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Regenerative Surgical Therapy of Peri-implantitis: An Umbrella Review of Answered/Unanswered Questions and Future Perspectives

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Purpose: To systemically summarize current knowledge about regeneration of peri-implant defects based on available systematic reviews.

Materials and Methods: A systematic search for review articles published between 2010 and 2020 in four databases was conducted. Only systematic reviews and meta-analyses were included. Based on the available literature, five questions of clinical importance on indication for regenerative approaches, surgical technique, methods of decontamination, outcome of therapy and adjunctive use of biological factors were formulated and answered.

Results: The electronic search resulted in 312 studies, from which 264 studies were published between 2010 and 2020. Finally, 18 systematic reviews and one consensus report were chosen. Data of the included studies were based on 58 to 840 implants. Data on over 4.904 implants were assessed. From the 19 studies that were included, 15 assessed the outcome of regenerative therapy; three, the surgical protocol of regenerative therapy; two, the use of laser in regenerative therapy; and one, the additional use of growth factors in regenerative peri-implant therapy. Three studies assessed more than one topic.

Conclusions: In general, a partial bone fill can be expected in 85% of regenerative procedures. Regeneration leads to a mean of 57% of greater bone fill, compared to open flap surgery only. Defect configuration plays a crucial role in the outcome, whereas the role and extent of benefit of different surgical protocols are still not clear.

Keywords: peri-implantitis, guided bone regeneration (GBR), regenerative dentistry, dental implant, infrabony defects

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INTRODUCTION

The placement of dental implants has become a routine procedure for the rehabilitation of patients with one or more missing teeth. High success rates of up to 97 and 75% after 10 (1) and 20 years (2), respectively, have been reported. However, in recent cases of implant placements, mainly biological complications in terms of peri-implant inflammation, known as mucositis and peri-implantitis, are increasingly reported in daily practice (3). Whereas, mucositis is limited to the

surrounding soft tissues, peri-implantitis results in progressive peri-implant bone loss (4). Today, peri-implantitis represents the main reason for late implant failure and removal (5). A meta-analysis (MA) estimated a considerable weighted mean prevalence of 22% (confidence interval: 14–30%) for disease development (6).

To treat this respective attachment loss, several treatment approaches are available. Whereas, non-surgical therapy has already been shown to be ineffective (7), open flap surgery seems to have more promising results, if indicated, regenerative procedures seem to have even better outcomes (8). With regard to regenerative procedures, mainly two parameters seem to still be of eminent interest: [1] the effective cleaning and decontamination of the affected implant sites (4), and [2] presence of suitable hard tissue defects allowing for stable augmentation, coverage, and healing (9).

A plethora of different surgical techniques including grafting materials and growth factors, have already been described in the literature (8), and experts agree that overall treatment outcomes improve after 6 months to 10 years, especially when considering clinical probing pocket depth (PPD) and radiographic measurements as primary outcome parameters.

This evidence-based update review was conducted with the aim of stocktaking the available current evidence, with a focus on regenerative peri-implantitis treatment, and highlighting the current and future research perspectives. For this purpose, the authors tried to formulate the most specific clinically relevant questions for this topic based on a systematic literature search.

MATERIALS AND METHODS

A systematic literature search for reviews and meta-analyses assessing regenerative treatment approaches of peri-implantitis bone defects was conducted in September 2020. It followed the focused question: what is the current knowledge about regeneration of peri-implant defects in human patients?

This review was written in accordance with the PRISMA statement for reporting systematic reviews of studies evaluating healthcare interventions and the methodology for summarizing systematic reviews (10).

The following databases were included: MEDLINE, Embase, Web of Science, and Scopus. The following search terms were applied: "Peri-implantitis" OR "peri-implantitis" OR "peri implantitis" AND "Reconstructive surgery" OR "regeneration" OR "reconstruct" OR "regenerat" OR "guided bone regeneration" OR "GBR" OR "augmentation" OR "augment" AND "Review."

Based on the available literature, five questions of clinical importance were formulated:

1) Augmentative procedures – for which defects and which patients?
2) (How) can infected implant surfaces be cleaned?
3) How can/should regeneration be achieved?
4) What is the outcome of regenerative therapy in peri-implantitis?
5) Should we apply additional biologicals or stem cells as adjunct measures?

