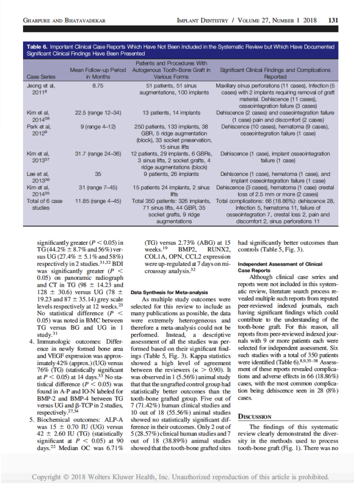

Case Series	Mean Follow-up Period in Months	Patients and Procedures With Autogenous Tooth-Bone Graft in Various Forms	Significant Clinical Findings and Complications Reported
Jeong et al, 2011[8]	8.75	51 patients, 51 sinus augmentations, 100 implants	Maxillary sinus perforations (11 cases), Infection (5 cases) with 2 implants requiring removal of graft material. Dehiscence (11 cases), osseointegration failure (3 cases)
Kim et al, 2014[38]	22.5 (range 12–34)	13 patients, 14 implants	Dehiscence (2 cases) and osseointegration failure (1 case) pain and discomfort (2 cases)
Park et al, 2012[9]	9 (range 4–12)	250 patients, 133 implants, 38 GBR, 5 ridge augmentation (block), 33 socket preservation, 15 sinus lifts	Dehiscence (10 cases), hematoma (9 cases), osseointegration failure (1 case)
Kim et al, 2013[37]	31.7 (range 24–36)	12 patients, 29 implants, 6 GBRs, 3 sinus lifts, 2 socket grafts, 4 ridge augmentations (block)	Dehiscence (1 case), implant osseointegration failure (1 case)
Lee et al, 2013[36]	35	9 patients, 26 implants	Dehiscence (1 case), hematoma (1 case), and implant osseointegration failure (1 case)
Kim et al, 2014[35]	31 (range 7–45)	15 patients 24 implants, 2 sinus lifts	Dehiscence (3 cases), hematoma (1 case) crestal loss of 2.5 mm or more (2 cases)
Total of 6 case studies	11.85 (range 4–45)	Total 350 patients: 326 implants, 71 sinus lifts, 44 GBR, 35 socket grafts, 9 ridge augmentations	Total complications: 66 (18.86%): dehiscence 28, infection 5, hematoma 11, failure of osseointegration 7, crestal loss 2, pain and discomfort 2, sinus perforations 11

Table 6. Important Clinical Case Reports Which Have Not Been Included in the Systematic Review but Which Have Documented Significant Clinical Findings Have Been Presented

significantly greater ($P < 0.05$) in TG (44.2% ± 8.7% and 56%) versus UG (27.4% ± 5.1% and 58%) respectively in 2 studies.[31,32] BDI was significantly greater ($P < 0.05$) on panoramic radiograph and CT in TG (98 ± 14.23 and 128 ± 30.6) versus UG (78 ± 19.23 and 87 ± 35.14) grey scale levels respectively at 12 weeks.[23] No statistical difference ($P < 0.05$) was noted in BMC between TG versus BG and UG in 1 study.[31]

4. Immunologic outcomes: Difference in newly formed bone area and VEGF expression was approximately 42% (approx.) (UG) versus 76% (TG) (statistically significant at $P < 0.05$) at 14 days.[33] No statistical difference ($P < 0.05$) was found in A-P and IO-N labeled for BMP-2 and BMP-4 between TG versus UG and β-TCP in 2 studies, respectively.[27,34]
5. Biochemical outcomes: ALP-A was 15 ± 0.70 IU (UG) versus 42 ± 2.60 IU (TG) (statistically significant at $P < 0.05$) at 90 days.[22] Median OC was 6.71% (TG) versus 2.73% (ABG) at 15 weeks.[19] BMP2, RUNX2, COL1A, OPN, CCL2 expression were up-regulated at 7 days on microassay analysis.[32]

Data Synthesis for Meta-analysis

As multiple study outcomes were selected for this review to include as many publications as possible, the data were extremely heterogeneous and therefore a meta-analysis could not be performed. Instead, a descriptive assessment of all the studies was performed based on their significant findings (Table 5, Fig. 3). Kappa statistics showed a high level of agreement between the reviewers (κ > 0.90). It was observed in 1 (5.56%) animal study that that the ungrafted control group had statistically better outcomes than the tooth-bone grafted group. Five out of 7 (71.42%) human clinical studies and 10 out of 18 (55.56%) animal studies showed no statistically significant difference in their outcomes. Only 2 out of 5 (28.57%) clinical human studies and 7 out of 18 (38.89%) animal studies showed that the tooth-bone grafted sites had significantly better outcomes than controls (Table 5, Fig. 3).

Independent Assessment of Clinical Case Reports

Although clinical case series and reports were not included in this systematic review, literature search process revealed multiple such reports from reputed peer-reviewed indexed journals, each having significant findings which could contribute to the understanding of the tooth-bone graft. For this reason, all reports from peer-reviewed indexed journals with 9 or more patients each were selected for independent assessment. Six such studies with a total of 350 patients were identified (Table 6).[8,9,35–38] Assessment of these reports revealed complications and adverse effects in 66 (18.86%) cases, with the most common complication being dehiscence seen in 28 (8%) cases.

Discussion

The findings of this systematic review clearly demonstrated the diversity in the methods used to process tooth-bone graft (Fig. 1). There was no

standardization in the source of procurement (autogenic, xenogenic or allogenic), treatment (materials used for demineralization and sterilization), composition (enamel, dentin, cementum, pulp) and graft dimensions (particle size). The absence of adequate uniformity and standardization in the processing of graft material not only makes comparison with other materials difficult but also undermines the clinical utility of the graft material.

