filled with hydrated particles of HBMA (Puros – Zimmer Dental) covered by a collagen membrane (Colla tape – Zimmer Dental) – 6 m healing | ABD (4) CHX (21) AID (4n) | % of vital new bone % of residual graft material % connective tissue | Early: 16 Delayed: 22 8 mm × 2 mm × 4 µm Decalcified, dehydrated, embedded in paraffin. Stained with Harris' hematoxylin and eosin. | Image analysis softwares to create layers (Photoshop Elements 7 + Image J) | No No No |
| # 16 | Kemas et al. (2010) | Esthetic alveolar ridge preservation with calcium phosphate and a collagen membrane: Preliminary report | CT/ University | 4 | 46.5 ± 10.2 years (range 25–57) 8 (3 m/5f) | 0 (0/0) | Test: Sockets filled with BCP (Bone Ceramic-Straumann) covered by two layer of collagen membrane (BioGide – Geistlich and Collaplug – Zimmer Dental) | ABD (7) CHX (14) AID (7) | % of new bone % of residual graft material % connective tissue | Test: 6 6 mm × 2 mm × 5 µm Fixed in 10% neutral buffered formalin, dehydrated in a series of graded alcohols, placed in xylene and embedded in paraffin. Stained with haematoxylin-eosin | Light microscope | No No No |
| # 17 | Pelegrine et al. (2010) | Clinical and histomorphometric evaluation of extraction sockets treated with an autologous bone marrow graft | RCT/ University | 6 | 47.5 ± 10.3 years (range 28–70) 13 (7 m/6f) | 0 (0/0) | Test: Sockets filled with autologous bone marrow Control: Any treatment | ? | % of mineralized bone | Test: 15 Control: 15 7 mm × 2 mm × 7 µm Fixed in 10% neutral buffered formalin, decalcified and embedded in paraffin. Stained with hematoxylin-eosin | Digital image analysis (Axiovision 4.6, Zeiss) | Yes Yes Yes |
| # 18 | Lee et al. (2009) | Comparative histomorphometric analysis of extraction sockets healing implanted with bovine xenografts, irradiated cancellous allografts and solvent-dehydrated allografts in human | CT/ Hospital | 4–6 | 54.8 ± 6.8 years (range 39–68) 20 (16 m/4f) | 0 (0/0) | A: Socket filled with DBBM (Bio-Oss, Geistlich Pharma) covered by a collagen membrane (Bio-Gide, Geistlich Pharma) B: Socket filled with HBMA (Rocky Mountain Tissue Bank) covered by a collagen membrane (Bio-Gide, Geistlich Pharma) C: Socket filled with HBMA (Puros – Zimmer Dental) covered by a collagen membrane (Bio-Gide, Geistlich Pharma) | ABD (7) AID (7) | % of new bone % of residual graft material % fibrous tissue | A: 7 B: 8 C: 4 2 mm × 2 mm × 4–6 µm Fixed in 10% neutral buffered formalin, decalcified with 5% formic acid and embedded in paraffin. Stained hematoxylin-eosin and masson trichrome | Projection microscope and a image analysis software (Image Pro Plus v4.5, Media Cybernetics) | No No No |
| # 19 | Aimetti et al. (2009) | Clinical and histological healing of human extraction sockets filled with calcium sulfate | RCT/ University | 3 | 51.27 ± 8.40 years (range 36–68) 40 (18 m/22f) | 0 (0/0) | Test: Sockets filled with MGCSH (Surgiplaster, Classimplant) Control: Any treatment | ABD (5) CHX (14) AID (5) | % of lamellar bone % of woven bone | Test: 22 cones Control: 18 cones 7 mm × 2.5 mm × 4 µm Fixed in 5% neutral buffered formalin, decalcified in ethylenediaminetetraacetic acid, dehydrated in ethanol and embedded in paraffin. Stained with hematoxylin-eosin, Giemsa and Gordon and Sweet's | Light microscope | No No No |
| # 20 | Ferek et al. (2009) | Comparison of dermal matrix and polytetrafluoroethylene membrane for socket bone augmentation: a clinical and histological study | CT/ University | 4 | 59.55 ± ? years (range 29–77) 20 (7 m/13f) | 0 (0/0) | A: Sockets filled with HBMA (Puros – Zimmer Dental) covered with ADM (AlloDerm, BioHorizons) B: Sockets filled with HBMA (Puros – Zimmer Dental) covered with a dPTFE membrane (Cyroplast, Osteogenics Biomedical) | ABD (7) AID (4n) | % of Bone % of new bone % of soft tissue % of Residual graft material | A: 9 cones B: 9 cones 9 mm × 2.75 mm × 45 µm Fixed in 10% neutral buffered formalin, dehydrated in alcohol for 9 days, embedded in light-curing resin. Stained with Stevenel's blue and Van Gieson's picric fuchsin | Light microscope and a combination of image software (Photoshop + Public NIH Image program) | No No No |

Table 1. Continued

| ID # | Author | Title | Design/ setting | Follow-up time (months) | Mean age ± SD, number of subjects and gender | Smokers (control/ test) | Groups | Pharmacological treatment (Days) | Outcomes | Biopsy core number per group, dimension (length × diameter × thickness), and treatment | Histomorphometrical analysis | Flap raised/ releasing incisions/closure |
|------|-------------------------------------|---|------------------------|-------------------------------|---|-------------------------------|--|--|---|--|---|--|
| # 21 | Crespi et al. (2009) | Magnesium-Enriched hydroxyapatite compared to calcium sulfate in the healing of human extraction sockets: radiographic and histomorphometric evaluation at 3 months | CT/ Hospital | 3 | 51.3 ± 7 years (range 28-72) 15 (6 m/7f) | 0 (0/0) | A: Sockets filled with MHA (SINTLife, FinCeramica) covered with a collagen membrane (?) B: Sockets filled with CaS (Easy Set, Sweden-Martina) covered with a collagen membrane (?) C: Sockets covered with a collagen membrane (?) | ABD (7) | % of vital bone % of graft material % of connective tissue | A: 15 cones B: 15 cones C: 15 cones Fixed in 4% buffered formaldehyde, dehydrated in alcohol, embedded in epoxy-resin. Stained with toluidine blue | Optical microscope and an image analysis software (Microcontrol – Alexasoft) | No No No |
| # 22 | Molly et al. (2008) | Bone Formation Following Implantation of bone Biomaterials Into extraction Sites | CT/ University | 6 | 53 ± 7 years (range 37-63) 8 (1 m/7f) | 0 (0/0) | A: Sockets filled with PPAS (Fisigrat – Ghimas) covered with a ePTFE membrane (GoreTex – Gore Biomaterials) B: Sockets filled with DBBM (Bio-Oss, Geistlich Pharma) covered with a ePTFE membrane (GoreTex – Gore Biomaterials) C: Sockets filled with natural coral derivative CaCO ₃ (Biocoral, Inotek) covered with a ePTFE membrane (GoreTex – Gore Biomaterials) Control: any treatment | ABD (7) AID (an) | % of vital bone % of graft material | A: 8 B: 6 C: 6 Control: 5 7 mm × 2 mm × 20 µm Fixed in a buffered formaldehyde/ethanol solution, dehydrated in graded ethanol series and embedded in methylmethacrylate. Stained with Stevenel's blue and van Gieson's picrofuchsin | Light microscope and an image analysis software (Image Pro Plus, Media Cybernetics) | Yes ? Yes |
| # 23 | Wang & Tsao (2008) | Histological evaluation of socket augmentation with mineralized human allograft | CT/ University | 5 | 56 ± 7 years (range 7-7) 5 (3 m/2f) | ? | Test: Sockets filled with HBMA (Puros – Zimmer Dental) covered by a collagen membrane (CollaPlug – Zimmer Dental) | AID(3) | % of bone % of residual graft material % connective tissue | Test: 7 10 mm × 2 mm × 5 µm Fixed in 10% neutral buffered formalin, dehydrated in series of alcohol. Stained with Hematoxylin-eosin and trichrome. | Image analysis software (Image Pro Express, Media Cybernetics) | No No No |
| # 24 | Neiva et al. (2008) | Effects of a Puty-Form Hydroxyapatite matrix Combined with The Synthetic Cell-Binding Peptide P-15 on alveolar Ridge Preservation | RCT/ University | 4 | 48.00/49.92 ± 14.89/ 14.20 years (range 25/36-69/ 76) 30 (13 m/17f) | 0 (0/0) | A: Socket filled with ABBM and peptide P-15 (PepGen P15 – Dentsply) covered by a collagen membrane (CollaPlug – Zimmer Dental) B: Socket covered by a collagen membrane (CollaPlug – Zimmer Dental) | ? | % of new bone % of residual graft material % connective tissue | A: 12 B: 12 10 mm × 2.7 mm × 5 µm Fixed in 10% neutral buffered formalin, dehydrated in a series of graded alcohols and embedded in glycol methacrylate. Stained with hematoxylin-eosin | ? ? ? | No No No |
| # 25 | Cardaropoli & Cardaropoli (2008) | Preservation of the post-extraction alveolar ridge: a clinical and histological study | CS/Private practice | 4 | 45.9 ± 7 years (range 27-63) 10 (6 m/4f) | ? | Test: Sockets filled with CPB (GenOs Osteobiol – Tecross) covered with a collagen membrane (Evolution Osteobiol – Tecross) | ABD (6) CHX (until sutures removal) | % Residual graft material | Test: 10 7 mm × 7 mm × 7 µm Fixed in 10% neutral buffered formalin, dehydrated in ethanol, embedded in methyl methacrylate resin. Stained with basic fuchsin and toluidine blue | ? ? ? | No No No |
| # 26 | Barone et al. (2008) | Xenograft vs.s extraction alone for ridge preservation after tooth removal: a clinical and histomorphometric study | RCT/ Hospital | 7 | >18 (range 26-29) 40 (16 m/24f) | 5 (3/2) | Test: Sockets filled with CPB (MP3 Osteobiol) covered with a collagen membrane (Evolution Osteobiol – Tecross) Control: Any treatment | ABD (4) CHX (21) AID (3) | % Trabecular bone % Connective tissue % Residual graft material | Test: 20 7 mm × 7 mm × 70-80 µm Fixed in 10% neutral buffered formalin, dehydrated in alcohol and embedded in methyl – methacrylate resin. Stained with fast green and acid fuchsin | Optical microscope and digital image analysis (Axiovision, Zeiss) | Yes Yes Yes |