Further, a hand search was conducted, and reference lists of included studies were screened.

Screening and Selection

First, both authors independently assessed the publications by title and abstract. The inclusion and exclusion criteria for the reviews were as follows:

Inclusion criteria: systematic reviews and meta- analyses including human studies published from January 2010 to September 2020.

Exclusion criteria: reviews on animal studies; all other publication forms other than reviews; publication before 2010; and reviews not in English.

Available titles and abstracts were collected and discussed before being finally included or excluded by the two authors.

The quality of included literature was assessed using AMSTAR 2 criteria (11).

Data Extraction

The following key points were collected for all included systematic reviews and summarized in **Tables 1**, **2**: name of authors, year of publication, topic of research, number of included implants, PICO (Population, Intervention, Comparison, Outcome), main results, and conclusions.

For each formulated focus question, a specific surrogate parameter or outcome variables were specified as follows:

1) defect configuration and host factors
2) efficacy of available surface cleaning protocols
3) indication and benefit of use of different biomaterials
4) expected outcome of regenerative treatment
5) benefit of use of bio-active materials or cell therapy.

Respective data (if available) and conclusions were collected.

RESULTS

Search

Search results are shown in **Figure 1**. The electronic search contained 312 articles, which included 264 articles published between 2010 and 2020. Finally, 18 systematic reviews and one consensus report were included. Consequently, 46 studies were excluded, because of their narrative and non-systematic methodology. Inter-examiner agreement of a Cohen's kappa (K) of 0.762 was achieved after the initial screening. The authors discussed discrepancies before reaching a consensus.

Studies

Table 1 describes the 18 included systematic reviews and one consensus report. **Table 2** contains the formulated PICO or focus question for each study with their corresponding main conclusions. Among the 19 included studies, 15 studies assessed the outcome of regenerative therapy; three, the surgical protocol of regenerative therapy; two, the use of laser in regenerative

TABLE 1 | Characteristics of the included studies (SR, Systematic Review; MA, Meta-Analysis; RCT, Randomized Clinical Trial; CCT, Case Control Studies).

Author (REF) & study-type	Included original studies (No. of implants)	Topic	Evid. for quest. no.	Quality assessment acc. to AMSTAR 2
Aljohani et al. (12) SR	5 RCTs ($n = 226$)	Outcome of regenerative therapy	3	Low quality
Chala et al. (13) SR	9 ($n =$ n.a.)	Use of laser in regenerative therapy	2	Low quality
Chan et al. (14) SR	21: 9 RCTs & 12 CS ($n = 467$)	Outcome of regenerative therapy	3	Moderate quality
Daugela et al. (15) MA	18 ($n = 713$)	Surgical protocol & outcome of regenerative therapy	3 & 5	Low quality
Esposito et al. (16) SR	9: 2 for surgical interventions ($n = 58$)	Outcome of regenerative therapy	3 & 4	High quality
Heitz-Mayfield et al. (9) SR	43 – 26 for surgical interventions ($n = >447$)	Surgical protocol & outcome of regenerative therapy	2 & 3	Moderate quality
Khoshkam et al. (17) MA	1 RCT – 11 Case series ($n = 407$)	Outcome of regenerative therapy	4	Moderate quality
Khoshkam et al. (18) MA	1 RCT – 5 Case series ($n = 152$)	Outcome of regenerative therapy	4	Moderate quality
Khouly et al. (19) MA	5 RCTs ($n = 220$)	Efficacy of growth factors	5	High quality
Khoury et al. (8) CR	4 Reviews	Surgical protocol & outcome of regenerative therapy	1, 2, & 3	NA
Lin et al. (20) MA	22: 6 RCTs, 16 Case series ($n = 698$)	Use of laser in regenerative therapy	2	Moderate quality
Mahato et al. (21) SR	20: 10 for surgical interventions (RCT & CCT)	Outcome of regenerative therapy	3	Low quality
Natto et al. (22) SR	13: 8 for surgical interventions (RCT & CCT) ($n = 70$)	Use of laser in regenerative therapy	2	Moderate quality
Ramanauskaite et al. (23) MA	29: 13 for regenerative interventions (RCT & CCT)	Outcome of regenerative therapy	1 & 4	Moderate quality
Ramanauskaite et al. (24) SR	24 ($n = 840$)	Outcome of regenerative therapy	1, 3, & 4	Moderate quality
Roccuzzo et al. (25) SR	18 ($n =$ n.a.)	Outcome of regenerative therapy	4	High quality
Sahrmann et al. (26) SR	17 ($n = 173$)	Outcome of regenerative therapy	2 & 4	Low quality
Schwarz et al. (27) MA	40: 6 for regenerative interventions (RCT & CCT) ($n = 317$)	Outcome of regenerative therapy	4	Moderate quality
Tomasi et al. (28) MA	16 RCTs ($n = 116$)	Outcome of regenerative therapy	4	High quality

