What is the Efficacy of Beta-tricalcium Phosphate as Graft Material in Periodontal Infra-bony Defects? Systematic Review and Meta-Analysis

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Abstract

Background: β-TCP is a synthetic grafting material (alloplasts)that can be used as allografts and xenografts in peridontal periodontal infra-bony defect. However, it is important to compare this material outcomes in such treatments when comparted to others Therefore, the aim of this review is to evaluate the effectiveness of β-TCP in the regeneration of periodontal infra-bony defect.

Methods: Three electronic databases (Cochrane, Pubmed, Embase) were searched up to March 2020. The inclusion criteria consist of regeneration of periodontal infra-bony defect via implementation of β-TCP in combination with other bone graft materials. Outcomes consisted of pocket depth reduction, clinical attachment level gain and bone fill.

Results: Five studies were included according to inclusion criteria. β-TCP found to be superior than debridement alone while it shown comparable result to other bone grafts materials in term of pocket depth reduction, clinical attachment level gain and bone fill. the outcomes of the regenerative procedures of periodontal infra-bony defect with the use of β-TCP in combination with other growth factors seems to be superior than alone.

Conclusion: β-TCP seems to be a promising material to be used in periodontal infra-bony defect regeneration. However, randomized clinical trials with larger sample size and more controlled study design are needed to support the findings.

Background

β-tricalcium phosphate (β-TCP) introduced in 1973 by Driskell [1] as a material to treat bone defects caused by trauma. Aminal studies proofed its uses in many fields in dentistry such as pulp capping and apixfication in endodontics [2] repair of cleft palates and orbital rim defects in maxillofacial surgery [3, 4] and repair of osseous lesions in periodontics [5]. β-TCP is a biocompatible [2, 4, 6] alloplastic bone grafting material that is resorbable with osteoconductive properties [7]. β-TCP was found to completely resorbed within a period of 0.5–1.5 year [8] when applied into various bony defects such as; intraosseous defect around natural teeth, edentulous defective alveolar ridges and maxillary sinuses [7, 9].

When grafted sites were histologically evaluated, β-TCP particles were found to be surrounded by and in intimate contact with osteoid. Furthermore, fragments of mature bone have been seen separate from the synthetic material with minimal trace of inflammation. These findings explained that β-TCP goes through complete resorption and replacement by mature bone in these. However, this process might take years to be completed [10]. Several attempts have been made to measure amount of mature bone formation with this grafting material within different periods of time. A histological study evaluating the re-osteointegration process of a bony defect around implants in the area of distal surface of 1st molar and mesial surface of 2nd molar, showed a bone gain of 1.90 mm and 1.41 mm around 1st and 2nd molars respectively [11].

Kishore et al. reported a mean bone fill of 3.6 mm and 4.4 mm with β-TCP alone after 6 and 9 months respectively [12]. When he combined β-TCP with membrane, the bone fill was 3.9 mm and 4.2 mm after 6 and 9 months respectively [13]. in a split mouth design study comparing β-TCP alone or in combination with PRP, found a linear bone fill with β-TCP alone to

Several studies utilizing the use of β-TCP alone or in combination with other grafting materials in several different surgical regenerative procedures, showed promising results of bone gain and new vital bone formation in a

comparable matter to other bone grafting materials such as allograft as well as xenografts [14–16]. On the other hand, other study reported an inferior outcome when β-TCP was compared others grafting materials [9]. It can be observed among literature that conflicting results as well as the lack of exact amount of bone fill in relation to different surgical regenerative procedures when using β-TCP. Therefor the aim of this systematic review is to evaluate the use of β-TCP alone or combined with other substitute for regeneration around natural teeth or implants.

Focused question

What is the difference in periodontal regenerative outcomes between grafts composed mainly of TCP and other grafting materials when used in guided tissue regeneration (GTR) of infra-bony defects around natural teeth?

Materials And Methods

Study design

A systematic review of studies focusing on the use of β-TCP in combination with other bone graft materials for regeneration of bone defect around natural teeth and implants. As currently recommended, we followed the PRISMA statements checklist for reporting a systematic review [17].

Registration

This systematic review protocol was specified in advance, registered with the International Prospective Register of Systematic Reviews (PROSPERO) on January 6, 2020.

Eligibility criteria for study inclusion

For the purpose of conducting a systematic review, we assessed all studies in which the primary objective was to evaluate the benefit of β-TCP combined with other bone graft in GTR around natural teeth and guided bone regeneration around implant. Randomized clinical trials, case series and case report were eligible for inclusion. Thereafter, the eligibility criteria (by applying the PICO framework):

Population:

Periodontal infra-bony defects (including 1,2, or 3 walls)

Intervention:

Graft material composed mainly of Tricalcium phosphate

Outcome:

- Primary—Probing depth reduction (PD reduction), clinical attachment level gain (CAL gain) and amount of bone fill (BF)

- Secondary— keratinized tissue width (KTW), gingival recession (GR), soft tissue thickness changes (Δ STT)

Search strategy

Comprehensive search strategies were established to identify studies for this systematic review. no language restrictions were applied. The MEDLINE (via PubMed), EMBASE and Cochrane databases were searched for papers published from 2019 and before based on the following search strategy prepared for MEDLINE: : (((((Periodontal regeneration) OR infra-bony defects) OR furcation defects) OR guided tissue regeneration) OR guided bone regeneration) OR bone augmentation))))) AND (((((((bone fill) OR periodontal pocket) OR clinical attachment level) OR keratinized tissue) OR bone regeneration) OR soft tissue regeneration) OR recession) OR furcation fill)))))))) ((Tri calcium phosphate) OR calcium phosphate) OR synthograft)

Assessment of validity

Two independent reviewers (A.S and F.S) screened the titles, abstracts and full tests of the papers that were identified. Disagreement between the reviewers was resolved through discussion and consensus was reached. Inter-reviewer agreement for the selection process was assessed by Cohen's Kappa score [18]. The reasons for excluding studies were recorded. Studies meeting the inclusion criteria underwent data extraction and validity assessment.

Data extraction

A pre-designed extraction forms were developed to assess the following data were extracted Author name(s), publication year and place, source of funding, conflict of interest, study design, sample size, follow-up period, source, selection and description of the study population (including age, gender, race and ethnicity, and presence and characteristics of gingival recession at baseline), definition and measurement method of the intervention, controls, and outcome, results and their variation, and risk of bias.

Data synthesis

The data were organized into evidence tables according to PRISMA guidelines [17] and a descriptive summary was created to determine study characteristics, study quality, and results. Descriptive statistical analysis according to the mean values was used to evaluate the outcomes (Table 1).