Table 1. Continued

| ID # | Author | Title | Design/ setting | Follow-up time (months) | Mean age ± SD, number of subjects and gender | Smokers (control/ test) | Groups | Pharmacological treatment (Days) | Outcomes | Biopsy core number per group, dimension (length × diameter × thickness), and treatment | Histomorphometrical analysis | Flap raised/ releasing incisions/closure |
|------|-------------------------|--|--------------------|-------------------------------|--|-------------------------------|--|--|--|---|---|--|
| # 27 | Serino et al. (2008) | Poly(lactide and polyglycolide) sponge used in human extraction sockets: bone formation following 3 months after its application | RCT/ University | 3 | ? ± ? years (range 32–64) 20 (8 m/12f) | ? | Test: Sockets filled with PPA5 (Fislograft – Ghimas) Control: Any treatment | CHX (14) AID (an) | % of mineralized bone % of graft material (for T Sites) % of non-mineralized tissue | Test: 7 3 mm × 6 mm × 30 µm Fixed in 10% neutral buffered formalin, dehydrated in alcohol and embedded in glycolmethacrylate resin. Stained with Von Kossa and basic fuchsin | Light microscope and a image analysis software (Image Pro Plus v4.5, Media Cybernetics) | Yes Yes No |
| # 28 | Luczynski et al. (2005) | Acellular dermal matrix and hydroxyapatite in prevention of ridge deformities after tooth extraction | CT/ University | 6 | ? ± ? years (range 35–60) 11 (7m/7f) | 0 (0/0) | A: Sockets filled with resorbable porous HA (Algipore, Dentsply – Friadent) covered with ADM (AlloDerm, BioHorizons) B: Sockets covered with ADM (AlloDerm, BioHorizons) | ABD(10) CHX (until soft tissue closure) | % of bone % of connective tissue | A: 15 B: 15 2 mm × 5 mm × 7 µm Fixed in 10% neutral formalin, decalcified in acid dehydrated, embedded in paraffin. Stained with hematoxylin-eosin | ? Yes Yes No | |
| # 29 | Fraum et al. (2004) | Extraction sockets and implantation of hydroxyapatites with membrane barriers. A histological study | RCT/ Hospital | 6–8 | 48.1 ± ? years (range 26–71) 15 (9 m/6f) | 0 (0/0) | A: Sockets filled with absorbable HA (OsteoGraf RLD – Dentsply) covered with ADM (AlloDerm) B: Sockets filled with absorbable HA (OsteoGraf RLD – Dentsply) covered with ePTFE membrane (GoreTex Regenerative) C: Sockets filled with ABBM (OsteoGraf R/M300 – Dentsply) covered with ADM (AlloDerm) D: Sockets filled with ABBM (OsteoGraf R/M300 – Dentsply) covered with ePTFE membrane (GoreTex Regenerative) | ABD (14) CHX (28) | % of vital bone % of graft material % of connective tissue | A: 4 B: 4 C: 4 D: 4 2.7 mm × 6 mm × 7 µm Fixed in 10% buffered formalin, decalcified. Stained with hematoxylin-eosin | Grid-overlay counting Yes Yes No | |
| # 30 | Vance et al. (2004) | Comparison of an allograft in an experimental putty carrier and a bovine-derived xenograft used in ridge preservation: a clinical and histological study in humans | RCT/ University | 4 | 56.0 ± 11 years (range 7–7) 24 (9 m/15f) | ? | A: Sockets filled with a putty binder composed of CMC and Cas mixed with DFDBA (50:50) covered with a Cas barrier (Capset – Lifecore Biomedical) B: Sockets filled with DBBM (Bio-Oss, Geistlich Pharma) covered with a collagen membrane (Bio-Gide, Geistlich Pharma) | ABD (?) CHX (?) AID (?) | % of Vital bone % of Graft % of Trabecular space % of Amorphous organic matrix N° of osteoblasts | A: 12 B: 12 2.7 mm × 6 mm × 7 µm Fixed in 10% buffered formalin, decalcified. Stained with hematoxylin-eosin | Light microscope and a 15× reticle eyepiece (Nikon) | Yes ? Yes |
| # 31 | Guarnieri et al. (2004) | Medical grade calcium sulfate hemihydrate in healing of human extraction sockets: clinical and histological observations at 3 months | CSM/Multi-centre | 3 | ? ± ? years (range 35–58) 10 (3 m/7f) | ? | Test: Sockets filled with MGCSH (Surgiplaster – Classimplant) Control: Any treatment ? | ABD (7) CHX (14) | % of trabecular bone | Test: 10 Control: 5 7 mm × 7 mm × 70 µm Fixed in 4% buffered formaldehyde, dehydrated in alcohol and embedded in methylmethacrylate resin. Stained with fast green, toluidine blue and modified Von Kossa | Image analysis software (KS 300, Kontron Electronics) | Yes No Yes |
| # 32 | Norton et al. (2003) | Efficacy of bovine bone mineral for alveolar augmentation: a human histological study | CT/ University | 6 | 53.66 ± 11.8 years (range 26–69) 15 (7 m/8f) | 3 | Test: Sockets filled with DBBM (Bio-Oss, Geistlich Pharma) plus autologous bone covered with a collagen membrane (Bio-Gide, Geistlich Pharma) | ABD (5) CHX (7) | % of new bone % of residual graft material % connective tissue | Test: 10 2.5 mm × 7 mm × 5 µm Fixed in 10% buffered formalin, decalcified in 10% formic acid/on exchange resin and embedded in paraffin. Stained with hematoxylin and eosin | Manual delimitation of each area and digital analysis (Q Win, Leica) | Yes Yes Yes |

Table 1. Continued

| ID # | Author | Title | Design/ setting | Follow-up time (months) | Mean age ± SD, number of subjects and gender | Smokers (control/ test) | Groups | Pharmacological treatment (Days) | Outcomes | Biopsy core number per group, dimension (length × diameter × thickness), and treatment | Histomorphometrical analysis | Flap raised/ releasing incisions/closure |
|------|--------------------------|--|----------------------------------|-------------------------------|--|-------------------------------|--|---|--|---|---|--|
| # 33 | Fugazzotto (2003a,b) | GBR using bovine bone matrix and resorbable and non-resorbable membranes. Part 1: Histological results | CT/Private practice | 3–13 | 7 ± 7 years (range 29–63) 90 (43 m/47f) | 0 (0/0) | A, B, C, D: Sockets filled with DBBM (Bio-Oss, Geistlich Pharma) plus sterile saline covered with a e-PDTE membrane (GoreTex) fixed with non-resorbable tacks (Frees Tack – Nobel Biocare) Test: Sockets filled with PPAS (Fisiograft – Ghimas) Control: Any treatment | ABD (10) CHX (21) AID (5) | % of Bone % of Residual graft material % of other tissues | A: 6 B: 40 C: 6 D: 7 2 mm × 7 mm × 7 μm | Grid-overlay counting | Yes Yes Yes |
| # 34 | Serino et al. (2003) | Ridge preservation following tooth extraction using a polylactide and a polyglycolide sponge as a space filler: a clinical and histological study in humans | CT/ University | 6 | 45.9 ± 7 years (range 35–64) 45 (14 m/31f) | ? | | CHX (14) AID (an) | % of mineralized bone % of graft material | Test: 10 Control: 3 3 mm × 6 mm × 30 μm Fixed in 10% formalin, dehydrated in alcohol and embedded in glycolmethacrylate resin. Stained with toluidine blue, Von Kossa and basic fuchsin | Light microscope and a image analysis software (Image Pro Plus v4.5, Media Cybernetics) | Yes No No |
| # 35 | Iasella et al. (2003) | Ridge preservation with freeze-dried bone allograft and a collagen membrane compared to extraction alone for implant site development: a clinic and histological study | RCT/7 | 4–6 | 51.5 ± 13.6 years (range 29–76) 24 (10 m/14f) | ? | Test: Sockets filled with FDBA (American Red Cross) + 50 mg/ml tetracycline solution covered by a collagen membrane (Biomend Extend – Centerplus Dental Division) Control: Any treatment A: Socket covered by a collagen membrane (Bio-Gide, Geistlich Pharma) – reentry at 4 months B: Socket filled with DBBM (Bio-Oss, Geistlich Pharma) covered by a collagen membrane (Bio-Gide, Geistlich Pharma) – reentry at 7 months Control: Any treatment – reentry at 1–15 years | ABD(14) CHX (until soft tissue closure) AID (7) | % of Vital bone % of non-vital tissue % of Trabecular space % of Amorphous organic matrix N° of osteoblasts % of lamellar bone % of residual graft material % of woven bone % of bone marrow % of connective tissue | Test: 12 Control: 10 2.7 mm × 6 mm × 30 μm Fixed in 10% buffered formalin, decalcified. Stained with hematoxylin-eosin | Light microscope and a 15× reticle eyepiece | Yes No No |
| # 36 | Carmagnola et al. (2003) | Healing of human extraction sockets filled with Bio-Oss | CT/ University | 4–180 | 56.5 ± 9.7 years (range 39–76) 21 (13 m/8f) | ? | | ? | % of residual graft material % of woven bone % of bone marrow % of connective tissue | A: 11 Control: 10 2.8 mm × 8–12 mm × 20–30 μm Fixed in 5% formaldehyde, dehydrated in ethanol, embedded in acrylic resin. Stained with toluidine blue | Light microscope and digital point counting procedure (O-500, Leica) | Yes ? |
| # 37 | Froum et al. (2002) | Histological comparison of healing extraction sockets implanted with Bioactive glass or demineralized freeze-dried bone allograft: a pilot study | RCT/ University | 6–8 | 54.9 ± 11.9 years (range 35–77) 19 (12 m/7f) | 0 (0/0) | A: Socket filled with a bioactive glass (Biogran – Orthovita) B: Socket filled with a DFDBA (University of Miami Bone Bank) Control: Any treatment – reentry at 1–15 years | ABD(14) CHX (31) | % of vital bone % of residual graft material % of connective tissue | A: 10 cones B: 10 cones Control: 10 cones 2 mm × 7 mm × 7 μm Stained with Steveland's blue and Von Gieson's picric fuchsin | Grid-overlay counting | Yes Yes Yes |
| # 38 | Artzi et al. (2000) | Porous bovine bone mineral in healing of human extraction sockets. Part 1: histomorphometric evaluations at 9 months | Individual cohort/ University | 3 | 7 ± 7 years (range 23–64) 15 (6 m/9f) | ? | Test: Sockets filled with DBBM (Bio-Oss, Geistlich Pharma) | ABD (7) CHX (14) AID (an) | % of bone % of connective tissue % of residual graft material | Test: 15 2.5 mm × 5–7 mm × 5 μm Fixed in 10% neutral buffered formalin, decalcified in formic acid. Stained with hematoxylin – eosin | Point – counting procedure with a projection microscope and a 64-square graticule | Yes No Yes |

CT, Clinical Trial; RCT, Randomized Clinical Trial; CS, Case Series; AID, Anti-inflammatory drugs; CHX, Chlorhexidine; ABD, Antibiotics drugs; an, As needed; DBBM, Demineralized Bovine Bone Mineral; CPB, Corticancellous porcine bone; MCBS, Mineral collagen bone substitute; EMD, Emdogain®; rhPDGF-BB, recombinant human platelet-derived growth factor; ADM, Acellular dermal matrix; CaS, Calcium sulfate; DFDBA, Demineralized Freeze-Dried Bone Allograft; FDBA, Freeze-dried bone allograft; DBM, Demineralized Bone Matrix; MHA, Magnesium-Enriched hydroxyapatite; HA, hydroxyapatite; dPTE, dense polytetrafluoroethylene; ePTE, expanded polytetrafluoroethylene; MGCSH, Medical grade calcium sulfate hemihydrate; β-TCP, beta-tricalcium phosphate; Ctg, type I collagen; EBM, Equine bone mineral; BCP, biphasic calcium phosphate; HBMA, Human bone mineral allograft; CaCO₃, Calcium Carbonate; PPAS, poly(lactide-polyglycolic acid) sponge; ABBM, Anorganic bovine bone material; CMC, Carboxymethyl Cellulose.