therapy; and one, the additional use of growth factors in regenerative peri-implant therapy. Three studies assessed more than one topic. In all, eight studies included a meta-analysis; nine studies, a systematic literature search; and one study, a consensus report. Eight of the 18 reviews included case control trials (CCT) data in addition to randomized control trials (RCT) data. The consensus report was based on the data of four reviews. The data of the included studies were based on 58 to 840 implants. Five studies did not mention the number of included implants. This umbrella review contains data on a total of over 4.904 implants. The quality of the included systematic reviews ranged from low ($n = 5$), moderate ($n = 9$), to high ($n = 4$), according to AMSTAR 2 criteria (11) (**Table 1**).

DISCUSSION

Question 1: Augmentative Procedures – for Which Defects and Which Patients?

The healing potential of regenerative therapy is mainly determined by the morphology of the underlying bone defects (29). Schwarz and co-workers (30) investigated the impact of defect configuration. Whereas class I defects represent well-defined infrabony defects with an additional sub-classification based on the inflicted lost walls and their configuration, class II defects describe suprabony, i.e., horizontal bone loss. Within class I defects, the Ie-configuration represents a circumferential crater-shaped self-containing defect and was defined as being the

TABLE 2 | Overview over the PICO (**P**opulation, **I**ntervention, **C**omparison, **O**utcome) question or the formulated focused question with corresponding main findings of each included review.

