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Surgical techniques for alveolar socket preservation: a systematic review of histological and histomorphometric outcomes

Tecniche chirurgiche per la preservazione dell'osso alveolare: revisione sistematica delle variabili istologiche e istomorfometriche

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Summary

After tooth extractions alveolar process resorption takes place with consequences for prosthetic therapy. The aim of this paper was to systematically review the literature for hystological data that provide information regarding the effect of alveolar ridge preservation procedures and biomaterials on healing after extraction in humans in terms of bone, connective tissues and residual graft percentages.

Search was conducted, till September 2012, consulting MEDLINE-PubMed and the Cochrane CENTRAL. Of 646, 38 papers were selected. As outcome variables were selected the mean percentage of Bone (%B), Connective Tissue (%CT) and Residual Graft Material (%RGM). Considering %B, best value is at 3 months with Allografts (54,4%) while the worst is with Xenografts at 5 months (23,6%). Considering %CT the highest and lowest values are shown at 7 months with Allografts (67%) and Alloplasts (27,1%). Considering %RGM lowest percentages are shown by Allografts (12,4% to 21,11%) while the highest are with Xenografts and Alloplasts at 7 months, 37,14% and 37,23%. In any case there aren't statistical differences.

The most impactful evidence is represented by the absence of statistical significant differences between various ARPs and control. So it is no necessary to wait further than 3-4 months, prior to implant insertion in preserved sites.

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Keywords: Alveolar ridge preservation, socket preservation, histolomorphometry, bone graft, membrane.

Riassunto

In seguito alle estrazioni dentarie avviene un processo di riassorbimento del processo alveolare con importanti conseguenze sulla terapia protesica. Lo scopo di questo studio è di revisionare sistematicamente i dati istologici presenti in letteratura che possano dare informazioni riguardo gli effetti delle procedure di preservazione dell'osso alveolare e dell'utilizzo di biomateriali sulla

guarigione postestrattiva nell'uomo in termini istomorfometrici.
La ricerca è stata effettuata, fino a settembre 2012, consultando i motori di ricerca MEDLINE-PubMed e Cochrane CENTRAL. Di 646 titoli, 38 studi sono stati selezionati. Sono state selezionate come variabili primarie la percentuale media di Osso (%B), di Tessuto Connettivo (%CT) e di Biomateriale Residuo (%RGM). Considerando la %B, i valori migliori si ottengono a 3 mesi con l'utilizzo di innesti omologhi (54,4%) mentre i peggiori si hanno a 5 mesi con l'utilizzo di innesti eterologhi (23,6%). In termini di %CT i valori limite sono espressi a 7 mesi con l'utilizzo di innesti omologhi (67%) e innesti alloplastici (27,1%). In termini di %RGM la percentuale più bassa si ha con l'utilizzo di innesti omologhi (da 12,4 a 21,11%) mentre quelle più alte si hanno a 7 mesi con l'utilizzo di innesti eterologhi e alloplastici, 37,14% e 37,23%. In ogni caso le differenze non sono statisticamente significative.
L'evidenza più importante risultante da questa metanalisi è rappresentata dall'assenza di differenze statisticamente significative nella composizione tissutale derivante dalle varie procedure di Preservazione dell'Osso Alveolare e dalla guarigione spontanea, che indicherebbe la necessità di non aspettare più di 3-4 mesi prima dell'inserimento di impianti nei siti preservati.

Introduction

After tooth extractions a consequent loss in height and width of the alveolar process always takes place (Araujo and Lindhe, 2005). Usually the amount of the horizontal bone loss is the greatest and occurs mainly on the buccal than on 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(Van der Weijden et al., 2009). This process 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 functional and esthetical consequences impairing the execution of both traditional and implant supported dentures (Pinho et al., 2006, Araujo and Lindhe, 2005, Cardaropoli et al., 2003, Bartee, 2001a, Bartee, 2001b). Thus various surgical procedures 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 (Ten Heggeler et al., 2011, Vignoletti et al., 2012, Vittorini et al. 2013). 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, Becker et al., 1996, Froum et al., 2002), xenografts, deproteinized bovine-bone mineral (DBBM) (Artzi et al., 2000), alloplasts (Serino et al., 2003) and bone morphogenic proteins (BMP) (Fiorellini et al., 2005). Furthermore guided bone regeneration (GBR) procedures with or without bone grafts, has also been evaluated (Mardas et al., 2010, Mardas et al., 2011, Barone et al., 2008, Iasella et al., 2003, Lekovic et al., 1998, Lekovic et al., 1997). Consequently 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" (Darby et al., 2008). Hence, since 2009 various systematic reviews have been published confirming the efficacy of different "ARPs" in preventing post-extraction dimensional changes of alveolar ridges.
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 for histological data that provide information with respect to the effect of socket preservation procedures and materials on healing patterns following tooth extraction in humans in terms of residual graft, bone and connective tissues percentages as compared with physiological processes in untreated sites.

Materials and Methods

Focused question

Which socket preservation technique in humans provides the best histological bone healing pattern prior to implant insertion?

Search strategy

Papers search was conducted, up to September 2012, consulting The National Library of Medicine, Washington, DC (MEDLINE-PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL), using the following search 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) NOT (trauma OR tumour OR injuries OR cancer OR "Cleft lip and palate"). This research was supplemented by cross-checking the reference lists of selected studies and review articles. "Grey literature" was investigated as well.

The inclusion criteria were:

- human studies;
- english pubblications;
- randomized Clinical Trials, Controlled Clinical Trials, prospective/retrospective CT or case series with a minimum of 4 biopsy cores per group;
- histomorphometrical evaluation of hard tissue healing over a period of 3 – 7 months after ARPs.

The exclusion criteria were:

- animal studies;
- following publications of the same study data;
- studies describing immediate implant placement in fresh extraction sockets;
- letters, narrative or historical review.

