

Systematic Review Pre-Implant Surgery

Titanium mesh associated with rhBMP-2 in alveolar ridge reconstruction

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Abstract. A systematic review of the literature was performed regarding the use of titanium mesh in association with recombinant human bone morphogenetic protein (rhBMP) for alveolar ridge reconstruction. The PubMed, Scopus, and Cochrane databases were searched for articles in English published up until June 2017. The inclusion criteria encompassed studies in humans – randomized clinical trials, prospective and retrospective studies, and case series. The screening and selection process was performed by three independent reviewers, with verification by a senior researcher in the case of disagreement. The initial search identified 92 studies. After removal of duplicates, 70 remained for title and abstract reading. Fifty-four articles were considered non-relevant, resulting in a total of 16 studies. Following application of the inclusion criteria, 10 studies were selected. An additional study was added after the hand search, giving a total of 11 articles. These reported on 106 patients who had undergone alveolar ridge augmentation with rhBMP and titanium mesh. There were 74 maxillary grafts and 22 mandibular grafts, and the success rate of rehabilitation was 93.4% to 100%. The most frequently reported complications were suture dehiscence and mesh exposure, but without graft loss. rhBMP associated with titanium mesh is a viable method for alveolar reconstruction with high success rates and low rates of local complications.

Key words: alveolar bone loss; alveolar bone grafting; bone morphogenetic protein 2; surgical mesh.

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Bone augmentation procedures are an important tool for oral rehabilitation with dental implants^{1–4}. Early tooth loss, hormonal changes, and increased age are some of the factors contributing to bone resorption, which impairs or even pre-

vents the installation of osseointegrated dental implants¹. Bone resorption represents a special problem for implant placement.

Several techniques for bone augmentation have been described over the past

three decades^{1,5}, including autogenous bone transplantation^{6–8}, allograft with fresh-frozen human bone⁹, bone substitutes of animal origin^{6,10,11}, and synthetic mineral materials¹. Despite these various alternatives, only autogenous bone

induces the three essential mechanisms for ideal bone augmentation: osteoconduction, osteoinduction, and osteogenesis^{7,12}. However, research on bone grafting is extensive, and proteins involved in the osteogenesis process have been isolated, i.e. the bone morphogenetic proteins (BMPs).

The BMPs were first described in 1965 by Urist¹³, but were only isolated from bovine bone in 1980, with BMP-2 being isolated in 1988¹⁴. Several animal studies have shown the efficacy of BMP-2 in bone formation^{15–18}. Although it was hypothesized that BMPs could be associated with malignant neoplasia, their safety has been proven^{19–21}. A variant of BMP, the recombinant human BMP-2 (rhBMP-2), has been used in medical procedures in the USA since 2002, and it was first indicated for use in the oral and maxillofacial region for alveolar ridge augmentation in 2007^{4,12,16,19}.

Difficulties controlling the amount of bone formation and graft resorption are similar when using BMPs as they are in all other bone augmentation procedures. Another problem is the control of soft tissue migration into the graft. Cell migration from the periosteum or mucosa into the graft probably occurs before the migration

of osteogenic cells. This could explain some graft and osseointegration failures or severe graft resorption^{22,23}.

Surgeons have attempted to prevent soft tissue migration through the use of artificial barriers. The most common barriers used and described in the literature include resorbable collagen membranes, non-resorbable polytetrafluoroethylene (PTFE) membranes, and titanium mesh^{5,12,22}. Tissue enzymes degrade resorbable membranes before sufficient time has passed for bone cells and blood vessels to reach the graft^{1,5}. PTFE membranes do not break down and remain in place covering the graft until a second procedure is done for their removal. However, they are highly malleable and do not provide a framework to maintain the graft form^{23,24}. Titanium mesh is a micro perforated mesh that combines plastic properties and porosity. These features allow graft nutrition and provide a scaffold to maintain the graft morphology²².

Despite the good results obtained with rhBMP-2 in animal and clinical studies^{18,24,25}, there is no compilation of data regarding the amount of new bone formation, outcomes, and dental implant placement after rhBMP-2/titanium mesh grafting procedures. The objective of this

study was to perform a systematic review of the literature to find and organize data on bone formation, success rate, and implant installation in alveolar ridges grafted with rhBMP-2/titanium mesh.

Materials and methods

The following question was raised to guide this study: Is the use of titanium mesh associated with bone morphogenetic protein (rhBMP) effective in volume augmentation for atrophic areas of the alveolar ridge in humans?