Author (REF)	PICO/Focused question	Main findings
Aljohani et al. (12)	**P:** Patients with peri-implantitis and classified according to the American Society of Anesthesiolo-gists or ASA physical Status I or II. **I:** Mechanical debridement + Laser (both in surgical and non-surgical modalities) **C:** Different surgical approaches **O:** Primary and secondary outcomes	Higher mean PPD reduction, if bone substitutes are used. Higher mean radiographic bone fill if bone substitutes are used. Lack of evidence which bone substitute material should be used.
Chala et al. (13)	**P:** Adults with peri-implantitis or peri-implant mucositis **I:** Mechanical debridement + Laser (both in surgical and non-surgical modalities) **C:** Mechanical debridement alone (both in surgical and non-surgical modalities); **O:** Pain; Healing; probing pocket depth (PPD), bleeding index (BI), etc.;	Shows no benefits for long-term outcome. All wavelengths show similar results.
Chan et al. (14)	**Focused Question:** What are the radiographic and clinical outcomes of different surgical interventions for the treatment of peri- implantitis?	Higher mean PPD reduction, if bone substitutes are used. Higher mean radiographic bone fill if bone substitutes are used.
Daugela et al. (15)	**Focused Questions:** 1.What are the overall treatment outcomes of reconstructive procedures in treating peri- implantitis? 2. Does the use of barrier membranes or submergence of the healing site provide beneficial clinical outcomes in the treatment of peri-implantitis?	A mixture of xenogenic and autogenous bone is suggested. No data for the use of EMD in peri-implantitis available. The use of PDGF shows tendency to highest bone fill, when used in bone regeneration.
Esposito et al. (16)	Not mentioned	No evidence indicating the most effective approach.
Heitz-Mayfield et al. (9)	**P:** Patients diagnosed with peri-implantitis **I:** Treatment **C:** Include both non-surgical and surgical treatment **O:** Resolution of disease: implant survival and absence of PD $\geq$ 5 mm with suppuration/BOP and no further bone loss	A pre-surgical hygiene phase seems beneficial. Through intrasurgical cleaning, blood clot stability, peri-operative infection control and post-operative maintenance are crucial.
Khoshkam et al. (17)	**Focused Question:** Do reconstructive surgical procedures provide beneficial clinical outcomes in comparison with other surgical techniques (respective surgeries and open flap debridement) in the treatment of peri-implantitis? As an alternative focused question, what are the overall treatment outcomes of reconstructive procedures in treating peri-implantitis?	Radiographic bone defect fill WMD 2.17 mm. PPD reduction WMD 2.97 mm. Attachment gain WMD 1.65 mm.
Khoshkam et al. (18)	**Focused Question:** How do the effects of regenerative treatment of peri-implantitis compare to those of other treatment modalities, such as open-flap debridement, after a minimum of healing time of 36 months in human subjects?	Lack of long term results. WMD bone defect fill of 2.41 mm after 36 months. WMD PPD reduction of 3.06 mm after 36 months.
Khouly et al. (19)	**P:** Adult human subject, undergoing treatment for peri-implant diseases **I:** Growth factors in combination with surgical/non-surgical treatment **C:** Comparative growth factor treatment OR no growth factor **O:** Inflammation resolution in terms of re-duction of bleeding on probing, probing depth, and bone level (primary outcomes), and related parame- ters (e.g., gingival recession, plaque index, complica- tions, etc.) (secondary outcomes)	Lack of evidence for additional benefit of growth factors in peri-implantitis treatment. PRF membranes seem to be inferior compared to collagene membranes.
Khoury et al. (8)	NA – consensus report	Infrabony defects can be augmented. No superiority of any bone graft material. No superiority of any decontamination method. Soft tissue augmentation may contribute to a positive outcome.
Lin et al. (20)	**P:** Comprised individuals with peri-implant mucositis or peri-implantitis **I:** Use of lasers alone or as adjuncts in surgical/non-surgical therapies **C:** No use of lasers **O:** Changes in: (1) PD, (2) CAL, (3) percentage of bleeding on probing (BOP), (4) plaque index (PI), (5) recession (REC), and (6) marginal bone level (MBL).	No clinical benefit over other methods. Might be of use when defect access is limited.

(Continued)

TABLE 2 | Continued

Author (REF)	PICO/Focused question	Main findings
Mahato et al. (21)	**P:** Patients diagnosed with peri-implantitis **I:** Treatment **C:** Non-surgical treatment with surgical treatment **O:** Resolution of disease: implant survival and absence of PD ≥4 mm with suppuration/BoP and no further bone loss	Adjunctive use of augmentative procedures shows positive outcomes. Complete bone fill is difficult to achieve. More long-term research needed.
Natto et al. (22)	Not mentioned	Need of more clinical research is needed in order to formulate clinical suggestions.
Ramanauskaite et al. (23)	What is the effectiveness of non-surgical and surgical treatment methods for clinical and radiographic peri-implantitis symptoms resolution with respect to PD, BOP, and marginal bone loss?	Whenever possible a regenerative approach should be seeked, showing most promising results.
Ramanauskaite et al. (24)	**P:** Patients diagnosed with peri-implantitis based on case definitions used in respective publications **I:** Surgical augmentative peri-implantitis measures **C:** Surgical non-augmentative measures **O:** Primary: changes in clinical parameters (i.e., bleeding on probing [BOP %] and peri-implant probing depth [PD (mm)]; secondary: radiographic defect fill [%] and/or defect reduction (mm)	Respective and regenerative procedures show similar outcomes in term of BOP and PPD reduction. Complications in 58.4% when non-resorbable or resorbable membranes were used. Implants with moderate rough surfaces undergoing regenerative therapy show significantly better outcomes compared to rough surfaces. The benefit of antibiotics has not been assessed.
Roccuzzo et al. (25)	**P:** Patients with osseointegrated dental implants that were diagnosed with and received treatment by investigators for peri-implantitis **I:** Enrolment in SPT for a minimum of 3 years following treatment for peri-implantitis **C:** Nil **O:** Implant loss for any reason (failure), recurrence of peri-implantitis	85% resp. 80% of implants treated for peri-implantitis might survive after 5 years and 7 years of treatment (irrespective for respective or regenerative treatment).
Sahrmann et al. (26)	Not mentioned	Partial bone fill occurs in 85% of regenerative procedures. No rinsing solution shows superiority to the other. Hydrogen peroxide has been widely used in literature.
Schwarz et al. (27)	**P:** Patients with peri-implant mucositis and peri-implantitis based on case definitions used in respective publications **I:** Alternative or adjunctive measures to non-surgical and surgical treatments **C:** Conventional measures for non-surgical and surgical treatments **O:** Changes in peri-implant mucosal inflammation	Augmentative procedures show higher radiographic bone fill, but similar PPD reduction compared with OFD.
Tomasi et al. (28)	**P:** Patients in good general health requiring treatment of peri-implantitis **I:** Reconstructive technique as adjunction to surgical therapy of peri-implantitis **C:** Surgical therapy of peri-implantitis alone (open-flap debridement) **O:** Changes of radiographic marginal bone level, clinical attachment level and soft tissue level. Reduction of probing depth and peri-implant bleeding on probing. Implant survival (in studies with a follow-up of ≥5 years)	Regeneration leads to 57% (WMD) of greater bone fill compared to OFD. Heterogenous study designs in the field.

