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LITERATURE REVIEW:

Efficacy of Bone Marrow Aspirates in Bone Regeneration Compared to Conventional Bone Grafts- A Systematic Review

Eficacia de los aspirados de médula ósea en la regeneración ósea en comparación con los Injertos óseos convencionales: una revisión sistemática

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ABSTRACT: The search for a superior bone graft substitute compared to the gold standard of harvesting autogenous bone grafts has plagued dentists for decades. With the advent of tissue engineering, the search has been aimed at bone graft substitutes with osteogenic potential and osteoinductive and osteoconductive properties. Bone Marrow Aspirates (BMAs) have evolved as a potential adjunct to conventional bone grafts that can substantially enhance the bone regeneration potential of these materials. This systematic review aims to explore and assess the literature on the efficacy of bone marrow aspirates in new bone formation. An electronic search of PubMed, Web of Science, and Scopus databases was conducted to identify articles that evaluated the efficacy of bone marrow aspirates for new bone formation, published until September 2022, and a supplementary manual search of references from these articles was also conducted. Case reports, case series, commentaries, letters to the editor, narrative or systematic reviews, and articles in languages other than English were excluded from consideration. The articles were assessed against the ROB-II tool for Randomised Controlled Trials (RCTs) for risk of bias assessment. GRADE assessment based on the Cochrane Handbook for quality assessment and a summary of findings table were used to present the results. In a comprehensive electronic search of 150 articles from the three databases, seven studies assessed new bone formation in healthy partially edentulous patients who underwent bone regeneration with bone marrow aspirates compared to conventional bone grafts - autogenous harvested bone, allogenic, and alloplastic substitutes.

This review concludes that adding bone marrow aspirates results in comparable results to bone graft alone. The results must be interpreted cautiously owing to their 'low quality' GRADE assessment. Future research with a greater sample size, homogenous populations, and comparable digital imaging and software may provide results that can be aptly applied to broader populations.

KEYWORDS: Bone grafts; Bone marrow aspirates; Bone regeneration; New bone formation, Osteogenic potential; Osteoinductive properties; Osteoconductive properties.

RESUMEN: La búsqueda de un sustituto de injerto óseo superior al método de referencia, la obtención de injertos óseos autógenos, ha sido una preocupación para los dentistas durante décadas. Con el advenimiento de la ingeniería de tejidos, la búsqueda se ha centrado en sustitutos de injerto óseo con potencial osteogénico y propiedades osteoinductoras y osteoconductoras. Los aspirados de médula ósea (AMO) se han convertido en un posible complemento a los injertos óseos convencionales, que pueden mejorar sustancialmente el potencial de regeneración ósea de estos materiales. Esta revisión sistemática tiene como objetivo evaluar la literatura sobre la eficacia de los AMO en la neoformación ósea. Se realizó una búsqueda electrónica en las bases de datos PubMed, Web of Science y Scopus para identificar artículos publicados hasta septiembre de 2022. Se excluyeron los informes de casos, las series de casos, los comentarios, las cartas al editor, las revisiones narrativas o sistemáticas y los artículos en idiomas distintos del inglés. Los artículos se evaluaron con la herramienta ROB-II para ensayos controlados aleatorizados (ECA) para la evaluación del riesgo de sesgo. Para presentar los resultados, se utilizó la evaluación GRADE basada en el Manual Cochrane para la evaluación de la calidad y una tabla de resumen de hallazgos. En una búsqueda electrónica exhaustiva de 150 artículos de las tres bases de datos, siete estudios evaluaron la neoformación ósea en pacientes sanos parcialmente edéntulos sometidos a regeneración ósea con aspirados de médula ósea, en comparación con injertos óseos convencionales. Esta revisión concluye que la adición de aspirados de médula ósea produce resultados comparables a los del injerto óseo solo. Los resultados deben interpretarse con cautela debido a su baja calidad en la evaluación GRADE. Investigaciones futuras podrían proporcionar resultados que se puedan aplicar adecuadamente a poblaciones más amplias.

