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Systematic Review

Regenerating Alveolar Bone for Implant Placement: The Efficacy of Autogenous Mineralized Dentin Matrix—A Systematic Review and Meta-Analysis

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Abstract: The preservation of the alveolar ridge has gained increasing importance for various types of rehabilitation, including dental implant placement. Consequently, researchers have explored different bone grafts, such as mineralized dentin matrix grafts. However, a comprehensive review of the efficacy of autogenous mineralized dentin (AMD) for alveolar ridge preservation remains lacking. In this review, we evaluated the efficacy of AMD as a method for alveolar ridge preservation in cases of delayed implant placement. A comprehensive search through PubMed, Google Scholar, Cochrane Library, and B-on repositories was conducted without time constraints up to July 2024 to identify peer-reviewed human studies. These studies assessed the percentage of newly formed bone and residual graft following bone regeneration with AMD grafts after tooth extraction, specifically in the context of delayed implant placement. Our analysis included four selected studies involving 55 patients and 67 sockets. The findings suggest that AMD grafts resulted in an average (and 95% confidence interval) of 43.8% [36.6%, 50.8%] newly formed bone, and delayed implant placement was a feasible surgical option for all patients. Although the available literature is scarce, AMD grafting has yielded promising outcomes as a method for bone reconstruction. Nevertheless, additional randomized controlled trials with larger sample sizes and longer follow-ups are required to substantiate these findings.

Keywords: mineralized dentin matrix; dentin graft; dental implants; alveolar ridge preservation

Citation: Meném, M.; Santos, A.; Mascarenhas, P. Regenerating Alveolar Bone for Implant Placement: The Efficacy of Autogenous Mineralized Dentin Matrix—A Systematic Review and Meta-Analysis. *Appl. Sci.* **2024**, *14*, 10018. https://doi.org/10.3390/app142110018

Academic Editor: Mario Taba Jr.

Received: 24 September 2024
Revised: 22 October 2024
Accepted: 29 October 2024
Published: 2 November 2024

1. Introduction

1.1. Dental Extraction

Tooth extraction is among dentistry's most frequently performed procedures [1]. The healing process following a tooth extraction is typically divided into four sequential yet overlapping phases: (1) hemostasis and coagulation, (2) inflammation, (3) proliferation, and (4) modeling/remodeling [2,3]. The first phase, hemostasis and coagulation, begins immediately after the tooth is extracted. Blood fills the extraction socket, leading to the formation of blood clots [3,4]. This clot is essential for initiating the subsequent phases of healing. The second phase, inflammation, starts approximately 48 to 72 h post-extraction. During this phase, inflammatory cells, including neutrophils, macrophages, and lymphocytes, migrate into the area in response to cytokines and growth factors released by platelets in the clot [2,3,5]. Within seven days, granulation tissue, rich in blood vessels, connective tissue, fibroblasts, and inflammatory cells, infiltrates the socket and completely replaces the clot [3–6]. The third phase, proliferation, is subdivided into two stages: fibroplasia and the formation of woven bone [3]. This stage is marked by an intense migration of fibroblasts, which leads to an increase in collagen synthesis and the production of extracellular matrix proteins [2]. At the periphery of the alveolus, connective tissue matures, and osteoblasts and osteogenic fibers form, contributing to the formation of osteoid tissue at the base of the socket [5,6]. Non-calcified bone spicules become identifiable by day seven, and immature bone forms within two weeks post-extraction. This immature bone will later be replaced by mature bone [3,6]. Osteoid tissue and non-calcified bone spicules play a crucial role in bone mineralization during the following two to three weeks, a process that begins at the base of the alveolus and continues toward the coronal portion, lasting up to six months post-extraction [4,7]. The final phase, modeling and remodeling, involves significant bone shape and architecture changes. During this phase, bone resorption occurs (modeling), along with the replacement of cancellous bone by lamellar bone (remodeling), without altering the overall shape [3]. Bone modeling continues for several months, with the most pronounced changes occurring within the first three months [8]. These phases are critical for understanding the tissue dynamics involved in post-extraction socket healing and provide a foundation for optimizing clinical outcomes in dental extractions.

1.2. Approaches to Minimize Alveolar Bone Resorption

Socket healing involves internal changes leading to bone formation and external changes leading to the bone resorption of the alveolar ridge, affecting its height and width [8]. These changes challenge clinicians, presenting esthetic issues and complicating implant placement, thus compromising future oral rehabilitation [9,10]. Over the past few decades, various techniques have been developed to mitigate bone changes after tooth extraction, such as partial tooth extraction, orthodontic extrusion, and alveolar ridge preservation [11].

1.2.1. Alveolar Ridge Preservation

Alveolar ridge preservation (ARP) techniques refer to any procedure performed after tooth extraction to minimize the external resorption of the alveolar bone ridge and maximize bone formation within the alveolus, within the limits of the alveolar space [4,12]. Most ARP procedures focus on ensuring minimally invasive dental extractions, preserving the integrity of the alveolar bone walls, and filling the socket with biomaterials, such as bone grafts, to maintain a favorable alveolar ridge for future dental implant placement [9,13].

Bone grafts have been used for decades to reconstruct and regenerate bone defects caused by traumatic extractions and periodontal or endodontic lesions [14]. Bone grafts can be classified as allografts, xenografts, alloplasts, or autogenous [9,15]. These grafts can be osteoinductive—promoting the recruitment of bone-forming cells, such as undifferentiated cells and pre-osteoblasts, and stimulating new bone formation through these cells; osteoconductive—where the graft provides a physical scaffold for bone regeneration; or osteogenic—where the cells within the graft promote new bone formation, even in the absence of mesenchymal stem cells [5,16,17]. Autogenous grafts are harvested and implanted in the same individual [18]. Autogenous bone is considered the gold standard due to its ideal properties of being osteoconductive, osteoinductive, and osteogenic [14,19]. Due to histocompatibility, these grafts reduce the risk of immune reactions, infections, and potential graft rejection [20,21]. However, the availability of autogenous bone grafts is limited, and they exhibit a high resorption rate when subjected to high loads and soft tissue stresses. Furthermore, their harvest requires an additional surgical site, increasing morbidity at the donor area [19,20,22].

1.2.2. Mineralized Dentin Graft

One type of autogenous graft that has garnered increasing attention is the use of a patient's extracted tooth. This approach offers a significant advantage by eliminating the need for a secondary bone harvesting site. Moreover, it is comparable to autogenous bone in both composition and the formation mechanism, making it a promising option for alveolar bone augmentation following tooth extraction [23].

Bone and dentin share similar biochemical compositions and formation mechanisms [24]. Both teeth and maxillofacial bones originate from neural crest cells during embryonic development [25]. Due to this biological similarity, dentin has been explored as a potential bone substitute since the 1960s. Its high mineral content, osteocompatibility, osteoconductivity, and osteoinductive properties make it suitable for bone grafting applications [26,27].