Table 2. Quality assessment of selected studies

| Validity | Study # quality criteria | # 1 Clozza et al. (2012a,b) | # 2 Perelman-Karmon et al. (2012) | # 3 Cardaropoli et al. (2012) | # 4 Wood & Mealey (2012)2 | # 5 Hoang & Mealey (2012) | # 6 Crespi et al. (2011a) | # 7 Nevins et al. (2011) | # 8 Crespi et al. (2011b) | # 9 Heberer et al. (2011) | |
|------------------------------------|---|---|-----------------------------------|---|--|--|---|---------------------------|---|---|-----|
| External | Representative population group | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | |
| | Eligibility criteria defined | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | |
| Internal | Random allocation | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | |
| | Allocation concealment | No | Yes | Yes | Yes | Yes | No | No | No | Yes | |
| | Blinded to the patient | No | ? | No | No | ? | No | No | ? | ? | |
| | Blinded to the examiner | No | ? | Yes | ? | Yes | ? | ? | ? | ? | |
| | Blinding during statistical analysis | No | ? | ? | ? | Yes | ? | ? | ? | ? | |
| | Reported loss to follow-up | ? | Yes | No | Yes | Yes | Yes | Yes | Yes | ? | |
| | # (%) of drop-outs | 0? | 0 | 0? | 8 | 10 | 0 | 0 | 0 | 0? | |
| Statistical | Treatment identical, except for intervention | Na | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | |
| | Sample size calculation and power | No? | No | Yes | Yes | Yes | No | No | Yes | No | |
| | Point estimates presented for primary outcome | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | |
| | Measures of variability for the primary outcome | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | |
| | Intention to treat analysis | No | No | No | No | No | No | No | No | No | |
| | Clinical aspects | Study design | CT | RCT | RCT | RCT | RCT | CT – Split mouth | RCT | RCT – Split mouth | RCT |
| | | Validated measurement | ? | ? | Yes | ? | ? | ? | ? | ? | ? |
| | | Calibration examiner | Yes | Yes | Yes | ? | ? | ? | ? | ? | ? |
| | | Reproducibility data shown | No | No | No | Yes | No | No | No | No | Yes |
| | Reason for extraction | ? | ? | ? | Root fracture, periodontal involvement, endodontic treatment failure and advanced caries | ? | Non-restorability, fracture, periodontal disease, failed endodontic procedure | ? | ? | ? | ? |
| Local inclusion/exclusion criteria | | 4 wall architecture, socket depth >5 mm, no peri-apical lesions | At least 2 wall maintained | No acute periodontitis or peri-apical lesions | Socket depth ≥10 mm, no acute periodontitis or peri-apical lesions | No buccal bone dehiscence extending >50% of the socket | No acute peri-apical infection | ? | Presence of 3 bone walls and loss of buccal plate | No severe periodontitis, acute perio lesions, peri-apical lesions and severe resorbed pockets | |
| Estimated potential risk of bias | | High | Moderate | Low | Moderate | Low | High | Moderate | Moderate | Moderate | |
| CEBM Level of evidence | | 3 (2c) | 2 (1b) | 2 (1b) | 2 (1b) | 2 (1b) | 3 (2c) | 2 (1b) | 2 (1b) | 2 (1b) | |
| Jadad score | NA | 2 | 2 | 3 | 3 | NA | 2 | 2 | 2 | | |
| Validity | Study # quality criteria | # 20 Fotek et al. (2009) | # 21 Crespi et al. (2009) | # 22 Molly et al. (2008) | # 23 Wang & Tsao (2008) | # 24 Neiva et al. (2008) | # 25 Cardaropoli & Cardaropoli (2008) | # 26 Barone et al. (2008) | # 27 Serino et al. (2008) | # 28 Luczynski et al. (2005) | |
| External | Representative population group | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | |
| | Eligibility criteria defined | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No | |
| Internal | Random allocation | No | No | No | No | Yes | ? | Yes | Yes | ? | |
| | Allocation concealment | No | ? | No | No | Yes | ? | ? | ? | ? | |
| | Blinded to the patient | No | ? | ? | No | Yes | ? | ? | ? | No | |
| | Blinded to the examiner | Yes | Yes | ? | No | Yes | ? | ? | ? | ? | |
| | Blinding during statistical analysis | No | ? | ? | No | Yes | ? | ? | ? | ? | |
| | Reported loss to follow-up | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | |
| | # (%) of drop-outs | 2 (10%) | 0 | 0 | 0 | ? | ? | 0 | 4 (20%) | 0 | |
| Statistical | Treatment identical, except for intervention | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | |
| | Sample size calculation and power | No | ? | No | No | Yes | ? | ? | ? | ? | |
| | Point estimates presented for primary outcome | No | Yes | Yes | Yes | Yes | ? | Yes | Yes | ? | |
| | Measures of variability for the primary outcome | No | Yes | Yes | Yes | Yes | Yes | Yes | ? | ? | |
| Intention to treat analysis | No | ? | No | No | No | Yes | ? | ? | ? | | |

| # 10 Ruga et al. (2011) | # 11 Nam et al. (2011) | # 12 Brkovic et al. (2012) | # 13 Checchi et al. (2011) | # 14 Park et al. (2010) | # 15 Beck & Mealey (2010) | # 16 Kesmas et al. (2010) | # 17 Pelegrine et al. (2010) | # 18 Lee et al. (2009) | # 19 Aimetti et al. (2009) |
|----------------------------|---|--|--------------------------------|--|---|---|----------------------------------|---|--|
| ? | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes |
| Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| No | ? | Yes | Yes | No | Yes | No | Yes | No | Yes |
| No | No | ? | ? | No | No | No | ? | No | ? |
| No | ? | ? | ? | No | ? | No | ? | No | Yes |
| No | ? | ? | Yes | No | ? | No | ? | No | Yes |
| No | ? | Yes | ? | No | ? | ? | ? | No | ? |
| Yes | Yes | Yes | No | Yes | Yes | Yes | No | Yes | ? |
| 10 | 2 | 0 | ? | 0 | 7 | 2 | ? | 1 | ? |
| Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes |
| No | No | No | No | No | Yes | No | No | No | Yes |
| Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| No | No | No | No | No | No | No | No | No | No |
| CT | CT | RCT | RCT | CT | CT | CT | RCT | CT | RCT |
| No | ? | ? | ? | No | ? | Yes | ? | ? | Yes |
| No | ? | ? | ? | No | ? | ? | ? | Yes | Yes |
| No | No | No | Yes | No | No | No | No | No | No |
| ? | Advanced periodontal and/or endodontic lesion | Fracture, endodontic failure and periodontal disease. | ? | Severe chronic periodontitis, apical lesions | ? | Periodontal disease, endodontic failure, advanced restorable caries or tooth fracture | ? | Periodontally hopeless prognosis | Root or crown fractures, non-restorable caries, residual roots |
| At least 3 wall maintained | ? | 4 walls architecture, socket depth >6 mm, no active peri-apical lesions, | No acute peri-apical infection | ? | At least 10 mm of bony support, no acute infection or peri-apical lesions | Presence of defect of the labial bone of >1/3 of mid width | No sockets with severe bone loss | No peri-apical lesions, acute abscesses and severe horizontal bone resorption | 4 walls architecture, no peri-apical or periodontal abscesses |
| High | Moderate | Moderate | Low | High | Moderate | High | Moderate | High | Low |
| 3 (2c) | 3 (2c) | 2 (1b) | 2 (1b) | 2 (1b) | 3 (2c) | 3 (2c) | 2 (1b) | 3 (2c) | 2 (1b) |
| NA | NA | 2 | 1 | NA | NA | NA | 1 | NA | 2 |
| # 29 Froum et al. (2004) | # 30 Vance et al. (2004) | # 31 Guarnieri et al. (2004) | # 32 Norton et al. (2003) | # 33 Fugazzotto (2003a,b) | # 34 Serino et al. (2003) | # 35 Iasella et al. (2003) | # 36 Carmagnola et al. (2003) | # 37 Froum et al. (2002) | # 38 Artzi et al. (2000) |
| Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| Yes | Yes | NA | NA | No | Yes | Yes | ? | Yes | No |
| Yes | No | NA | NA | No | ? | ? | ? | ? | No |
| ? | No | ? | No | No | ? | ? | ? | ? | No |
| ? | Yes | ? | No | No | ? | Yes | ? | ? | No |
| ? | No | ? | No | ? | ? | ? | ? | ? | No |
| Yes | ? | Yes | Yes | No | Yes | Yes | No | Yes | ? |
| 0 | ? | 0 | 0 | ? | 9 (20%) | 0 | ? | 0 | ? |
| Yes | Yes | NA | NA | Yes | Yes | Yes | Yes | Yes | No |
| No | No | ? | No | No | ? | Yes | ? | ? | No |
| Yes | Yes | Yes | Yes | Yes | Yes | Yes | ? | Yes | Yes |
| Yes | Yes | Yes | Yes | Yes | Yes | Yes | ? | Yes | Yes |
| No | No | ? | No | No | ? | ? | ? | ? | No |

Table 2. Continued

| Validity | Study #quality criteria | # 20 Fotek et al. (2009) | # 21 Crespi et al. (2009) | # 22 Molly et al. (2008) | # 23 Wang & Tsao (2008) | # 24 Neiva et al. (2008) | # 25 Cardaropoli & Cardaropoli (2008) | # 26 Barone et al. (2008) | # 27 Serino et al. (2008) | # 28 Luczyszyn et al. (2005) |
|------------------|---------------------------------------|---|--|--------------------------|---|---|---|---------------------------|---|------------------------------|
| Clinical aspects | Study design | CT | CT – Split-mouth | CT – Split-mouth | CT | RCT | CS | RCT | CT | CT – Split-mouth |
| | Validated measurement | ? | ? | ? | ? | Yes | ? | ? | No | ? |
| | Calibration examiner | ? | ? | ? | ? | Yes | ? | ? | No | ? |
| | Reproducibility data shown | No | No | No | No | Yes | No | No | ? | No |
| | Reason for extraction | Endodontic failure, tooth fracture | ? | Advanced periodontitis | Fractures, endodontic complications and periodontal disease | ? | Root fractures, periodontal, endodontic failures, advanced caries lesions | ? | Periodontal disease | ? |
| | Local inclusion/exclusion criteria | No peri-apical lesions or inadequate bone height for future implant | 3 walls maintained, no buccal plate presence, no acute periodontal infection | ? | ? | Residual pockets with <80% bone loss in all dimensions, no acute infections | ? | ? | At least 8 mm of residual alveolar bone, no acute abscesses | ? |
| | Estimated potential risk of bias CEBM | Low | Moderate | Low | High | Low | High | Moderate | Moderate | High |
| | Level of evidence | | | | | | | | | |
| | Jadad score | 3 (2c) | 3 (2c) | 3 (2c) | 3 (2c) | 2 (1b) | 4 (4) | 2 (1b) | 3 (2c) | 3 (2c) |

and 180 months, but only 3- to 7-month results have been recorded for this SR and meta-analysis.