Selection criteria

Published studies involving the use of titanium mesh associated with rhBMP were selected according to the following inclusion criteria after reading the title and abstract: studies in English; studies in humans; randomized clinical trials, prospective and retrospective studies, and case series. There was no limitation on publication year.

The inclusion criteria were selected to provide broad results, with no specific surgical technique, grafting area, or type of implant–prosthesis rehabilitation performed.

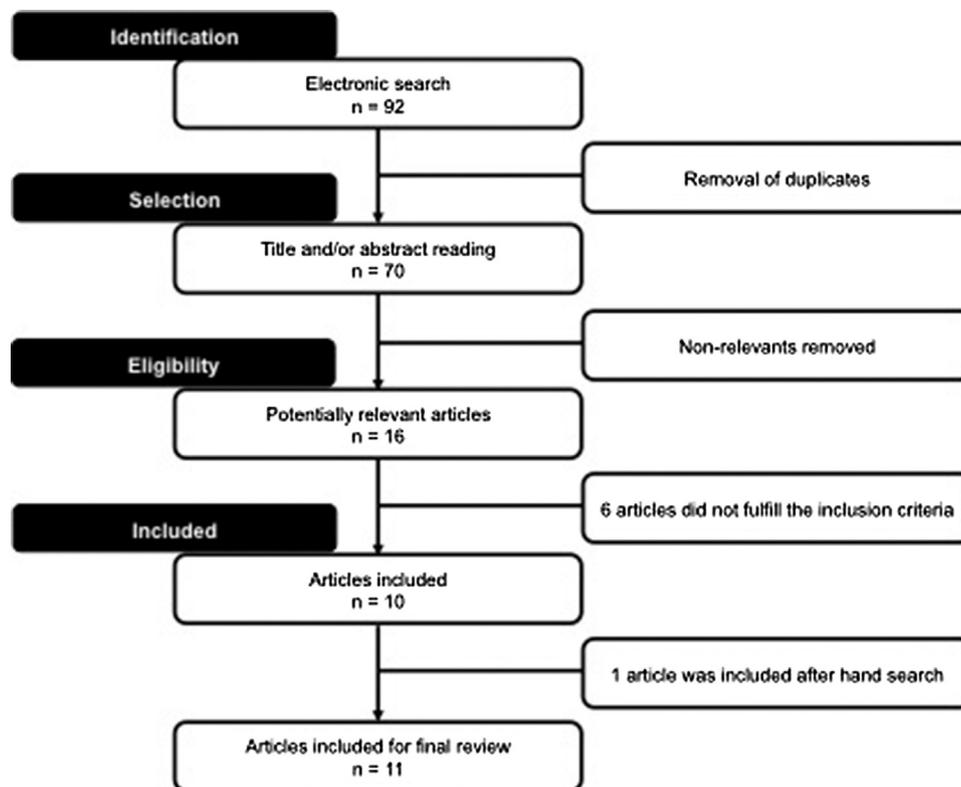


Fig. 1. Flowchart of the systematic review.

Search strategy

The search was performed in the PubMed, Scopus, and Cochrane databases, with the combination of the following terms: “Bone Morphogenetic Proteins”; “BMP”; “rhBMP-2*”; “Bone morphogenetic protein-2”; “Titanium mesh”; “Titanium shell”; “Mesh”; “Alveolar ridge augmentation”; “Alveolar ridge grafting”; “Alveolar ridge graft”; “Alveolar bone graft”; “jaw OR jaws OR mandibular OR maxillary”; “bone graft”. The terms were combined for the construction of two search lines:

- (bone morphogenetic proteins OR BMP OR rhBMP-2* OR bone morphogenetic protein-2) AND (titanium mesh OR titanium shell OR mesh) AND (alveolar ridge augmentation OR alveolar ridge grafting OR alveolar ridge graft OR alveolar bone graft).
- (bone morphogenetic proteins OR BMP OR rhBMP-2* OR bone morphogenetic protein-2) AND (titanium mesh OR titanium shell OR mesh) AND (jaw OR jaws OR mandibular OR maxillary) AND (bone graft)

The titles and abstracts were assessed by three independent reviewers (GST, DVM, and PHAC).

Data extraction

After full-text reading of the selected articles, the reviewers extracted the following data from each study: study design; number of patients and grafts; types of graft; types of mesh and/or membrane; the carrier used; bone defect localization; bone gain and volume of resorption; implant–prosthesis rehabilitation; complications; success and failures rates; expected time to re-intervention. Any further relevant information was also collected from each study.