Dentin is composed of approximately 70% inorganic material, predominantly hydroxyapatite. The organic component constitutes 20% of the total composition, with 90% being collagen. Most of the collagen is type I, with smaller amounts of types III and V also present. The remaining portion of the organic matrix comprises non-collagenous proteins (NCPs), a variety of growth factors, including bone morphogenetic proteins (BMPs), transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF), and platelet-derived growth factors (PDGFs), as well as lipids. Furthermore, dentin comprises 10% water [28–30].

NCPs regulate mineral deposition, ensure dentin's proper structural organization, and are involved in bone calcification whilst dentin's collagen matrix provides a scaffold for the formation and deposition of minerals, cell adhesion and differentiation, and preserving the integrity of dentin [29–31]. These proteins fill the spaces between collagen fibers and accumulate on the periphery of dentinal tubules [29]. The main NCPs are dentin phosphoprotein (DPP), dentin matrix protein 1 (DMP1), osteonectin, osteocalcin, bone sialoprotein (BSP), osteopontin (OPN), extracellular matrix phosphoglycoprotein, proteoglycans, and some serum proteins [28,29]. NCPs and growth factors such as BMPs, LIM mineralization protein 1, and insulin-like growth factors are responsible for the osteoinductive property of this graft [31].

In this context, three different methods of dentin processing have been developed: demineralized dentin matrix (DDM), partially demineralized dentin matrix (PDDM), and mineralized dentin (ADM) [31].

The first documented human study using a dentin graft was performed by researcher Masaru Murata during a maxillary sinus lift surgery in 2003 [28,32]. Building on this foundation, Kim et al. introduced a procedure for autogenous demineralized dentin grafting (DDM) [33]. The demineralization process allows for the exposure of organic components (collagen fibrils, non-collagenous proteins, and growth factors), reducing the graft's crystallinity while increasing its porosity and surface area, which leads to enhanced osteoinductive activity [33–35]. However, the demineralization process increases both the preparation time and the associated costs compared to mineralized dentin due to the complexity of the procedure [23].

As a result, mineralized dentin graft provides mechanical stability, forming a stable foundation for implant placement [36]. While its osteoinductive properties may take longer to manifest, the low crystallinity of dentin hydroxyapatite supports gradual bone remodeling [33].

A streamlined method for preparing an autogenous mineralized dentin matrix graft was introduced in 2014, offering a cost-effective and efficient alternative.

The first step is carried out by the practitioner and involves removing all restorations, crowns, carious lesions, discolored dentin, tartar, or periodontal ligament remnants with a high-speed irrigated tungsten bur immediately after extraction. Any practitioner is well-versed in such a process. For multi-radicular teeth, the roots are sectioned [36].

Infection control is critical at this stage, ensuring that no infected or carious material enters the grinder. Proper cleaning and sterilization protocols are essential to manage the risk of contamination [37].

The second step, the cleansing process, is standardized using the cleanser kit provided by the manufacturer. The two solutions treat the dentin to eliminate all organic elements including bacteria, viruses, and cellular remnants on the mineral's surface or within the dentin's tubules. This step has been shown to be highly effective and renders the dentin graft material cleansed to a rate that can be considered sterile [36].

Avoiding human error during this process is vital, and strict adherence to protocols reduce variability and potential mistakes.

The tooth is dried and placed in a sterilized grinding chamber, such as the Smart Dentin Grinder™ (Kometa Bio ltd., Holon, Israel), where it is ground and sorted to select particles of 300–1200 microns for grafting. The particles below 300 microns fall into a waste drawer because it is considered as a non-efficient size [36].

Subsequently, the particles are treated with sodium hydroxide and alcohol to remove any residual organic debris and open the dentinal tubules [36].

Patient-specific safety should be considered, as while the material is autologous, ensuring that no diseased or pathological material is used is crucial. Pre-procedural evaluations are essential to confirm the absence of systemic or oral infections.

Finally, the graft material is rinsed with buffered saline to neutralize and adjust the pH, completing the process within 15–20 min [36].

The combination of the steps described above prep, clean, and standardize the readiness of the dentin graft regardless of the user [36].

Although there is no standardized external supervision, the responsibility for the pre-processing lies with the dental professional performing the procedure, and internal protocols, training, and visual inspections serve as safeguards to ensure safety and quality [37].

The literature remains inconsistent regarding which grafts offer the most advantages. However, some authors advocate for a patient-specific approach, recommending DDM in cases where the socket walls have already been damaged or are expected to be resorbed because of their higher rate of bone formation [38,39]. MMD, due to its superior mechanical stability, is suggested for situations that allow for earlier dental implant placement [36].

1.3. Oral Rehabilitation with Dental Implants

Since the concept of osseointegration was introduced over 50 years ago, oral rehabilitation with dental implants has evolved from an experimental procedure to a treatment with predictable outcomes and success in replacing edentulous spaces [40,41].

Dental implants' success depends on local and systemic favorable factors [42]. The requirements for the successful placement of dental implants include the osseointegration of the implant and insertion in the ideal three-dimensional position, achieving appropriate contours of hard and soft tissues, sufficient bone volume, a favorable architecture of the alveolar bone ridge for surgery, and proper surgical technique [4]. In cases where dental implants are planned following dental extraction, the procedure should be performed to maximize the preservation of the alveolar bone ridge [9].

The primary objective of this systematic review and meta-analysis is to evaluate, based on current scientific evidence, whether autogenous mineralized dentin (AMD) is effective in preserving the alveolar ridge for subsequent dental implant placement following a healing period of at least four months.

2. Materials and Methods

2.1. Search Strategy

The protocol of this review was registered in PROSPERO with the number CRD42024 571848. The planning process of this systematic review followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [43].

The PI(C)OT question for this systematic review was "In adult patients (Population) who undergo alveolar ridge preservation with AMD for delayed dental implant placement (Intervention), what are the percentages of newly formed bone and residual graft (Outcomes) after a follow-up period of at least 4 months (Time)?".

The search algorithm was then formulated: ("mineralized dentin matrix" OR "mineralized dentin graft" OR "mineralized dentin") AND ("bone graft" OR "dental graft" OR "xenograft" OR "allograft" OR "graft" OR "autologous graft" OR "autogenous graft") AND ("dental implant" OR "dental implants") and applied to PubMed, Cochrane Library, Google Scholar, and B-on aggregator (included sources are listed at https://www.b-on.pt/colecoes/ accessed on 1 July 2024). A manual search of the references of selected articles and reviews was also performed to identify sources not found in the electronic search but meeting the inclusion criteria. Searches were performed without applying a time filter, with the latest search conducted on 1 July 2024.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria included the following: human studies of patients who had undergone bone regeneration with AMD graft after extraction and delayed implant placement, with information on the procedure and outcomes such as newly formed bone and residual graft. Articles could be written in Portuguese, English, or Spanish.

Articles were rejected if they met the following exclusion criteria: animal studies, in vitro studies, case reports, case series, expert opinions, or studies without information on the procedure and relevant outcomes.