Histological examination of the grafted sites from multiple studies revealed the formation of a dentin-bone complex, where tooth-bone graft was surrounded by newly forming bone.[19,24,25,28,29] The amount of time required for resorption of the graft varied considerably, and the histologic studies showed a characteristic picture of graft particles encased in newly formed bone. All studies failed to show complete resorption of the graft material and its replacement by newly formed bone. Another study in extraction sockets of dogs showed granular tissue with fibroblast cells and collagen fibers and sparse bone formation in the vicinity of the tooth-bone graft particles.[5] Thus, histologic analysis from the studies included in this review clearly demonstrated diverse findings without any clear evidence of complete resolution of the tooth-bone graft. The portion of residual tooth-bone graft ranged from 29.00% at 6 months[15] to 6.15% at 6 months.[6] However, this was not significantly different from bovine bone. With duration of studies ranging from 2 weeks to 6 months, it would be difficult to predict the actual remodeling time required for complete resorption of the graft particles. Lack of uniform resorption time affects the predictably of the material and poses obstacles in treatment planning, especially in cases where implants are needed to be placed at the grafted sites.

Many studies in this review compared tooth-bone graft with controls using their radiologic presentation.[23,30,31] Because the tooth-bone graft was made up of dentin and/or enamel, it appeared more radio-opaque and dense that the surrounding bone. Such comparisons of radio-opacities might not be good indicators to judge the clinical success of the graft material.

Four studies in this review assessed immunological, immunohistological, and biochemical outcomes such as vascular response.[33,34] expression of factors such BMP,[27,32] RUNX, and OPN.[32] These studies recorded the expression of the mentioned factors over 3 weeks. They provided significant insight in the initial period of bone healing at the tooth-bone grafted sites. The studies were designed to determine the osteogenic potential of the graft material in the initial phase only and could not assess the long-term clinical outcomes that are critical for success.

In the animal studies, multiple sites were utilized to assess the tooth-bone graft such as parietal bone,[21,30] femoral bone,[4,26] mandibular bone,[19,20,28,29] extraction sockets,[27,33] and the maxillary sinus.[25] The results from studies using distant sites such as femoral bone might be of lower significance as compared to others using intraoral sites due to differences in composition of bone, vascular supply, and healing.[39]

Among the 4 RCTs assessed in this study, one study clearly demonstrated that tooth-bone graft provided no added benefit in treatment of bone loss seen in periodontal defects.[11] This study provided substantial insight into the long-term clinical success of the material as the cases were followed up for a period of 12 months. In the study by Jun et al 2014, no significant difference was found between bovine bone and tooth-bone graft placed in maxillary sinus augmentation cases. The maxillary sinus, being a well-enclosed cavity, shows a high success rate for grafting procedures independent of the biomaterial used.[40] Thus, the grafting site also played a significant part in the clinical presentation of the tooth-bone graft in this study. The other 2 RCTs demonstrated satisfactory results when tooth-bone graft was compared to bovine graft[6] and beta-tricalcium phosphate graft and ungrafted sites.[7]

There were number of complications seen in the studies included in this systematic review. In the animal studies, premature exposure and separation of the mineralized block graft were noted in 9 tooth-bone grafted sites (28.3%) as compared to 2 autogenous bone controls,[19] 11 tooth-bone grafted sites (34.38%) as compared to 3 autogenous bone controls,[28] and 3 tooth-bone grafted sites (18.75%) as compared to 2 autogenous bone controls.[29] In these studies, a lack of primary implant stability was noted in 13.04% (3/23) sites,[19] 4.76% (1/21) sites,[28] and 15.38% (2/13) sites.[29] Additionally, the clinical cohort study[41] demonstrated wound dehiscence in 7 (12.96%) implants, failure of osseointegration in 4, hematoma in 1, and marginal bone loss greater than 1 mm at 1 year in 5 cases. Thus, a total number of complications of 17 (31.48%) was noted in 54 implants placed in 37 patients. In addition to the studies included in the systematic review, an independent assessment of case reports also demonstrated complications in 18.86% cases, with the most common complication being dehiscence seen in 8% cases (Table 6). All these studies clearly indicate that the tooth-bone graft is susceptible to exposure and dehiscence.

The risk of bias analysis demonstrated that only 50% of the clinical studies (Table 3) had a low risk of bias. The animal studies on the other hand demonstrated a high risk in 21.11% entries, an unclear risk in 15.56% entries, and a low risk in 63.33% entries (Table 4). Thus, based on this analysis, the likelihood that the reported findings had a potential bias in favor of the tooth-bone graft cannot be ruled out.

As per the distribution of the studies in this review based on the statistical comparison between tooth-bone graft and controls (Table 5, Fig. 3), 5 out of 7 (71.42%) human clinical studies and 10 out of 18 (55.56%) animal studies reported no significant difference in outcomes. Based on the assessment of the entire body of evidence on the subject, it can be clearly seen that the tooth-bone graft does not provide any additional benefit over other graft materials. Also, the lack of predictability in terms of resorption time and clinical success and the absence of standardized methods for processing limit the use of this material in clinical practice.

The findings of this systematic review clearly demonstrated the diversity in the methods used to process tooth-bone graft .There was no standardization in the source of procurement (autogenic, xenogenic or allogenic), treatment (materials used for demineralization and sterilization), composition (enamel, dentin, cementum, pulp) and graft dimensions (particle size). The absence of adequate uniformity and standardization in the processing of graft material not only makes comparison with other materials difficult but also undermines the clinical utility of the graft material

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