Screening process

A three stage screening process was performed independently by two reviewers (V.D.R., G.V.O.). Initially, all the titles were screened to eliminate irrelevant publications and reviews. During the second stage, all the selected publications were analysed as abstracts and consequently the full texts of articles fulfilling the inclusion criteria were obtained. In the 3rd stage, through the analysis of all of the selected full texts, the included articles were chosen. After this search, 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). Any disagreements between the two reviewers was resolved after additional discussion with a third reviewers (M.C.).

Assessment of heterogeneity

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). This combination resulted in the quality criteria mentioned in Table 2. A given study was classified as low risk of bias when: a) random allocation, b) defined

inclusion/exclusion criteria, c) blinding to patient and examiner, d) balanced experimental groups, e) an identical treatment between groups except for intervention, and f) report of follow-up were specified. When one of these six criteria were missing the study was classified as having a moderate potential risk of bias; when two or more of those were missing, it resulted in a high potential risk. Moreover CEBM document for "Levels of Evidence" and Jadad score (Jadad et al., 1996), for RCTs, were used to assess the methodological quality of included studies.

Data extraction and analysis

Data extracted from the selected studies was 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 (A.M.) if only raw data were reported. For all studies the pooled weighted means were reported and a respective approximation of confidence interval at 95% was computed. Proportion meta-analysis of both B, CT and RGM mean percentages were performed using software StatsDirect. A statistical homogeneity test was applied and the fixed effect or random effect estimate of the pooled mean was used to evaluate the heterogeneity between studies. The level of significance was set at $p<0,05$.

Results

Search Results

The search resulted in 624 papers. After title screening, 446 publications were excluded. Of 178 abstracts analyzed 104 were excluded on the basis of the inclusion criteria; most of them were concerned with immediate implant placement or did not demonstrate histological measurements as outcomes. From reference lists and "grey literature" other 22 papers were selected for screening. A total of 96 full-text papers were analyzed. Of them, 38 papers fulfill the inclusion criteria and were processed for data extraction (figure 1) (Clozza et al., 2012a, Clozza et al., 2012b, Perelman-Karmon et al., 2012, Cardaropoli et al., 2012, Wood and Mealey, 2012, Hoang and Mealey, 2012, Crespi et al., 2011a, Nevins et al., 2011, Crespi et al., 2011b, Heberer et al., 2011, Ruga et al., 2011, Nam et al., 2011, Brkovic et al., 2012, Checchi et al., 2011, Park et al., 2010, Beck and Mealey, 2010, Kesmas et al., 2010, Pelegrine et al., 2010, Lee et al., 2009, Aimetti et al., 2009, Fotek et al., 2009, Crespi et al., 2009, Molly et al., 2008, Wang and Tsao, 2008, Neiva et al., 2008, Cardaropoli and Cardaropoli, 2008, Barone et al., 2008, Serino et al., 2008, Luczyszyn et al., 2005, Froum et al., 2004, Vance et al., 2004, Guarnieri et al., 2004, Norton et al., 2003, Fugazzotto, 2003a, Fugazzotto, 2003b, Serino et al., 2003, Iasella et al., 2003, Carmagnola et al., 2003, Froum et al., 2002, Artzi et al., 2000). The selected studies showed a considerable heterogeneity and these characteristics are presented in Table 1.

Tab. 1

ID#	Author	Design/ setting	Follow-up time (months)	Mean age ± SD, number of subjects and gender	Smokers (control/ test)	Groups	Pharmacologycal treatment (Days)	Flap raised/ releasing incisions/ closure
# I	Clozza et al. 2012	CT / University	6	55 ± 10 y (range 41-76) 13 (3m/10f)	0 (0/0)	Test: Alloplast	Anti-inflammatory (AN) Chlorexidine (14)	? ? No
# II	Perelman et al. 2012	RCT / University	9	? ± ? y (range 26-68) 23 (7m/16f)	0 (0/0)	A: Xenograft B: Xenograft + membrane	Anti-inflammatory (14) Chlorexidine (14)	Yes Yes Yes
# III	Cardaropoli et al. 2012	RCT / Private Practice	4	47,2 ± 12,9 y (range 24-71) 41 (24m/17f)	0 (0/0)	Test: Xenograft + membrane Control: any treatment	Antiobiotics (6) Anti-inflammatory (3) Chlorexidine (7) Hyaluronic acid and amino acids gel (3)	No No No
# IV	Wood et Mealey 2012	RCT / University	5	56.7 ± ? y (range 20 -78) 33 (13m/20f)	0 (0/0)	A: Allograft + membrane B: Allograft + membrane	Antiobiotics (7) Chlorexidine (14)	No No ?
# V	Hoang et Mealey 2012	RCT / University	5	56.1 ± ? years (range 29 -76) 30 (15m/15f)	?	A: Allograft + membrane B: Allograft + membrane	Antiobiotics (7) Anti-inflammatory (AN) Chlorexidine (7)	No No No
# VI	Crespi et al. 2011	CT / University	4	53,7 ± ? y (range 32-70) 15 (?m/?f)	0 (0/0)	A: Alloplast + membrane B: Xenograft + membrane C: membrane	Antiobiotics (7) Anti-inflammatory (7) Chlorexidine (7)	No No No
# VII	Nevins et al. 2011	RCT / University	5	? ± ? years (range 18-70) 15 (?m/?f)	?	A: Alloplast B: Alloplast C: Alloplast D: Alloplast	Antiobiotics (5) Chlorexidine (14)	Yes Yes ?
# VIII	Crespi et al. 2011	RCT / University	4	53.7 ± ? years (range 32-70) 15 (?m/?f)	0 (0/0)	A: Xenograft + membrane B: membrane	?	? ? ?
# IX	Heberer et al. 2011	RCT / University	3	49.9 ± ? y (range 36 -67) 25 (15m/10f)	0 (0/0)	Test: Xenograft Control: any treatment	NONE	No No No
# X	Ruga et al. 2011	CT / University	3	47.8 ± ? y (range 18 -69) 35 (9m/26f)	?	Test: Alloplast	Antiobiotics (5) Anti-inflammatory (3) Corticosteroids (3) Chlorexidine (10)	Yes Yes Yes
# XI	Nam et al. 2011	CCT / University	6	? ± ? y (range 36-65) 42 (20m/22f)	?	A: Xenograft + membrane B: Xenograft +membrane	Antiobiotics (7) Chlorexidine (7)	Yes Yes Yes
# XII	Brkovic et al. 2011	RCT / University	9	49/46 ± 15/13y (range 20-55) 20 (8m/12f)	0 (0/0)	A: Alloplast B: Alloplast + membrane	Antiobiotics (7) Anti-inflammatory (7)	Yes Yes Yes
# XIII	Checchi et al. 2011	RCT / University	6	54 ± 8 y (range 43-76) 10 (0m/10f)	0 (0/0)	A: Alloplast + membrane B: Alloplast + membrane	Chlorexidine (10) Anti-inflammatory (AN)	? ? No
# XIV	Park et al. 2010	CT / University	6	? ± ? y (range ?-?) 4 (?m/?f)	?	Test: Xenograft + membrane	Antiobiotics (14) Chlorexidine (28)	Yes Yes Yes
# XV	Beck and Mealey 2010	CT / University	3-6	57.4 ± ? y (range 39-76) 33 (13m/20f)	?	A: Allograft + membrane B: Allograft + membrane	Antiobiotics (4) Chlorexidine (21) Anti-inflammatory (AN)	No No No
# XVI	Kesmas et al. 2010	CT / University	4	46.5 ± 10.2 y (range 25-57) 8 (3m/5f)	0 (0/0)	Test: Alloplast + membrane	Antiobiotics (7) Chlorexidine (14) Anti-inflammatory (7)	No No No