2.3. Study Selection

The search results were imported into Mendeley Desktop Citation Manager software version 1.206.0 to remove duplicates. Two independent reviewers (M.M. and P.M.) undertook the initial screening of the titles and abstracts of the remaining articles. Following this preliminary screening, the same reviewers conducted the final selection of studies by independently reviewing the full texts of the articles in accordance with the pre-established selection criteria. Should any discrepancies arise between the reviewers, these were resolved through discussion with a third reviewer (A.S.). The same process was subsequently employed in the manual search.

2.4. Data Extraction

Data extracted from the selected articles included study design, patient demographics (such as mean age and sex ratio), treatment plan, graft type, time from treatment to follow-up, outcomes, investigations performed, and study conclusions. The quantitative results were converted as applied and reported as the mean ± standard deviation.

2.5. Risk of Bias Assessment

The risk of bias assessment was carried out using the ROBINS-I tool: The Risk of Bias in Non-Randomized Studies—of Interventions [44] and the JBI Critical Appraisal Tools—Checklist for Randomized Controlled Trials [45].

2.6. Statistical Analysis

Random-effects meta-analyses were performed with OpenMetaAnalyst for Windows 10 (64-bit) using the DerSimonian–Laird method. Statistical analysis included newly formed bone (%, mean ± standard deviation) and residual graft (%, mean ± standard deviation). All articles included in the systematic review were included in the meta-analysis. The magnitude of heterogeneity was assessed using the I^2 index, and the associated significance was evaluated using Cochran's Q test. Sources of heterogeneity were explored by random effects meta-regressions against covariates such as mean age and male/female ratio. The significance of the meta-regression coefficients was checked using the Wald test.

3. Results

3.1. Search Results

A flowchart illustrating the search strategy is provided (Figure 1). The search yielded 447 articles (identification phase). After duplicates were removed (n = 80), 367 articles remained to be reviewed. Next, 337 articles were excluded after title or abstract screening, leaving 30 articles to be assessed for eligibility through full-text review, of which 28 were excluded. A manual search was performed, and 27 articles were assessed for eligibility, of which two were included. At the final stage, four studies from 2020, 2021, and 2022 were included in this review [23,46–48].

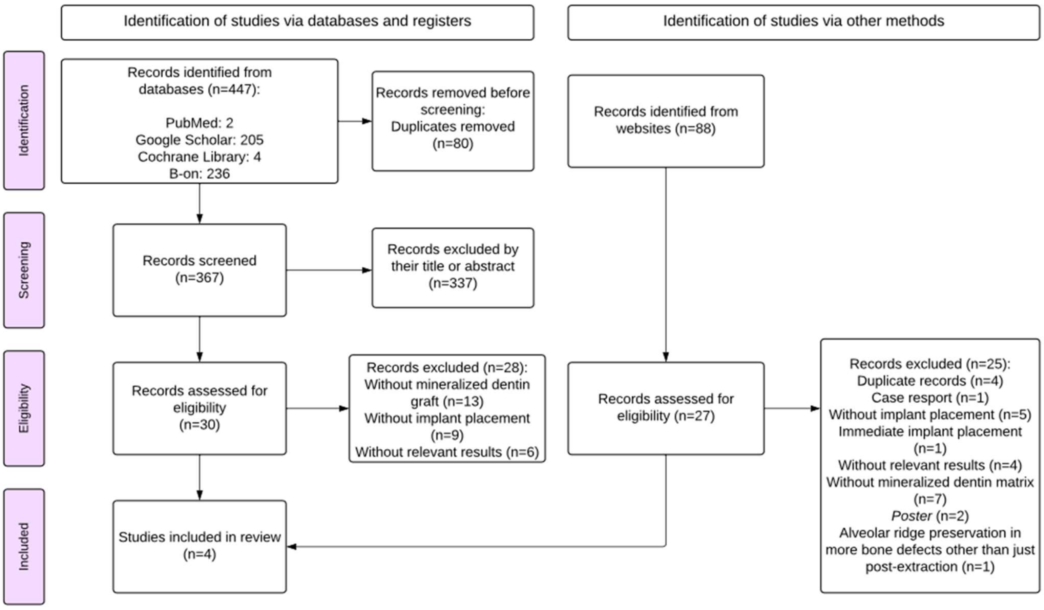

Figure 1. Flowchart diagram showing the search strategy (adapted from the PRISMA flow diagram) [43].

3.2. Data Extracted

The selected studies included 55 patients. The sample size varied from 10 to 32 sockets after extraction, totaling 67 sockets. The mean age of all patients was 54 years in Andrade et al. [47], 33.5 years in Elfana et al. [48], 56.8 years in Santos et al. [23], and 50.2 years in Artzi et al. [46]. The sex ratio (male to female) was 0% in Andrade et al. [47] because no males were included in the study, 30% in Elfana et al. [48], 42.2% in Santos et al. [23], and 53.3% in Artzi et al. [46]. The data extracted from the studies was summarized in Table 1.

Table 1. Summary data from selected articles.

	Study Design	Patient Data	Treatment Plan	Type of Graft	Time Between Treatments	Exams Performed	Study Conclusions
Andrade et al. [47]	Prospective experimental	4 patients, 10 sockets Ages: 44–63 years old (mean: 54 years old) Sex M∣F: 0∣4.	Dental extraction. Graft preparation. Preparation of L-PRF membrane and liquid fibrinogen. Graft placed inside socket. Delayed implant placement.	Mineralized dentin matrix, liquid fibrinogen, and L-PRF membrane.	Delayed implant placement at 4–6 months follow-up.	CBCT, clinical exam, bone biopsy, and histological and histomorphometric analysis.	AMD graft was able to promote adequate quantity and quality for delayed implant placement.

Table 1. *Cont.*

	Study Design	Patient Data	Treatment Plan	Type of Graft	Time Between Treatments	Exams Performed	Study Conclusions
Elfana et al. [48]	Prospective experimental	10 patients, 10 sockets.	Dental extraction. Graft placed inside socket. Resorbable collagen membrane was placed (Hypro-Sorb, Bioimplon GmbH, Gießen, Germany). Delayed implant placement.	Mineralized dentin matrix and collagen membrane.	Delayed implant placement at 6 months follow-up.	CBCT, bone biopsy, and histological and histomorphometric analysis.	AMD and ADD are equally effective in ARP. Both are biocompatible and osteoconductive with ADD seeming more osteoinductive.
		(mean age: 33.5 years old) Sex M∣F: 3∣7.					
Santos et al. [23]	Prospective experimental	26 patients, 32 sockets.	Dental extraction. Graft preparation. Graft placed inside socket. Resorbable collagen membrane was placed (Bio-Gide, Geistlich, Wolhusen, Switzerland). Delayed implant placement.	Mineralized dentin matrix and collagen membrane.	Delayed implant placement at 6 months follow-up.	CBCT, bone biopsy, implant stability, radiographic analysis, histomorphometric analysis, and patient-related outcomes.	Implants placed showed similar stability in socket grafted with AMD and xenograft; AMD showed higher quantities of newly formed bone and less residual graft than xenograft ($p < 0.001$).
		Age: 28–75 years old (mean: 56.8 years old) Sex M∣F: 11∣15.					
Artzi et al. [46]	Prospective experimental	15 patients, 15 sockets.	Dental extraction. Graft preparation. Graft placed inside socket. Resorbable membrane placed (Bio-Gide, Geistlich, Wolhusen, Switzerland). Delayed implant placement.	Mineralized dentin matrix and collagen membrane.	Delayed implant placement at 6 months follow-up.	Alveolar ridge height measurement, periapical radiography, CBCT, bone biopsy, and histomorphometric analysis.	Biocompatible, excellent osteoconductive properties; alveolar ridge was ready for delayed implant placement.
		Age: 27–71 years old (mean: 50.2 years old) Sex M∣F: 8∣7.					