PALABRAS CLAVE: Injertos óseos; Aspirados de médula ósea; Regeneración ósea; Formación de hueso nuevo; Potencial osteogénico; Propiedades osteoinductoras; Propiedades osteoconductoras.

INTRODUCTION

Bone grafts have been an integral part of regenerative dentistry for centuries. They have found a multitude of applications, including but not limited to the reconstruction of bony defects due to trauma, infections, neoplasia, ridge preservation, vertical and horizontal augmentation of resorbed alveolar ridges, and sinus floor augmentations (1). Current statistics propose that about 2.2 million bone graft procedures, with an annual market of 664 million dollars, are being performed globally. The trend, as mentioned above, seems to grow exponentially at the rate of 13 percent annually (2). Autogenous bone grafts have been regarded as the gold standard for bone regeneration in dentistry. Autogenous graft materials, with their excellent osteogenic potential in addition to their osteoinductive and osteoconductive characteristics, have reported high success rates (3). The outcome of autologous grafting depends on numerous factors, such as the defect size or recipient site volume,

and may also influence the donor site selection. For instance, a minor defect may be reconstructed with intraoral autogenous chips, blocks, or cortical shields harvested from the chin and ramus. In contrast, a large defect requiring two-dimensional augmentation may require a considerable amount of graft material and may necessitate extra-oral graft harvesting via iliac crest, rib, or calvaria (4). Researchers have been in pursuit of a comparable, if not superior, bone graft substitute to overcome the shortcomings of harvesting autogenous bone grafts (5).

With the advancement in technology and the advent of tissue engineering, research has been directed at stem cells and progenitor cells in bone regeneration. A growing body corroborates the enhanced bone regeneration following treatment with bone marrow-derived Mesenchymal Stem Cells (MSCs) in conjunction with bone substitutes for bone regeneration and osseointegration of implants (1, 6, 7).

Bone Marrow Aspirate Concentrates (BMACs) are biological derivatives obtained from the bone marrow that have proven efficacious and may be clinically more applicable than culture-grown mesenchymal stem cells. Freshly obtained bone marrow is subjected to density gradient centrifugation to harvest these BMACs, without any additional *in vitro* culturing. The preparation process takes approximately 20-30 minutes, thus making intra-operative harvesting and delivery viable and practical (8). BMACs are superior to MSCs for two reasons. Firstly, they do not contain any foreign serum or growth factors. Secondly, in addition to MSCs, they comprise pro-regenerative growth factors such as osteoprotegrin (9, 10).

The present systematic review aims to explore and analyze the literature on the efficacy of bone marrow aspirates in new bone formation.

METHODOLOGY

SEARCH STRATEGY

The present systematic review was conducted following the PRISMA guidelines (11). The review was conducted with the focused question, "Can bone marrow aspirates enhance bone regeneration compared to conventional bone grafts alone?"

The following Boolean strategy was used to carry out a methodical search: (“bone marrow”[MeSH Terms] OR “bone marrow” OR marrow) AND (aspirate OR aspirated OR aspirates OR aspirating OR aspiration) AND (“dental health services”[MeSH Terms] OR dentistry) AND (regenerate OR regenerated OR regenerating OR regeneration[MeSH Terms]).

Both the all-fields search ALL=(bone marrow aspirates dental regeneration) and an extra simplified search string, bone AND marrow AND aspirates AND dental AND regeneration, were utilised.

INCLUSION CRITERIA

Population (P): Patients undergoing bone regeneration
Intervention (I): Bone marrow aspirates
Control (C): Conventional Bone grafts
Outcome (O): New bone formation
Studies (S): Human clinical trials, prospective studies

EXCLUSION CRITERIA

Letters to the editor, commentaries, and reviews, including narrative and systematic reviews, case reports, and case series were excluded from the present systematic review. Articles in languages other than English were excluded.

A comprehensive electronic search was performed to identify articles published until September 2022 across three databases, inclu-

ding PubMed, Scopus, and Web of Science. Table 1 enlists the keywords used to perform the search across the databases.