Data correlation

After data extraction, the clinical importance of collected variables was correlated with complication and failures rates.

Quality assessment – PRISMA

The quality assessment was performed in accordance with the PRISMA statement²⁶, with the aim of verifying the strength of scientific evidence. The potential risk of bias of each study was classified according to established criteria commonly used in previous systematic reviews: random sam-

ple selection; definition of inclusion and/or exclusion criteria; report of losses to follow-up; validated measurements obtained; statistical analysis. Studies that fulfilled all of these criteria were classified as having a low risk of bias. Those in which only one criterion was not fulfilled were classified as having a moderate risk of bias. In the case of two or more criteria not being fulfilled, the study was classified as having a high risk of bias.

Results

Following the PRISMA guidelines, the electronic database search resulted in the identification of 92 articles. After the removal of duplicates, 70 articles remained for title and abstract reading. Fifty-four of these articles were found to be non-relevant and were excluded, resulting in a total of 16 articles. After applying the inclusion criteria, 10 were selected. One more article was then added after a hand search. Thus a total of 11 articles reporting 11 studies were included in this review. A flowchart of the systematic review process is presented in Fig. 1.

Following the evaluation of quality, two studies were considered as having a low risk of bias (de Freitas et al., 2013; Marx et al., 2013)^{4,27}, one was considered as having a moderate risk of bias (de Freitas et al., 2016)²⁸, and eight studies were considered as having a high risk of bias (Misch et al., 2015; Ribeiro-Filho et al., 2015; Butura and Galindo, 2014; Luiz et al., 2014; Hart and Bowles, 2012; Misch, 2011; Herford and Boyne, 2008; Ferretti and Ripamonti, 2002)^{3,12,23,25,29–32} (Table 1).

As expected, the data collected were not the same for all studies. Some studies reported a large amount of information and some reported just the basics. All results are presented in Tables 2–5.

Discussion

With every new surgical technique and biomaterial for bone grafting, questions are raised regarding their efficacy and associated features^{2,5,14}. For this reason, the present systematic review was performed to collect data on the main characteristics of alveolar rhBMP-2/titanium mesh when used for alveolar ridge augmentation.

Furthermore, the limitations and contradictions of autogenous bone grafting in critical defects for reconstruction of the jaws has led to the search for new guided bone regeneration (GBR) materials and techniques²⁷. An absorbable collagen

Table 1. Quality assessment of the studies.

Year	Authors	Random selection in population	Defined inclusion/exclusion criteria	Report of loss to follow-up	Validated measurements	Statistical analysis	Estimated potential risk of bias
2016	de Freitas et al. ²⁸	Yes	Yes	No	Yes	Yes	Moderate
2015	Misch et al. ²⁹	No	No	Yes	Yes	No	High
2015	Ribeiro Filho et al. ³	No	Yes	Yes	Yes	No	High
2014	Butura and Galindo ³¹	No	Yes	Yes	Yes	No	High
2014	Luiz et al. ³⁰	No	Yes	Yes	No	No	High
2013	de Freitas et al. ⁴	Yes	Yes	Yes	Yes	Yes	Low
2013	Marx et al. ²⁷	Yes	Yes	Yes	Yes	Yes	Low
2012	Hart and Bowles ²³	No	No	Yes	No	No	High
2011	Misch ³²	No	No	Yes	No	No	High
2008	Herford and Boyne ²⁵	No	No	Yes	No	No	High
2002	Ferretti and Ripamonti ¹²	Yes	No	Yes	No	No	High

Table 2. Details of the studies collected for analysis: type of study and patient demographic data.

Year	Authors	Study design	Number of patients	Number of grafts	Age (years)	Sex
2016	de Freitas et al. ²⁸	RCT	12	12	>18	NR
2015	Misch et al. ²⁹	Retrospective review	15	16	NR	NR
2015	Ribeiro Filho et al. ³	Case series; prospective	5	5	49.4 ± 20.8	1 M, 4 F
2014	Butura and Galindo ³¹	Case series; retrospective	7	8	46.1 (22–78)	4 M, 3 F
2014	Luiz et al. ³⁰	Case series	2	2	51 (40–62)	1 M, 1 F
2013	de Freitas et al. ⁴	RCT	12	12	rhBMP-2: 42.4 ± 10.1 (36–50)	rhBMP-2: 4 M, 8 F
2013	Marx et al. ²⁷	RCT	20	20	NR	NR
2012	Hart and Bowles ²³	Case series	8	10	40.5 (25–52)	7 M, 1 F
2011	Misch ³²	Case series	5	5	NR	NR
2008	Herford and Boyne ²⁵	Case series	14	14	NR	NR
2002	Ferretti and Ripamonti ¹²	RCT	6	6	34 (14–56)	4 M, 2 F

F, female; M, male; NR, not reported; RCT, randomized clinical trial; rhBMP-2, recombinant human bone morphogenetic protein 2.