Table 1
Qualitative description of included studies

Name of author	Country	Population	Intervention	Follow up	Comparison	Outcomes
Strub et al. [19]	Switzerland	Patients: 8 Age: 28-55 years Gender: 5 M, 3F Bony defects: 47 Defect Type: 1,2, 3 walls defects or horizontal bone loss. Pre-surgical Preparation: - OHI* - SRP* - Occlusal adjustment - splinting - Re-evaluation after 4-6 weeks Antibiotic use: 4 m/IU Oral Penicillin 1 day pre-surgery	TCP* Form: TCP was mixed with sterile distilled water (38.5% powder to 61.5% water) to form a paste	12 months	Frozen allogenic graft	Primary outcomes: · PD* reduction (TCP): 1.8mm (allograft): 2.0mm · Re-entry BF* (TCP): 1.2mm (allograft): 1.5mm Secondary outcomes: . Radiographic BF (TCP): 1.05mm (allograft): 0.9mm . Residual pocket deeper than 3 mm (TCP): 38% (allograft): 22%
Snyder et al. [9]	USA	Patients:10 Age: unknown Gender: unknown	TCP Form:	18 months	None	Primary outcomes:

		Bony defects:10 Defect type:1 or 2 walls, furcation areas Pre-surgical Preparation: - Initial phase therapy - Occlusal analysis - Antibiotics: Tetracycline 250mg tablets, q.i.d 10 days post-surgery	die-pressed to form discs 2 inches in diameter x 1/8-inch thick and fired at 2000°F for 2 hours. The discs were then crushed in an alumina mortar and pestle, with the resulting powder being sieved to recover the 200/+325 mesh size fraction.			· PD reduction: 3.6mm · CAL* gain: 1.2mm · Re-entry BF: 2.8mm
Zafiropoulos et al. [20]	Germany	Patient: 64 Age: 30-71years Gender: 31M,34F Smoking status: 28 S *, 37NS* Bony defects: 93 Defect type: 2 or 3 walls. Pre-surgical Preparation: - Non-surgical therapy - Re-evaluation Antibiotics: Diclofenac, 100 mg per day for 4 days, started 1 day pre-surgery	HA/b-TCP+ASB * Form: *Bone Ceramic:* HA and ß-TCP (60/40%)#	12 months	1- ASB* ASB +BDX*	Primary outcomes: · CAL gain: (HA/b-TCP+ASB): 3.2 mm (ASB): 3.4mm (BDX): 3.2mm · Re-entry BF: (HA/b-TCP+ASB): 1.6 mm (ASB): 2.8mm (BDX): 1.5mm Secondary outcomes: · BOP* redcution:

						(HA/b-TCP+ASB): 13.8 % (ASB): 14.7% (BDX): 20.0% · PLI* reduction: (HA/b-TCP+ASB): 27.6% (ASB): 26.5% (BDX): 30.0% · RBG* percentage: (HA/b-TCP+ASB): 82.3% (ASB): 69.3% (BDX): 83.3%
Rajesh et al. [21]	India	Patient: 60 Age: 20-45 years Gender: Not mentioned Bony defects: 60 Defect Types:2 or 3 walls Pre-surgical Preparation: - OHI* - SRP* - Occlusal adjustment - Re-evaluation after 4 weeks	CPC Form: Chitra Calcium Phosphate Cement in the form cement	months	1-Debritment only (Deb) 2-Hydroxyapatite cement granules (HA)	Primary outcomes · PD reduction: (CPC): 6.20mm (HA): 4.05mm (Deb): 2.95mm · CAL gain: (CPC): 5.80mm (HA): 3.55mm

		Antibiotics: Doxycycline 100mg, BID for the 1st day followed by 100mg OD for 5 days				(Deb): 2.30mm Secondary outcome · GR* reduction: (CPC): 0.15mm (HA): 0.15mm (Deb): 0.20mm
Sukumar et al. [22]	Czech Republic	Patient: 21 Age: 21-53years Gender: 8M, 13F Smoking status: 7 S, NS Bony defects: 39 Defect Types: 2 or 3 walls Pre-surgical Preparation: OHI* SRP* Elimination of local factor Occlusal adjustment Re-evaluation after 2 weeks	TCP/ $CaSO_4$* Form: Composite material consisted of β-TCP + calcium sulphate	12 months	None	Primary outcomes: · PD reduction: (TCP/ $CaSO_4$): 1.98mm · CAL gain: (TCP/ $CaSO_4$): 1.68mm Secondary outcomes: · GR reduction: (TCP/ $CaSO_4$): 0.31mm

	Antibiotics: Amoxi-Amoxacillin 250 mg with clavulanic acid 125 mg or clarithromycin 500 mg) were prescribed to the patients for 7–14 days

Quality and risk of bias assessment

The methodological quality of the trials included was assessed and recorded into tables according to PRISMA, focusing on the following points: 1. Method of randomization (e.g. the method used to generate the randomization sequence): (i) adequate, when random number tables, tossed coin or shuffled cards were used; (ii) inadequate, when other methods were used, such as alternate assignment, hospital number or odd/even date of birth; and (iii) unclear, when the method of randomization was not reported or explained. 2. Allocation concealment (e.g. how the randomization sequence was concealed from the examiners): (i) adequate, when examiners were kept unaware of the randomization sequence (e.g. by means of central randomization or opaque envelopes); (ii) inadequate, when other methods were used, such as alternate assignment or hospital number; and (iii) unclear, when the method was not reported or explained. 3. Blindness of examiners with regard to the treatment procedures used in the study period was assessed. 4. Completeness of the follow up was based on the following question: Was the number of subjects at baseline and at completion of the follow-up period reported. In addition, the presence of explanations (reasons) for dropouts was checked. Studies that did not report completeness of the follow up were not included. 5. Similarity between groups at baseline. 6. Assessment of any analysis done to control confounding factors that can affect the final outcomes (Table 2). The risk of bias was graded as low, high, or unclear for each domain based on the criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0

Table 2
Risk of bias assessment of included studies

Authors/year	Randomization	Blinding	Incomplete outcome data	Selective outcome reporting	Similarity of groups at baseline	Control of confounding and interaction	Conflict of interest
Strub et al. [19]	NO	NO	NO	NO	Yes, split mouth design	NO	None
Snyder et al. [9]	NO	NO	NO	NO	N/A	NO	None
Zafiropoulos et al. [20]	NO	Yes, single blinding	Yes, CAL gain	NO	No	NO	None
Rajesh et al. [21]	Yes, Random number table method	NO	NO	NO	No	NO	Yes, the study was supported by graft material company*
Sukumar et al. [22]	NO	NO	NO	NO	N/A	NO	None
*Sree Chitra Tirunal Institute for Medical Sciences and Technology							

