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## Cleft alveolar bone graft materials: literature review

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# The Cleft Palate-Craniofacial Journal

## Cleft alveolar bone graft materials: Literature review

Journal:	<i>The Cleft Palate-Craniofacial Journal</i>
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Keywords:	Bone grafting, Bone regeneration, Computerized tomography, Maxilla, Osteogenesis
Abstract:	<p>Since the early stages alveolar bone grafting development, multiple types of materials have been used. To date iliac cancellous bone graft (ICBG) seems to remain the gold standard.</p> <p>Methods : A systematic review of literature is conducted in order to describe the different possibilities of bone filling, autologous or not, and to assess their effectiveness, compared to ICBG. This review focused on studies reporting volumetric assessment of the alveolar cleft graft result (by CT-scan or CBCT).</p> <p>Results: Grafting materials could be divided in 3 types: autologous bone grafts, iliac cancellous bone graft supplementary material and bone substitutes. Among autologous materials, no study could show a superiority of any other bone origins over iliac cancellous bone. Yet ICBG gives inconsistent results and presents donor site morbidity. Concerning supplementary material, only three studies could show a benefit of adding PRF (one study) and adding PRP (2 studies) to ICBG, which remains controversial for most studies. There is a lack of 3-D assessment in most articles concerning the use of scaffolds. Only one study could show an improvement of the graft when adding Acellular Dermal Matrix to ICBG. Looking at bone substitutes highlights failures among bioceramics alone, side-effects of BMP-2 composite materials and difficulties in cell therapy set-up. Studies assessing cell therapy-based substitutes show a comparable efficacy with iliac cancellous bone graft but remain too few.</p> <p>Conclusion: This review highlights the lack of 3-dimensionnal assessments in alveolar bone graft materials field and also could not remove ICBG from its current Gold standard position.</p>

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## Abstract:

*Introduction:* Since the early stages of alveolar bone grafting development, multiple types of materials have been used. To date iliac cancellous bone graft (ICBG) seems to remain the gold standard.

*Design / Methods:* A systematic review of literature is conducted in order to describe the different possibilities of bone filling, autologous or not, and to assess their effectiveness, compared to ICBG. This review focused on studies reporting volumetric assessment of the alveolar cleft graft result (by CT-scan or CBCT).

*Results:* Grafting materials could be divided in 3 types: autologous bone grafts, iliac cancellous bone graft supplementary material and bone substitutes. Among autologous materials, no study could show a superiority of any other bone origins over iliac cancellous bone. Yet ICBG gives inconsistent results and presents donor site morbidity. Concerning supplementary material, only three studies could show a benefit of adding PRF (one study) and adding PRP (2 studies) to ICBG, which remains controversial for most studies. There is a lack of 3-D assessment in most articles concerning the use of scaffolds. Only one study could show an improvement of the graft when adding Acellular Dermal Matrix to ICBG. Looking at bone substitutes highlights failures among bioceramics alone, side-effects of BMP-2 composite materials and difficulties in cell therapy set-up. Studies assessing cell therapy-based substitutes show a comparable efficacy with iliac cancellous bone graft but remain too few.

*Conclusion:* This review highlights the lack of 3-dimensionnal assessments in alveolar bone graft materials field and also could not remove ICBG from its current Gold standard position for the moment.

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7 **Key Words**  
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10 bone grafting, bone regeneration, maxilla, osteogenesis, computerized tomography  
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## Text:

## Introduction

Cleft Lip and palate are usually closed in the 18 months after birth. Alveolar cleft stays open not to impair on maxillary growth (Robertson and Jolleys, 1968) until the time of well-established secondary alveolar bone grafting (Boyne and Sands, 1972).

Despite the small volume of alveolar cleft (Feichtinger et al., 2008; Dissaux et al., 2016), a full reconstruction of alveolar bone can't be done only using gingivoperiostoplasty. The neo-osteogenesis occurring in that case is different from fracture healing (Meyer et al., 2006) as two cortical bone surfaces are involved and bone synthesis in this small alveolar cleft space cannot occur only by abrading cortical bone. Thus, a bone graft should be done to restore adapted bone dimensions in alveolar cleft.

Since the early stages of alveolar bone grafting development, multiple types of materials, autogenous or not, have been used.

A systematic review of literature is conducted in order to describe the different possibilities of bone filling and to assess their effectiveness. First an overview of all autologous fillers is described. Then the review focuses on iliac cancellous bone graft (ICBG) supplementary material and finally on bone substitutes.