SELECTION OF STUDIES

The articles obtained from the database search were screened to eliminate duplicates. Two reviewers independently conducted the primary screening of the articles based on titles and abstracts. Full-text records were obtained of the articles that cleared the primary screening. Two reviewers vetted the full-text records independently to screen articles that met the inclusion criteria. A manual search of the bibliography of included articles was performed to supplement the electronic search to incorporate articles that were undiscovered on the electronic search. Disagreements were resolved through discussion with a third reviewer until a consensus was reached. Studies that met the PICOS criteria were subjected to data extraction and validity assessment.

DATA COLLECTION

Data extraction was carried out by two reviewers independently, and a third reviewer corroborated the data for accuracy. Details of the studies, including author, year, country of origin, sample size, intervention and control groups, outcome assessment, results, and inferences, were noted onto a customized template (Microsoft Word, Microsoft Inc, Redwood, CA, USA).

QUALITY ASSESSMENT

The quality of the studies included in the present systematic review was assessed by two reviewers independently based on the Cochrane Handbook for Systematic Reviews for Interventions (12). The studies were evaluated against the ROB-II tool for Randomised Control Trials (RCTs). ROB-2 is a modified tool that assesses the validity of the RCTs based on five specific domains. The domains included were bias in the randomization process, deviation from intended intervention, missing outcome, variable outcome measures, and selective reporting. Each response was evaluated as 'low,' 'high,' or 'some concern' (13). Disagreements were resolved by discussion with a third reviewer until a consensus was reached. Agreement between the two reviewers was assessed using kappa statistics.

QUALITY OF EVIDENCE FOR OUTCOMES IN THE SUMMARY OF FINDINGS TABLE

Each outcome in the summary of findings table was assessed based on the recommendations mentioned in the Cochrane Handbook for Systematic Reviews for Interventions (12, 14). The GRADE system was applied by one reviewer, and the ratings were applied after a discussion with the other two reviewers. After a consensus was reached among the three review members, the final ratings were applied. To begin with, each outcome for RCTs was graded as 'high' quality. The evidence rating was subsequently downgraded by one level based on five parameters, i.e., the risk of bias, indirectness of evidence, imprecision of results, inconsistent results, and publication bias.

RESULTS

A total of 150 articles were identified on an electronic search of the three aforementioned databases. Following the removal of duplicates, the remaining 100 articles were screened based on titles and abstracts. The 18 articles that cleared primary screening were subjected to full-text analysis to determine their eligibility. Seven studies that met the PICOS criteria were included in the present systematic review (15-21). Figure 1 shows the PRISMA flow diagram for the same.

CHARACTERISTICS OF INCLUDED STUDIES

All articles included in the present systematic review were human randomized trials that examined 101 patients across seven studies (15-21). The studies were predominantly conducted across Europe and Central America (Brazil (16, 18-20), Austria (15, 17), and Germany (21)). The studies included healthy, partially edentulous patients with ridge deficiencies or extraction sockets undergoing bone regeneration procedures, older than 18 years of age. Five studies out of seven were conducted on sinus augmentation procedures, (15, 17, 18, 20, 21), while one study was conducted on horizontal augmentation (16) and the other on extraction sockets (19). Table 1 summarises the characteristics of the studies included in the present systematic review.