ID#	Author	Design/ setting	Follow-up time (months)	Mean age ± SD, number of subjects and gender	Smokers (control/ test)	Groups	Pharmacologycal treatment (Days)	Flap raised/ releasing incisions/ closure
# XVII	Pelegrine et al. 2010	RCT / University	6	47.5 ± 10.3 y (range 28-70) 13 (7m/6f)	0 (0/0)	Test: Autograft Control: any treatment	?	Yes Yes Yes
# XVIII	Lee et al. 2009	CT / Hospital	4-6	54.8 ± 6.8 years (range 39-68) 20 (16m/4f)	0 (0/0)	A: Xenograft + membrane B: Allograft + membrane C: Allograft + membrane	Antiobiotics (?) Anti-inflammatory (?)	No No No
# XIX	Aimetti et al. 2009	RCT / University	3	51.27 ± 8.40 y (range 36-68) 40 (18m/22f)	0 (0/0)	Test: Alloplast Control: any treatment	Antiobiotics (5) Chlorexidine (14) Anti-inflammatory (5)	No No No
# XX	Fotek et al. 2009	CT / University	4	59/55 ± ? y (range 29-77) 20 (7m/13f)	0 (0/0)	A: Allograft + membrane B: Allograft + membrane	Antiobiotics (7) Anti-inflammatory (AN)	No No No
# XXI	Crespi et al. 2009	CT /Hospital	3	51.3 ± ? y (range 28-72) 15 (8m/7f)	0 (0/0)	A: Alloplast + membrane B: Alloplast + membrane C: membrane	Antiobiotics (7)	No No No
# XXII	Molly et al. 2008	CT / University	6	53 ± ? y (range 37-63) 8 (1m/7f)	0 (0/0)	A: Alloplast + membrane B: Xenograft + membrane C: Alloplast + membrane Control: any treatment	Antiobiotics (7) Anti-inflammatory (AN)	Yes ? Yes
# XXIII	Wang & Tsao 2008	CT / University	5	56 ± ? y (range ?-?) 5 (3m/2f)	?	Test: Allograft + membrane	Anti-inflammatory (3)	No No No
# XXIV	Neiva et al. 2008	RCT / University	4	48.00/49.92 ± 14.89/14.20 y (range 25/36-69/76) 30 (13m/17f)	0 (0/0)	A: Xenograft + membrane B: membrane	?	No No No
# XXV	Cardaropoli et al. 2008	CS / Private practice	4	45.9 ± ? y (range 27-63) 10 (6m/4f)	?	Test: Xenograft + membrane	Antiobiotics (6) Chlorexidine until sutures removal	No No No
# XXVI	Barone et al. 2008	RCT / Hospital	7	>18 (range 26-29) 40 (16m/24f)	5 (3/2)	Test: Xenograft + membrane Control: any treatment	Antiobiotics (4) Chlorexidine (21) Anti-inflammatory (3)	Yes Yes Yes
# XXVII	Serino et al. 2008	RCT / University	3	? ± ? y (range 32-64) 20 (8m/12f)	?	Test: Alloplast Control: any treatment	Chlorexidine (14) Analgesics (AN)	Yes Yes No
# XXVIII	Luczyszyn et al. 2005	CT/ University	6	? ± ? y (range 35-60) 11 (?m/?f)	0 (0/0)	A: Alloplast + membarne B: membrane	Antiobiotics (10) Chlorexidine until soft tissue closure	Yes Yes No
# XXIX	Froum et al. 2004	RCT / Hospital	6-8	48.1 ± ? y (range 26-71) 15 (9m/6f)	0 (0/0)	A: Alloplast + membrane B: Alloplast + membrane C: Xenograft + membrane D: Xenograft + membrane	Antiobiotics (14) Chlorexidine (28)	Yes Yes No
# XXX	Vance et al. 2004	RCT / University	4	56.0 ± 11 y (range ?-?) 24 (9m/15f)	?	A: Allograft + membrane B:Xenograft + membrane	Antiobiotics (?) Chlorexidine (?) Anti-inflammatory (?)	Yes ? Yes
# XXXI	Guarnieri et al. 2004	CS / Multi-centre	3	? ± ? y (range 35-58) 10 (3m/7f)	?	Test: Alloplast Control: any treatment	Antiobiotics (7) Chlorexidine (14)	Yes No Yes
# XXXII	Norton et al. 2003	CT / University	6	53.66 ± 11.8 y (range 26-69) 15 (7m/8f)	3	Test: Xenograft + membrane	Antiobiotics (5) Chlorexidine (7)	Yes Yes Yes
# XXXIII	Fugazzotto 2003	CT /Private practice	3-13	? ± ? y (range 29-63) 90 (43m/47f)	0 (0/0)	A, B, C, D: Xenograft + membrane	Antiobiotics (10) Chlorexidine (21) Anti-inflammatory (5)	Yes Yes Yes