Population epidemiology, tooth types, and reason for extraction

The selected studies included a number of subjects ranging between 4 and 90. Ten studies do not report the mean age of patients (# 2, 7, 11, 14, 26–28, 31, 33 and 38), while only three do not report the age range of subjects (# 14, 23 and 30). Five studies do not report information about gender (# 6–8, 14, 28). Reasons for extraction are reported in 18 studies (# 3, 5, 11, 12, 14, 16, 18–20, 22, 23, 25, 27, 29, 32, 34, 36, and 37), while local criteria for inclusion/exclusion are clearly reported in 22 papers (# 1–6, 8–10, 12, 13, 15–21, 24, 27, 31, and 38). Most studies evaluated effects of ARPs on anterior or single-rooted teeth. Seven studies included molars (# 3, 6, 8, 10, 12, 21, 25), study # 5 included only molars, eleven included all kinds of teeth (# 9, 11, 13, 18, 22, 23, 29, 32, 34, 36 and 37). Three studies do not report any information regarding tooth type (# 7, 14, and 33). Twenty-one studies did not include smokers: twelve because of a clear exclusion criteria (# 3, 8, 9, 16–18, 20–22, 24, 28, 33). Furthermore, studies # 26 and 32 included smokers, 5 and 3, respectively, whereas fifteen studies did not report the smoking status of the participants (# 5, 7, 10, 11, 14, 15, 23, 25, 27, 30, 31, 34–36, 38).

Intervention and pharmacological treatment

All the extracted data belonged to test groups of studies evaluating the effect of

different ARPs without immediate implant placement. Among these groups most evaluated the use of a combination of GRAFT and BARRIER, whereas thirteen evaluated the use of a GRAFT alone (studies # 1, 2, 7, 9, 10, 12, 17, 19, 27, 31, 34, 37, 38) and only six evaluated the use of a BARRIER alone (studies # 6, 8, 21, 24, 28, and 36). Four studies did not provide any information about post-operatively drug administration (# 8, 17, 24, and 36), while in study # 9 no drugs were prescribed. Twenty-seven studies provided antibiotic administration for the immediate post-extraction healing period, in addition of chlorhexidine mouth-rinses as antiseptic. Only fourteen studies (# 2, 3, 6, 10, 12, 16, 18, 19, 23, 26, 30, 33, 35, and 38) provided NSAID administration. All studies described the extraction procedure as less traumatically possible. A flap was raised for extraction in 21 studies (# 2, 7, 10, 11, 12, 14, 17, 22, 26–38). Among these, in only thirteen releasing incisions were performed (# 2, 7, 11, 12, 14, 17, 26–29, 32, 33, and 37). In the remaining studies, extractions were conducted without flaps. After extraction, primary soft tissue closure was achieved in fourteen studies (# 2, 10–12, 14, 17, 22, 26, 30–33, 37, and 38).

Evaluation parameters and methods

Only data regarding histomorphometry were extracted from selected studies. Most of studies evaluated all the outcomes described as primary in this review, while other five eval-

uated the % B only (# 2, 7, 17, 19, and 31), two evaluated % B and % RGM (# 22, 34), whereas study # 25 and 28 evaluated % RGM and % B -% CT, respectively.

Assessment of quality

Assessment of quality is presented in Table 2. The estimated risk of bias is defined as LOW in ten studies (# 3, 5, 13, 19, 20, 22, 24, 29, 30, and 35), as MODERATE in fourteen (# 2, 4, 7, 8, 9, 11, 12, 15, 17, 21, 26, 27, 37, and 38) and as HIGH in the remaining fourteen. Eight studies presented a combination of a low potential risk and a 2(1b) level of evidence (OCEBM 2011). Nine studies scored 2(1b) and presented a moderate potential risk (# 2, 4, 7, 8, 9, 12, 17, 26, and 27). Studies # 25 and 31 presented a combination of high potential risk and a level of evidence score of 4(4). Study # 38 is classified as moderate with a score of 3(2b). Remaining studies scored 3(2c): twelve were classified as having high potential risk of bias, four as moderate and two as low (# 20 and 22). About JADAD evaluation two studies out of seventeen RCTs (# 30, 35) scored 4, five studies (# 4, 5, 24, 29, 37) scored 3, eight (# 2, 3, 7, 8, 9, 12, 19, 26) scored 2 and only two studies (# 13 and 17) scored 1.

Loss to follow-up

Twelve studies did not report any information regarding loss to follow-up (# 1, 3, 9, 13, 17, 19, 24, 25, 30, 35, 36, 38). So lost to follow-up are reported in 26 studies. Of them, sixteen had no drop-outs (# 2, 6, 7, 8, 12, 14, 21–23, 26, 28, 29, 31, 32, 35, and 37).

| # 29 Froum et al. (2004) | # 30 Vance et al. (2004) | # 31 Guarnieri et al. (2004) | # 32 Norton et al. (2003) | # 33 Fugazzotto (2003a,b) | # 34 Serino et al. (2003) | # 35 Iasella et al. (2003) | # 36 Carmagnola et al. (2003) | # 37 Froum et al. (2002) | # 38 Artzi et al. (2000) |
|------------------------------------|--------------------------|------------------------------|--|---------------------------|---------------------------------|----------------------------|--|------------------------------------|--|
| RCT | RCT | CS | CT | CT – Parallel | CT – Split-mouth | RCT | CT – Parallel | RCT | Individual cohort |
| ? | Yes | ? | ? | Yes | ? | ? | ? | ? | Yes |
| ? | Yes | ? | ? | Yes | ? | ? | ? | ? | No |
| Yes | Yes | No | No | Yes | No | No | No | No | Yes |
| Periodontal and prosthetic reasons | ? | ? | Periodontal disease, endodontic failure and trauma | ? | Periodontally compromised teeth | ? | Periodontal and/or endodontic lesions or root fracture | Periodontal and prosthetic reasons | ? |
| ? | ? | No severe bone loss (>50%) | ? | ? | ? | ? | ? | ? | 3-4 walls architecture, no peri-apical lesions, abscesses and severe ridge resorption (>50%) |
| Low | Low | High | High | High | High | Low | High | Moderate | Moderate |
| 2 (1b) | 2 (1b) | 4 (4) | 3 (2c) | 3 (2c) | 3 (2c) | 2 (1b) | 3 (2c) | 2 (1b) | 3 (2b) |

Study outcomes

The study outcomes are presented in Tables 3. All the rough data are referred to site treated. For every primary outcome four proportion meta-analysis were performed at different healing stages (3–7 months): test groups were assimilated in order to nature of the graft used into three different ARPs, Allo-grafts, Xenografts, or Alloplasts. Untreated sites were used as control. If samples were constituted by one test/control group data reported on papers were used for comparison. Results are shown in Figs 2–4. All the Pooled Proportions were calculated using Fixed Effect estimate. For each kind of graft used the Spearman's correlations coefficient (r) over time was calculated. Analyzing % B (Fig. 2) best mean value is shown at 3 months using Alloplasts (54.4–95% CI = 26.75–57.18%), while the worst one is obtained by those ARPs adopting Xenografts at 5 months (23.6–95% CI = 2.13–66.71%). Considering % CT (Fig. 3) the highest and lowest mean values are shown at 7 months by groups testing Allografts (67–95% CI = 32.09–91.80%) and Alloplasts (27.1–95% CI = 10.78–47.69%). During time no statistical relevant differences arise among the performances of different kind of graft material and Control sites, both for % B and % CT. With regard to % CT in every group, even including controls, there is a trend toward a slight decrease. Referring to % RGM the lowest percentages are produced by Allografts (12.4–21.11%), whereas the highest percentages are obtained at

7 months by Xenografts and Alloplasts, with 37.14% (95% CI = 21.27–54.59%) and 37.23% (95% CI = 5.42–77.57%), respectively. Also regarding % RGM no statistical differences are shown (Fig. 4).

Discussion

The aim of this article was to carry out a systematic review regarding histological data derived from human studies reporting the effect of ARPs on healing patterns following tooth extraction. Different study on humans (Amler et al. 1960; Evian et al. 1982; Devlin & Sloan 2002; Trombelli et al. 2008) have identified the key processes of tissue modeling and remodeling after tooth extraction that eventually lead to a reduction on the overall ridge dimensions with significant bone height changes in both the buccal and lingual sides. They reported that whereas tissue modeling appeared to be a comparatively fast process, remodeling of the newly formed hard tissue was seemingly slow and unpredictable. In the study by Trombelli et al. (2008), conducted on 27 biopsies, representative of the early (2–4 weeks), intermediate (6–8 weeks,) and late phases (12–24 weeks) of healing, the mature bone organization and architecture was not completed even at 24 weeks after tooth extraction. Furthermore, a significant heterogeneity was observed in the composition of the specimens within each observational interval. They concluded that a great vari-

ability exists in man with respect to hard tissue maturation within extraction sockets.

In our systematic review, nine meta-analyses were performed referring to the three selected primary outcomes: residual graft, bone, and connective tissues percentages. Also, a comparison was conducted with histomorphometry regarding results of physiological healing processes in untreated sites.

Drawing conclusions across the studies is difficult, since test groups differed in many aspects, including considerable differences in surgical techniques (bone substitute into the socket alone or covered at the top by a barrier), in biomaterials used, in flap management (flapless, no primary closure/mucoperiosteal flap, primary closure), in follow-up duration and, above all, in type of biopsy retrieval. Nevertheless, some important speculations may rise.