^aAge reported as the mean ± standard deviation, or mean (range).

sponge soaked with rhBMP has been shown to be an alternative for such situations, as was demonstrated by the articles included in this systematic review^{3,4,12,23,25,27–32}.

Although in 2002 Ferretti and Ripamonti had already presented what appears to be a precursor to the new material in jaw reconstructions, the use of rhBMP-2 for maxillofacial reconstructions was only authorized by the US Food and Drug Administration in 2007^{4,12}. For this reason, the great majority of studies involving the use of this protein were conducted relatively recently, in the last two decades^{3,4,23,25,27–35}.

Ten studies were performed in the last 10 years^{3,4,23,25,27–32}, while only one was performed more than 15 years ago¹². Six studies were case series reports^{3,25,25,30–32}, four were randomized clinical trials^{4,12,27,28}, and one was a retrospective review²⁹. Altogether, the studies included 106 patients who underwent 110 reconstruction procedures. There were 74 maxillary grafts and 22 mandibular grafts. Marx et al. (2013)²⁷ performed the study with the largest number of patients, with a total of 20 grafting procedures in 20 patients. In contrast, Luiz et al. (2014)³⁰ performed only two grafting surgeries in two patients and this was the study with the least patients and grafts. Patients of both sexes were included in the studies, and they ranged in age from 14 to 78 years (Table 2).

In only two of the 106 patients were autogenous bone grafts associated with rhBMP-2^{12,23}. Five studies worked with rhBMP-2 by itself^{3,4,23,25,28}, and six studies used rhBMP-2 with additional biomaterials^{12,27,29–32}. Among the biomaterials used were mineralized bone allograft (MinerOss, BioHorizons)^{29,32}, anorganic bovine bone (Bio-Oss, Geis-

tlich)^{30,31}, crushed cancellous freeze-dried allogeneic bone (ccFDAB)²⁷, and demineralized frozen human cortical bone¹². All biomaterials were used in their particulate form (Table 3).

All but one study used an absorbable collagen sponge as rhBMP-2 carrier¹². Titanium mesh was used in all studies; however Hart and Bowles (2012)²³ used two types of a titanium-reinforced porous polyethylene mesh with different thicknesses: 0.8 mm and 1 mm. Four studies used a 0.2-mm thick titanium mesh^{3,4,29,32}, and the others did not specify the thickness of the mesh used^{12,25,27,28,30,31}. Moreover, two studies covered the titanium mesh with a collagen membrane (AlloDerm; Colla Tape)^{30,31}.

Ferretti and Ripamonti (2002)¹² had the osseointegration material formulated specially for their study and used a concentration of 2 mg of derived bovine BMPs and 8 mg for the largest defect. The remaining studies used the material according to the extent of the defects and following the manufacturer's recommendations regarding the size of the kit^{3,4,23,25,27–32} (XX small^{3,27,29,31}, X small^{28,32}, small^{4,32}, medium^{25,31}, and large²⁵). Furthermore, Misch et al. (2015)²⁹ added platelet-rich plasma (PRP) in 11 grafts and Marx et al. (2013)²⁷ associated their grafts with 50% by volume of ccFDAB and 7 ml of activated PRP.

Grafting was performed in both the maxilla and the mandible. Five studies involved only the maxilla^{3,4,27,28,30}, and three involved only the mandible^{12,25,32}. Among these, four reconstructed the anterior maxilla^{3,4,28,30}, and one reconstructed different maxillary regions²⁷. Moreover, one study reconstructed the posterior region of the mandible³², and two reconstructed different regions^{12,25}. Three

studies included reconstruction of both maxilla and mandible^{23,29,31} (Table 4).