CHARACTERISTICS OF INTERVENTIONS

The studies included in the present systematic review consisted of a test group that received bone marrow aspirates along with conventional bone graft materials. In the majority of the studies, the bone marrow aspirates were obtained from the iliac crest (15, 16, 18-21), except for the study by Payer *et al.*, in which tibial bone marrow aspirates were obtained (17). The bone marrow was collected from the patients under sedation through a puncture 2cm laterocaudally from the posterior-superior aspect of the iliac crest with an 11-gauge needle (15, 16, 18-21). The tibial bone marrow aspirates were harvested through a stitch incision at the proximal medial aspect of the condyle of the tibia with a bone marrow biopsy needle (17). Heparin was added to the bone marrow aspirates to prevent coagulation. De Oliviera *et al.*, in their study, assessed the difference in bone regeneration potential that occurs due to differences in the centrifugation process. The study had two test groups: single centrifugation group (SCG) and double centrifugation group (DCG) (18). For the control group, three out of seven studies treated the patients with xenogenic bovine bone mineral (Bio-oss, Geistlich Materials, Wolhusen, Switzerland). While one study treated the patients with allogenous block bone grafts that were adapted and fixed to the defects with titanium screws (Kopp Dental Industry Products) (16), another study used bovine bone mineral in conjunction with autogenous bone graft (21). One study applied Platelet Rich Fibrin (PRF) harvested from blood obtained from the antecubital vein (19).

CHARACTERISTICS OF OUTCOME MEASURES

All studies in the present systematic review examined new bone formation as the primary outcome. The studies evaluated the percentage of mineralized tissue on histomorphometric analysis. The specimen obtained after the biopsy was stained in Haematoxylin and Eosin dye (H&E staining) in three studies, while the remaining studies employed Azur II Pararosanilin (15, 21), Mason-trichome (20), and Levai-Lackzo staining, respectively (17). The photographs of the specimen were subsequently subjected to histomorphometric analysis to measure the quantity of mineralized and non-mineralized tissue following digitization with a digital camera and computer software. Areas of new bone formation were identified by excluding old pristine bone from overlapping images of the mineralized tissue in the specimen. DaCosta *et al*. also examined the tomographic parameters at baseline and six months post-operatively (16). While the study by Fontes *et al*. evaluated the immunohistochemical reaction for the expression of RUNX2 and osteocalcin (19), Payer *et al*. applied commercial monoclonal antibodies for further cell characterization (FACS analysis) and differentiation assays (osteogenic and adipogenic differentiation) using flow cytometric analysis (17). The authors further evaluated the osseointegration of implants based on the Periotest values and radiographic examination (17).

CHARACTERISTICS OF OUTCOMES

Four out of seven studies included in the present systematic review reported a null effect for the test and control groups. The studies reported no significant difference in the outcomes when bone grafts were used, irrespective of the addition of bone marrow aspirates (15, 17, 18, 21). The results were corroborated by the study conducted by Rickert *et al*., which evaluated the efficacy of the combination of a bovine bone matrix (Bioss) and bone marrow aspirates (BMAs) in comparison to the bovine bone matrix (Bioss 70%) and autologous bone (30%) (22). Three studies differed in their judgment and reported significant enhancement with the adjunctive use of bone marrow aspirates in mineralized tissue formation (16, 19, 20). Histomorphometric analysis was used in all seven trials to assess bone formation. When compared to the corresponding control groups, the results demonstrated varying effects of bone marrow aspirates (BMA) on bone development. With a mean bone growth of 4.60±1.43, the test group in the Costa *et al*. trial demonstrated a considerable improvement in bone regeneration, outperforming the comparison group (16). Histomorphometric analysis revealed a statistically significant increase in mineralised tissue in the test group (55.15±20.91%) compared to the control group in the Pasquali *et al*. study (19). In comparison to the control group, the test group showed noticeably more bone increase (54.20±4.31%), demonstrating the beneficial impact of bone marrow aspirates on bone formation (20). Four studies found no statistically significant difference in bone development between the bone marrow aspirate-treated locations and their corresponding control groups, even though they used the same histomorphometric techniques. In these investigations, the regeneration results were similar for both groups (15, 17, 18, 21). The volume of autogenous bone or bovine bone matrix used in conjunction with the bone marrow aspirates was not specified in most of the studies. Inconsistency in the volume of the graft material may have also skewed the results. The disparity in the outcomes may be attributed to the lack of standardization in the surgical approach and the healing time, i.e., the time elapsed between healing and a precocious second intervention in the form of reopening of the wound for biopsy sampling (8, 20). The discrepancy in the digitization of images and the software used for the analysis may also have inadvertently impacted the outcome of the studies.