most favorable one for a regenerative approach. In addition, with a mean prevalence of 55%, it also represents the most common defect encountered in patients suffering from peri-implantitis (30). In accordance with periodontal defect characteristics, the assumption based on the existing body of literature is that the more walls are present and the more self-containing these defects are, the more promising the potential bone regeneration is (31). In contrast to this optimal situation, regeneration of suprabony class II defects seems—as in line with periodontal defects—not to be a predictably achievable goal yet (8). This means that exposed implant shoulders and threads can only be managed by non-regenerative or maybe respective means, i.e., implantoplasty (32). A combination of a respective approach with guided bone regeneration (GBR) may be considered, if defects show supra- and infrabony components (21, 29). Notably, only 50% of patients treated with such a combined approach of implantoplasty and GBR showed no sign of inflammation after 2 years (32). Of course, with regard to the overall eligibility of a patient for regenerative and augmentative therapy and the overall outcome prognosis, the most relevant systemic and environmental factors, such as smoking, oral hygiene, and medical condition, must be considered (31).

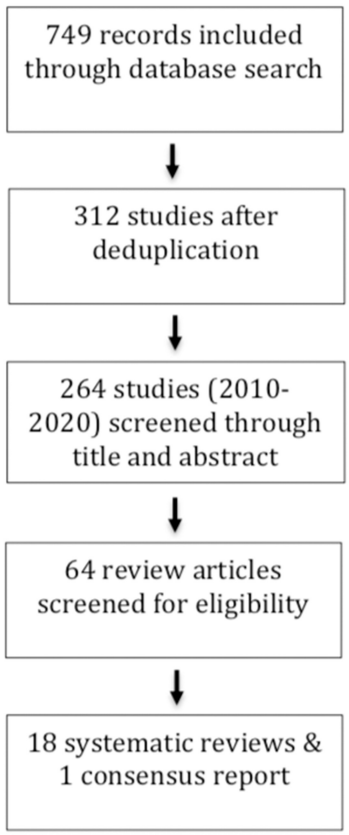

FIGURE 1 | Flow diagram of literature search and selection.

Question 2: (How) Can Infected Implant Surfaces Be Cleaned?

Various decontamination methods, such as mechanical, physical, and chemical approaches and combinations, have been described in the literature (27). All methods commonly aim to remove biofilm and/or calculus and create a biocompatible surface, which conceptually leads to successful re-osseointegration (33). Despite various materials and protocols, none seems capable of complete and reliable decontamination of implant surfaces (29), and no single rinsing solution has shown any superiority over the others (8). Therefore, most protocols represent a combination of mechanical and chemical debridement methods combining the thought advantages of each approach (34).

From a conceptual point of view, any mechanical instrument, such as hand instruments and ultrasonic tips, used for debridement should be softer than the treated implant material to prevent damage to the implant surface (35). For this purpose, tips have been modified or coated with different materials, such as carbon fibers, plastic, and silicon. Unfortunately, most of these instruments have often been judged as ineffective in thoroughly removing biofilm (36). In addition, material remnants and contaminations are possible, which should not be neglected in this context.