## Methods

A systematic literature review using MEDLINE (Via OVID; 1948 To June 2019) and SCIEDIRECT was conducted, using MESH terms as “Cleft Palate, Cleft Lip, Bone Transplantation, Alveolar Bone Grafting, Bone Substitutes, Ilium”, associated with free words in order to get the most extensive research. This review focused on studies reporting volumetric assessment of the alveolar cleft graft result (by CT-scan or CBCT). In order to describe all the disposable grafting materials, certain studies providing only 2D analysis were added but are specified and are exceptional. In fact, studies only evaluating the bone graft result on standard 2D-Xray (dental panoramic or retro-alveolar X-Ray) most often overestimate the result of the graft in terms of height and anteroposterior width (Hamada et al., 2005).

Abstracts and their original article, in English or French, were selected for review when they met the following inclusion criteria: (1) Studies on human-being of all ages, (2) Alveolar bone grafting realized on patients with cleft lip, alveolar and palate or with only cleft lip and alveolar, either unilateral or bilateral forms, (3) Randomized trials or cohort study or prospective or retrospective study, (4) 3-D analysis of the alveolar bone graft result (by CBCT or CT-scan), (5) Reported result as a comparison between pre- and post-operative volumes or as a ratio of bone graft volume over alveolar cleft initial volume, (6) Analysis comparing a grafting material with a controlled group using an other material (most of the time ICBG), (7) Analysis of the residual bone graft volume at a minimum of 3-months post-operatively. Exclusion criteria were: (1) Animal studies, (2) Case-report, (3) No available volumetric analysis.

## Autologous bone grafts

Histocompatible and non-immunogenic, autologous bone reduces the autoimmune reaction against transplanted material and the risk of infectious diseases transmissions.

Autologous bone harvested from different donor sites may differ in terms of cell viability and absorption rate. Moreover, harvesting methods and their complications may vary in function of donor sites.

### ***Iliac cancellous bone graft***

Several studies suggest that iliac cancellous bone graft harvested from anterior iliac crest is the most common grafting material in secondary alveolar bone grafting. It can be collected easily and in abundance. In addition, it allows double team work, one harvesting iliac bone while the other one prepares the alveolar bone graft site (Bajaj et al., 2003). Iliac cancellous bone is preferred to cortico-cancellous samples. Indeed, it shows faster revascularization in 3 weeks on average (Pinholt et al., 1994; Kerwin et al., 1996) and brings a high potential of osteoprogenitor cells and pluripotent cells. These cells are assumed to potentiate neo-osteogenesis occurring at an early stage after bone grafting (Sadove et al., 1990).

Iliac bone can be harvested by direct exposure or using a trephine to core-drill a sample.

Literature has focused on donor site morbidity as the main disadvantage of iliac bone graft.

Yet this morbidity is quite difficult to assess because it really relies on habits of each surgeon and on the way in which harvesting is performed. Major criticism of iliac donor site is based on the pain caused at the iliac crest. Nevertheless, several studies agree to say that this pain is often overestimated (Kalk et al., 1996; Eufinger and Leppänen, 2000; Joshi and Kostakis,



2004; Rawashdeh 2008). Most patients report low-intensity pain relieved by paracetamol. Kalk et al. (1996) and Eufinger et Leppänen (2000) notice that respectively 26% (n=17) and 38% (n=19) of their patients complain more about their hip than their mouth. Baquain et al. (2009) and Matsa et al. (2012) report that patients could walk within 24 hours post-operatively and recover normal gait in a maximum of 10 days. Matsa also specifies that harvesting has no impact on hip growth. The length of hospital stay was initially quite long at the time of Bergland (1986) or Hall and Posnick (1983) but has been then reduced to 1 or 2 days (Perry et al., 2005). Cancellous iliac bone harvesting for alveolar cleft bone grafting still remains nowadays the Gold standard for most of the teams (Abyholm et al., 1981; Ennemark et al., 1987; Kalk et al., 1996; Eufinger and Leppänen, 2000; Eppley and Sadove, 2000; Joshi and Kostakis, 2004; Perry et al., 2005; Rawashdeh 2007 and 2008; Khojasteh et al., 2015) but its resorption potential, up to 40% in 1 year (Van der Meij, 2001; Feichtinger et al., 2008; Khojasteh et al., 2015) drive some surgeons towards other autogenous harvesting sites.