SUMMARY OF THE ADVERSE EFFECTS RELATED TO BONE MARROW ASPIRATES

Although the side effects of bone marrow aspirates (BMA) in bone regeneration are usually minor and self-limiting, they should nevertheless be recognised. The most frequent consequence is donor-site morbidity, which usually manifests as temporary discomfort, oedema, or bruising near the iliac crest. Haematoma formation, superficial infection, and transient sensory abnormalities are less common consequences (24). Compared to conventional autologous bone graft harvesting, rare but more significant events like deep infec-

tion, nerve damage, or excessive bleeding occur at lower rates. When compared to traditional bone transplant operations, the safety profile of BMA is generally regarded as favourable, with far fewer donor-site problems (24-26).

RISK OF BIAS

The present review utilized the ROB-II tool, as shown in Figure 2, for the assessment of the risk of bias for the included studies. Six out of seven studies were evaluated to have a 'high risk of bias (15-18, 20, 21), while one study was evaluated to have a serious concern regarding the risk of bias (19). The assessment was mainly due to considerable deficiencies in the randomization process and the assessment and reporting of the outcomes in most of the studies. One study reported significant patient dropout and had to be eliminated from evaluation due to late implant placement, leading to inadvertent attrition bias (21). Since the studies showed serious concerns in one or more critical domains, they were judged to have an overall high risk of bias.

QUALITY OF THE EVIDENCE

The present systematic review included seven articles involving 101 patients. The quality of evidence for bone gain was 'low' as per the GRADE assessment. The quality of evidence was downgraded by one level to reflect the high risk of bias primarily due to inadequacies in the randomization process, attrition bias, and the assessment and reporting of the outcomes in the included studies. The majority of the studies in the present review reported a null effect for the primary outcome, which further jeopardized the quality of the evidence. Table 2 depicts the summary of findings using the GRADE system.

Table 1. Summary of characteristics of the included studies.

Author and Year	Sample Size	Study Design	Intervention	Control	Time of Outcome measurement	Outcome Assessment	Conclusion	Inference
Costa *et al.* (2010)(16)	10 patients	Control group: 5 (allogenic block graft); Test group: 5 (allogenic block graft impregnated with autologous Illiac BM Aspirate)	Block graft + Illiac Crest Bone Marrow Aspirates	Block graft	Six months post-surgery, tomographic examination was carried out	New bone formation as percentage area on histomorphometric and tomographic analysis	The test group showed statistically significant bone gain of 4.60±1.43 mm ($p<0.05$)	Bone marrow aspirates can increase the regeneration potential of bone grafts.
Sauerbier *et al.* (2011)(21)	26 patients, 45 sites	Control group: 11 patients, 11 sites; Test group: 25 patients, 34 sites (partial crossover design)	Block graft + Illiac Crest Bone Marrow Aspirates	Bio-Oss+ Autogenous bone	An early time point was selected following a healing phase that lasted only three to four months	New bone formation as percentage area on histomorphometric analysis	No significant difference was seen in new bone formation ($p=0.333$). The test group showed 14.3±1.8 and control group showed 12.6±1.7% new bone formation	Bone marrow aspirates may not significantly increase the regeneration potential of bone grafts
Payer *et al.* (2013)(17)	6 patients; 12 sites	Split mouth study: Control group: 6 sites; Test group: 6 sites	Bio-Oss + Tibial Bone Marrow Aspirates	Bio-Oss	Histomorphometric analysis of biopsies taken from the enhanced sites three and six months after implantation	New bone formation as percentage area on histomorphometric analysis	No significant difference was seen in new bone formation ($p=0.535$). At three months, test group showed 10.36±11.83 and control group showed 9.45±4.15% new bone formation	Bone marrow aspirates may not significantly increase the regeneration potential of bone grafts
Wildburger *et al.* (2013)(15)	7 patients; 14 sites	Split mouth study: Control group: 7 sites; Test group: 7 sites	Bio-Oss + Illiac Crest Bone Marrow Aspirates	Bio-Oss	After 3 and6 months, biopsies were performed	New bone formation as percentage area on histomorphometric analysis	No significant difference was seen in new bone formation ($p=0.535$). At three months, test group showed 11.8 % and control group showed 7.4% new bone formation	Bone marrow aspirates may not significantly increase the regeneration potential of bone grafts