Only four studies specified the bone gain in numbers^{3,4,28,29}. The others reported bone volume gain, but did not report the values. No study reported the graft reabsorption rate. Six studies reported a success rate of 100% for implant osseointegration after reconstruction^{3,4,29–32}. One study reported a success rate of 93.4%²⁷. One study reported implant installation but did not present the success rate²⁸. Two studies did not show any data about implant installation^{23,25}, and in one study the dental rehabilitation was performed with a chrome cobalt removable prosthesis¹². A delay of 6 months before surgical site re-exposure was reported in four studies^{4,23,28,32}; this delay was 6.5 months in two studies^{30,31} and 7 months in another³. Four studies did not report this information^{12,25,27,29} (Table 4).

Regarding undesirable results, five studies reported the absence of any complications during the rehabilitation process^{3,12,29,30,32}. One study did not mention this issue²⁸. Two studies reported titanium mesh exposure but not leading to major problems^{4,31}. One study reported two cases of dehiscence followed by infection resulting in loss of the graft and three cases of dehiscence without affecting the grafted area²⁷. One study reported one case of membrane exposure after 2 weeks, leading to insufficient vertical bone gain and two cases of graft exposure, after 2 weeks and 3 months, leading to no bone gain at all²³. Only one study referred to complications without specifying what kind²⁵ (Table 5).

There is evidence at the proof of principle level for the combined use of mesh and BMP-2, but no comparative data with other treatment options.

Table 3. Data collected regarding the bone graft.

Year	Authors	Graft used	Mesh used	rhBMP dose	Carrier
2016	de Freitas et al. ²⁸	rhBMP-2 (test group)	Titanium mesh	rhBMP-2 at 1.5 mg/ml; total dose 4.2 mg	ACS
2015	Misch et al. ²⁹	rhBMP-2 + particulate mineralized bone allograft	Titanium mesh, 0.2 mm thick	1.05 mg of 1.5 mg/ml rhBMP-2 per site involving two teeth	ACS
2015	Ribeiro Filho et al. ³	rhBMP-2	Titanium mesh, 0.2 mm thick	0.7 ml of 1.5 mg/ml rhBMP-2 for 15 min	ACS
2014	Butura and Galindo ³¹	rhBMP-2 + anorganic bovine bone (Bio-Oss)	Titanium mesh	Extra-extra small kit for one defect; medium kit for maxilla and mandible defects	ACS
2014	Luiz et al. ³⁰	rhBMP-2 + anorganic bovine bone (Bio-Oss)	Titanium mesh	NR	ACS
2013	de Freitas et al. ⁴	rhBMP-2 (test group)	Titanium mesh, 0.2 mm thick	rhBMP-2 at 1.5 mg/ml; total dose 4.2 mg per site (small kit)	ACS
2013	Marx et al. ²⁷	rhBMP-2 + ccFDAB (allogeneic bone)	Titanium mesh	1.05 mg of 1.5 mg/ml rhBMP-2 per site involving two teeth	ACS
2012	Hart and Bowles ²³	rhBMP-2 + autogenous bone (1); rhBMP-2 (9)	Titanium-reinforced porous polyethylene	NR	ACS
2011	Misch ³²	rhBMP-2 + particulate mineralized bone allograft	Titanium mesh, 0.2 mm thick	Four extra-small kits and one small kit (1.5 mg/ml rhBMP-2)	ACS
2008	Herford and Boyne ²⁵	rhBMP-2	Titanium mesh	1.5 mg/ml for a total dose of 4.2 mg (medium and large kits)	ACS
2002	Ferretti and Ripamonti ¹²	rhBMP-2 + autogenous bone (rib) (1); rhBMP-2 + allogeneic bone (5)	Titanium mesh	2 mg of derived bovine BMPs; 8 mg of naturally derived bovine BMPs for the largest defect	NR

ACS, absorbable collagen sponge; BMP, bone morphogenetic protein; ccFDAB, crushed cancellous freeze-dried allogeneic bone; NR, not reported; rhBMP-2, recombinant human bone morphogenetic protein 2.

Table 4. Data collected regarding success.