### ***Tibial graft***

Tibia is considered as an alternative harvesting site because it also provides cancellous bone. Lexer performed in 1908 the first maxillary graft using cortico-cancellous tibial graft, along with its periosteum. This donor site has been first developed in orthopedics and then in cranio-maxillo-facial surgery for reconstructive, orthognathic or cleft surgeries (O'Keefe et al., 1991; Catone et al., 1992). This donor site was first preferred for adults before it was considered to be used on children. Indeed, taking cancellous bone from the tibial epiphysis represents a risk of damage to the growth center. Besly and Ward Booth (1999) describe the harvesting technique on children. Nevertheless, the available quantity of harvested bone is

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3 much lower of the one obtained from iliac crest. For an adult, the samplings are limited to  
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5 25mL (Ilankovan et al., 1998; Chen et al., 2006). In the case of a child, harvesting could be  
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7 performed on both legs if an important quantity of bone is required (Hughes and Revington,  
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9 2002; Chen et al., 2006). This offsets the low morbidity which is advanced for this donor site  
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11 (Van Damme and Merckx, 1996; Chen et al., 2006). In addition, patients are asked not to  
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13 perform any sport activity for 3 months. Tibial cancellous alveolar bone graft seems to give  
14  
15 equivalent results as iliac cancellous bone graft, but available studies only provide 2D  
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17 assessment on standard X-ray and could not be conclusive (Sivarajasingam et al., 2001; Al  
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19 Harbi et al., 2012). Even if an equivalent result could be proved, morbidity of this donor site,  
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21 especially in children, does not place tibia as a first choice.  
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### 30 ***Calvarial graft***

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32 The success of calvaria as bone donor site in maxillofacial surgery (Jackson et al., 1986;  
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34 Tessier et al. 1982 and 2005) prompted surgeons to use it for clefts (Wolfe and Berkowitz,  
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36 1983; Kortebein et al., 1991; Denny et al., 1999). Calvarial bone is an attractive option at first  
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38 sight because of its embryological origin close to the recipient site and its membranous  
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40 ossification process like alveolar bone's one. However, onlay grafts of calvarial bone, which  
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42 provides good results, remain different from the particular case of alveolar cleft bone  
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44 grafting, where the surgeon performs inlay grafts. Rosenthal and Buchman (2003)  
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46 developed the work of Ozaki et al. (1998, 1999) and compared inlay bone grafts of cortical  
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48 and cancellous iliac bone (endochondral origin) with mandibular bone grafts (membranous  
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50 origin) in rabbits. Four critical size defects were performed on the rabbits' skulls, the first  
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52 filled with cortical iliac bone, the second with cancellous iliac bone, the third with  
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54 mandibular cortical bone and the last one left empty as control. The animals were killed at 3,  
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3 8 and 16 weeks for histological analysis. A microCT-scan study was also carried out. The  
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5 three types of inlay grafts in this experiment increased in terms of volume. Interestingly the  
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7 authors noted that the best result was obtained with iliac cancellous bone. This study  
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9 highlights that the mechanisms of inlay grafts are different from onlay ones. Thus, if onlay  
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11 grafts of calvarial bone obtain excellent results in reconstructive maxillo-facial and pre-  
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13 implant surgery, the particular case of alveolar cleft is different. Alveolar bone grafting must  
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15 be considered as an inlay graft as it fills and is molded into the defect in between alveolar  
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17 processes and the edge of the piriform orifice, and not as a typical onlay graft of the maxilla.  
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19 This important statement could explain the conclusions of several authors, as Sadove et al.  
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21 (1990), Kortebein et al. (1991), or La Rossa et al. (1995) showing better results of alveolar  
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23 bone grafting, when cancellous iliac bone is used in comparison with calvarial grafts. Even if  
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25 cancellous bone as cortical one could be harvesting on calvaria (Wolfe et Berkowitz, 1983;  
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27 Denny et al., 1999; Han et al., 2017), this act could be longer, trickier and less productive  
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29 than on iliac crest. Complications rate vary from 0.25% (Tessier et al., 2005) to 5.5% (Jackson  
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31 et al., 1986) in literature and can be potentially severe compare to the ones occurring in iliac  
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33 crest harvesting: calvaria osteomyelitis, dura mater exposure, cerebro-spinal fluid leakage,  
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35 extra- or subdural hematoma and neurological complications (Kline et Wolfe, 1995; Fearon,  
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37 2000). In addition, hiding the scar in the hair, which at first could be considered as an  
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39 advantage, could be difficult to handle for a child who had multiple operations on his face.  
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41 Finally, this site does not enable two surgeons to work at the same time.  
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### ***Mandibular graft***