Air-polishing devices have, therefore, been suggested for non-surgical and intra-surgical debridement procedures. The efficacy of mechanical and ultrasonic curettage seems to be inferior to that of air-polishing systems (35). However, air-polishing devices have to be applied with care, as a certain risk exists for the generation of an iatrogenic emphysema (8, 26). The extent of re-osseointegration of titanium implants after air polishing therapy has been reported to be between 39 and 46% with increased clinical implant attachment and PPD reduction (35).

Lasers (Diode, Er:YAG, Nd:YAG, Er,Cr:YSGG) have also been suggested for peri-implant therapy (22). Evidence supports the ability of lasers for tissue debridement, cell proliferation (photobiomodulation), bacterial inactivation (antimicrobial photodynamic therapy), and calculus ablation to comparable levels of conventional mechanical instrumentation. In a systematic review and meta-analysis (20), less effectiveness of lasers for surgical treatment of peri-implant diseases was described; i.e., the test group did not show any clinical benefits over the control groups without laser (20). These findings are consistent with those of a recent systematic review showing strong scientific evidence that both treatments, regenerative procedures with or without additional laser disinfection, result in the same outcome in the long-term (13). Although lasers show no significant advantage over other decontamination methods, they might possess some advantages, especially when the access to mechanical instruments is compromised (29).

Regarding chemical agents, different rinsing solutions have been suggested for decontamination of implant surfaces. However, none has been proven to be superior to the other (29). Among the most frequently used and investigated chemicals, the following substances are commonly recommended: hydrogen peroxide, citric acid, sodium chloride, chloramines, tetracycline hydrochloride, and chlorhexidine gluconate. Additionally, based on the available evidence, no single method has been proven to be superior (29), but undoubtedly, the adjunct use of rinsing, as such, is clinically considered an important adjunctive step in cleaning the affected areas. Owing to its availability, efficacy, and safety, hydrogen peroxide, applied on the implant surface for 2 min, has been the substance most widely used for chemical decontamination (26).

Question 3: How Can/Should Regeneration Be Achieved?

The use of bone substitute materials alone or in combination with barrier membranes has been investigated in several studies (12, 15).

With respect to the selection of bone substitute materials, autogenous bone has been used and described as gold standard as in many other augmentative procedures. However, a recent meta-analysis suggested that its use—despite its potential osteoinductive and osteogenic properties—leads to the least bone gain, when compared to synthetic and xenogenic bone grafts, and a resorption of up to 40% of the original volume has been reported (15, 37). Synthetic or xenogenic materials show higher volume stability in the presence of a low or no

resorption rate. Most authors, therefore, still suggest a mixture of materials to combine advantages and concurrently overcome disadvantages (15), as mentioned above. However, no recent systematic review still could show any significant superiority of a specific material (12).

Noteworthy, due to limited amounts of human histologies, no final conclusion can be drawn, with respect to re-osseointegration of previously exposed implant surfaces after GBR procedures (32).

When assessing the additional use of a membrane, the studies could not show an improvement of the outcome when membranes were used, especially in self-containing (class-Ie) defects. In contrast, membranes tended to exhibit more complications during healing by developing wound dehiscence. Complications have been reported in 58.4% of all cases, when non-resorbable or resorbable membranes were used (24). Resorbable membranes alone would surely show a lower complication rate, as mostly non-resorbable membranes show a higher rate of wound- dehiscence (38). Membrane fixation and stabilization, in combination with pins, have been suggested for more complex defects, including bone dehiscence, to contain and stabilize the bone substitute material (32). Based on the question, if submerged or unsubmerged healing of the augmented implant site is preferable, evidence showing any superiority of one approach to the other is lacking. However, from a clinical viewpoint, seeking a submerged healing whenever possible to enable an uninterrupted healing seems rational (8). Certainly, due to patients' chewing comfort and other reasons, sometimes this cannot be achieved.