Quantitative analysis

The Meta- analysis was done for the three variables (PD-reduction, CAL gain and Bone Fill). As these variables are quantitative (continuous), mean and standard deviation were used to describe these variables. The Standardized mean difference (SMD) was used as a summary pooled statistic where the pooled effect of 0.2= small, 0.5= medium & 0.8 and above as large effect was considered. Student's t-test for single sample was used to the statistical significance of SMD. Cochran's Q was used to identify the heterogeneity in the pooled data and also I^2 to observe the percentage of total variation across the studies included in the meta- analysis. A cut-off values of I^2 > 50% was used to rule out the higher levels of unexplained variability in the effect sizes. The pooled estimates were obtained by using the fixed effect and random effect models. A p-value of ≤ 0.05 and 95% confidence intervals were used to report the statistical significance and precision of estimates. Graphical presentation of results was shown using Forest plots (overall effect using both fixed and random effect models) for the studies included in the meta-analysis. The analysis was carried out using MedCalc for windows version 15.0 (MedCalc Software, Ostend, Belgium).

Results

Reviewers agreement and kappa score

Electronic searches yielded 74 articles of which 10 were selected for full-text evaluation after screening their titles and abstracts. 5 articles were further excluded, and reasons are listed in Fig. 1. The k value for inter-reviewer agreement for potentially relevant articles was 0.91 for full- text article reviewing, indicating a "almost perfect" agreement between the 2 reviewers.

Study design and patient features

Five studies were included as shown in Table 1. The studies published between 1979–2010, in the following countries Switzerland, USA, German, India, and Czech Republic. Four of them were prospective studies [9,19-21] while one was retrospective [22]. One study used split mouth design compared between β-TCP vs allograft [19]. 171 was the total number of participants included in the studies [9,19-22]. Age of participant ranged from 20 to 71 years old. The total number of treated sites were 254. Type of bone defects varied between; 1-wall, 2-wall, or 3-wall defect. In regards to gender, it was not specified in two studies [9,21], while the remaining three studies gave a total number of female was 50 and the male was 44 [19,20,22]. Smoking status of the participants was not defined [9,19,21]. Zafiropoulos study defined smoking status as participant who smokes 10 cigarettes or more as smoker, while participants who smokes less than 10 cigarettes as non-smokers. number of smokers in his study was 28 smokers while the non-smokers was 37. However they did not considered the smoking status during data analysis and the two groups were pooled together giving a justification that the total sample size was small and moreover the number of smokers participants were small [20]. Sukumar study mentioned that 7 out of his participants were medium smokers, however they did not give a clear definition for smoking status. the Follow up period was 12 months in 3 of the studies, 18 months in one study and not applicable in one [22].

Pre- surgical preparation

In Strub's study, they considered cause-related phase which comprise of oral hygiene instructions, scaling and root planning, occlusal adjustment, splinting, and re-evaluation after 4-6 weeks [19]. While in Snyder's trial, initial phase therapy and occlusal analysis were conducted [9]. Zafiropoulos's study, initial phase therapy and re-evaluation [20]. Furthermore, In Rajesh et al, oral hygiene instructions, scaling and root planning, occlusal adjustment and re-evaluation after 4 weeks were performed [21]. Similarly, Sukumar's study, oral hygiene instructions, scaling and root planning, elimination of local factor, occlusal adjustment and re-evaluation after 2 weeks [22].

Comparison groups

Three studies compare different types of bone grafts used to fill the defects. Strub et al. compared TCP powder to frozen allogenic bone [19]. Zafiropoulos study, compared between autogenous spongiosa (ASB) alone, ASB combined with HA/ B-TCP or ASB combined with BDX [20]. Finally, Rajesh compared calcium phosphate cement versus hydroxyapatite cement and used debridement alone as a control group [21].

Types of Intervention

Strub et al. used β-TCP mixed with sterile distilled water with ratio of 38.5% powder to 61.5% water giving a form of paste [19]. Snyder et al. convert TCP to powder form by specific preparation [9]. Zafiropoulos et al. consume biphasic calcium phosphate (which is a mixture of 60% HA and 40% of β-TCP) mixed with autogenous spongiosa bone graft in particulate form [20]. Rajesh et al. utilized a Chitra calcium phosphate cement as intervention in a butty form [21]. Sukumar et al. the intervention group composed of β-TCP with calcium sulphate [22]. The material placed in a butty form (based on the manufacturer instruction).

Surgical approach

In Strub et al. study, a small palatal full thickness flap was initiated followed by. granulation tissue removal from the bony defect with root planning. Bleeding was induced in the defect area followed by placement of β-TCP/frozen allogenic graft [19]. In Snyder et al. trial, an internal bevel incision with buccal and lingual full thickness flap were initiated. Bone defects were debrided with root planning. Then intra-marrow penetration was performed and grafting Tricalcium phosphate cement was placed [9]. Intrasulcular incision with full thickness flap were performed along with vertical incision was implemented when needed. Granulation tissues were removed and root planning. Roots surfaces adjacent to the defect were conditioned with tetracycline suspension (100 mg/per mL). all autogenous bone graft materials were harvested from the retromolar area. autogenous spongiosa alone (ASB), ASB mixed with bovine derived zenograft or ASB mixed synthetic composite (β-TCP + HA) were placed. Augmented areas were covered with collagen membrane [20]. Rajesh et al. performed an intrasulcular incision with full thickness flap. defect areas were debrided, and root planning was done. Roots surfaces adjacent to the defect were conditioned with tetracycline suspension (100mg/per mL) bone graft materials were placed [21].

Finally, Sukumar et al initiated cervicular incision with facial and lingual full thickness flap and vertical incision as needed. Root debridement and granulation tissues removal was followed. Root surface conditioning was done using 2.5 % tetracycline HCl, then TCP/ $CaSO_4$ was packed into defects [22].

Although the systematic review covered a large period of time the surgical procedures were almost the same as illustrated from the included studies.