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55 Also attractive by its same embryological origin and its membranous ossification, mandibular  
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57 bone has been proposed as a donor site by several surgeons. Bosker and van Dijk in 1980  
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(Borstlap et al., 1990) were the first to describe the use of the mandibular symphysis as a donor site for alveolar bone graft. They published their preliminary results on 25 cases in 1989 (Koole et al., 1989) and confirmed that the mandibular symphysis represented an attractive donor site by its ease of access and gave good results in terms of alveolar cleft bone grafting. One operating site, invisible scar, reduction in post-operative pain and in length of hospital stay, represent major advantages (Koole, 1994; Booij et al., 2005; Andersen et al., 2014). Several teams (Freihofer et al., 1993; Koole, 1994; Park and Lee, 2016; Attar et al., 2017) describe good results using mandibular graft, comparable to ones obtained with iliac bone, but most of their assessments are realized in 2 dimensions and cannot be conclusive. Moreover, most of the authors report that the harvested bone volume on mandibular symphysis is often insufficient in case of large or bilateral clefts (Freihofer et al., 1993, Bähr and Coulon, 1996; Weijs et al., 2010; Shirzadeh et al., 2018). Adding  $\beta$ -TCP is often required to obtain an adequate volume (Weijs et al., 2010; Shirzadeh et al., 2018). A higher rate of included canines (31%) is also found in children transplanted from mandibular bone compared to iliac bone (Schultze-Mosgau et al., 2003). Main risks of this donor site are potential lesions of dental gums or teeth roots, especially when graft is realized at an early age (Ennemark et al., 1987; Koole, 1994; Booij et al., 2005). In addition, harvesting mandibular symphysis in adults could result in long-term persistent defect of mandibular shape (Dik et al., 2010).

### ***Other autogenous donor sites***

The other sites are represented by costal bone (nowadays abandoned) and olecranon, which remains anecdotal. Nadal et al. (2010) described harvesting a cortico-cancellous sample on olecranon but does not provide any three-dimensional analysis of their results.

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6 To date iliac cancellous bone remains the Gold Standard of autologous materials in  
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8 secondary alveolar cleft bone grafting. As it is still presenting morbidity and inconstant  
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10 results, surgeons try to potentiate graft results by adding supplementary material.  
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## 17 Iliac cancellous bone graft supplementary material (Table 1)

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21 Iliac bone resorption rate in the specific case of alveolar cleft grafting can reach 40 to  
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23 50% (Sindet-Pedersen and Ennemark, 1990; Maamon and Telfah, 2008; Janssen et al.,  
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25 2014; Khojasteh et al., 2015). These figures should be considered approximations because  
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27 the authors never assess during the operation whether they fill the entire volume of the  
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29 alveolar cleft or not. Several studies have attempted to identify factors that could identify  
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31 this resorption as platelet concentrates or scaffolds.  
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### 38 **PRP/ PRF**