ID#	Author	Design/ setting	Follow-up time (months)	Mean age ± SD, number of subjects and gender	Smokers (control/ test)	Groups	Pharmacologycal treatment (Days)	Flap raised/ releasing incisions/ closure
# XXXIV	Serino et al. 2003	CT / University	6	45.9 ± ? y (range 35-64) 45 (14m/31f)	?	Test: Alloplast Control: any treatment	Chlorexidine (14) Anti-inflammatory (AN)	Yes No No
# XXXV	Iasella et al. 2003	RCT / ?	4-6	51.5 ± 13.6 y (range 28-76) 24 (10m/14f)	?	Test: Allograft + membrane Control: any treatment	Antiobiotics (14) Chlorexidine until soft tissue closure Anti-inflammatory (7)	Yes No No
# XXXVI	Carmagnola et al. 2003	CT / University	4-180	56.5 ± 9.7 y (range 39-76) 21 (13m/8f)	?	A: Membrane B: Xenograft + membrane Control: any treatment	?	Yes ? No
# XXXVII	Froum et al. 2002	RCT / University	6-8	54.9 ± 11.9y (range 35 -77) 19 (12m/7f)	0 (0/0)	A: Alloplast B: Allograft Control: any treatment	Antiobiotics (14) Chlorexidine (31)	Yes Yes Yes
# XXXVIII	Artzi et al. 2000	Individual cohort/ University	3	? ± ? y (range 23-64) 15 (6m/9f)	?	Test: Xenograft	Antiobiotics (7) Chlorexidine (14) Anti-inflammatory (AN)	Yes No Yes

Of the selected studies, seventeen were RCT, nineteen are CT. Study # XXV, XXXI and XXXVIII are Case Series or Individual Cohort Clinical Trial. Two studies have a Parallel design (# XXXIII, XXXVI) and six have a Split-Mouth design (# VI, VIII, XXI, XXII, XXVIII, XXXIV). Follow-up periods ranged between 3 and 180 months, but only 3-7 months results were recorded.

The studies included a number of subjects ranging between 4 and 90. Eleven studies did not report the mean age of patients, while only three did not report the age range of subjects. Five studies did not report information about gender. Reasons for extraction are reported in eighteen studies, while local criteria for inclusion/exclusion are clearly reported in twenty-two of them. Most studies evaluated effects of socket preservation on anterior or single-rooted teeth while seven studies included molars. Study # V was conducted including only molar teeth. Eleven of them included all kinds of teeth. Three studies did not report this information. Twenty-one studies did not include smokers. In twelve of them it was a clear exclusion criteria. Studies # XXVI and XXXII included smokers, 5 and 3 respectively, whereas fifteen studies did not report the smoking status of the participants.

Among these groups most evaluated the use of a combination of graft and barrier, whereas seventeen evaluated the use of a graft alone and only six evaluated the use of a barrier alone. Four studies did not provide any information about post-operatively drug subministration while in 1 study no drugs were prescribed. Twenty-seven studies provided antibiotic administration and the same used chlorexidine as antiseptic. Only fourteen studies provided NSAID administration. All studies described the extraction procedure as less traumatically possible. A flap was raised for extraction in twenty-one studies. Among these, in only thirteen releasing incisions were performed. In the remaining studies, extractions were conducted without flaps. After extraction, primary soft tissue closure was achieved in fourteen studies.

Only data regarding histomorphometry were extracted from selected studies. Most of studies evaluated all the outcomes described as primary in this review. Of others, five evaluated only the %B (# II, VII, XVII, XIX and XXXI), two evaluated %B and %RGM (# XXII, XXXIV), whereas study # XXV and XXVIII evaluated respectively %RGM and %B-%CT.

Assessment of quality

Assessment of quality is presented in Table 2. The estimated risk of bias is defined as low in ten studies, as moderate in fourteen and as high in the remaining fourteen. Eight studies presented

a combination of a low potential risk and a 2(1b) level of evidence. Nine studies scored 2(1b) and presented a moderate potential risk Studies # XXV and XXXI presented a combination of high potential risk and a level of evidence score of 4(4). Study #XXXVIII is classified as moderate with a score of 3(2b). All other studies scored 3(2c); among them twelve were classified, in order of potential risk, as high, four as moderate and two as low. Regarding Jadad evaluation two studies out of seventeen RCTs scored 4, five studies scored 2and only two studies scored 1.
Loss to follow-up are reported in twenty-six studies. Of them sixteen had no drop-outs.