Antibiotic use

For those studies that used pre-surgical antibiotic protocols, Strub et al. prescribed Penicillin 4 million IU orally one day before the surgery [19]. Zafiropoulos et al. started the use one day before the surgery chlorhexidine 0.1% [20]. Furthermore, Strub et al. chlorhexidine 0.2% mouth wash twice a day for two weeks [19]. Snyder et al. tetracycline tablets 250 mg 4 times a day for 10 days [9]. Zafiropoulos et al. chlorhexidine 0.1% twice a day for 3 weeks [20]. Rajesh et al. doxycycline 100mg twice a day for the 1^{st} day followed by 100 mg once a day for 5 days and chlorhexidine 0.2% mouth wash [21]. Sukumar et al. Augmentin 375 mg or Clarithromycin 500 mg for 7-14 days. After 2 weeks hydrogen peroxide 3% were applied during sutures removal. Listerine mouth wash for 2 weeks [22].

Post-operative management

In Strub et al. trial, periodontal dressing and cyanoacrylate tissue adhesive were placed [19]. While in Snyder et al. trial, only periodontal dressing was placed [9]. Zafiropoulos et al. oral diclofenac 100mg per day for 4 days [20]. Rajesh et al. non-eugenol periodontal dressing was placed for one week and Ibuprofen 400mg t.i.d for 3 days [21].

Risk of bias assessment

The result of the bias assessment of the included studies are presented in Table 2. All studies overall obtained a low score in quality analysis (Fig. 2). Randomization and conflict of interest were reported in Rajesh et al. study [21]. Single blinding and incomplete outcome data were present in Zafiropoulos et al. study [20]. Details regarding to groups similarity at baseline was not mentioned in Snyder et al. [9] and Sukumar et al. [22] studies.

Outcome measured:

A) Primary outcomes:

1- PD reduction:

Strub et al. when compared between frozen allogenic graft versus TCP powder found a net change of 2 mm for the allogenic graft with an average of 22% pocket deeper than 3mm while in the TCP group net change found to be 1.8mm with 38% as an average of pocket deeper than 3mm [19]. Snyder et al. reported a 3.6mm of pocket depth reduction for the TCP treatment with no other group to compare [9]. As for Rajesh et al. pocket depth reduction for the CPC, HA, and debridement alone found to be 6.2 mm, 4.05 mm, and 2.95 respectively [21]. Sukumar et al. reported 1.98mm pocket depth reduction for TCP with no comparison group [22].

2- CAL gain:

Snyder et al. found a net gain of 1.2 mm for the TCP with no comparison [9]. Zafiropoulos et al. found than the net gain of CAL for the three groups HA/b-TCP + ASB, ASB alone and ASB + BDX to be 3.2 mm, 3.4 mm and 3.2 mm, respectively. However, the former did not compare CAL results between the three groups [20]. Sukumar et al. net CAL gain of 1.68 mm for the TCP with no comparison [22].

3- BF:

Strub et al. at the re-entry found 1.2mm gain for the TCP treated site while for the allogenic group found to be 1.5 mm [19]. Zafiropoulos et al. reported a gain of 1.6 mm for HA/b-TCP + ASB, 2.8 mm for ASB alone and 1.5 mm for ASB + BDX [20].

B) Secondary outcomes:

1- GR reduction

Rajesh et al. found gingival recession reduction to be 0.15 mm for CPC, 0.15 mm for HA and 0.2 mm for debridement group [21]. Sukumar et al. reported 0.31mm increase of the gingiva recession for the TCP group with no comparison [22].

Meta-analysis results

A) 2 walls Infra-bony defects:

For one of the outcome variables “PD reduction”, the statistical significance was assessed by combining the difference in its mean values which were extracted from 2 studies [19,21] which were compared between two groups. The results show statistically significant difference favoring β-TCP in the values of standardized mean difference

(SMD) by fixed effect but not by random effect criteria. (t=3.730, p=0.001; t=1.844, p=0.075). The Cochran's Q value is not statistically significant (Q=3.707, p=0.0542) and I^2 value (73.02%) is higher, but not statistically significant, which implies no heterogeneity in the 2 studies which included in the analysis. Hence, the pooled SMD by fixed effect was used to infer significant difference in the mean values of PD reduction between the two groups (SMD =1.555, t=3.730, p=0.001). The overall effect (1.555) is a large effect (Table 3). The corresponding forest plot for PD reduction shows the effect size of each of the two studies and combined effect size by fixed and random effects models (Fig. 3A).

For another outcome variable "CAL gain", the results show statistically significant difference favoring β-TCP as well in the values of standardized mean difference (SMD) by fixed effect but not by random effect criteria. (t=2.119, p=0.042; t=0.617, p=0.542). The Cochran's Q value is statistically significant (Q=9.499, p=0.002) and I^2 value (89.47%) is higher, and statistically significant, which implies heterogeneity in the 2 studies which included in the analysis. Hence, the pooled SMD by random effect was used to infer no significant difference in the mean values of CAL gain between the two groups (SMD =0.734, t=0.617, p=0.542). The overall effect (0.734) is a medium effect (Table 3). The corresponding forest plot for CAL gain shows the effect size of each of the two studies and combined effect size by fixed and random effects models (Fig. 3B).

For the third outcome variable "Bone Fill", the results show statistically significant difference toward control groups (allograft and autograft) and in the values of standardized mean difference (SMD) by both the fixed effect and random effect criteria. (t=2.673, p=0.013; t=2.673, p=0.013). The Cochran's Q value is not statistically significant (Q=0.2425, p=0.622) and I^2 value (0.00%) which implies no heterogeneity in the 2 studies which included in the analysis. Hence, the pooled SMD by fixed effect was used to infer significant difference in the mean values of Bone Fill between the two groups (SMD =1.189, t=2.673, p=0.013). The overall effect (1.189) is a large effect (Table 3). The corresponding forest plot for Bone Fill shows the effect size of each of the two studies and combined effect size by fixed and random effects models (Fig. 3C; Table 3).