Successful and long-lasting outcomes of different GBR procedures are well documented in literature (Dragoo & Sullivan 1973; Evian et al. 1982; Simion et al. 1994; Zitzmann et al. 2001) and led to the assumption that enhancing ARPs with multiple biomaterials, such as distinct kind of bone grafts and barriers (absorbable and non absorbable) might cause a more rapid bone formation inside extraction sockets by means of a double mechanism. First, in a mechanical fashion, stabilizing the blood clot, acting as a scaffold with a space-maintaining effect and avoiding epithelial

Table 3. Histomorphometrical results

| ID # | Study | # of teeth (maxillar/mandibular)/type | # of cores per group | Follow-up time (months) | % total bone (mineralized) | % residual graft | % connective/fibrous tissue (matrix) |
|------|-------------------------------|---------------------------------------|---|--------------------------|--|--|---|
| # 1 | Ciozza et al. (2012a, b) | 32 (18 + 14) I/C | Group Test (active bioglass): 6 | 6 | Test: 54.00 ± 31.00 | Test: 8.10 ± 7.80 | Test: 37.90 ± 25.60 |
| # 2 | Perelman-Karmon et al. (2012) | 23 (18 + 5) I/P | Group A (DBBM): 13 Group B (DBBM + Collagen): 10 | 9 | A: 29.7 ± 7.21 B: 40.8 ± 10.61 | ∅ | ∅ |
| # 3 | Cardaropoli et al. (2012) | 48 P/M | Group Test (DBBM Collagen + Collagen): 24 Group Control: 24 | 4 | Test: 26.34 ± 16.91 Control: 43.82 ± 12.23 | Test: 18.46 ± 11.18 Control: 0.0 ± 0.0 | Test: 55.19 ± 11.45 Control: 56.17 ± 12.23 |
| # 4 | Wood & Mealey (2012) | 32 (26 + 6) I/C/P | Group A (DFBDA + collagen): 16 Group B (FDBA + collagen): 16 | 5 | A: 38.42 ± 11.48 B: 24.63 ± 13.65 | A: 8.88 ± 12.83 B: 25.42 ± 17.01 | A: 52.71 ± 7.96 B: 49.94 ± 11.07 |
| # 5 | Hoang & Mealey (2012) | 30 (8 + 21) M | Group A (DBM-55 + collagen): 16 Group B (DBM-MS+ collagen): 14 | 5 | A: 48.8 ± 18.7 B: 52.7 ± 13.1 | A: 8.2 ± 4.7 B: 5.4 ± 4.5 | A: 43.1 ± 18.6 B: 41.9 ± 11.5 |
| # 6 | Crespi et al. (2011a) | 45 P/M | Group A (MHA + collagen): 15 Group B (CPB + collagen): 15 Group C (collagen): 15 | 4 | A: 36.5 ± 2.6 B: 38.0 ± 16.2 C: 30.3 ± 4.8 | A: 32.2 ± 3.2 B: 36.6 ± 4.8 C: 0.0 ± 0.0 | A: 33.3 ± 1.5 B: 25.3 ± 9.4 C: 58.3 ± 7.1 |
| # 7 | Nevins et al. (2011) | 16 | Group A (MCBS): 4 Group B (MCBS + rhPDGF-BB): 4 Group C (MCBS + EMD): 4 Group D (EMD + BCP): 4 | 5 | A: 28.3 ± 17.2 B: 39.6 ± 11.3 C: 23.9 ± 9.3 D: 21.4 ± 4.2 | ∅ | ∅ |
| # 8 | Crespi et al. (2011b) | 30 (15 + 15) P/M | Group A (CPB + collagen): 15 Group B (collagen): 15 | 4 | A: 39.6 ± 9.4 B: 29.5 ± 5.0 | A: 34.4 ± 5.1 B: 0.0 ± 0.0 | A: 26.0 ± 9.9 B: 57.7 ± 6.9 |
| # 9 | Heberer et al. (2011) | 39 (24 + 15) I/C/P/M | Group Test (DBBM Collagen): 20 Group Control: 19 | 3 | Test: 24.4 ± 10.80 Control: 44.21 ± 24.88 | Test: 14.75 ± 6.98 Control: 0.0 ± 0.0 | Test: 60.85 ± 8.78 Control: 55.78 ± 24.88 |
| # 10 | Ruga et al. (2011) | 60 P/M | Group Test (CaS): 19 | 3 | Test : 65.26 ± ? | Test : 30.00 ± ? | Test : 4.74 ± ? |
| # 11 | Nam et al. (2011) | 44 (25 + 19) I/C/P/M | Group A (coated DBBM + Collagen): 7 Group B (DBBM + Collagen): 5 | 6 | A: 10.4 ± 4.6 B: 5.3 ± 8.3 | A: 18.7 ± 7.0 B: 16.4 ± 12.2 | A: 70.8 ± 8.7 B: 78.3 ± 19.5 |
| # 12 | Brkovic et al. (2012) | 20 (9 + 11) C/P/M | Group A (β-TCP/Cig): 8 Group B (β-TCP/Cig + collagen): 7 | 9 | A: 42.4 ± 14.6 B: 45.3 ± 14.5 | A: 9.7 ± 7.3 B: 12.5 ± 6.6 | A: 47.1 ± ? B: 42.1 ± ? |
| # 13 | Checchi et al. (2011) | 10 I/C/P/M | Group A (biomimetic MHA + collagen): 5 Group B (nanocrystalline HA + collagen): 5 | 6 | A: 54.0 ± 22.0 B: 49.0 ± 28.0 | A: 8.0 ± 7.0 B: 14.0 ± 7.0 | A: 39.0 ± ? B: 41.0 ± ? |
| # 14 | Park et al. (2010) | 4 | Group Test (EBM+ collagen): 4 | 6 | Test : 9.88 ± 6.57 | Test : 42.62 ± 6.57 | Test : 47.50 ± 9.28 |
| # 15 | Beck & Mealey (2010) | 38 (16 + 22) I/C/P | GroupA (HBMA + collagen): 16 Group B (HBMA + collagen): 22 | Group A: 3 Group B: 6 | A: 45.8 ± 22.4 B: 45.0 ± 19.8 | A: 14.6 ± 12.9 B: 13.5 ± 12.2 | A: 39.6 ± 13.0 B: 41.3 ± 14.6 |
| # 16 | Kemas et al. (2010) | 8 I | Group Test (BCP + collagen): 6 | 4 | Test : 28.00 ± 36.75 | Test : 15.83 ± 8.70 | Test : 65.50 ± 25.85 |
| # 17 | Pelegrine et al. (2010) | 30 I/C | Group Test (autologous bone marrow): 15 Group Control: 15 | 6 | Test: 42.87 ± 11.33 Control: 45.47 ± 7.21 | ∅ | ∅ |
| # 18 | Lee et al. (2009) | 20 I/C/P/M | Group A (DBBM + collagen): 7 Group B (HBMA + collagen): 8 Group C (HBMA + collagen): 4 | 5 | A: 23.6 B: 17.2 C: 12.0 | A: 25.4 B: 12 C: 11.5 | A: 34.1 B: 45.9 C: 46.3 |
| # 19 | Aimetti et al. (2009) | 40 I/C | Group Test (MGCSH): 22 Group Control: 18 | 3 | Test: 58.8 ± 3.5 Control: 47.2 ± 7.7 | ∅ | ∅ |
| # 20 | Fotek et al. (2009) | 20 I/P | Group A (HBMA + ADM): 9 Group B (HBMA + dPTFE): 9 | 4 | A: 27.89 B: 32.63 | A: 13.93 B: 14.73 | A: 58.19 B: 52.64 |
| # 21 | Crespi et al. (2009) | 45 M/P | Group A (MHA + collagen): 15 Group B (Ca5 + collagen): 15 Group C (collagen): 15 | 3 | A: 40.0 ± 2.7 B: 45.0 ± 6.5 C: 32.8 ± 5.8 | A: 20.2 ± 3.2 B: 13.9 ± 3.4 C: 0.0 ± 0.0 | A: 41.3 ± 1.3 B: 41.5 ± 6.7 C: 64.6 ± 6.8 |
| # 22 | Molly et al. (2008) | 36 I/C/P/M | Group A (Fisiograft + e-PTFE): 8 Group B (DBBM + e-PTFE): 6 Group C (CaCO3 + e-PTFE): 6 Group Control: 5 | 6 | A: 27.9 ± 20.6 B: 20.7 ± 15.8 C: 24.0 ± 22.0 Control: 29.4 ± 17.1 | A: 5.6 ± 8.9 B: 20.2 ± 17.0 C: 12.0 ± 16.4 Control: 0.0 ± 0.0 | ∅ |