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41 In recent years, clinical research protocols have been particularly interested in recent years  
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43 in fibrin glues and in platelet concentrates such as PRP (Platelet-Rich Plasma) and finally PRF  
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45 membranes (Platelet-Rich Fibrin). These second-generation platelet concentrates are  
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47 obtained from centrifugation of the patient's blood. Whereas PRF is collected on a dry tube  
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49 and does not require anticoagulant or the addition of thrombin. It appears as a fibrin  
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51 membrane which has trapped a large amount of growth factors. PRP also came from blood  
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53 centrifugation but with the use of special commercial kits. After centrifugation, an  
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55 anticoagulant and/or thrombin are added in order to obtain PRP, which comes as a gel. This  
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57 gel is more or less fluid depending on the kit. As well, PRP growth factors composition relies  
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3 on the type of kit and on the initial platelet concentration. Platelet concentration is an  
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5 important factor considering PRP studies. The results of a study are comparable only if the  
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7 type of kit and/or the same initial platelet concentrations are equivalent. PRP and PFR  
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9 contains various amounts of growth factors, such as PDGF (Platelet-Derived Growth Factor),  
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11 VEGF (Vascular Endothelial Growth Factor), TGF- $\beta$  (Transforming Growth Factor beta). These  
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13 factors could, in theory, improve wound healing and neoangiogenesis, promote bone growth  
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15 and so reduce graft resorption (Marukawa et al., 2011).  
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20 Two studies report a decreased resorption rate when PRP is added to iliac cancellous bone  
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22 graft, but these studies only concern adults (Oyama et al., 2004; Marukawa et al., 2011).  
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26 Concerning a younger population, no statistically significant difference in graft stability could  
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28 be identified between the groups iliac cancellous bone graft (ICBG) alone and PRP (Gupta et  
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30 al., 2013; Sakio et al., 2017). One study on PRF by Shawky and Seifeldin (2016) reported a  
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32 statistically significant increase in the percentage of newly formed bone when PRF was  
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34 added to ICBG. However, controversies remain because in 2018 Saruhan and Ertas could not  
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36 find any difference with or without PRF. A modification of bone density was also noticed in  
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38 Gupta et al. (2013) and Huang et al. (2018) studies.  
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45 Fibrin glue is a degradable bio-adhesive, composed of fibrinogen and prothrombin, which  
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47 are supposed to improve cell migration and neoangiogenesis. This review only found one  
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49 study by Segura-Castillo et al. (2005) which added fibrin glue to ICBG in alveolar cleft bone  
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51 grafting. The 2-dimensionnal analysis does not conclude to any benefit adding fibrin glue.  
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### 55 56 ***Scaffolds*** 57 58 59 60

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3 Two types of scaffolds added to iliac cancellous bone graft can be identified: simple  
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5 “scaffolds” guiding neo-osteogenesis and “membrane barriers” which also block the  
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7 ingrowth of soft tissue.  
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10 Strictly speaking scaffolds could be of several types: deproteinized bovine bone (DBB), human  
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12 demineralized bone matrix (DBM), demineralized dentinal matrix (DDM). This review only  
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14 identifies one study for each scaffold where the effectiveness of combining the scaffold with  
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16 ICBG is assessed compared to ICBG alone. While DBB does not appear to provide any benefit  
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18 over ICBG alone (Thuaksuban, 2010), DBM might enhance ICBG result (Maclsaac et al., 2012).  
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20 However, a 2-D assessment could not, once again, lead to a conclusion.  
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28 Membrane barriers guide bone growth block soft tissues and growth and so tend to isolate  
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30 and preserve the bone graft volume. Several types of membrane barriers are found in  
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32 literature: Polylactic-polyglycolic acid membranes (Peled et al., 2005), Bio-Gide membranes  
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34 (Deng et al., 2007) and Acellular Dermal Matrix (ADM). The only 3-D volumetric study entails  
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36 on Acellular Dermal Matrix membrane. Described by Clavijo-Alvarez et al. in 2018, ADM  
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38 belongs to the process called “guided bone regeneration”. The ADM membrane is used to  
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40 block the invasion of surrounding tissue, allowing osteoblastic cells to have enough time to  
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42 proliferate in this "preserved" space and thus generate neo-bone. This membrane is  
43  
44 completely absorbed in 4 to 6 months. Clavijo-Alvarez et al. (2018) only carried out a clinical  
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46 study on the tolerance of ADM membrane. He concludes to an equivalent rate of complication  
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48 and graft exposure when ADM is added to ICBG or not. Only Xiao et al. (2016) realized a  
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50 randomized comparative trial with volumetric assessment of two groups: one alveolar bone  
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52 graft group using ADM combined with ICBG and a control group using ICBG alone (Table 1).  
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57 This study concerned 60 patients and assess bone graft resorption rate using CBCT at 1 week,  
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3 and 6 months post-operatively. The bone resorption rate was significantly reduced for the  
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5 “ADM + ICBG” group compared to the control group (31.69% versus 36.50%,  $p = 0.017$ ). The  
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8 only significant bias in this study stands in the unspecified age of patients.  
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## 17 Bone substitutes

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22 This review identifies 3 different types of bone substitutes: Bioceramics, BMP-2 composite  
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24 bone substitutes and cell therapy.  
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### 30 *Bioceramics*