Year	Authors	Site	Bone gain ^a	Expected time to re-intervention	Implant/success rate
2016	de Freitas et al. ²⁸	Anterior region of the maxilla	Horizontal bone gain: rhBMP-2: 3.2 ± 0.9 mm (middle) rhBMP-2: 1.5 ± 0.7 mm (2 mm) rhBMP-2: 2.9 ± 0.8 mm (6 mm) rhBMP-2: 1.7 ± 0.9 mm (10 mm)	6 months	Reported installation without details
2015	Misch et al. ²⁹	Maxilla (9) Mandible (7)	Vertical bone gain: 8.53 ± 3.5 mm (range 4.4–16.3 mm)	NR	100% (40 implants)
2015	Ribeiro Filho et al. ³	Anterior region of the maxilla	Horizontal bone gain: 3.83 ± 0.69 mm (range 3.03–5.13 mm)	7 months	100% (10 implants)
2014	Butura and Galindo ³¹	Anterior region of the maxilla (6) Mandible (2)	NR	6.5 months	100% (14 implants)
2014	Luiz et al. ³⁰	Anterior region of the maxilla	NR	6.5 months	100%
2013	de Freitas et al. ⁴	Anterior region of the maxilla	Horizontal bone gain: Clinical observation at 6 months: rhBMP-2: 3.2 ± 0.9 mm Radiographic measurements at 3 months: rhBMP-2: 1.5 ± 0.7 mm (2 mm) rhBMP-2: 3.0 ± 0.8 mm (6 mm) rhBMP-2: 1.9 ± 0.9 mm (10 mm) Radiographic measurements at 6 months: rhBMP-2: 1.5 ± 0.7 mm (2 mm) rhBMP-2: 2.9 ± 0.8 mm (6 mm) rhBMP-2: 1.7 ± 0.9 mm (10 mm)	6 months	100% (rhBMP-2: 32 implants)
2013	Marx et al. ²⁷	Maxilla	Bone gain reported, but not specified	NR	61 (3.4/bone graft) rhBMP-2: success in 57/61
2012	Hart and Bowles ²³	Maxilla (8) Mandible (2)	NR	6 months	NR
2011	Misch ³²	Posterior region of the mandible	NR	6 months	100% (10 implants)
2008	Herford and Boyne ²⁵	Mandible	NR	NR	NR
2002	Ferretti and Ripamonti ¹²	Mandible	NR	NR	Rehabilitation with removable prosthesis

NR, not reported; rhBMP-2, recombinant human bone morphogenetic protein 2.

^a Bone gain reported as the mean ± standard deviation.

Table 5. Data collected regarding failures.

Year	Authors	Reabsorption ^a	Complications	Implant installation not possible, or new graft required	Further observations
2016	de Freitas et al. ²⁸	NR	NR	NR	None
2015	Misch et al. ²⁹	NR	None	No	PRP was added in 11 patients
2015	Ribeiro Filho et al. ³	NR	None (moderate oedema and erythema during the postoperative period)	No	None
2014	Butura and Galindo ³¹	NR	2 mesh exposure without major problems	No	The initial volume was reported; titanium mesh was covered by AlloDerm (BioHorizons)
2014	Luiz et al. ³⁰	NR	None	No	Titanium mesh was covered by a collagen membrane (Colla Tape, Zimmer Dental)
2013	de Freitas et al. ⁴	NR	1 titanium mesh exposure without major problems; oedema and erythema	No	None
2013	Marx et al. ²⁷	NR	Dehiscence followed by infection (2 bone grafts were lost in each group)	1 patient out of 18 treated with rhBMP-2 lost two implants and had to undergo another rhBMP-2 bone graft surgery	Information about morbidity; the bone graft was associated with 50% by volume of ccFDAB and 7 ml of activated PRP
2012	Hart and Bowles ²³	NR	Dehiscence (3 cases in each group; however the bone grafts were not affected)	3 cases: there was no gain (2) or an insufficient vertical gain (1)	0.8 mm thick Synpore titanium-reinforced fan plates (3) (Synthes); 1.0 mm thick MTB surgical implants (7) (Porex Surgical)
2011	Misch ³²	NR	3/10: 1 mesh exposure (2 weeks after); 2 bone graft exposure (2 weeks for one and 3 months for the other)	No	None
2008	Herford and Boyne ²⁵	NR	Reported without specifying	NR	For defects greater than 3.5 mm, 2 large BMP kits were used; for smaller defects, the medium size kit was used
2002	Ferretti and Ripamonti ¹²	NR	None	No	Trauma and pathology – major reconstructions; the osseointegration material was formulated for this study

ccFDAB, crushed cancellous freeze-dried allogeneic bone; NR, not reported; PRP, platelet-rich plasma.

^a Reabsorption, measured in millimetres or as a percentage, was not reported in any study.

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Competing interests

None.

Ethical approval

Not required.

Patient consent

Not required.

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