Tab. 2

Study # quality criteria	# I Clozza et al. (2012)	# II Perelman et al. (2012)	# III Cardaropoli et al. (2012)	# IV Wood, Mealey. (2012)	# V Hoang, Mealey. (2012)	# VI Crespi et al. (2011)	# VII Nevins et al. (2011)	# VIII Crespi et al. (2011)	# IX Heberer et al. (2011)	# X Ruga et al. (2011)	# XI Nam et al. (2011)	# XII Brkovic et al. (2011)	# XIII Checchi et al. (2011)
Representative population group	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes
Eligibility criteria defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Random allocation	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	?	Yes	Yes
Allocation concealment	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	?	?
Blinded to the patient	No	?	No	No	?	No	No	?	?	No	?	?	?
Blinded to the examiner	No	?	Yes	?	Yes	?	?	?	?	No	?	?	Yes
Blinding during statistical analysis	No	?	?	?	Yes	?	?	?	?	No	?	Yes	?
Reported loss to follow-up	?	Yes	No	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes	No
# (%) of drop-outs	0?	0	0?	8	10	0	0	0	0?	10	2	0	?
Treatment identical, except for intervention	na	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample size calculation and power	no?	No	Yes	Yes	Yes	No	No	Yes	No	No	No	No	No
Point estimates presented for primary outcome	Yes	Yes	Yes	Yes	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	Yes	Yes	Yes	Yes
Intention to treat analysis	No	No	No	No	No	No	No	No	No	No	No	No	No
Study design	CT	RCT	RCT	RCT	RCT	CT	RCT	RCT	RCT	CT	CT	RCT	RCT
Validated measurement	?	?	Yes	?	?	?	?	?	?	No	?	?	?
Calibration examiner	Yes	Yes	Yes	?	?	?	?	?	?	No	?	?	?
Reproducibility data shown	No	No	No	Yes	No	No	No	No	Yes	No	No	No	Yes
Estimated potential risk of bias	H	M	L	M	L	H	M	M	M	H	M	M	L
CEBM Level of evidence	3 (2c)	2 (1b)	2 (1b)	2 (1b)	2 (1b)	3 (2c)	2 (1b)	2 (1b)	2 (1b)	3 (2c)	3 (2c)	2 (1b)	2 (1b)
Jadad score	NA	2	2	3	3	NA	2	2	2	NA	NA	2	1

Study # quality criteria	# XIV Park et al. (2010)	# XV Beck, Mealey. (2010)	# XVI Kesmas et al. (2010)	# XVII Pelegrine et al. (2010)	# XVIII Lee et al. (2009)	# XIX Aimetti et al. (2009)	# XX Fotek et al. (2009)	# XXI Crespi et al. (2009)	# XXII Molly et al. (2008)	# XXIII Wang & Tsao (2008)	# XXIV Neiva et al. (2008)	# XXV Cardaropoli et al. (2008)	# XXVI Barone et al. (2008)
Representative population group	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Eligibility criteria defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Random allocation	No	Yes	No	Yes	No	Yes	No	No	No	No	Yes	?	Yes
Allocation concealment	No	No	No	?	No	?	No	?	No	No	Yes	?	?
Blinded to the patient	No	?	No	?	No	Yes	No	?	?	No	Yes	?	?
Blinded to the examiner	No	?	No	?	No	Yes	Yes	Yes	?	No	Yes	?	?
Blinding during statistical analysis	No	?	?	?	No	?	No	?	?	No	Yes	?	?
Reported loss to follow-up	Yes	Yes	Yes	No	Yes	?	Yes	Yes	Yes	Yes	No	No	Yes
# (%) of drop-outs	0	7	2	?	1	?	2 (10%)	0	0	0	?	?	0
Treatment identical, except for intervention	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample size calculation and power	No	Yes	No	No	No	Yes	No	?	No	No	Yes	?	?
Point estimates presented for primary outcome	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	?	Yes
Measures of variability for the primary outcome	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Intention to treat analysis	No	No	No	No	No	No	No	?	No	No	No	Yes	?
Study design	CT	CT	CT	RCT	CT	RCT	CT	CT	CT	CT	RCT	CS	RCT
Validated measurement	No	?	Yes	?	?	Yes	?	?	?	?	Yes	?	?
Calibration examiner	No	?	?	?	Yes	Yes	?	?	?	?	Yes	?	?
Reproducibility data shown	No	No	No	No	No	No	No	No	No	No	Yes	No	No
Estimated potential risk of bias	H	M	H	M	H	L	L	M	L	H	L	H	M
CEBM Level of evidence	2 (1b)	3 (2c)	3 (2c)	2 (1b)	3 (2c)	2 (1b)	3 (2c)	3 (2c)	3 (2c)	3 (2c)	2 (1b)	4 (4)	2 (1b)
Jadad score	NA	NA	NA	1	NA	2	NA	NA	NA	NA	3	NA	2

Study # quality criteria	# XXVII Serino et al. (2008)	# XXVIII Luczyszyn et al. (2005)	# XXIX Froum et al. (2004)	# XXX Vance et al. (2004)	# XXXI Guarnieri et al. (2004)	# XXXII Norton et al. (2003)	# XXXIII Fugazzotto (2003)	# XXXIV Serino et al. (2003)	# XXXV Iasella et al. (2003)	# XXXVI Carmagnola et al. (2003)	# XXXVII Froum et al. (2002)	# XXXVII Artzi et al. (2000)
Representative population group	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Eligibility criteria defined	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Random allocation	Yes	?	Yes	Yes	NA	NA	No	Yes	Yes	?	Yes	No
Allocation concealment	?	?	Yes	No	NA	NA	No	?	?	?	?	No
Blinded to the patient	?	No	?	No	?	No	No	?	?	?	?	No
Blinded to the examiner	?	?	?	Yes	?	No	No	?	Yes	?	?	No
Blinding during statistical analysis	?	?	?	No	?	No	?	?	?	?	?	No
Reported loss to follow-up	Yes	Yes	Yes	?	Yes	Yes	No	Yes	Yes	No	Yes	?
# (%) of drop-outs	4 (20%)	0	0	?	0	0	?	9 (20%)	0	?	0	?
Treatment identical, except for intervention	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	No
Sample size calculation and power	?	?	No	No	?	No	No	?	Yes	?	?	No
Point estimates presented for primary outcome	Yes	?	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
Study design	CT	CT	RCT	RCT	CS	CT	CT	CT	RCT	CT	RCT	Individual cohort
Validated measurement	No	?	?	Yes	?	?	Yes	?	?	?	?	Yes
Calibration examiner	No	?	?	Yes	?	?	Yes	?	?	?	?	No
Reproducibility data shown	?	No	Yes	Yes	No	No	Yes	No	No	No	No	Yes
Estimated potential risk of bias	M	H	L	L	H	H	H	H	L	H	M	M
CEBM Level of evidence	3 (2c)	3 (2c)	2 (1b)	2 (1b)	4 (4)	3 (2c)	3 (2c)	3 (2c)	2 (1b)	3 (2c)	2 (1b)	3 (2b)
Jadad score	NA	NA	3	4	NA	NA	NA	NA	4	NA	3	NA