31  
32 Several bioceramics have been used in cleft alveolar grafting, such as Glass-bone (Graillon et  
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34 al., 2018), hydroxyapatite (Benlidayi et al., 2012), and beta-tricalcium phosphate ( $\beta$ -TCP) (Chen  
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36 et al., 2012). They present good biocompatibility and osteoinduction potential. In the specific  
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38 case of alveolar cleft, bioceramics might be considered as ideal bone substitutes because they  
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40 provide a matrix that is slowly absorbed and this way interesting for neo-osteogenesis. This  
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42 statement is only hypothetical because each type of bioceramics is only supported by only  
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44 one study using a 2-D assessment. Thus, this literature review cannot promote for the  
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46 moment the use of bioceramics instead of autologous bone in alveolar cleft grafting.  
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54 A bone critical-size defect is relatively poor in osteoprogenitor cells. This way osteoconductive  
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56 substitutes alone are not sufficient to produce osteoinductive signals to promote bone  
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3 regeneration. The regenerative approach involves combining the use of biomaterials, such as  
4  
5 a biodegradable scaffold, and growth factors and/or stem cells.

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8 During conventional bone repair, the osteoprogenitor cells, differentiate into osteoblasts  
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10 producing the osteoid bone matrix. Mineralization of this matrix over time results in the  
11  
12 formation of lamellar bone. The objective of the following two substitutes is to stimulate the  
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14 arrival and activation of osteoprogenitor cells (BMP-2) or to bring these cells directly to site.  
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### 20 ***BMP-2 composite bone substitutes (Table 2)***

21  
22 BMP-2 (Bone Morphogenic Protein-2) is the most well-known growth factor inducing bone  
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24 formation (Bessa et al., 2008). This growth factor is usually combined to scaffolds or barrier  
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26 membranes such as ACS (Acellular Collagen Sponge),  $\beta$ -TCP, Hydrogel or DBM (Demineralized  
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28 Bone Matrix). The most commonly-used concentration of BMP-2, in literature, is 1.5mg/ml.  
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30 (Herford et al., 2007; Dickinson et al., 2008; Alonso et al., 2010; Canan et al., 2012; Neovius et  
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32 al., 2013; Trujillo et al. 2018). Below this concentration, a complete failure of the bone  
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34 substitute occurs (Neovius et al., 2013). This review reports that BMP-2 combined with ACS is  
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36 the most studied BMP-2 composite bone substitutes. While Alonso et al. in 2010 gets a worse  
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38 result using BMP2/ACS compared to ICBG, most studies show a similar efficacy to ICBG in  
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40 terms of bone volume regeneration and tooth eruption capacity (Herford et al., 2007; Canan  
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42 et al., 2012). Other BMP-2 supports, such as  $\beta$ -TCP, Hydrogel or DBM, show equivalent results  
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44 as well (Neovius et al., 2013; Hammoudeh et al., 2017; Trujillo et al. 2018). Dickinson et al.  
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46 (2008) is the only one to describe a mild superiority of BMP-2/ACS compared to ICBG, but this  
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48 result only concerns an adult population and not a younger population presenting deciduous or  
49  
50 mixed dentition. Hammoudeh et al., 2017 did not realize a volumetric assessment but the  
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52 study involves a very important number of patients. Thus, it is important to take into account,  
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3 especially to evaluate tolerance of BMP-2 composite bone substitute. One important fact  
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5 highlighted by the review is edema as a common side effect of using BMP-2 composite bone  
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7 substitutes (Alonso et al., 2010; Neovius et al., 2013; Hammoudeh et al.,2017); some studies  
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9 even had to stop using it (Neovius et al., 2013).  
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### 20 ***Cell therapy (Table 3)***

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22 Cell therapy has the benefit to provide a non-antigenic solution, able to completely  
23  
24 reconstruct the alveolar process in terms of form and function. Autologous osteoblastic cells  
25  
26 and Bone Marrow Mesenchymal Stem Cells (BMMSC) are the most commonly used cells in  
27  
28 humans (Pradel and Lauer, 2012; Du et al., 2017; Al-Ahmady et al., 2018).  
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32 Research on cell therapy in bone regeneration has been developed in recent years. Yet  
33  
34 preparation and culture of BMMSC are usually difficult and delicate. Thus, clinical trials are  
35  
36 rare. This review only reports three volumetric studies in humans. Only two of them really  
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38 describe cells preparation (Pradel and Lauer, 2012; Al-Ahmady et al., 2018). These studies  
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40 could not identify any difference of results in between cell therapy and ICBG (Pradel and  
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42 Lauer, 2012; Du et al., 2017); but the residual bone volume obtained are poor compared to  
43  
44 other studies using autogenous bone or other bone substitutes. Modification of the support  
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46 or addition of growth factors will surely bring promising results, but more studies are  
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48 required (Al-Ahmady et al., 2018).  
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## Conclusion