Table 3
Meta-analysis of PD-reduction, CAL-gain & Bone-Fill variables related to 2-wall intra-bony defects

PD-reduction	**Group1**			**Group2**			**SMD**	**95% CI**	
Study	Total	Mean	SD	Total	Mean	SD			
Strub et al. [19]	10	1.9	0.5	3	1.5	0.8	0.657	-0.720,2.034	
Rajesh et al. [21]	10	6.2	1.1	10	4.3	0.27	2.272	1.097,3.446	
Overall effect								Weight (%)	
Fixed effects: Total N=33; SMD=1.555(95% CI: 0.705,2.405); t=3.730; p=0.001								Fixed	Random
Random effects: Total N=33; SMD=1.489(95% CI: -0.158,3.135); t=1.844; p=0.075								44.40	48.49
Test for heterogeneity: Q=3.707; p=0.0542; I^2=73.02% (95% CI:0.00, 93.93%)								55.60	51.51
CAL-gain	Group1			Group2			SMD	95% CI	
Study	Total	Mean	SD	Total	Mean	SD			
Rajesh et al. [21]	10	5.6	1.2	10	3.3	1.1	0.524	0.812, 3.015	
Zafiropoulos et al. [20]	4	4.0	0.8	9	4.4	0.8	-0.465	-1.711,0.781	
Overall effect								Weight (%)	
Fixed effects: Total N=33; SMD=0.815 (95% CI:0.031,1.60); t-value=2.119; p=0.042								Fixed	Random
Random effects: Total N=33; SMD=0.734 (95% CI: -1.692,3.159); t-value=0.617; p=0.542								53.83	50.40
Test for heterogeneity: Q=9.499; p= 0.002; I^2= 89.47% (95% CI:60.84, 97.17%)								46.17	49.60
Bone Fill	Group1			Group2			SMD	95% CI	
Study	Total	Mean	SD	Total	Mean	SD			
Strub et al. [19]	10	1.2	0.6	3	2.4	1.3	0.674	-2.922,0.045	
Zafiropoulos et al. [20]	4	6.5	1.7	9	7.7	0.8	0.592	-2.30,0.306	
Overall effect								Weight (%)	
Fixed effects: Total N=26; SMD= -1.189(95% CI: -2.107, -0.271); t-value=-2.673; p=0.013								Fixed	Random
Random effects: Total N: 26; SMD=- 1.189(95% CI: -2.107, -0.271); t-value=-2.673; p=0.013								43.55	43.55
Test for heterogeneity: Q=0.2425; p=0.622; I^2= 0.00% (95% CI:0.00,0.00)								56.45	56.45

B) 3-walls Infra-bony defects:

For the outcome variable “PD reduction”, the results showed not statistically significant difference in the values of standardized mean difference (SMD) by both fixed effect and random effect criteria. (t=0.744, p=0.464; t=0.322, p=0.750). The Cochran’s Q value is not statistically significant (Q=1.873, p=0.171) and I^2 value (46.61%) is low, and not statistically significant, which implies no heterogeneity in the 2 studies which included in the analysis. Hence, the pooled SMD by fixed effect was used to infer no significant difference in the mean values of PD reduction between the two groups (SMD =0.273, t=0.744, p=0.464). The overall effect (0.273) is a low effect (Table 4). The

corresponding forest plot for PD reduction shows the effect size of each of the two studies and combined effect size by fixed and random effects models (Fig. 4A).

For the outcome variable “CAL gain”, the results show statistically significant difference favoring β-TCP in the values of standardized mean difference (SMD) by fixed effect but not by random effect criteria. (t=2.206, p=0.031; t=1.376, p=0.173). The Cochran’s Q value is not statistically significant (Q=3.636, p=0.056) and I^2 value (72.50%) is higher, but not statistically significant, which implies no heterogeneity in the 2 studies which included in the analysis. Hence, the pooled SMD by fixed effect was used to indicate the significant difference in the mean values of CAL gain between the two groups (SMD =0.532, t=2.206, p=0.031). The overall effect (0.532) is a medium effect (Table 4). The corresponding forest plot for CAL gain shows the effect size of each of the two studies and combined effect size by fixed and random effects models (Fig. 4B).

For the outcome variable “Bone Fill”, the results show statistically significant difference toward β-TCP in the values of standardized mean difference (SMD) by only fixed effect and not significant be random effect criteria (t=3.388, p=0.001; t=0.057, p=0.955). The Cochran’s Q value is highly statistically significant (Q=12.50, p=0.0004) and I^2 value (92.00%) which implies high heterogeneity in the 2 studies which included in the analysis. Hence, the pooled SMD by random effect was used to infer no statistically significant difference in the mean values of Bone Fill between the two groups (SMD =0.088, t=0.057, p=0.955). The overall effect (0.088) is a low effect (Table 4). The corresponding forest plot for Bone Fill shows the effect size of each of the two studies and combined effect size by fixed and random effects models (Fig. 4C; Table 4).

Table 4
Meta-analysis of PD-reduction, CAL-gain & Bone-Fill variables related to 3-walls Infra-bony defects

PD-reduction	**Group1**			**Group2**			**SMD**	**95% CI**	
Study	Total	Mean	SD	Total	Mean	SD			
Strub et al. [19]	3	1.9	0.6	3	1.5	0.7	0.667	-1.361,2.340	
Rajesh et al. [21]	10	3.5	1.2	10	4.5	1.9	0.439	-1.524,0.319	
Overall effect								Weight (%)	
Fixed effects: Total N=26; SMD=-0.273(95% CI: -1.029,0.484); t=-0.744; p=0.464								Fixed	Random
Random effects: Total N=26; SMD=-0.172(95% CI: -1.274,0.930); t=-0.322; p=0.750								30.22	39.44
Test for heterogeneity: Q=1.873; p=0.171; I^2=46.61% (95% CI: 0.00, 0.00%)								69.78	60.56
CAL-gain	Group1			Group2			SMD	95% CI	
Study	Total	Mean	SD	Total	Mean	SD			
Rajesh et al. [21]	10	5.9	1.2	10	3.8	1.8	1.315	0.315,2.315	
Zafiropoulos et al. [20]	25	4.7	0.8	25	4.5	0.7	0.262	-0.300,0.824	
Overall effect								Weight (%)	
Fixed effects: Total N=35; SMD=0.532 (95% CI:0.051,1.013); t-value=2.206; p=0.031								Fixed	Random
Random effects: Total N=35; SMD=0.718(95% CI: -0.323,1.759); t-value=1.376; p=0.173								25.65	43.30
Test for heterogeneity: Q=3.636; p= 0.056; I^2= 72.50% (95% CI: 0.00, 93.81%)								74.35	56.70
Bone Fill	Group1			Group2			SMD	95% CI	
Study	Total	Mean	SD	Total	Mean	SD			
Strub et al. [19]	3	1.2	0.5	3	2.4	0.6	-1.734	-4.015,0.547	
Zafiropoulos et al. [20]	25	7.7	0.9	25	6.3	1.1	1.371	0.747,1.995	
Overall effect								Weight (%)	
Fixed effects: Total N=56; SMD= 0.983(95% CI:0.401,1.565) ; t-value=3.388; p=0.001								Fixed	Random
Random effects: Total N: 56; SMD=- 0.088(95% CI: -3.195,3.019); t-value=-0.057; p=0.955								12.49	47.00
Test for heterogeneity: Q=12.500; p=0.0004; I^2= 92.00% (95% CI: 72.42,97.68%)								87.51	53.00