Table 3. Continued

| ID # | Study | # of teeth (maxillar/mandibular)/type | # of cores per group | Follow-up time (months) | % total bone (mineralized) | % residual graft | % connective/fibrous tissue (matrix) |
|------|----------------------------------|---------------------------------------|---|--|---|--|---|
| # 23 | Wang & Tsao (2008) | 7 I/CP/M | Group Test (HBMA + Collagen): 17 | 5 | Test: 68.45 ± 6.12 | Test : 3.81 ± 3.55 | Test : 27.72 ± 5.60 |
| # 24 | Neiva et al. (2008) | 24 (24 + 0) P | Group A (ABBM – P15 + collagen): 15? Group B (collagen): 15? Group Test (CPB + collagen): 10 | 4 | A: 29.92 ± 8.46 B: 36.54 ± 7.73 | A: 6.25 ± ? B: 0.0 ± 0.0 | A: 65.25 ± 6.41 B: 62.67 ± 7.41 |
| # 25 | Cardaropoli & Cardaropoli (2008) | 10 M/P | Group Test (CPB + collagen): 20 | 4 | ∅ | Test : 24.50 ± 11.65 | ∅ |
| # 26 | Barone et al. (2008) | 40 I/CP | Group Control: 20 | 7 | Test : 35.5 ± 10.4 Control: 25.7 ± 9.5 | Test : 29.2 ± 10.1 Control: 00.0 ± 0.0 | Test : 36.6 ± 12.6 Control: 59.1 ± 10.4 |
| # 27 | Serino et al. (2008) | 16 I/CP | Group Test (FISIOGRAFT): 7 Group Control: 9 | 3 | Test : 59.9 ± 22.4 Control: 48.8 ± 14.4 | Test : 00.0 ± 0.0 Control: 00.0 ± 0.0 | Test : 40.07 ± 22.43 Control: 51.16 ± 14.43 |
| # 28 | Luczynsyn et al. (2005) | 30 I/CP | Group A (HA + ADM): 15 Group B (ADM): 15 | 6 | A : 1.0 B: 46.0 | A: 42.0 B: 00.0 ± 0.0 | A: 57.0 B: 54.0 |
| # 29 | Froum et al. (2004) | 16 I/CP/M | Group A (HA + ADM): 4 Group B (HA + ePTFE): 4 Group C (ABBM + ADM): 4 Group D (ABBM + ePTFE): 4 | 7 | A: 34.5 ± 16.76 B: 27.60 ± 11.12 C: 41.65 ± 18.28 D: 17.87 ± 7.18 | A: 61.75 ± 16.82 B: 60.60 ± 11.85 C: 45.47 ± 13.76 D: 60.70 ± 14.00 | A: 10.75 ± 13.69 B: 11.87 ± 6.80 C: 12.85 ± 13.57 D: 21.42 ± 8.34 |
| # 30 | Vance et al. (2004) | 24 I/CP | Group A (CMC/Ca5/DFDBA+CaS): 12 Group B (DBBM + Collagen): 12 Group Test (MGCSH): 10 | 4 | A: 61 ± 9 B: 26 ± 20 Test: 58.1 ± 6.2 med. Control: ≤ 46 | A: 3 ± 3 B: 16 ± 7 ∅ | A: 36 ± ? B: 59 ± ? ∅ |
| # 31 | Guarnieri et al. (2004) | 15 I/CP | Group Control: 5 | 3 | Test: 26.90 ± ? A: 19.4 | Test: 25.60 ± ? A: 59.1 | Test: 47.40 ± ? A: 21.5 |
| # 32 | Norton et al. (2003) | 30 I/CP/M | Group Test (DBBM + Collagen): 30 | 6 | B: 34.5 C: 69.1 D: 68.8 | B: 18.7 C: 11.3 D: 0.13 | B: 46.8 C: 19.6 D: 31.1 |
| # 33 | Fugazzotto (2003a,b) | 59 | Group A (DBBM + e-PTFE): 6 Group B (DBBM + e-PTFE): 40 Group C (DBBM + e-PTFE): 6 Group D (DBBM + e-PTFE): 7 | 8 | | | |
| # 34 | Serino et al. (2003) | 39 I/CP/M | Group Test (FISIOGRAFT): 10 Control: 3 | 6 | Test: 66.7 ± 14.31 Control: 43.66 ± 10.69 | Test : 0.0 ± 0.0 Control: 0.0 ± 0.0 | ∅ |
| # 35 | Iasella et al. (2003) | 24 I/CP | Group Test A (FDBA + collagen): 5 Group Test B (FDBA + collagen): 7 Group Control A: 5 Group Control B: 5 | Test A: 4 Test B: 6 Control A: 4 Control B: 6 | Test A: 31 ± 9 Test B: 25 ± 17 Test comb: 28 ± 14 Control A: 58 ± 11 Control B: 50 ± 14 Control comb: 54 ± 12 A: 53.0 ± ? B: 34.4 ± ? Control: 43.5 ± ? | Test A: 32 ± 19 Test B: 41 ± 18 Test comb: 37 ± 18 Control A: 0.0 ± 0.0 Control B: 0.0 ± 0.0 Control comb.: 0 ± 0 A: 0.0 ± 0.0 B: 21.1 ± 20.0 Control: 0.0 ± 0.0 | Test A: 37 ± ? Test B: 34 ± ? Test comb: 37 ± ? Control A: 42 ± ? Control B: 50 ± ? Control comb.: 46 ± ? A: 46.0 ± ? B: 44.3 ± ? Control: 43.0 ± ? |
| # 36 | Carmagnola et al. (2003) | 31 I/CP/M | Group A (Collagen): 11 Group B (DBBM + Collagen): 7 Group Control: 10 | A: 4.5 B: 8 Control: > 9 | A: 59.5 ± 14.3 B: 34.7 ± 7.9 Control: 32.4 ± 6.0 Test: 46.3 ± 9.81 | A: 5.5 ± 1.2 B: 13.5 ± 3.6 Control: 0.0 ± 0.0 Test: 30.8 ± 7.82 | A: 35.3 ± 14.1 B: 67.0 ± 8.1 Control: 51.6 ± 36.1 Test: 22.9 ± 12.28 |
| # 37 | Froum et al. (2002) | 30 I/CP/M | Group A (Bioactive glass): 10 Group B (DFDBA): 10 Group Control: 10 | 7 | | | |
| # 38 | Artzi et al. (2000) | 15 I/CP | Group Test (DBBM): 15 | 3 | | | |

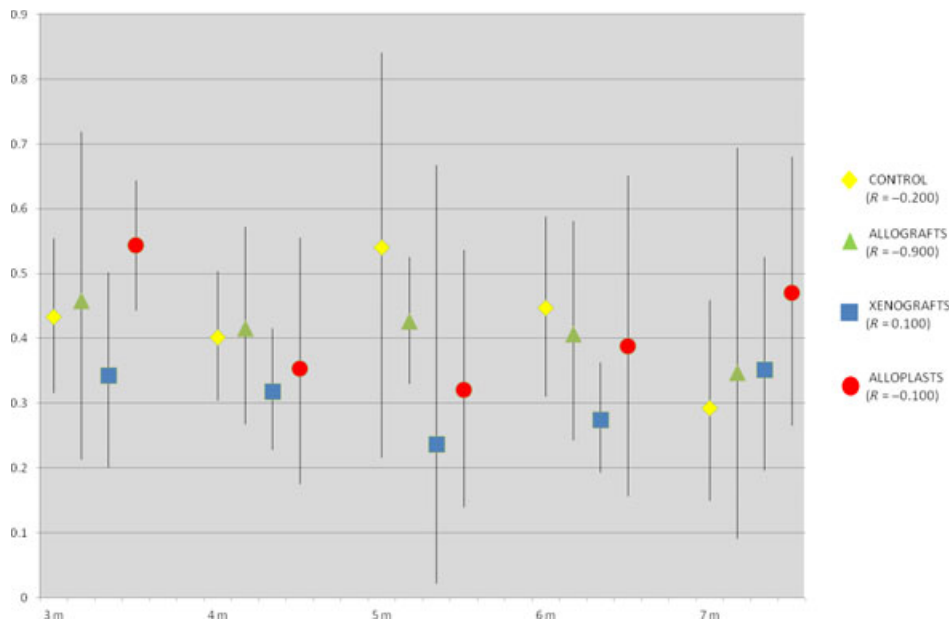


Fig. 2. Percentage bone over healing time (yellow, healed bone; green, allografts; blue, xenografts; red, alloplasts). R = simple linear Spearman's correlations coefficient.

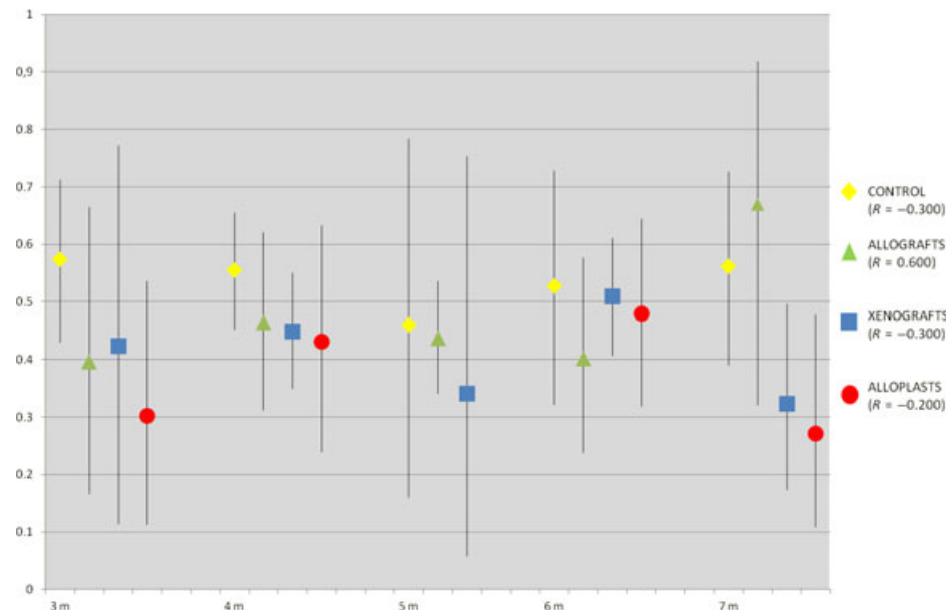


Fig. 3. Percentage CT over healing time (yellow, healed bone; green, allografts; blue, xenografts; red, alloplasts). R = simple linear Spearman's correlations coefficient.

ingrowth; secondly, biologically, providing an extra source of collagen, minerals, and growth factors.

All the recent systematic reviews (Ten Heggeler et al. 2010; Vignoletti et al. 2012; Horvath et al. 2013; Vittorini Orgeas et al. 2013) and an international consensus (Hammerle et al. 2012) on this topic seem to agree on confirming somewhat beneficial clinical outcome when adopting ARPs. Accordingly, our research corroborates this positive trend, even from a histological stand point. In fact, during healing time, no statistical relevant differences have been

shown among the performances of each kind of graft material and control sites, both for % B and % CT. On the other hand, when adopting ARPs, the possibility to maintain the dimension of alveolar crest or, at least, to reduce its resorption has been described.

Our results seem to be consistent with those suggested by Horvath et al. (2013), although our approach has been specifically focused on comparing histomorphometric data, thus including more papers as well. It is noteworthy that, to the best of our knowledge, this research is the first system-

atic review performing several meta-analyses on histological data referring to ARPs performance.

Accordingly to current literature, a suggestive result regards the variations in RGM %: in fact xenografts and alloplasts showed the highest amount of residual particles, still over 35% at 7 months post-op, while allografts presented the lowest rate, thus suggesting an hypothetical clinical preference in case of graft selection. Furthermore, considering B %, the best mean value is produced at 3 months by allografts unlike xenografts showed the worst % still after 5 months; it is interesting to notice how these results suggest a likely, peculiar inflammatory foreign body reaction induced by graft particles as previously proposed by Araujo et al. (2008).

In respect to clinical implications related to dental implant insertion, the most relevant evidence is represented by the absence of statistical significant differences between various ARPs and control sites in terms of B and CT percentages, even considering the different follow-up times. This finding should be considered when an implant placement is scheduled after an ARP therapy (Hammerle et al. 2004). In fact, such procedures seem to be as unable to accelerate as to delay the physiological healing process in extraction sockets, just because they do not improve the histological modifications in treated sites. Consequently, it might be argued that providing for a longer healing period, prior to implant insertion, is not mandatory, even with the aim of achieving a complete maturation and mineralization of bone tissue. In particular placement could be performed after just 3 or 4 months.

However, several critical issues arise from a thorough interpretation of our results. First of all, in most of the selected studies, a small sample size limits the possibility of drawing any strong conclusions. A complete lack of standardization in follow-up timing among the examined papers, impairs a comprehensive overview of the entire healing process and a consequent solid understanding of its progression month by month. In addition, all the analyzed researches show different biopsy retrieval techniques, thus, considering as a staple a trephine core sampling, it appears clear that multiple locations of bone core retrievals, for instance, may not coincide exactly with the precise position of the original dental alveola, impairing a correct data evaluation.