Study outcomes

The study outcomes are presented in Tables 3. For every primary outcome four proportion meta-analysis were performed at each healing stage (3 to 7 months): test groups were assimilated in order to nature of the graft used into three different ARPs, Allografts, Xenografts or Alloplasts. No treated sites were used as control. If samples were constituted by one test/control group data reported on papers were used for comparison. All the Pooled Proportions were calculated using Fixed Effect estimate. For each ARP the simple linear Pearson's correlations coefficient (r) over time was calculated. Considering %B (Fig. 2) best mean value is shown at 3 months with Allografts (54,4%-95%CI=26,75% to 57,18%) while the worst is shown by Xenografts

at 5 months (23,6%-95% CI=2,13% to 66,71%). Considering %CT (Fig. 3) the highest and lowest mean values are shown at 7 months by Allografts (67%-95%CI=32,09% to 91,80%) and Alloplasts (27,1%-95%CI=10,78% to 47,69%). During time no statistical relevant differences are shown among the performances of each kind of ARPs and Control sites, both for %B and %CT. For %CT in every group, including controls, there is a tendency to decrease. Considering %RGM lowest percentages are shown by Allografts (12,4% to 21,11%) whereas the highest percentages are shown at 7 by Xenografts and Alloplasts, 37,14% (95%CI=21,27% to 54,59%) and 37, 23% (95%CI=5,42% to 77,57%) respectively. For %RGM also no statistical differences are shown (Fig. 4).

Tab. 3

ID#	Study	# of teeth (maxillar/ mandibular)/ type	# of cores per group	Follow-up time (months)	% total bone (mineralized)	% residual graft	% connective / fibrous tissue (matrix)
# I	Clozza et al. 2012	32 (18+14) I / C	Test (active bioglass):6	6	Test : 54.00 ± 31.00	Test : 8.10 ± 7.80	Test : 37.90 ± 25.60
# II	Perelman et al. 2012	23 (18+5) I / P	A (DBBM): 13 B (DBBM + Collagen): 10	9	A: 29.7 ± 7.21 B: 40.8 ± 10.61	Ø	Ø
# III	Cardaropoli et al. 2012	48 P / M	Test (DBBM Collagen + Collagen): 24 Control: 24	4	Group Test: 26.34 ±16.91 Group 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
# IV	Wood et Mealey 2012	32 (26+6) I / C / P	A (DFBDA + collagen): 16 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
# V	Hoang et Mealey 2012	30 (8+21) M	A (DBM-SS + collagen): 16 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
# VI	Crespi et al. 2011	45 P / M	A (MHA + collagen): 15 B (CPB + collagen): 15 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
# VII	Nevins et al. 2011	16	A (MCBS): 4 B (MCBS + rhPDGF-BB): 4 C (MCBS + EMD): 4 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	Ø	Ø
# VIII	Crespi et al. 2011	30 (15+15) P / M	A (CPB + collagen): 15 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
# IX	Heberer et al. 2011	39 (24+15) I / C / P / M	Test (DBBM Collagen): 20 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
# X	Ruga et al. 2011	60 P / M	Test (CaS):19	3	Test : 65.26 ± ?	Group Test : 30.00 ± ?	Test : 4.74 ± ?
# XI	Nam et al. 2011	44 (25+19) I /C / P / M	A (coated DBBM + Collagen): 7 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
# XII	Brkovic et al. 2011	20 (9+11) C / P / M	A (β-TCP/Clg): 8 B (β-TCP/Clg+ 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 ± ?
# XIII	Checchi et al. 2011	10 I / C / P / M	A (biomimetic MHA + collagen): 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 ± ?
# XIV	Park et al. 2010	4	Test (EBM+ collagen): 4	6	Test : 9.88 ± 6.57	Test : 42.62 ± 6.57	Test : 47.50 ± 9.28
# XV	Beck et Mealey 2010	38 (16+22) I / C / P	A (HBMA + collagen): 16 B (HBMA + collagen): 22	A: 3 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
# XVI	Kesmas et al. 2010	8 I	Test (BCP + collagen):6	4	Test : 28.00 ± 36.75	Test : 15.83 ± 8.70	Test : 65.50 ± 25.85
# XVII	Pelegrine et al. 2010	30 I / C	Test (autologous bone marrow): 15 Control: 15	6	Test: 42.87 ±11.33 Control: 45.47 ± 7.21	Ø	Ø
# XVIII	Lee et al. 2009	20 I / C / P / M	A (DBBM + collagen): 7 B (HBMA + collagen): 8 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
# XIX	Aimetti et al. 2009	40 I / C	Test (MGCSH): 22 Control: 18	3	Test: 58.8 ± 3.5 Control: 47.2 ± 7.7	Ø	Ø