Discussion

The present review was conducted to evaluate the periodontal regenerative outcomes of β-TCP alloplast use and compare findings with other bone substitutes used to treat infra-bony defects. To the best of the author's knowledge, this is considered the first systematic review focusing on the comparing β-TCP alloplast to other regenerative materials. Among an extensive literature search, very few studies were found in relation to this alloplastic material. Only five studies have been included in this systematic review, furthermore three of those had been classified with low risk heterogeneity and were involved in meta-analysis. Overall β-TCP showed favorably result over debridement alone. However, using it alone or in combination with other bone substitutes showed comparable outcome to other

bone grafts. Furthermore, Meta-analysis revealed that in regards to two wall defects, a statistical significant difference was shown in the PD reduction, CAL gain favoring the use of β-TCP, while the same was not presented with BF .When the same was measured in three walls defects, no statistical significant difference was revealed in PD reduction for both random and fixed effect models. While, CAL gain and BF showed statistically significant difference in the fixed effect model favoring the use of β-TCP. Overall amount of PPD, CAL and BF was still inferior to well recognized autogenous and allografts [23]. Reynold et al. found that the amount bone fill showed similar result between alloplast and allograft [23]. However, in other systematic review done in 2015 by Sculean reported that the amount of bone fill of using of autograft, allograft, Xenograft and alloplast is comparable between all bone substitute materials except for alloplast which revealed inferior result than the others [24]. Similar results were reported in another systematic review by Calin et al.; When looking into β-TCP alone group, comparable results were reported to the present findings in terms of showing of amount gain PPD reduction & CAL gain and the same of having BF amount less shown. On the other hand, they reported that when growth factor was added to β-TCP with growth factors it gave superior outcomes that can be comparable to autogenous and allogenous grafts [25].

Furthermore, it was worthwhile comparing the present outcomes of B-TCP with another well documented alloplast which is Hydroxyapatite (HA). A systematic review focuses on whether HA has significant clinical effect on periodontal bony defect regeneration remains unclear. It showed no significant difference between the use of HA and open flap debridement. However, when the HA combined with β-TCP gave a better result [26].

Overall, it can be noticed that although autograft and allograft showed superior results in term of regeneration especially with more challenging defects such two wall-defects due to being less predictable and need more demand to approach successful regenerative outcomes. β-TCP can be considered as a promising alternative regenerative material in such situation where optimum grafts cannot be used due to unavailability or cost issues.

Furthermore, it is possible to enhance β-TCP grafts materials outcomes when combined with either alloplast or growth factors to reach similar outcomes to autografts and allografts [23–26].

Several limitations had been observed in this systematic review including small number of included studies, and no randomized clinical trials was found. Sample size of the included studies was small as well.

Conclusion

Based on the present systematic review, β-TCP is a valid alternative bone substitute material when it used alone for the treatment of periodontal infra-bony defect and it is result can be improved with the addition of growth factors or other alloplastic materials. Further randomized controlled trials are recommended focusing to β-TCP to confirm findings.

Abbreviations

β-TCP, β-tricalcium phosphate

GTR, guided tissue regeneration

PD, Probing depth

CAL, clinical attachment level

KTW, keratinized tissue width

GR, gingival recession

STT, soft tissue thickness

SMD, Standardized mean difference

ASB, autogenous spongiosa

HA, Hydroxyapatite

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

R.J. initiated the aim and idea for present study, F.S. and A. S. had conducted the data searching process, data extraction and table constructions as well risk of bias assessment. Meta-analysis was performed by R.J. and final manuscript write up and revision was done among all authors in an equal manner.