Author and Year	Sample Size	Study Design	Intervention	Control	Time of Outcome measurement	Outcome Assessment	Conclusion	Inference
Pasquali *et al.* (2015)(20)	16 patients	Control group:8; Test group:8	Bio-Oss + Illiac Crest Bone Marrow Aspirates	Bio-Oss	Bone biopsies were taken 6 months following the grafting surgeries	New bone formation as percentage area of mineralized tissue on histomorphometric analysis	The test group showed statistically significant vital bone formation of (55.15±20.91 %) compared to control group (27.30±5.55 %) ($p<0.05$)	Bone marrow aspirates can increase the regeneration potential of bone grafts
Oliviera *et al.* (2016)(18)	21 patients	Control:7, Test1:7; Test2:7	Test 1: Xenogenous Bone Graft+ single centrifugation Illiac crest BMAC; Test 2: Xenogenous Bone Graft+ Double centrifugation Illiac crest BMAC	Bio-Oss	6 months after the grafting procedures, bone samples were performed	New bone formation as percentage area of mineralized tissue on histomorphometric analysis	Comparable amount of new bone formation was seen in all three groups i.e. Single Centrifugation Group (SCG) 47.87±6.31, Double Centrifugation Group (DCG) 45.73±7.33, Control Group 49.90±7.64. The differences were not statistically significant ($p>0.05$)	Bone marrow aspirates may not significantly increase the regeneration potential of bone grafts
Fontes *et al.* (2020)(19)	15 patients	Control group: 5 (Spontaneous healing); Test 1: 5 (PRF); Test 2: 5 (PRF+ BMAC)	PRF+ BM Aspirate Concentrate from Illiac crest	PRF	Bone biopsy specimens were collected 6 months following the grafting surgeries.	New bone formation as percentage area of mineralized tissue on histomorphometric analysis	The test group showed statistically significant bone gain of 54.20±4.31 % ($p=0.0283$) compared to control group 40.60±5.98 % ($p=0.0090$)	Bone marrow aspirates can increase the regeneration potential of bone grafts

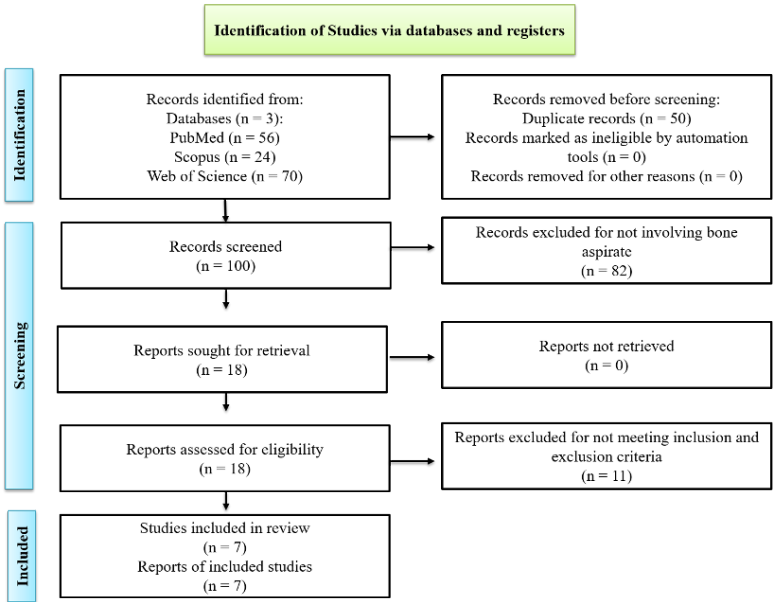

Figure 1. PRISMA flow chart.