3.3. Main Results from Studies

3.3.1. Radiography Analysis

Andrade et al. [47] used CBCT (Cone Beam Computer Tomography) for this analysis. The dimensions of the alveolar ridge before tooth extraction were 9.68 mm in buccal height, 5.01 mm in lingual height, and 9.69 mm in width in the selected tooth.

Four months after tooth extraction and grafting with AMD, the alveolar ridge measured 11.38 mm in buccal height, 7.13 mm in lingual height, and 11.33 mm in width. These measurements were also taken 6 months after implant placement and showed alveolar ridge dimensions of 11.30 mm in buccal height, 6.49 mm in lingual height, and 10.26 mm in width.

Elfana et al. [48] used CBCT for this analysis. The baseline dimensions for the test group (AMD) were 7.86 ± 1.16 mm in width, 9.25 ± 1.9 mm in buccal height, and 9.53 ± 176 mm in lingual height. As for the control group (ADD), the baseline dimensions were 8.11 ± 1.3 mm in width, 8.95 ± 1.6 mm in buccal height, and 8.86 ± 1.54 mm in lingual height. The differences in baselines between both groups were not statistically significant ($p > 0.05$).

After 6 months, the mean loss in terms of buccolingual ridge width was 0.85 ± 0.38 mm for the AMD group and 1.02 ± 0.45 mm for the test group ($p = 0.36$). The buccal height had a mean loss of 0.61 ± 0.20 mm in the AMD group and 0.72 ± 0.27 mm in the test group ($p = 0.31$). The lingual height had a mean loss of 0.66 ± 0.31 mm in the AMD group and 0.56 ± 0.24 mm in the test group ($p = 0.43$). The mean losses were higher in the test group regarding the width and buccal height, although none of the differences were statistically significant.

3.3.2. Histomorphometric Analysis

Andrade et al. [47] reported the highest mean newly formed bone at 56.5 ± 22.2%, showing a steady increase from 26.3% at four months to 56.5% at five months, and ultimately reaching 66.5% at six months. Residual graft percentages declined over time starting from 10.4% and reduced to just 0.9% by the six-month mark, with 40% of the sockets presenting no residual graft after six months.

Elfana et al. [48] observed a mean newly formed bone of 37.6 ± 8.9% in the AMD group, the lowest newly formed bone mean out of all four studies, and 48.4 ± 11.6% in the ADD group. Regarding residual graft percentages, the AMD group showed 17.1 ± 5.6%, while the ADD group exhibited 11.5 ± 4.1%.

In contrast, Santos et al. [23] found a mean newly formed bone of 47.3 ± 14.8% in the AMD group, which was significantly higher than the 34.9 ± 13.2% reported for the xenograft group ($p < 0.001$). The residual graft percentage was also significantly lower in the AMD group (12.2 ± 7.7%) compared to the xenograft group (22.1 ± 10.9%, $p = 0.001$).

Artzi et al. [46] reported a mean newly formed bone of 38.4 ± 16.5% and the highest residual graft percentage of 29.9 ± 14.4%. Their study also included a detailed analysis of the interaction between bone and dentin particles, with a mean direct contact of 69.1 ± 22.8% between new bone and dentin particles.

Thus, while all studies demonstrate bone formation over time, Andrade et al. [47] reported the most favorable outcomes in terms of both bone formation and minimal residual graft, followed by Santos et al.'s [23] AMD group, with Artzi et al. [46] presenting the higher residual graft levels and Elfana et al. [48] showing the lowest newly bone mean.

3.3.3. Implant-Related Results

Santos et al. [23] found no significant differences in keratinized gingiva width, mucositis, and peri-implantitis. Primary implant stability, secondary stability, and changes in implant stability showed no significant differences between groups. However, significant differences were observed in the length of implants placed: in the AMD group, the mean length of implants placed was 11.1 ± 0.8 mm; in the xenograft group (control group), the mean length of implants placed was 11.6 ± 0.8 mm ($p = 0.004$). Radiodensity was greater in the control group ($p < 0.001$).

In the study by Artzi et al. [46], all implants had excellent primary implant stability with at least 30 Ncm of torque. Follow-up confirmed that all implants placed had an appropriate function and peri-implant health.

3.4. Studies' Conclusions

In a comparative analysis of graft materials, Andrade et al. [47] concluded that AMD effectively promotes new bone formation without provoking an immunologic response from the host, noting a favorable relationship between dentin absorption and bone formation, and reporting that all patients achieved adequate bone quantity and quality for delayed implant placement. Elfana et al. [48] concluded that AMD and ADD showed equal efficiency in ARP, reducing dimensional losses after 6 months, with no adverse effects. Both grafts were biocompatible and osteoconductive, although ADD showed higher osteoinductive properties. Santos et al. [23] found that implants placed in areas grafted with AMD exhibited comparable stability to those in areas grafted with xenograft while demonstrating greater newly formed bone and lesser residual graft, leading to similar clinical results and patient-related outcomes. Complementing these findings, Artzi et al. [46] highlighted the utility of AMD grafts as a biomaterial for alveolar ridge preservation, showcasing their biocompatibility and excellent osteoconductivity; notably, sockets grafted with AMD were adequately prepared for delayed implant placement at the six-month follow-up.

Collectively, these studies underscore the efficacy of AMD in enhancing bone regeneration and its potential as a preferred grafting material in clinical applications.

3.5. Risk of Bias Results

The study of the risk of bias made it possible to verify whether there were methodological flaws in the studies included in this systematic review while also evaluating the quality of this review. The tools used to assess the risk of bias allowed used a precise scale to correctly analyze possible bias in the studies included in this systematic review and meta-analysis. The results were presented in two ways: traffic light plot (Figure 2) and summary plot (Figure 3) for the risk of bias for non-randomized studies; and traffic light plot (Figure 4) and summary plot (Figure 5) for randomized studies.