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Not applicable

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Figures

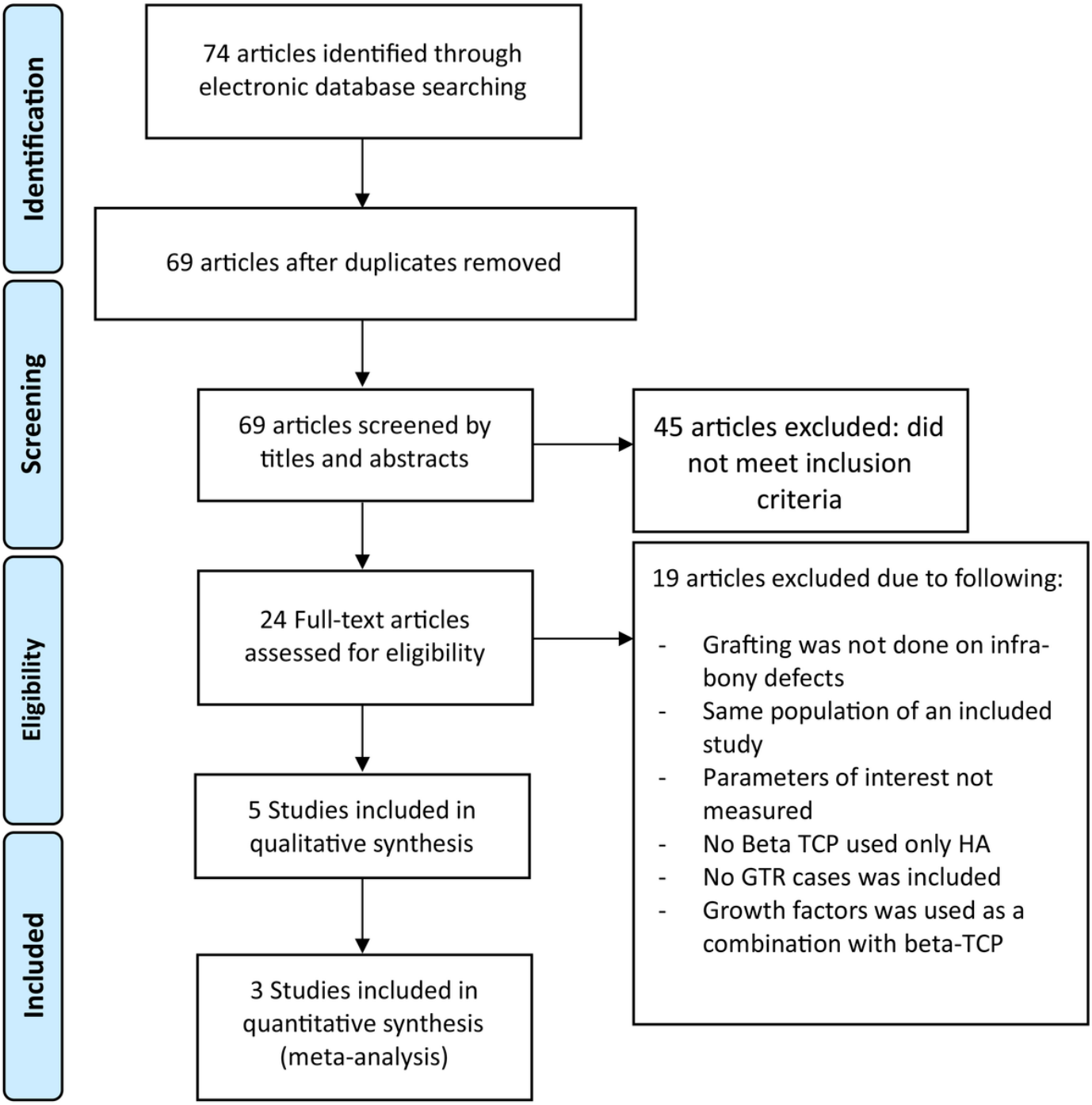

Figure 1

PRISMA Flow Diagram

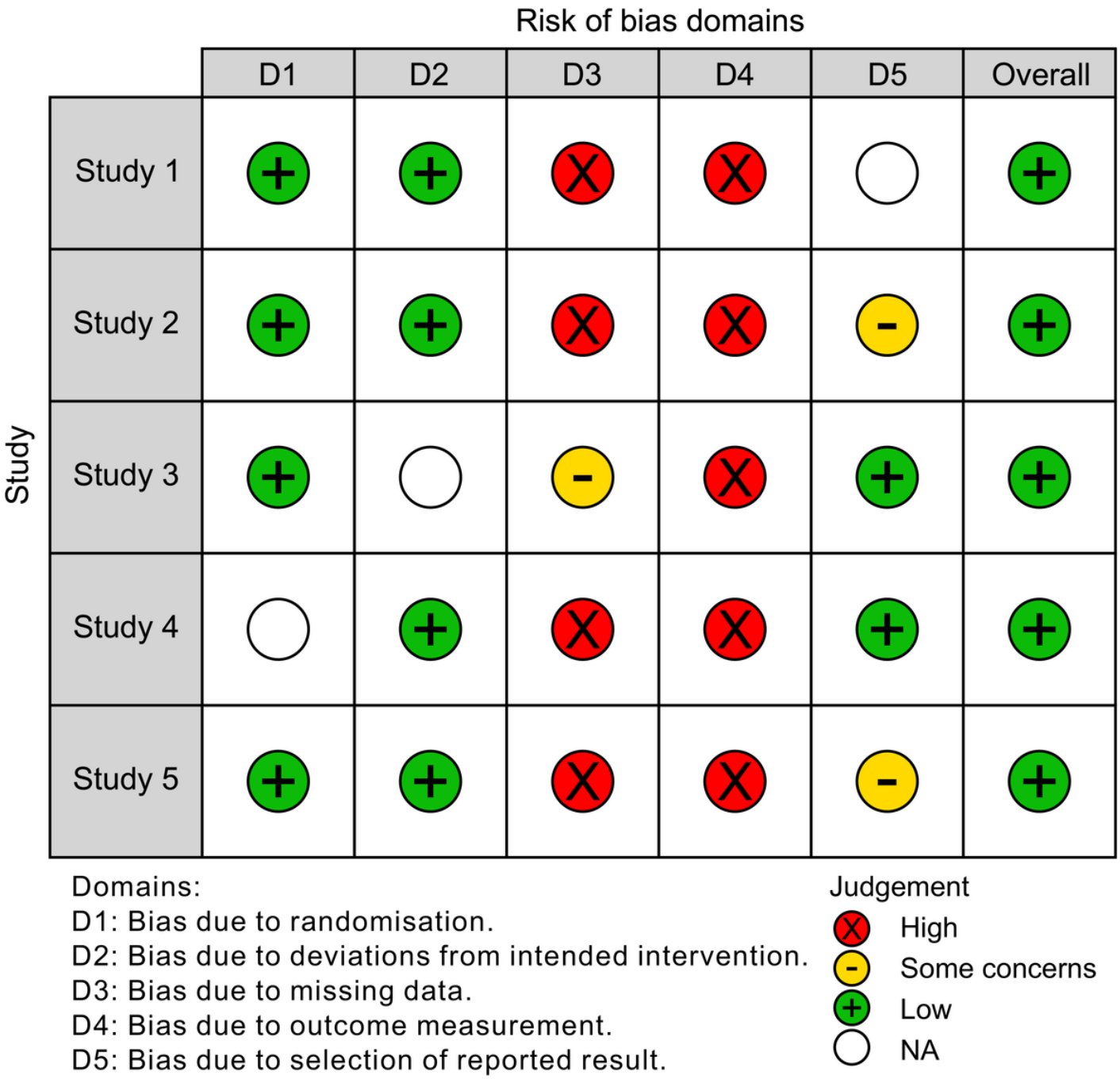

Figure 2

Risk of bias assessment (Traffic Light Plot). Overall, all the included studies showed low risk of bias