Table 2. Summary of the findings table.

	Quality Assessment					Summary of findings		
Outcome	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**No of participants (Studies)**	**Certainty of evidence (GRADE)**
New bone formation	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	Our confidence in the effect estimate is limited	101 (7)	Low

[a]Most of the studies showed serious concern due to the lack of a clear randomization process, assessment, and reporting of the outcome.
[b]Four out of seven studies showed a null effect for the outcome.

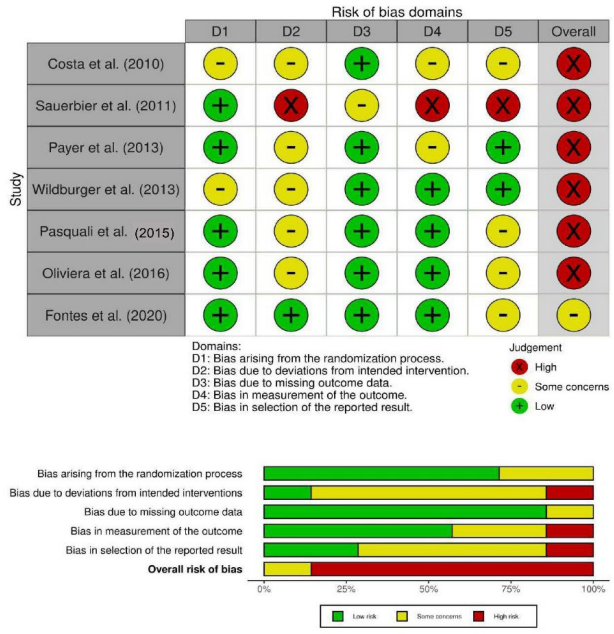

Figure 2. Summary of the risk of bias assessment.

DISCUSSION

Autogenous bone grafts are regarded as the gold standard for bone regeneration procedures in dentistry. The process of harvesting autogenous bone grafts involves a second surgical site. The morbidity and risk of complications associated with the harvesting of autogenous bone grafts significantly impact their utility (5). The use of bone graft substitutes was proposed to elude these complications. Despite their excellent osteoconductive and osteoinductive properties, allogenic grafts lack osteogenic potential (24, 25). Over the last decade, studies in the field of tissue engineering aimed at bone marrow stromal cells and their potential to create an osteogenic environment have been garnering interest (26, 27). A growing body of evidence suggests that bone marrow aspirate concentrates (BMACs) are a viable biological product for bone regeneration that contains pro-regenerative growth factors, including Platelet-derived Growth Factor (PDGF), Osteoprotegerin (OPG), Vascular-Endothelial Growth Factor (VEGF), aside from Mesenchymal Stem Cells (MSCs) (9, 10). The present systematic review evaluates the evidence for the efficacy addition of bone marrow aspirates for new bone formation in patients undergoing bone regeneration compared to bone grafts alone. The results from this systematic review are based on the seven articles that include randomized controlled trials. All the studies included in this review examined the extent of new bone formation in partially or completely edentulous patients with and without the use of bone marrow aspirates.

The majority of the studies included in this review reported that both treatment modalities show a similar new bone formation, irrespective of the addition of bone marrow aspirate concentrates (BMACs). The results were corroborated by a systematic review of the efficacy of chairside bone marrow aspirate concentrates on implant site development. The authors concluded that although favorable outcomes were reported, the addition of chairside harvested bone marrow aspirate concentrates did not significantly and predictably increase new bone formation compared to the control group (28). Studies have reported a reduced rate of postoperative bone graft resorption with the use of bone marrow aspirates in conjunction with corticocancellous iliac crest bone graft (1).