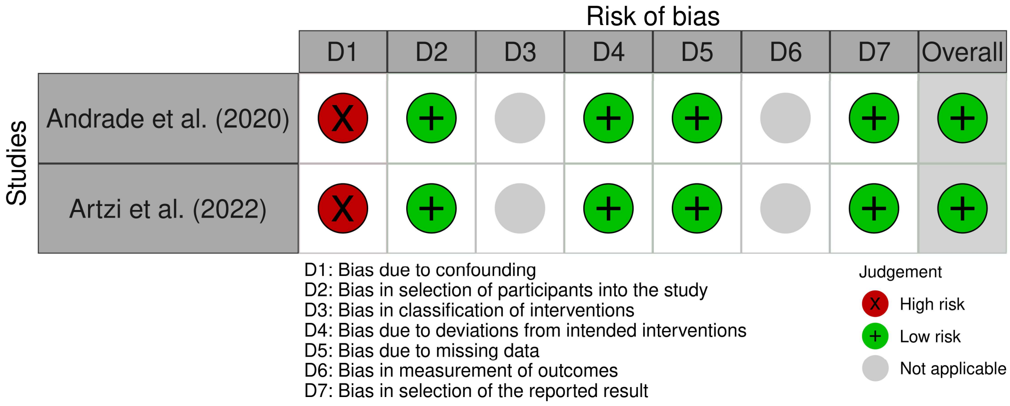

Figure 2. Traffic light plot of the risk of bias analysis of non-randomized studies [46,47].

Both non-randomized studies did not present possible confounding factors that could alter the results or the way they were controlled; therefore, both received a "high risk" rating in domain 1. The traffic plot with the ROBINS-I (https://sites.google.com/site/riskofbiastool/welcome/home/current-version-of-robins-i/robins-i-tool-2016 accessed on 13 October 2024) results is shown in Figure 2. The summary plot is shown in Figure 3.

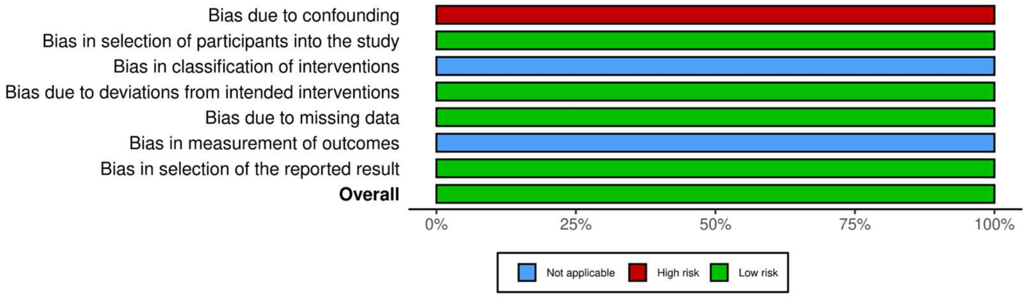

Figure 3. Summary plot of the risk of bias analysis of non-randomized studies.

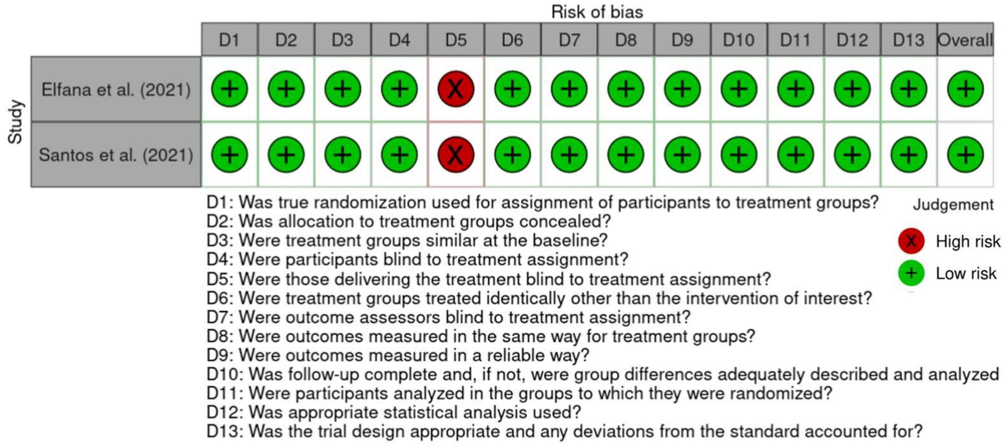

Figure 4. Traffic light plot of the risk of bias analysis of the randomized controlled trials [23,48].

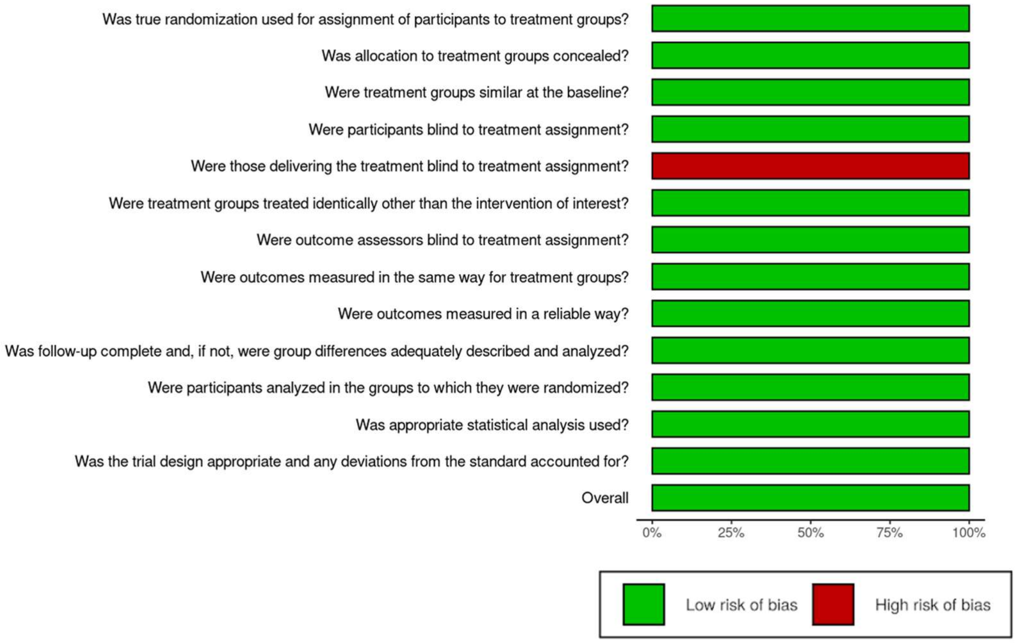

Figure 5. Summary plot of the risk of bias analysis of the randomized controlled trials.

Both Elfana et al. [48] and Santos et al. [23] received a "high risk" rating in domain 5 (dentist blinding) of the JBI tool (https://jbi.global/critical-appraisal-tools accessed on 31 October 2024) because the dentist knew which intervention was given to which patient (Figure 4). All included studies had an overall low risk of bias.

3.6. Meta-Analyses

Two meta-analyses were conducted: one to examine the percentage of newly formed bone at follow-up and another to examine the percentage of residual graft at follow-up. All studies included in the systematic review were included in both meta-analyses [23,46–48].

3.6.1. Meta-Analysis on the Percentage of Newly Formed Bone

The graph obtained from the first meta-analysis is represented in Figure 6.