This review reveals that certain bone substitutes show a comparable efficacy with iliac cancellous bone graft. However, the studies on the bone substitutes with comparable effect remain too few and none of the substitute seem to show a superiority. Their preparation is sometimes difficult. Thus, iliac cancellous bone graft still stands to these days the Gold Standard material for alveolar bone grafting, but research is tending to change this status. Autologous cancellous iliac bone graft used for decades has shown its effectiveness but stays relatively unclear concerning its mechanisms and characteristics of integration. Moreover, mechanical impairment on bone graft results remains poorly known, as witnessed by multiple studies and controversies about mechanotransduction (Dissaux et al., 2019). Based on this review a model is needed to better understand bone graft integration (Spingarn et al., 2017; Sheidaei et al., 2018; George et al., 2017, 2018, 2019) and how compaction force could influence it (Dissaux C. et al., 2019).

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## 28 Tables legend

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34 Table 1: Iliac cancellous bone graft supplementary materials (Summary of 3-D assessments  
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41 Table 2: BMP-2 composite bone substitutes (Summary of 3-D assessments trials found in  
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48 Table 3: Cell therapy substitutes (Summary of 3-D assessments trials found in literature)  
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Article	U or B Cleft	Nbr of pat.	Pat. age	Type of investigated material	Control group	Imaging	Postop evaluation timing	Studied parameters	Rando-mized trial	Results	Tooth eruption	Comments
Marukawa et al., 2011	U	20	20-30 y	PRP + ICBG (n=14)	ICBG (n=6)	CT	1M, 6M, 12M	Dental arch dimensions (height and antero-posterior dimension)	yes	Lesser resorption in antero-posterior width with PRP +ICBG at 6 M (16% versus 24%) and at 1y (26% versus 35%) than ICBG alone Lesser height decrease as well (2.1 versus 1.4%)	/	Detailed article about PRP preparation and platelet concentration
Oyama et al., 2004	U	12	16-18 y	PRP + ICBG (n=7)	ICBG (n=5)	CT	6M	Residual Bone Graft Volume	No	Residual Bone Graft Volume 80.19% with PRP versus 63.67% without PRP	/	Unknow technique of PRP preparation Unknown initial and final platelet conc.
Gupta et al., 2013	U+B	20	8-30 y	PRP + ICBG (n=10)	ICBG (n=10)	CT	3M, 6M	Bone density	Yes	Better mean density in PRP group at 6M: 1028+/- 11 HU versus 859 +/- 27	NS	Unknow technique of PRP preparation Unknown initial and final platelet concentrations Bias: wide age panel
Sakio et al., 2017	U	29	09-10 y	PRP + ICBG (n=23)	ICBG (n=6)	CT	1M, 6M, 12M	Percentage of new-formed bone over alveolar cleft	No	No difference	Canine eruption 100%	Unknow technique of PRP preparation
Saruhan et Ertas, 2018	U+B	22	NS	PRF + Cortico-cancellous BG	Cortico-cancellous BG	CBCT	6M	Percentage of new-formed bone over alveolar cleft	No	No difference (PRF: 68.2% +/-10 and without PRF : 64.6% +/-9%)	NS	Unknow technique of PRP preparation
Shawky et Seifeldin, 2016	U	24	9-14 y	PRF + ICBG (n=12)	ICBG (n=12)	CT	6M	Percentage of new-formed bone over alveolar cleft	Yes	PRF + ICBG : 82.6% +/- 3.9%, ICBG alone : 68.38% +/- 6.67%	NS	Detailed PRF preparation technique but no info on platelet conc.
Huang et al., 2017	U+B	20	8-25 y	CGF + ICBG (n=11)	ADM + ICBG (n=9)	CBCT	6M	Bone resorption rate +improved bone density rate	Yes	No difference in bone resorption rate but better density in CGF + ICBG group (61.6% vs 27%)	NS	CGF equivalent to PRF Well-detailed preparation
Xiao et al., 2016	U	60	NS	ADM + ICBG	ICBG	CT	1 W, 3M, 6M	Bone resorption rate	Yes	ADM+ICBG: resorption rate 31.69% vs 36.50% for ICBG (p= 0.017)	NS	Bias: no precision on age