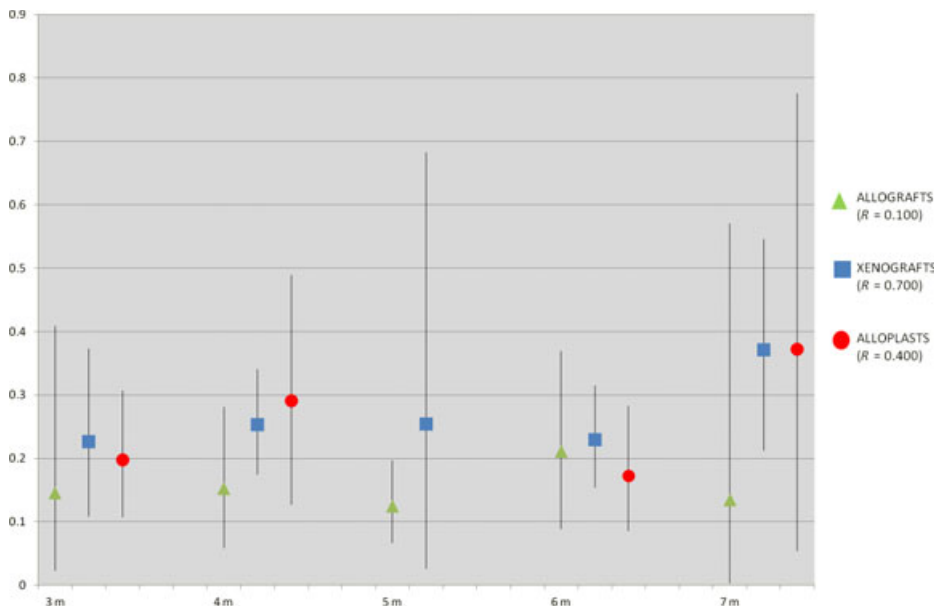


Fig. 4. Percentage RGM over healing time (green, allografts; blue, xenografts; red, alloplasts). R = simple linear Spearman's correlations coefficient.

Conclusion

With the limitations of this study, due to the considerable differences among studies

analyzed, it can be concluded that an absence of significant statistical differences between various ARPs and spontaneous healing are present in terms of percentage

References

- Aimetti, M., Romano, F., Griga, F.B. & Godio, L. (2009) Clinical and histologic healing of human extraction sockets filled with calcium sulfate. *The International Journal of Oral & Maxillofacial Implants* **24**: 902–909.
- Amler, M.H., Johnson, P.L. & Salman, I. (1960) Histological and histochemical investigation of human alveolar socket healing in undisturbed extraction wounds. *Journal of the American Dental Association* **61**: 32–44.
- Araujo, M., Linder, E., Wennstrom, J. & Lindhe, J. (2008) The influence of Bio-Oss Collagen on healing of an extraction socket: an experimental study in the dog. *The International Journal of Periodontics & Restorative Dentistry* **28**: 123–135.
- Araujo, M.G. & Lindhe, J. (2005) Dimensional ridge alterations following tooth extraction. An experimental study in the dog. *Journal of Clinical Periodontology* **32**: 212–218.
- Artzi, Z., Tal, H. & Dayan, D. (2000) Porous bovine bone mineral in healing of human extraction sockets. Part 1: histomorphometric evaluations at 9 months. *Journal of Periodontology* **71**: 1015–1023.
- Barone, A., Aldini, N.N., Fini, M., Giardino, R., Calvo Guirado, J.L. & Covani, U. (2008) Xenograft versus extraction alone for ridge preservation after tooth removal: a clinical and histomorphometric study. *Journal of Periodontology* **79**: 1370–1377.
- Bartee, B.K. (2001a) Extraction site reconstruction for alveolar ridge preservation. Part 1: rationale and materials selection. *The Journal of Oral Implantology* **27**: 187–193.
- Bartee, B.K. (2001b) Extraction site reconstruction for alveolar ridge preservation. Part 2: membrane-assisted surgical technique. *The Journal of Oral Implantology* **27**: 194–197.
- Beck, T.M. & Mealey, B.L. (2010) Histologic analysis of healing after tooth extraction with ridge preservation using mineralized human bone allograft. *Journal of Periodontology* **81**: 1765–1772.
- Becker, W., Becker, B.E. & Caffesse, R. (1994) A comparison of demineralized freeze-dried bone and autologous bone to induce bone formation in human extraction sockets. *Journal of Periodontology* **65**: 1128–1133.
- Becker, W., Urist, M., Becker, B.E., Jackson, W., Parry, D.A., Bartold, M., Vincenzi, G., De Georges, D. & Niederwanger, M. (1996) Clinical and histologic observations of sites implanted with intraoral autologous bone grafts or allografts. 15 human case reports. *Journal of Periodontology* **67**: 1025–1033.
- Brkovic, B.M., Prasad, H.S., Rohrer, M.D., Konandreas, G., Agrogiannis, G., Antunovic, D. & Sander, G.K. (2012) Beta-tricalcium phosphate/type I collagen cones with or without a barrier membrane in human extraction socket healing: clinical, histologic, histomorphometric, and immunohistochemical evaluation. *Clinical Oral Investigations* **16**: 581–590.
- Cardaropoli, G., Araujo, M. & Lindhe, J. (2003) Dynamics of bone tissue formation in tooth extraction sites. An experimental study in dogs. *Journal of Clinical Periodontology* **30**: 809–818.
- Cardaropoli, D. & Cardaropoli, G. (2008) Preservation of the postextraction alveolar ridge: a clinical and histologic study. *The International Journal of Periodontics & Restorative Dentistry* **28**: 469–477.
- Cardaropoli, D., Tamagnone, L., Roffredo, A., Gaveglione, L. & Cardaropoli, G. (2012) Socket preservation using bovine bone mineral and collagen membrane: a randomized controlled clinical trial with histologic analysis. *The International Journal of Periodontics & Restorative Dentistry* **32**: 421–430.
- Carmagnola, D., Adriaens, P. & Berglundh, T. (2003) Healing of human extraction sockets filled with Bio-Oss. *Clinical Oral Implants Research* **14**: 137–143.
- Cecchi, V., Savarino, L., Montevecchi, M., Felice, P. & Cecchi, L. (2011) Clinical-radiographic and histological evaluation of two hydroxyapatites in human extraction sockets: a pilot study. *International Journal of Oral & Maxillofacial Surgery* **40**: 526–532.
- Clozza, E., Biasotto, M., Cavalli, F., Moimas, L. & Di Lenarda, R. (2012a) Three-dimensional evaluation of bone changes following ridge preservation procedures. *The International Journal of Oral & Maxillofacial Implants* **27**: 770–775.
- Clozza, E., Pea, M., Cavalli, F., Moimas, L., Di Lenarda, R. & Biasotto, M. (2012b) Healing of fresh extraction sockets filled with bioactive glass

of bone and connective tissue. So in preserved sites, it seems to be no longer necessary to wait a different time of healing from untreated sites prior to implant insertion. Furthermore, such procedures seem to be ineffective in improving tissue quality for following implant placement, so their clinical effect in limiting dimensional alterations of ridge, and evaluation of the cost/benefit ratio should be taken into greater account. However, other researches are needed to clearly define the effects of such procedures.