ID#	Study	# of teeth (maxillar/ mandibular)/ type	# of cores per group	Follow-up time (months)	% total bone (mineralized)	% residual graft	% connective / fibrous tissue (matrix)
# XX	Fotek et al. 2009	20 I / P	A (HBMA + ADM): 9 B (HBMA + dPTFE): 9	4	A: 27.89 B: 32.63	A: 13.93 B: 14.73	A: 58.19 B: 52.64
ID#	Study	# of teeth (maxillar/ mandibular)/ type	# of cores per group	Follow-up time (months)	% total bone (mineralized)	% residual graft	% connective / fibrous tissue (matrix)
# XXI	Crespi et al. 2009	45 M / P	A (MHA + collagen): 15 B (CaS + collagen): 15 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
# XXII	Molly et al. 2008	36 I / C / P / M	A (Fisiograft + e-PTFE): 8 B (DBBM + e-PTFE): 6 C (CaCO3 + e-PTFE): 6 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	Ø
# XXIII	Wang & Tsao 2008	7 I / C / P / M	Test (HBMA + Collagen): 17	5	Test : 68.45 ± 6.12	Test : 3.81 ± 3.55	Test : 27.72 ± 5.60
# XXIV	Neiva et al. 2008	24 (24+0) P	A (ABBM - P15 + collagen): 15? B (collagen): 15?	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
# XXV	Cardaropoli et al. 2008	10 M / P	Test (CPB + collagen): 10	4	Ø	Group Test : 24.50 ± 11.65	Ø
# XXVI	Barone et al. 2008	40 I / C / P	Test (CPB + collagen): 20 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
# XXVII	Serino et al. 2008	16 I / C / P	Test (FISIOGRAFT): 7 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
# XXVIII	Luczyszyn et al. 2005	30 I / C / P	A (HA + ADM): 15 B (ADM): 15	6	A : 1.0 B: 46.0	A: 42.0 B: 00.0 ± 0.0	A : 57.0 B: 54.0
# XXIX	Froum et al. 2004	16 I / C / P / M	A (HA + ADM): 4 B (HA + ePTFE): 4 C (ABBM + ADM): 4 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
# XXX	Vance et al. 2004	24 I / C / P	A (CMC/CaS/DFDBA + CaS): 12 B (DBBM + Collagen): 12	4	A: 61 ± 9 B: 26 ± 20	A: 3 ± 3 B: 16 ± 7	A:36 ± ? B: 59 ± ?
# XXXI	Guarnieri et al. 2004	15 I / C / P	Test (MGCSH): 10 Control: 5	3	Test : 58.1 ± 6.2 med. Control: ≤ 46	Ø	Ø
# XXXII	Norton et al. 2003	30 I / C / P / M	Test (DBBM + Collagen): 30	6	Test : 26.90 ± ?	Test : 25.60 ± ?	Test : 47.40 ± ?
# XXXIII	Fugazzotto 2003	59	A (DBBM + e-PTFE): 6 B (DBBM + e-PTFE): 40 C (DBBM + e-PTFE): 6 D (DBBM + e-PTFE): 7	A: 4 B: 6 C: 8 D: 12	A: 19.4 B: 34.5 C: 69.1 D: 68.8	A: 59.1 B: 18.7 C: 11.3 D: 0.13	A: 21.5 B: 46.8 C: 19.6 D: 31.1
# XXXIV	Serino et al. 2003	39 I / C / P / M	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	Ø
# XXXV	Iasella et al. 2003	24 I / C / P	Test A (FDBA + collagen): 5 Test B (FDBA + collagen): 7 Control A: 5 Control B: 5	Test A: 4 Test B: 6 Control A: 4 Control B: 6	Test A: 31 ± 9 Test B: 25 ± 17 Control A: 58 ± 11 Control B: 50 ± 14	Test A : 32 ± 19 Test B: 41 ± 18 Control A: 0.0 ± 0.0 Control B: 0.0 ± 0.0	Test A: 37 ± ? Test B: 34 ± ? Control A: 42 ± ? Control B: 50 ± ?
# XXXVI	Carmagnola et al. 2003	31 I / C / P / M	A (Collagen): 11 B (DBBM + Collagen): 7 Control: 10	A: 4,5 B: 8 Control: > 9	A: 53.0 ± ? B: 34.4 ± ? Control: 43.5 ± ?	A: 0.0 ± 0.0 B: 21.1 ± 20.0 Control:0.0 ± 0.0	A: 46.0 ± ? B: 44.3 ± ? Control: 43.0 ± ?
# XXXVII	Froum et al. 2002	30 I / C / P / M	A (Bioactive glass): 10 B (DFDBA): 10 Control: 10	7	A: 59.5 ± 14.3 B: 34.7 ± 7.9 Control: 32.4 ± 6.0	A: 5.5 ± 1.2 B: 13.5 ± 3.6 Control: 0.0 ± 0.0	A: 35.3 ± 14.1 B: 67.0 ± 8.1 Control: 51.6 ± 36.1
# XXXVIII	Artzi et al. 2000	15 I / C / P	Test (DBBM): 15	3	Test : 46.3 ± 9.81	Test : 30.8 ± 7.82	Test : 22.9 ± 12.28