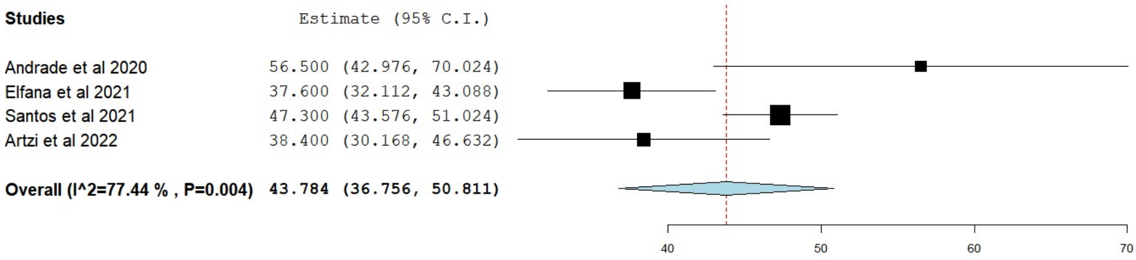

Figure 6. Forest plot graph of newly formed bone (%). I^2 represents the heterogeneity index. The dashed red line represents the meta-analytic mean [23,46–48].

The global meta-analytical value suggests that the AMD graft resulted in an average newly formed bone percentage of 43.8%, with a 95% confidence interval ranging from 36.6% to 50.8%.

Both Elfana et al. [48] and Artzi et al. [46] showed results bellow the meta-analytic mean but within the confidence interval (37.6% and 38.4%, respectively). Andrade et al. [47] and Santos et al. [23] showed results above the meta-analytic mean (56.5% and 47.3%, respectively), with Andrade et al. [47] being the most discordant study regarding the mean in this first meta-analysis. The heterogeneity was 77.4%, indicating a high degree of variability between the studies (Cochran's Q test, $p = 0.004$).

Meta-regressions were conducted to evaluate covariables that could have influenced the results. The covariables chosen were mean age and sex ratio.

The first meta-regression studied the effect of the mean age, shown in Figure 7. The second meta-regression studied the effect of the sex ratio, shown in Figure 8.

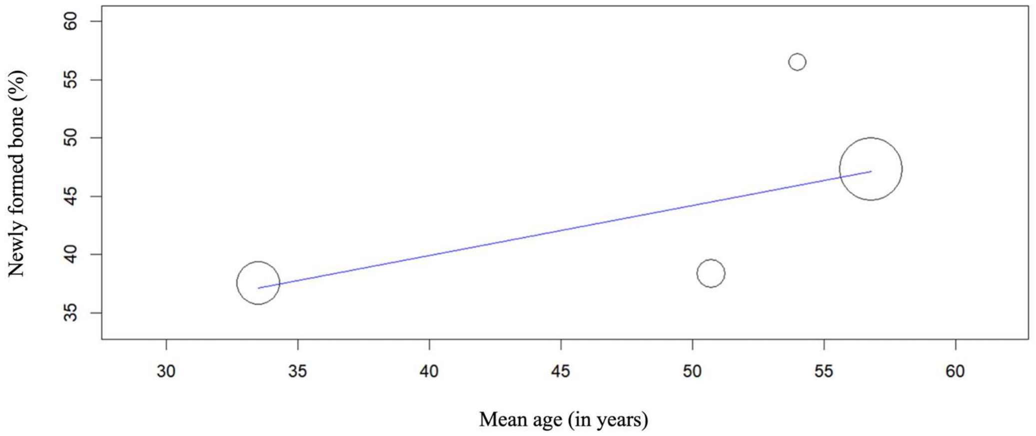

Figure 7. Meta-regression of the effect of mean age on the percentage of newly formed bone.

The meta-regression shown in Figure 7 indicates that, with an increase in mean age, there is a mean increase tendency in the percentage of newly formed bone (Wald test, $p = 0.003$).

As shown in Figure 8, this meta-regression reveals that as the sample female ratio decreases, there seems to decrease the percentage of newly formed bone. However, there is not sufficient evidence to statistically support this relationship (Wald test, $p = 0.194$).

It is clear from Figure 8 that even when one study is removed, the 95% confidence interval still includes the overall result, suggesting that no single study drastically changes the overall effect estimate.

A leave-one-out meta-analysis was also performed, as shown in Figure 9.

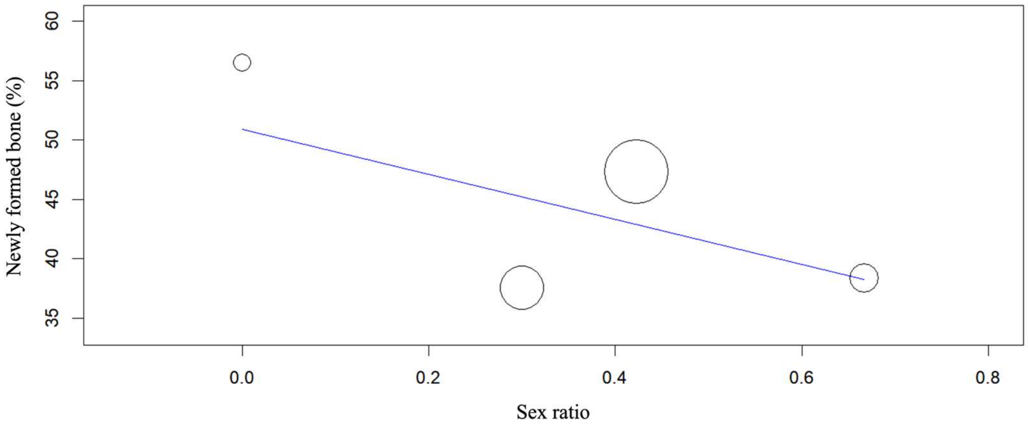

Figure 8. Meta-regression of the effect of male/female sex ratio on the percentage of newly formed bone.

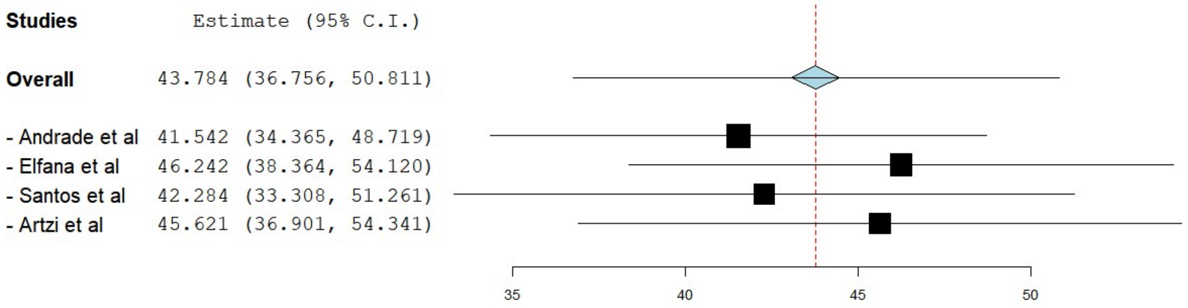

Figure 9. Leave-one-out meta-analysis for newly formed bone (%). The dashed red line represents the overall meta-analytic mean [23,46–48].