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- particles: histological findings in humans. *Clinical Implant Dentistry and Related Research*. Epub Ahead of Print Jun 12.
- Crespi, R., Cappare, P. & Gherlone, E. (2009) Magnesium-enriched hydroxyapatite compared to calcium sulfate in the healing of human extraction sockets: radiographic and histomorphometric evaluation at 3 months. *Journal of Periodontology* **80**: 210–218.
- Crespi, R., Cappare, P. & Gherlone, E. (2011a) Comparison of magnesium-enriched hydroxyapatite and porcine bone in human extraction socket healing: a histologic and histomorphometric evaluation. *The International Journal of Oral & Maxillofacial Implants* **26**: 1057–1062.
- Crespi, R., Cappare, P., Romanos, G.E., Mariani, E., Benasciutti, E. & Gherlone, E. (2011b) Cortico-cancellous porcine bone in the healing of human extraction sockets: combining histomorphometry with osteoblast gene expression profiles in vivo. *The International Journal of Oral & Maxillofacial Implants* **26**: 866–872.
- Darby, I., Chen, S. & De Poi, R. (2008) Ridge preservation: what is it and when should it be considered. *Australian Dental Journal* **53**: 11–21.
- Devlin, H. & Sloan, P. (2002) Early bone healing events in the human extraction sockets. *International Journal of Oral and Maxillofacial Surgery* **31**: 641–645.
- Dragoo, M.R. & Sullivan, H.C. (1973) A clinical and histological evaluation of autogenous iliac bone grafts in humans. I. Wound healing 2 to 8 months. *Journal of Periodontology* **44**: 599–613.
- von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gotsche, P.C., Vandenbroucke, J.P. & Initiative, S. (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* **370**: 1453–1457.
- Esposito, M., Coulthard, P., Worthington, H.V. & Jokstad, A. (2001) Quality assessment of randomized controlled trials of oral implants. *The International Journal of Oral & Maxillofacial Implants* **16**: 783–792.
- Evian, C.I., Rosenberg, E.S., Coslet, J.G. & Corn, H. (1982) The osteogenic activity of bone removed from healing extraction sockets in humans. *Journal of Periodontology* **53**: 81–85.
- Fiorellini, J.P., Howell, T.H., Cochran, D., Malmquist, J., Lilly, L.C., Spagnoli, D., Toljanic, J., Jones, A. & Nevins, M. (2005) Randomized study evaluating recombinant human bone morphogenetic protein-2 for extraction socket augmentation. *Journal of Periodontology* **76**: 605–613.
- Fotek, P.D., Neiva, R.F. & Wang, H.L. (2009) Comparison of dermal matrix and polytetrafluoroethylene membrane for socket bone augmentation: a clinical and histologic study. *Journal of Periodontology* **80**: 776–785.
- Froum, S., Cho, S.C., Elian, N., Rosenberg, E., Rohrer, M. & Tarnow, D. (2004) Extraction sockets and implantation of hydroxyapatites with membrane barriers: a histologic study. *Implant Dentistry* **13**: 153–164.
- Froum, S., Cho, S.C., Rosenberg, E., Rohrer, M. & Tarnow, D. (2002) Histological comparison of healing extraction sockets implanted with bioactive glass or demineralized freeze-dried bone allograft: a pilot study. *Journal of Periodontology* **73**: 94–102.
- Fugazzotto, P.A. (2003a) GBR using bovine bone matrix and resorbable and nonresorbable membranes. Part 1: histologic results. *The International Journal of Periodontics & Restorative Dentistry* **23**: 361–369.
- Fugazzotto, P.A. (2003b) GBR using bovine bone matrix and resorbable and nonresorbable membranes. Part 2: Clinical results. *The International Journal of Periodontics & Restorative Dentistry* **23**: 599–605.
- Guarnieri, R., Pecora, G., Fini, M., Aldini, N.N., Giardino, R., Orsini, G. & Piattelli, A. (2004) Medical grade calcium sulfate hemihydrate in healing of human extraction sockets: clinical and histological observations at 3 months. *Journal of Periodontology* **75**: 902–908.
- Hammerle, C.H., Araujo, M.G. & Simion, M. Osteology Consensus Group 2011. (2012) Evidence-based knowledge on the biology and treatment of extraction sockets. *Clinical Oral Implants Research* **23** Suppl 5: 80–82.
- Hammerle, C.H., Chen, S.T., Wilson, T.J. Jr. (2004) Consensus statement and recommended clinical procedures regarding the placement of implants in extraction sockets. *The International Journal of Oral & Maxillofacial Implants* **19**(Suppl): 26–28.
- Heberer, S., Al-Chawaf, B., Jablonski, C., Nelson, J.J., Lage, H. & Nelson, K. (2011) Healing of ungrafted and grafted extraction sockets after 12 weeks: a prospective clinical study. *The International Journal of Oral & Maxillofacial Implants* **26**: 385–392.
- Higgins, J.P.T. & Green, S. & Cochrane Collaboration. (2008) *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK; Hoboken, NJ: Wiley-Blackwell, pp. xxi, 649 p.
- Hoang, T.N. & Mealey, B.L. (2012) Histologic comparison of healing after ridge preservation using human demineralized bone matrix putty with one versus two different-sized bone particles. *Journal of Periodontology* **83**: 174–181.
- Horvath, A., Mardas, N., Mezzomo, L.A., Needleman, I.G. & Donos, N. (2013) Alveolar ridge preservation A systematic review. *Clinical Oral Investigations* **17**: 341–363.
- 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. *Journal of Periodontology* **74**: 990–999.
- Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J. & McQuay, H.J. (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* **17**: 1–12.
- Kesmas, S., Swasdison, S., Yodsanga, S., Sessirisombat, S. & Jansisanont, P. (2010) Esthetic alveolar ridge preservation with calcium phosphate and collagen membrane: preliminary report. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* **110**: e24–e36.
- Lee, D.W., Pi, S.H., Lee, S.K. & Kim, E.C. (2009) Comparative histomorphometric analysis of extraction sockets healing implanted with bovine xenografts, irradiated cancellous allografts, and solvent-dehydrated allografts in humans. *The International Journal of Oral & Maxillofacial Implants* **24**: 609–615.
- Lekovic, V., Camargo, P.M., Klokkevold, P.R., Weinlaender, M., Kenney, E.B., Dimitrijevic, B. & Nedic, M. (1998) Preservation of alveolar bone in extraction sockets using bioabsorbable membranes. *Journal of Periodontology* **69**: 1044–1049.
- Lekovic, V., Kenney, E.B., Weinlaender, M., Han, T., Klokkevold, P., Nedic, M. & Orsini, M. (1997) A bone regenerative approach to alveolar ridge maintenance following tooth extraction. Report of 10 cases. *Journal of Periodontology* **68**: 563–570.
- Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J. & Moher, D. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *British Medical Journal* **339**: b2700.
- Luczyszyn, S.M., Papalexioiu, V., Novaes, A.B., Jr, Grisi, M.F., Souza, S.L. & Taba, M., Jr. (2005) Acellular dermal matrix and hydroxyapatite in prevention of ridge deformities after tooth extraction. *Implant Dentistry* **14**: 176–184.
- Mardas, N., Chadha, V. & Donos, N. (2010) Alveolar ridge preservation with guided bone regeneration and a synthetic bone substitute or a bovine-derived xenograft: a randomized, controlled clinical trial. *Clinical Oral Implants Research* **21**: 688–698.
- Mardas, N., D'Aiuto, F., Mezzomo, L., Arzoumanidi, M. & Donos, N. (2011) Radiographic alveolar bone changes following ridge preservation with two different biomaterials. *Clinical Oral Implants Research* **22**: 416–423.
- Moher, D., Cook, D.J., Eastwood, S., Olkin, I., Rennie, D. & Stroup, D.F. (1999) Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* **354**: 1896–1900.
- Moher, D., Schulz, K.F. & Altman, D.G. CONSORT Group. (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Journal of the American Podiatric Medical Association* **91**: 437–442.
- Molly, L., Vandromme, H., Quirynen, M., Schepers, E., Adams, J.L. & van Steenberghe, D. (2008) Bone formation following implantation of bone biomaterials into extraction sites. *Journal of Periodontology* **79**: 1108–1115.
- Nam, H.W., Park, J.B., Lee, J.Y., Rhee, S.H., Lee, S.C., Koo, K.T., Kim, T.I., Seol, Y.J., Lee, Y.M., Ku, Y., Rhyu, I.C., Park, Y.J. & Chung, C.P. (2011) Enhanced ridge preservation by bone mineral bound with collagen-binding synthetic oligopeptide: a clinical and histologic study in humans. *Journal of Periodontology* **82**: 471–480.
- Needleman, I. (1999) CONSORT. Consolidated Standards of Reporting Trials. *British Dental Journal* **186**: 207.

- Neiva, R.F., Tsao, Y.P., Eber, R., Shotwell, J., Billy, E. & Wang, H.L. (2008) Effects of a putty-form hydroxyapatite matrix combined with the synthetic cell-binding peptide P-15 on alveolar ridge preservation. *Journal of Periodontology* **79**: 291–299.
- Nevins, M.L., Camelo, M., Schupbach, P., Nevins, M., Kim, S.W. & Kim, D.M. (2011) Human buccal plate extraction socket regeneration with recombinant human platelet-derived growth factor BB or enamel matrix derivative. *The International Journal of Periodontics & Restorative Dentistry* **31**: 481–492.
- Norton, M.R., Odell, E.W., Thompson, I.D. & Cook, R.J. (2003) Efficacy of bovine bone mineral for alveolar augmentation: a human histologic study. *Clinical Oral Implants Research* **14**: 775–783.
- OCEBM Levels of Evidence Working Group*. (2011). "The Oxford Levels of Evidence 2" Oxford Centre for Evidence-Based Medicine. Available at: <http://www.cebm.net/index.aspx?o=5653>.
- Park, J.Y., Koo, K.T., Kim, T.I., Seol, Y.J., Lee, Y.M., Ku, Y., Rhyu, I.C. & Chung, C.P. (2010) Socket preservation using deproteinized horse-derived bone mineral. *Journal of Periodontal & Implant Science* **40**: 227–231.
- Pelegri, A.A., da Costa, C.E., Correa, M.E. & Marques, J.F., Jr. (2010) Clinical and histomorphometric evaluation of extraction sockets treated with an autologous bone marrow graft. *Clinical Oral Implants Research* **21**: 535–542.
- Perelman-Karmon, M., Kozlovsky, A., Liloy, R. & Artzi, Z. (2012) Socket site preservation using bovine bone mineral with and without a bioresorbable collagen membrane. *The International Journal of Periodontics & Restorative Dentistry* **32**: 459–465.
- Pinho, M.N., Roriz, V.L., Novaes, A.B., Jr, Taba, M., Jr, Grisi, M.F., de Souza, S.L. & Palioto, D.B. (2006) Titanium membranes in prevention of alveolar collapse after tooth extraction. *Implant Dentistry* **15**: 53–61.
- Ruga, E., Galesio, C., Chiusa, L. & Boffano, P. (2011) Clinical and histologic outcomes of calcium sulfate in the treatment of postextraction sockets. *The Journal of Craniofacial Surgery* **22**: 494–498.
- Serino, G., Biancu, S., Iezzi, G. & Piattelli, A. (2003) Ridge preservation following tooth extraction using a polylactide and polyglycolide sponge as space filler: a clinical and histological study in humans. *Clinical Oral Implants Research* **14**: 651–658.
- Serino, G., Rao, W., Iezzi, G. & Piattelli, A. (2008) Polylactide and polyglycolide sponge used in human extraction sockets: bone formation following 3 months after its application. *Clinical Oral Implants Research* **19**: 26–31.
- Simion, M., Baldoni, M., Rossi, P. & Zaffe, D. (1994) A comparative study of the effectiveness of e-PTFE membranes with and without early exposure during the healing period. *The International Journal of Periodontics & Restorative Dentistry* **14**: 166–180.
- Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A. & Thacker, S.B. (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *The Journal of American Medical Associations* **283**: 2008–2012.
- Tan, W.L., Wong, T.L., Wong, M.C. & Lang, N.P. (2012) A systematic review of post-extraction alveolar hard and soft tissue dimensional changes in humans. *Clinical Oral Implant Research* **23** (Suppl. 5): 1–21.
- Ten Heggeler, J.M., Slot, D.E. & Van der Weijden, G.A. (2010) Effect of socket preservation therapies following tooth extraction in non-molar regions in humans: a systematic review. *Clinical Oral Implants Research* **22**: 779–788.
- Trombelli, L., Farina, R., Marzola, A., Bozzi, L., Liljenberg, B. & Lindhe, J. (2008) Modeling and remodeling of human extraction sockets. *Journal of Clinical Periodontology* **35**: 630–639.
- Van der Weijden, F., Dell'Acqua, F. & Slot, D.E. (2009) Alveolar bone dimensional changes of post-extraction sockets in humans: a systematic review. *Journal of Clinical Periodontology* **36**: 1048–1058.
- Vance, G.S., Greenwell, H., Miller, R.L., Hill, M., Johnston, H. & Scheetz, J.P. (2004) Comparison of an allograft in an experimental putty carrier and a bovine-derived xenograft used in ridge preservation: a clinical and histologic study in humans. *The International Journal of Oral & Maxillofacial Implants* **19**: 491–497.
- Vignoletti, F., Matesanz, P., Rodrigo, D., Figuero, E., Martin, C. & Sanz, M. (2012) Surgical protocols for ridge preservation after tooth extraction. A systematic review. *Clinical Oral Implants Research* **23**(Suppl. 5): 22–38.
- Vittorini Orgeas, G., Clementini, M., De Risi, V. & de Sanctis, M. (2013) Surgical techniques for alveolar socket preservation: a systematic review. *The International Journal of Oral & Maxillofacial Implant* **28**: 1049–1061.
- Wang, H.L. & Tsao, Y.P. (2008) Histologic evaluation of socket augmentation with mineralized human allograft. *The International Journal of Periodontics & Restorative Dentistry* **28**: 231–237.
- Wood, R.A. & Mealey, B.L. (2012) Histologic comparison of healing after tooth extraction with ridge preservation using mineralized versus demineralized freeze-dried bone allograft. *Journal of Periodontology* **83**: 329–336.
- Zitzmann, N.U., Scharer, P., Marinello, C.P., Schupbach, P. & Berglundh, T. (2001) Alveolar ridge augmentation with Bio-Oss: a histologic study in humans. *The International Journal of Periodontics & Restorative Dentistry* **21**: 288–295.