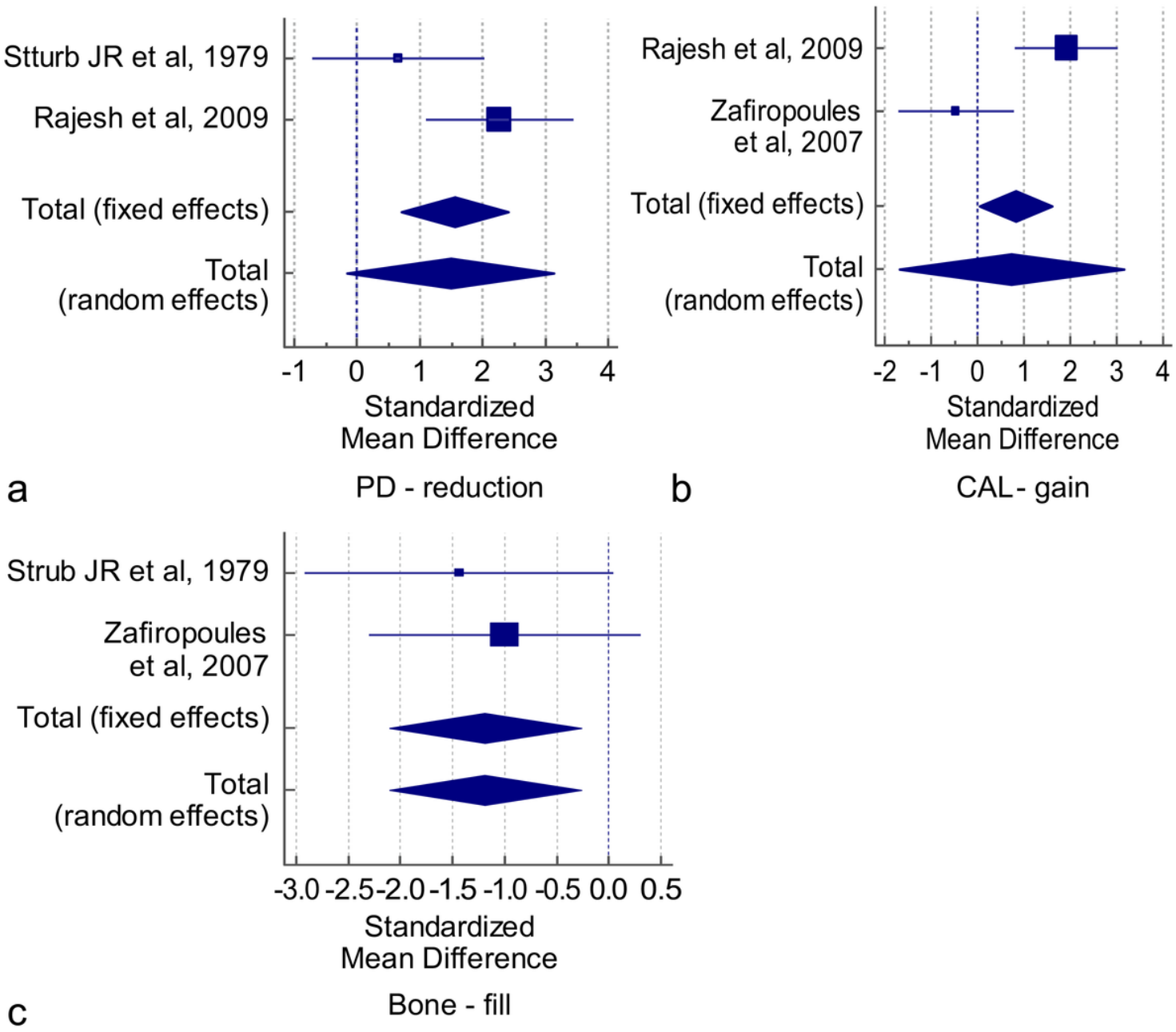

Figure 3

Forest plot for primary outcome variables for 2-walls infra-bony defects (A) PD-reduction, (B)CAL-gain, (C) Bone-fill

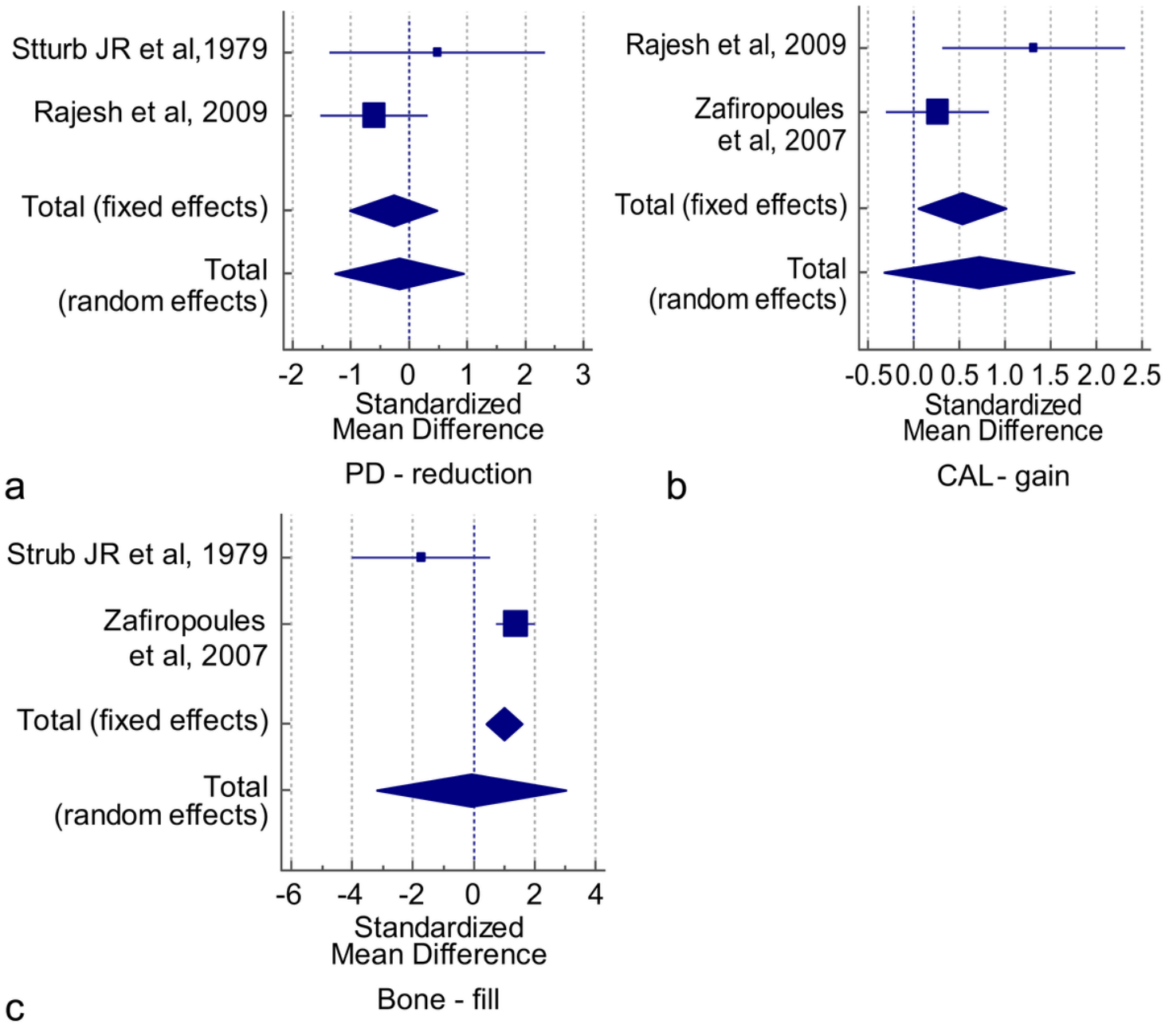

Figure 4

Forest plot for primary outcome variables of 3 walls infra-bony walls defects

Supplementary Files

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- PRISMAchecklist16.9.2020.doc