3.6.2. Meta-Analysis on the Percentage of Residual Graft

The graph obtained from the residual graft (%) meta-analysis is represented in Figure 10. The global meta-analysis mean residual graft was 15.2%, with a 95% confidence interval ranging from 7.2% to 23.2%.

In this meta-analysis, Andrade et al. [47] and Artzi et al. [46] were the most discordant studies, positioned at opposite extremes. Andrade et al. [47] reported the lowest result, while Artzi et al. [46] reported the highest, with both findings falling outside the confidence interval (3.6% and 29.9%, respectively). Meanwhile, Santos et al. [23] reported results below the meta-analytic mean, while Elfana et al. [48] reported results above it (12.2% and 17.1%, respectively). However, both were relatively close to the mean in this meta-analysis.

The heterogeneity (I^2) was 93.8%, indicating extremely high heterogeneity, demonstrating high discordance and variability between studies. Given the high heterogeneity, meta-regressions were performed to evaluate whether the covariate’s mean age and sex ratio might have influenced the results.

The first meta-regression examined the effect of mean age, shown in Figure 11. The second meta-regression investigated the effect of sex ratio, shown in Figure 12.

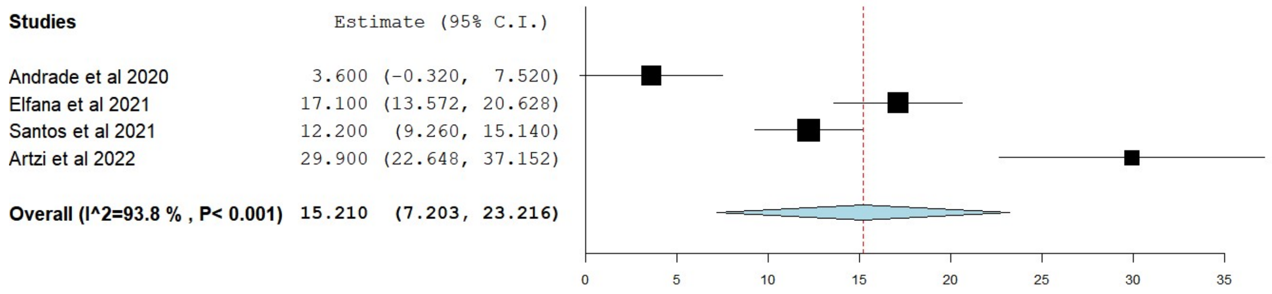

Figure 10. Forest plot graph of residual graft (%). I^2 represents the heterogeneity index. The dashed red line represents the meta-analytic mean [23,46–48].

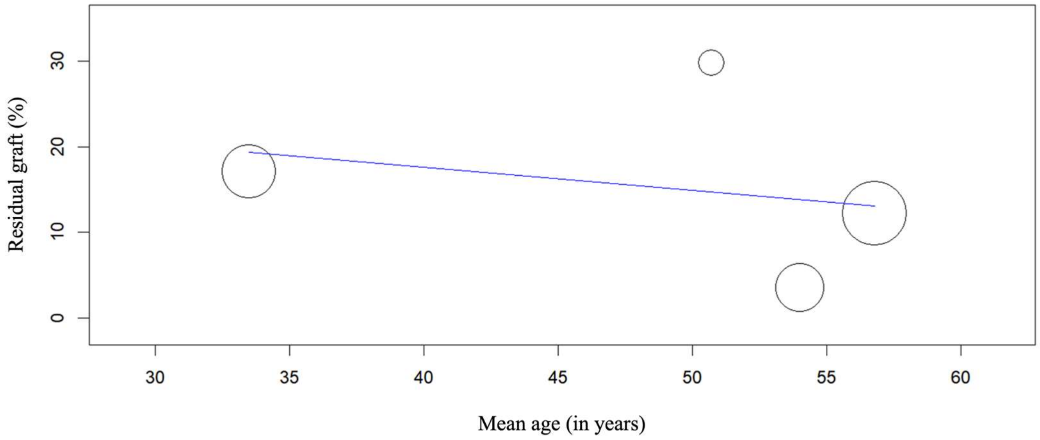

Figure 11. Meta-regression of the effect of mean age on the percentage of residual graft.

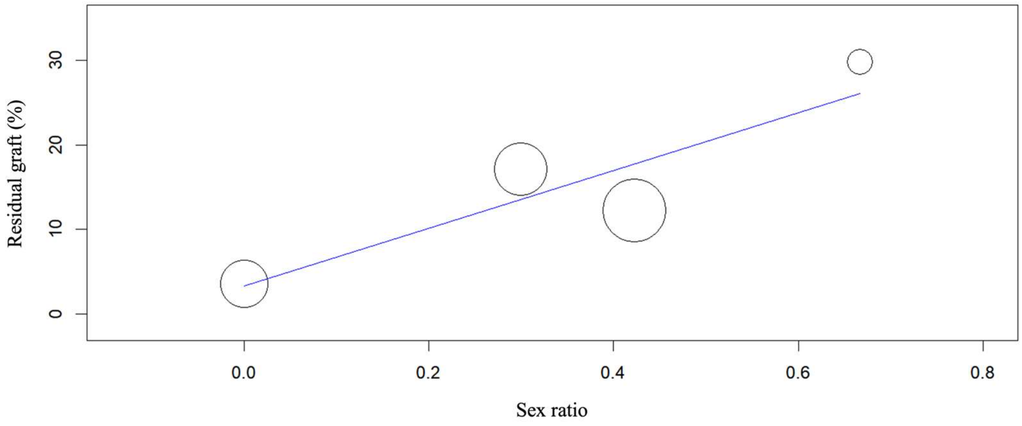

Figure 12. Meta-regression of the effect of the sex ratio on the percentage of residual graft.

In this meta-regression, with the increase in mean age, there is a decrease in the quantity of residual graft (%). However, this relationship did not show significant results (Wald test, $p = 0.569$).

This meta-regression shows that with the increase in males in the study, there is an increase in the percentage of residual graft at the follow-up. This relationship is significant (Wald test, $p < 0.001$).

A leave-one-out meta-analysis was also performed, as shown in Figure 13.

Once again, it is clear from Figure 12 that, even when one study is removed, the 95% confidence interval still includes the overall result, suggesting that no single study drastically changes the overall effect estimate.

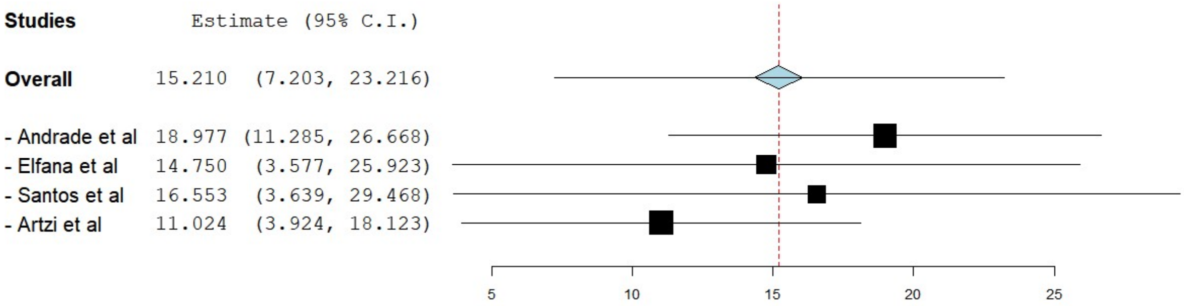

Figure 13. Leave-one-out meta-analysis for residual graft (%). The dashed red line represents the overall meta-analytic mean [23,46–48].