**Table 1 :** Iliac cancellous bone graft supplementary materials (Summary of 3-D assessments trials found in literature)

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*Y= years, NS= not specified, CT= Computed tomography, CBCT = Cone Beam computed Tomography, M=months, CGF=concentrate growth factor, conc.=concentration, Nbr=Number, pat.= patients, Tooth eruption = tooth eruption through the grafted site, U= Unilateral, B= Bilateral*

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Article	U or B Clefts	Nbr of pat.	Pat. age	Type of investigated material	Control group	Imaging	Postop evaluation timing	Studied parameters	Rando-mized trial	Results	Tooth eruption
Alonso et al, 2010.	U	16	8-12 y.	BMP-2/ACS (n=8)	ICBG (n=8)	TDM	6M and 12M post-op	Bone graft height/ alveolar cleft height, Volume of alveolar bone defect	yes	Superiority of ICBG (85% of BG / AC height vs 65% for substitute). More edema for bone substitute	Yes both groups
Canan Jr et al., 2012	U	18	8-12 y.	BMP-2/ACS (n=6)	ICBG (n=6) GPP (n=6, grp 3)	TDM	3,6 and 12M	Bone graft height, Volume of alveolar bone defect volume of newly-formed bone, bone density	yes	No difference between ICBG and BMP-2/ACS Poor results for GPP	NS
Herford et al., 2007	U	12	8-11 y.	BMP-2/ACS (n=10)	ICBG (n=2)	TDM	4M	Bone graft height, ratio bone graft volume/ alveolar cleft volume	no	No difference	NS
R. Trujillo et al., 2018	U+B	25	9-17 y.	rhBMP-2/betaTCP (n=9)	Mandibular bone (n=9). ICBG (n=6)	CBCT	6M	ratio bone graft volume/ alveolar cleft volume	no	85.47% ICBG, 80.56% symphysis, 81.22% RHBMP2/bTCP but no significant difference	NS
Dickinson et al., 2008	U	21	20-50 y.	BMP-2/ACS	ICBG	TDM	12M	ratio bone graft volume/ alveolar cleft volume	yes	Superiority BMP2/ACS vs ICBG (95 vs 63%)	NS
Neovius et al., 2012	U	7	8-11 y.	BMP-2/Hydrogel (5)	ICBG (3)	TDM	6M	ratio bone graft volume/ alveolar cleft volume	no	No difference (study had to stop because of important edema as side effect)	NS
Hammoudeh et al., 2017	U+B	501	NS	rhBMP-2/DBM (n=258)	ICBG (n=243)	Clinical evaluation / simple X-ray	2-4y	Complications, tooth eruption, necessity of new bone graft	no	No difference in terms of new BG necessity : 28 for ICBG vs 23. More edema in rhBMP2 group	No difference for canine eruption

**Table 2 : BMP-2 composite bone substitutes (Summary of 3-D assessments trials found in literature, except Hammoudeh et al., 2017)**  
 NS : Not specified, GPP : gingivoperiostoplasty, pat. = patients, Nbr= number, M= months, y=years

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Article	U or B Clefts	Nbr of pat.	Pat. age	Type of investigated material	Control group	Imaging	Postop evaluation timing	Studied parameters	Rando- mized trial	Results	Tooth eruption	Comments
Pradel and Lauer, 2012	U + B	8	8-11 y.	Osteoblasts/ACS (n=4)	ICBG (n=4)	CBCT	6M	Cleft volume (CBCT preop), newly-formed bone volume	no	No difference between groups but poor residual newly-formed bone ratio ( 40.9% versus 36.6% for ICBG)	NS	
Du et al., 2017	U	20	8-16 y.	Bone marrow MSC (n=10)	ICBG (n=10)	TDM	6M	Ratio Newly-formed bone graft volume/ alveolar cleft volume	NS	No significant difference : 58% In both groups	NS	No description of cell preparation
Al-Ahmady et al., 2018	U	20	8-15y.	BMMSC + nanohydroxyapatite + PRF (n=10)	ICBG (n=10)	TDM and X-ray	12M	No real volumetric evaluation despite TDM but notion of bone union or not	yes	Bone bridge in 90% for substitute group vs 70% ICBG	NS	No real volumetric evaluation. No notion about postop.edema

*Table 3: Cell therapy substitutes (Summary of 3-D assessments trials found in literature)*