Only little is known about the role of soft tissues in regeneration. Although evidence is lacking, ensuring the availability of adequate amounts of keratinized tissue in the surgical area seems rational. Providing both, stability to the blood clot and enabling the patient to clean the area properly after regeneration (39).

The administration of antibiotics, combined with regenerative procedures, was investigated in several studies, but none actually evaluated the possible positive effect on the regenerative outcome (24).

Question 4: What Is the Outcome of Regenerative Therapy in Peri-Implantitis?

As mentioned already, non-surgical therapy—especially in advanced peri-implantitis defects—seems rather ineffective and unpredictable. However, it should be considered a pre-surgical hygiene phase under any circumstances (9, 26). Similar to regenerative periodontal treatment, thorough intrasurgical cleaning, blood clot stability, peri-operative infection control, and post-operative maintenance seem to be crucial in the regeneration of peri-implant bone defects (9). As compared to periodontitis and inflammations around teeth, peri-implantitis, in general, progresses faster, explaining the need to treat patients without delay to avoid further bone or even implant loss (29).

An early systematic review showed complete bone fill after regenerative peri-implantitis therapy in only roughly 10% of the cases, whereas partial bone fill was described in almost 86% and no bone fill in 4% (26). Therefore, the authors concluded that a complete bone fill represents no predictable therapy outcome, while at least a partial bone fill can be expected (26). In a more recent systematic review, an additional mean bone-level-gain of 1.7 mm and a weighted mean difference (WMD) in bone fill of 57% was observed, when comparing regenerative procedures with open flap surgery (OFD) after 1 year. Surprisingly, no difference in PPD or bleeding on probing (BOP) reduction was observed (28). This was consistent with the observation of other authors stating that augmentative procedures show higher radiographic bone fill but similar PPD and BOP reduction to OFD (24, 27). A recent systematic review showed the highest mean PPD reduction (2.8–3.1 mm) and mean bone defect fill (up to 3.6 mm) in groups using bone substitute materials, compared to OFD (mean PPD reduction of 1.2 mm) alone (12). These findings corroborated the conclusions of other systematic reviews (14, 17, 23).

In spite of an initial successful regeneration of bony defects, cases of implant loss and disease recurrence have been described (24). Furthermore, implants with moderate rough surfaces undergoing regenerative therapy showed significantly better outcomes than rough surfaces (24).

With respect to long-term results, only limited data are available. One systematic review analyzed outcomes after 3 years. A WMD in bone defect fill of 2.4 mm and PPD reduction of 3.1 mm were observed (18). Irrespective of a respective or regenerative approach, Roccuzzo et al. (25) found a survival rate of implants treated for peri-implantitis of 85% resp. Eighty percent after 5 and 7 years of treatment.

In general, available data on peri-implant defect regeneration in humans have been shown to be limited, as a high number of available clinical studies seems to be, unfortunately, case series (28). The mentioned reviews, in addition to the low number of controlled trials, found that study designs and materials used in the different studies were very heterogeneous, leading to difficulties when trying to draw conclusions and formulate clinical suggestions (14, 16, 28).

Question 5: Should We Apply Additional Biologicals or Stem Cells as Adjunctive Measures?

Various bio-active materials or cell therapies, as innovative approaches, are used in many dental and medical fields, and are currently also investigated in the field of peri-implantitis therapy.

Especially, growth factors are frequently used in regenerative dentistry to enhance clinical outcomes. Regeneration stimulating factors include platelet-derived factors, such as platelet-rich fibrin (PRF), plasma rich in growth factors (PRGF), and enamel matrix derivative (EMD). In the following section, the most promising therapeutic options are shortly described (19). Unfortunately, the evidence of systematic reviews is still scarce. Therefore, this part was supplemented with data from narrative reviews to highlight potential future perspectives and the actual status of research.

Autologous Platelet Concentrates

One meta-analysis, including three original studies, observed a higher bone gain when platelet-derived-growth-factor (PDGF) was adjunctively used (15). Nevertheless, it was not proven whether defects treated with adjunctive PDGF actually had more

TABLE 3 | Model treatment step-by-step based on the available evidence.