4. Discussion

In the present systematic review and meta-analysis, four articles were included, comprising a total of 55 patients who underwent ARP with autogenous mineralized dentin, followed by dental implant placement after a healing period of at least 4 months. A variety of methodologies were employed in order to assess the characteristics of AMD. All studies followed the previously outlined protocol for the preparation of dentin [36]. However, Andrade et al. [47], Santos et al. [23], and Artzi et al. [46] employed the Smart Dentin Grinder™ Device (KometaBio, Fort Lee, NJ, USA), while Elfana et al. [48] employed the Gold Bone Mill (MCT Bio, Seoul, Republic of Korea). In the studies by Elfana et al. [48], Santos et al. [23], and Artzi et al. [46], only mineralized dentin and a resorbable collagen membrane were utilized. In contrast, Andrade et al.'s [40] study incorporated mineralized dentin, liquid fibrinogen, and leukocyte- and platelet-rich fibrin (L-PRF) membrane.

In the study by Castro et al. [49], the combination of liquid fibrinogen with an L-PRF membrane demonstrated the continuous release of growth factors for up to 14 days after applying these biomaterials, highlighting their potential as bioactive agents. Concurrently, this combination exhibited strong bactericidal activity, indicating its potential efficacy in combating postoperative infections [50].

The research by Dohan Ehrenfest et al. [51] examined the effects of a platelet-rich fibrin (PRF) membrane. It concluded that it releases growth factors gradually for at least one week, thus stimulating the healing environment during a significant remodeling period. Furthermore, this study evaluated the effects of leukocytes, which have been demonstrated to produce substantial amounts of Transforming Growth Factor Beta 1 (TGF-β1) and vascular endothelial growth factor (VEGF) and can, therefore, be considered an active source of growth factors [51]. The VEGF produced by leukocytes plays a role in the healing process and promotes angiogenesis [51]. These characteristics may help explain why the study by Andrade et al. [47] yielded the best results, demonstrating the highest percentage of newly formed bone and the lowest percentage of residual dentin.

The studies present similar protocols; however, notable differences exist among them. These variations in study design, methodologies, and procedures can introduce substantial heterogeneity, complicating the interpretation of results and limiting the ability to draw robust conclusions. Differences in patient selection criteria may result in variations in initial characteristics, such as age and sex distribution, which were consequently selected as covariates for the meta-regressions conducted.

Similarly, discrepancies in the preparation of the mineralized dentin graft may lead to different effects, complicating direct comparisons of results between studies. The timing of follow-up is another crucial factor. The study by Andrade et al. [47], which evaluated patients at 4, 5, and 6 months post-extraction, may have observed varying effects due to this difference, adding further complexity to comparisons among studies.

In the meta-analysis related to the mean percentage of newly formed bone, it was concluded that there is a positive effect of mineralized dentin (Cochran's Q test, $p = 0.004$) and that the clinical implications of these results are significant. The ability of AMD to promote newly formed bone without eliciting an immunologic response suggests its potential as a biomaterial for alveolar ridge preservation [21].

The age analysis revealed a significant relationship between the mean age of patients and the amount of newly formed bone (Wald test, $p = 0.003$). Similarly, the sex ratio analysis showed a significant association between the proportion of male participants and the percentage of residual graft, with a higher proportion of males linked to an increase in the percentage of residual graft (Wald test, $p < 0.001$). The small sample size on which these results are based implies the need for external validation. If confirmed, these findings suggest the need for further investigation to explore the biological, hormonal, or behavioral factors that may contribute to the observed differences.

Despite the encouraging outcomes, several limitations warrant consideration. First, the heterogeneity observed across both meta-analyses indicates variability among the included studies. This variability constrains the generalizability of the findings.

Moreover, the short follow-up durations, despite the classification of delayed implant placement as greater than six months, preclude the evaluation of long-term outcomes for this procedure. Another limitation is the relatively small number of studies included in this review. However, it was determined that case series and case reports would not be incorporated to preserve a high level of evidence.

Recently, systematic reviews have been conducted to study the efficacy of mineralized and/or demineralized dentin grafts in post-extraction sockets with subsequent dental implant placement. However, none have specifically focused solely on mineralized dentin, as this systematic review does [52–54].

Demineralized dentin is created by removing the mineral phase and immunogenic components while preserving a small fraction of minerals, the majority of type I collagen, NCPs, and growth factors such as bone morphogenetic proteins (BMPs) [55]. This demineralization process compromises the structural integrity of the dentin [56]. In contrast, due to its retained mineral content, mineralized dentin undergoes slower resorption, providing a stable scaffold that supports gradual and sustained new bone formation over time [32].

This study is pioneering in that it represents the inaugural systematic review with meta-analysis to include mineralized dentin exclusively. No studies have explicitly focused on this area, rendering this research unique and innovative.

Further research is needed to address the above limitations. Long-term studies with larger patient groups and diverse patient populations are further needed to validate externally the efficacy of AMD for alveolar ridge preservation. Standardized protocols for preparing and applying AMD should be established to minimize variability and improve potential comparability between studies.

5. Conclusions

Within the limitations of this review and given the limited number of studies available, AMD shows a promising trend in promoting newly formed bone. Additionally, AMD appears to be effective and safe, indicating its potential as an alternative to other bone graft materials in ARP procedures prior to dental implant placement. However, the high degree of heterogeneity across studies underscores the sensitivity and variability of these findings. Further randomized controlled trials with larger sample sizes and longer follow-ups are required to corroborate these findings.

Author Contributions: Conceptualization, M.M., A.S., and P.M.; methodology, M.M., A.S., and P.M.; software, M.M. and P.M.; validation, M.M., A.S., and P.M.; formal analysis, M.M. and P.M.; investigation, M.M.; data curation, M.M. and P.M.; writing—original draft preparation, M.M., A.S., and P.M.; writing—review and editing, M.M., A.S., and P.M.; visualization, M.M.; supervision, A.S. and P.M.; project administration, M.M., A.S., and P.M.; funding acquisition, M.M., A.S., and P.M. All authors have read and agreed to the published version of the manuscript.

Funding: The authors thank FCT/MCTES for the financial support to CiiEM (10.54499/UIDB/04585/2020) through national funds.

Data Availability Statement: Data that support these findings are available from the corresponding author upon reasonable request.

Conflicts of Interest: One of the articles included in this systematic review (Santos et al., 2021) [23] was authored by one of the authors of the current review. To reduce potential bias, the article selection and data extraction process were performed independently by other team members who were not involved in the authorship of the selected article. Any disagreements were resolved by discussion with a third independent reviewer. The authors declare that they have no other conflicts of interest.

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