The majority of the studies included in the review obtained Bone Marrow Aspirates (BMAs) from the posterior iliac crest (15, 16, 18, 19), except one in which tibial BMAs were obtained (17). The difference in the site from which the BMAs were harvested could have impacted the outcome of the studies. Takemoto *et al.*, in their clinical trial, analyzed the mRNA levels of Bone Morphogenetic Proteins (BMPs) and their receptors in BMAs harvested from three sites-iliac crest, proximal humerus, and proximal tibia (29). The authors reported no statistically significant differences among the groups and concluded that the proximal tibia and femur are viable sites for harvesting BMAs. Contrarily, Bulgin *et al.* suggested that the difference in the clinical outcomes may arise due to the complex process

of bone tissue healing and may not be assessed by mRNA levels alone. Although the exact mechanism of BMAs on tissue regeneration could not be clarified, the authors proposed a significant role of both cellular components and growth factors released from the BMAs in the outcome (30).

OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

All the studies included in the present systematic review were human clinical studies. All seven studies included in the review reported on new bone formation. However, none of the studies reported on patient-related outcomes of pain and discomfort. Patient choices could be affected by the effectiveness, safety, and morbidity associated with the intervention. Future studies should include this as an important outcome to be examined, as this information can augment the applicability of bone marrow aspirates for bone regeneration.

There was a discrepancy in the site and approach for the bone marrow aspiration. The digitization of images and the software used for the analysis also varied across the studies. The non-standardization of the surgical procedure, the postoperative sample processing, and the digital platform for the analysis may have significantly influenced the results, giving rise to the disparity in the outcome across the studies.

QUALITY OF EVIDENCE

The evidence consisted of seven studies, with a majority of them showing a significant risk of bias primarily due to inadequacies in the randomization process, measurement, and reporting of outcomes. Some studies lacked relevant information regarding the randomization procedure or had concerns regarding the blinding of assessors. A majority of the studies reported a null effect on the efficacy of bone marrow aspirates in new bone formation. Therefore, there was a significant imprecision in the quality of evidence owing to the disparity in the primary outcomes of the studies included in the present systematic review.

The quality of the evidence for the primary outcome, i.e., new bone formation, was low based on the GRADE assessment. This limits our confidence in the effect estimates, suggesting that the true estimate and effect estimate may vary considerably. A high risk of bias due to lack of randomization and blinding of assessors may skew the intervention effect and is the primary reason for a low assessment of the available evidence. Three studies out of seven reported a null impact on new bone formation (primary treatment outcome). This suggests an imprecision in the certainty of the effect of treatment that cannot be explained. For the reasons mentioned above, the quality of evidence for the present systematic review was assessed as 'low.' Overall, the methodological flaws within the studies lead to significant bias.

The present review derives its strength from a comprehensive electronic search of three databases supplemented by a manual search of the bibliography of included articles to identify relevant articles. Three reviewers adhered to a well-planned inclusion criterion for ascertaining the eligibility of the studies included in the present review. The review was conducted following the Cochrane Handbook for Systematic Reviews for Interventions, and the evidence was assessed for its quality.

Despite the author's best efforts, the present systematic review is not without its limitations. The review included articles published originally in English, as articles translated into English may lack veracity. This may have inadvertently resulted in publication bias. The studies included in the review had inadequacies in their randomization process and failed to satisfactorily explain the blinding of assessors and measurement of the outcomes. The studies used a range of digital imaging tools and computer software for the assessment of new bone

formation. The dissimilarity in the software may have contributed to the inconsistency in the outcomes. The patient population was eclectic, with a wide age group, and the interventions varied in the site and collection of bone marrow aspirates.

Further research with a larger sample size, a homogenous patient population, and analogous computer software for evaluating the outcomes is warranted to precisely assess the effect of adjunctive bone marrow aspirates with conventional bone grafts in new bone formation.

CONCLUSION

Based on the limited available evidence, the supplementation of conventional bone grafts with bone marrow aspirates may not significantly enhance their regeneration potential. The evidence offered in the present systematic review must be interpreted with caution owing to its 'low' quality. The limitations in the review warrant future research with a greater sample size to accurately estimate the effect of bone marrow aspirates on new bone formation.

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