Fig. 1

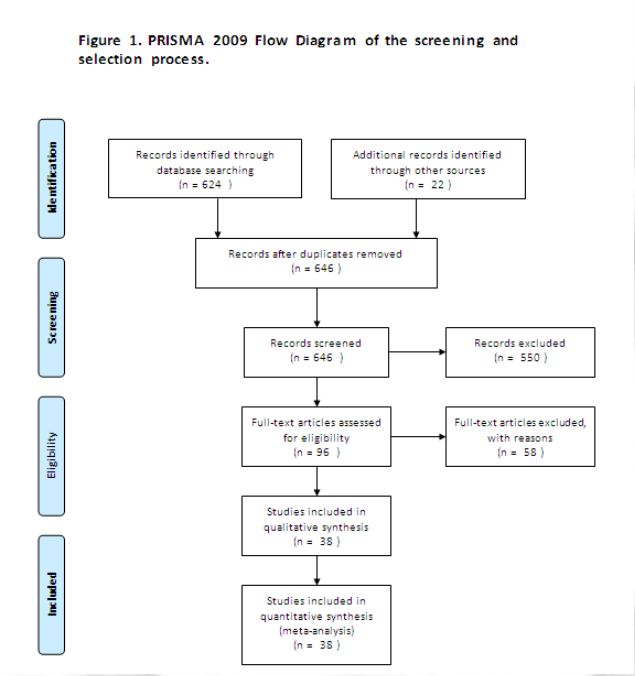


Fig. 2

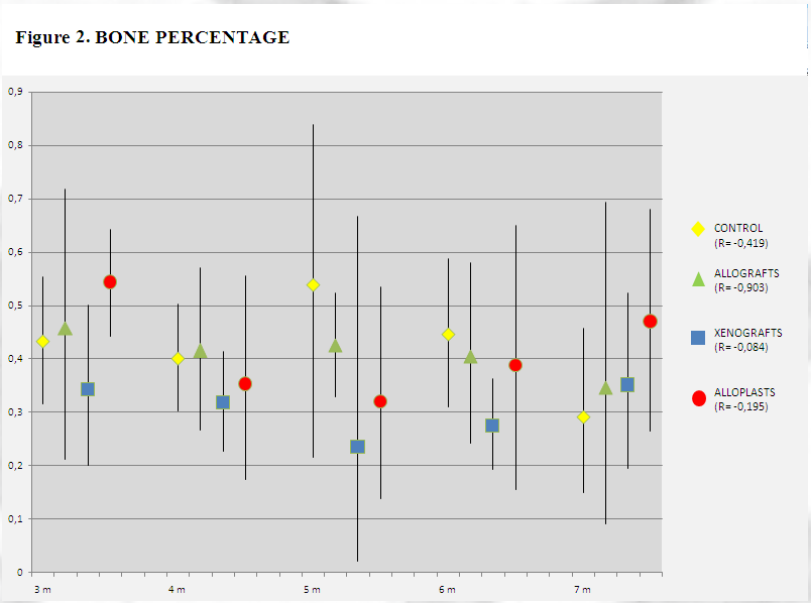


Fig. 3

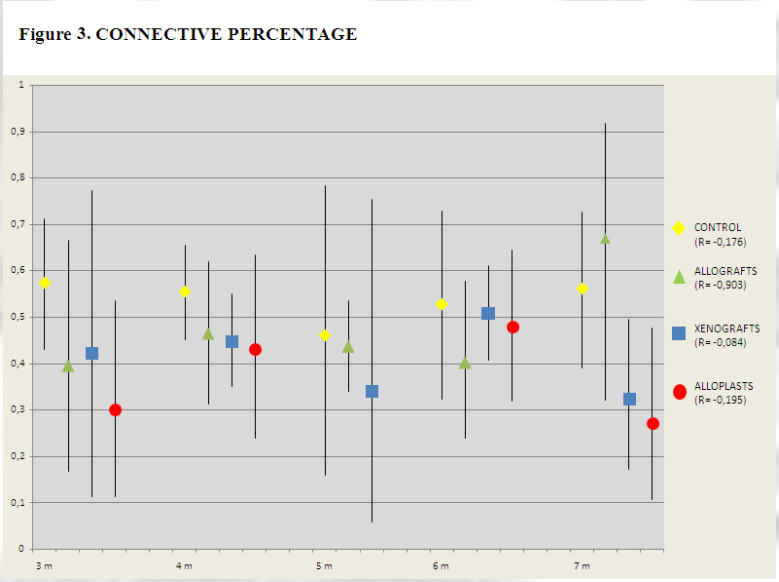
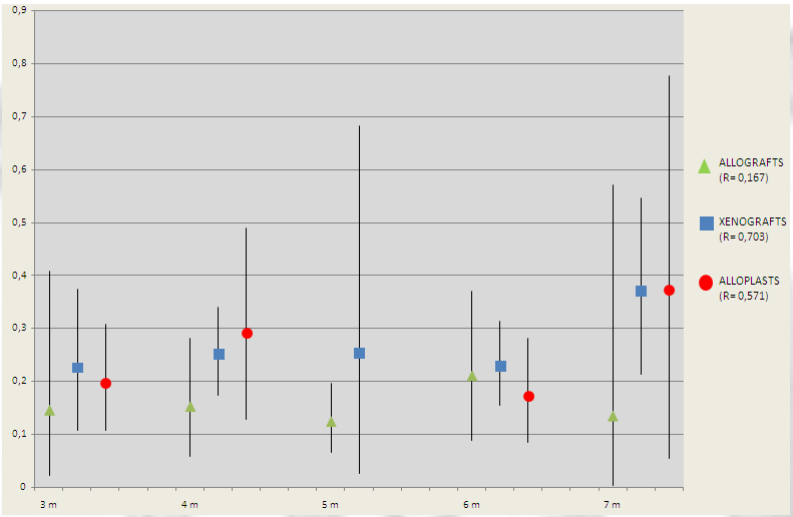


Fig. 4

Figure 4. RESIDUAL GRAFT MATERIAL PERCENTAGE



Conclusions

The aim of this paper was to set a systematic review regarding histological data derived from studies reporting the effect of ARPs on healing patterns following tooth extraction in humans. Thus a total of 12 meta-analyses were performed, referring to the 3 selected primary outcome(residual graft, bone and connective tissues percentages), regarding sites treated by means of allografts, xenografts, alloplastic materials and untreated sites.

Drawing conclusions across the studies is difficult since the test groups differed in many respects compared with each other, including considerable differences in surgical technique (bone substitute only/GBR graft), in bio-materials used (MGCSH/porcine bone with collagen membrane), 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 up.

Successful and long-lasting outcomes of different GBR procedures are well documented in literature (Dragoo and 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. Firstly, in a mechanical fashion, stabilizing the blood clot, acting as a scaffold with a space-maintaining effect and avoiding epithelial ingrowth, secondly in a biological way providing an extra source of collagen, minerals and growth factors.

All the recent SRs and consensus on this topic seem to agree on confirming somewhat of benefit when adopting ARPs. Accordingly our research corroborate this positive trend, even from an histological stand point.

Several critical issues arise from a thorough interpretation of our results. First of all, in the most part of the selected studies, a small sample size limits the possibility of spreading any conclusions. Then a complete lack in standardization of 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 clearly how multiple locations of bone core retrievals may not coincide exactly with the precise position of the original dental alveola, impairing a correct data evaluation.

Nevertheless our results seem to be consistent with those suggested recently in a systematic

review by Horvath et al.(Horvath et al., 2012), despite our approach has been especially focused on comparing histomorphometric data, thus including more papers too. It is noteworthy that, to the best of our knowledge, this research is the first SR 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 Lindhe et al (Araujo et al., 2008). In respect to clinical implications related to dental implant insertion the most impactful 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. Consequently it might be argued that it is no more so mandatory waiting further than 3-4 months, aiming to achieve a complete maturation and mineralization of bone tissue, prior to implant insertion. In fact ARPs seem to be unable to accelerate the physiological healing process in extraction sockets, just because they do not improve the histological modifications in treated sites.

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