1	Defect configuration: Host factors:	• Infrabony defect, preferable Class-Ie. • Patient should be non-smoker, healthy and show a reasonable oral hygiene &motivation.
2	Desinfection of implant surfaces:	• Any disinfection method can be used, but a combination of mechanical and chemical debridement is recommended.
3	Use of bone-substitutes: Use of membranes: Use of bioactive substances or cell therapies:	• Indicated. A mixture of autologous and xenogenic bone is discussed. • Primarily, if defect is not self-containing. • In general, no strong evidence. • Additional use of PDGF might be beneficial.
4	Soft tissue management:	• Submerged healing, if possible. • Presence/creation of attached mucosa (at least 2 mm) desirable.

bone fill. Remaining bone substitute materials could not be differentiated from real bone on radiographs.

Platelet-rich plasma (PRP) has been investigated mainly in animal peri-implantitis models, and it shows no additional benefit for the main therapy outcomes (40).

While we can rely on a lot of positive evidence in the use of PRF in periodontology, available data on peri-implant regeneration are very limited (41). PRF-membranes in one randomized controlled clinical trial have been shown to be inferior to collagen membranes (19). The adjunctive use of PRF to OFD showed beneficial outcomes in terms of clinical attachment level (CAL) after 3 and 6 months (19).

Enamel Matrix Derivatives (EMD)

The biologic effect of EMD with its acceleration of wound healing (42), osteopromotive (43), and antibacterial (44) properties has already been shown in several studies, especially in the field of periodontitis and dental traumatology (43). One systematic review revealed no actual clinical benefit in regenerative peri-implantitis therapy (19).

One randomized clinical trial, including 25 patients, is also available and noteworthy (45). This trial revealed a promising benefit of the EMD-group, in terms of bone level changes after 1 year. However, this advantage was not valid after 3 and 5 years of follow-up, respectively (45).

Stem Cells

Stem cells are known to be important for maintenance and regeneration of tissues within the periodontium (46). A similar role for maintenance and regeneration of peri-implant tissues can, therefore, be anticipated (46). Mainly, the use of dental pulp stem cells in bone regeneration therapy around dental implants has been investigated, showing the most osteogenic potential as a source for tissue-engineered bone around implants (47). However, stem cells are not considered an evidence-based treatment protocol currently, but might play a major role in the future.

Experimental Approaches

A recent narrative review also picked up the role of epigenetics in regenerative peri-implantitis therapy (48). Epigenetic modifications, such as methylation and histone modifications of cells, were concluded to have the potential to represent a target for promotion of bone regeneration. MicroRNAs are judged to be promising therapeutic agents, but not safe to be used currently. Scientific evidence for preventing MicroRNAs from interfering with unwanted target genetic pathways, which may cause adverse effects, is still lacking. Further profound investigations are still needed (48).

Future Developments

In the future, improvements should be expected in the field of smart and carrier materials, which may be able to release active substances, such as antibacterial and cell-stimulating substances. Further, the role of soft tissue management in regeneration should be precisely assessed.

More clinical research is needed to verify a possible advantage in adding EMD, autologous platelet concentrates, or stem cells to regenerative procedures.

Most importantly, the cleaning of the implant remains a critical pillar of any successful treatment, and promising developments in this field may also lead to optimized processes. One example, for instance, is the use of electrolytic systems to clean the implant surface (49). However, to date, no evidence-based justification of such treatment is available.

CONCLUSION

In assessing current literature, the following evidence-based bullet points can be formulated:

- Whereas, infrabony defects can be regenerated, suprabony defects cannot be predictably augmented.
- Air-polishing seems to be more effective than ultrasonic or hand instrumentation, in terms of implant surface debridement.
- No rinsing solution has been proven to be more efficient than another.
- A mixture of xenogenic and autogenous bone is discussed as the most suitable.
- Membranes should be primarily used in complex not self-containing defects.
- Evidence for biologicals and the use of stem cells is still lacking.
- In general, a partial bone fill can be expected in 85% of regenerative procedures.
- Regeneration leads to a mean of 57% of greater bone fill than in open flap surgery only.

Table 3 shows a step-by-step approach for a regenerative peri-implantitis treatment based on the herein gathered evidence.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AS and PS conducted the literature research, screened the studies, carefully read, and approved the final text. AS drafted the manuscript. PS validated the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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