RESEARCH PAPER

Enhancing the Soft Tissue Augmentation Around Dental Implants Using Amino Acid Infused Polysaccharide Scaffolds: A Systematic Review

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ABSTRACT

Background

Amino acid-infused polysaccharide scaffolds have been proposed as a promising method of enhancing soft tissue augmentation in dentistry, but currently the effects of this scaffold on soft tissue regeneration remain undefined and a systematic review of the available literature is required. In the current study, we will evaluate the efficacy of the scaffold in soft tissue regeneration by conducting a systematic review of the available literature on the use of amino acid infused polysaccharide scaffold in vivo in dental implant region.

Aim

The aim of the study was to conduct a systematic review of the existing knowledge on effectiveness of amino acid-infused polysaccharide scaffolds in improving the soft tissue augmentation around dental implants, relative to the conventional grafting procedures and non-modified scaffolds.

Materials and Methods

This was a systematic review that has been conducted in accordance with PRISMA. The electronic databases included PubMed/MEDLINE, Scopus, Web of Science, Embase, and Cochrane Library. Inclusion criteria included human clinical trials, animal trials, and in vitro mechanistic trials assessing the ability of polysaccharide amino-enriched scaffold in soft tissue augmentation around implants. Primary outcomes: soft tissue thickness, kinesthetic mucosa width, peri-implant soft tissue stability, esthetic indices. Secondary outcomes: histologic/histomorphometric data, inflammatory reaction, and the rates of complications. Study selection, data extraction and risk-of-bias were done by two independent reviewers using RoB-2 (clinical studies) and the tool of SYRCLE (animal studies). A narrative synthesis was done because of the heterogeneity of the types of scaffolds and outcome measures.

Data Collection and Analysis

Two authors independently extracted data in the included studies and then collated them. Data attributes were obtained through data collection forms but the quality of the study was determined through RoB tools.

Results

Majority of the studies described how amino acid-modified polysaccharide scaffolds displayed improvements over controls in terms of cell proliferation, fibroblast attachment, neovascularization and collagen deposition. Clinical and preclinical trials were successful showing an increase in soft tissue thickness and keratinized mucosa width and a decrease in postoperative morbidity. Nevertheless, there was a great difference in scaffold composition, amino acid concentration and follow-up period, and it was not possible to make direct comparisons.

Conclusion

Recent findings indicate that polysaccharide scaffolds with amino acids have positive potential in the enhancement of peri-implant soft tissue augmentation, and stability as an alternative to the autogenous grafts due to its biologically-oriented nature. Although positive results are achieved, the heterogeneity of studies, and the lack of high-quality clinical trials shows the necessity to standardize scaffold formulations and human studies with a long-lasting duration to determine the clinical efficacy.

Keywords: Dental implants, Soft tissue augmentation, Amino acids, Polysaccharide scaffolds, Collagen synthesis, Peri-implant esthetics, Biomaterials

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INTRODUCTION

To preserve peri- health and enhance aesthetics, methods to augment mucosal thickness around implant locations are frequently employed. Soft tissue grafting techniques may be carried out at stages including prior to or, during implant insertion throughout the healing period or following the placement of final restorations.[1]

Increasing mucosal thickness offers these benefits: (i) the return of the convex ridge shape during the healing period given that soft tissue grafting can contribute as much as 40% of the ultimate volume and (ii) the maintenance of peri-implant health over time evidenced by stable marginal bone heights or minimal alterations in marginal bone along, with reduced probing depths, plaque accumulation and bleeding indices(6–8). When the periimplant mucosal thickness is thin (<2 mm), mucosal thickness augmentation can also improve the aesthetic result by masking the tissue discolouration caused by metallic abutments. Furthermore, it seems that soft tissue augmentation supports the mucosal margin's stability.[2]

According to the scientific data available, autogenous SCTGs are considered as the grafting material of choice for augmentation of mucosal thickness. Positive outcomes with SCTGs have been achieved, mainly due to the enhancement of the soft tissue esthetics at the implant sites. To be noted, because employing an SCTG requires an additional surgical procedure for harvesting and is limited in supply, employing one will most definitely lead to higher morbidity [1]. It can be argued that the optimal option may not necessarily be the one showing the highest efficacy in randomized clinical trials, but the one that fulfills the patient's values and preferences.[3] As such, more focus is directed towards the patients' preferences, commonly referred to as PROMS or patient-reported outcome measures which are increasingly being considered when deciding on the intervention to utilize. Consequently, several pre-clinical and clinical studies have been conducted to assess soft tissue substitutes from various sources.[4]The morbidity of the patients is less when soft tissue substitutes are used compared to autogenous soft tissue grafts according to short-term results. Hence, it heavily depends on long-term data. [9]

A scaffold should be composed of biocompatible materials and designed to facilitate the repair of the bone defect, as well as to have an interconnected macroporous structure. The scaffold should also possess the ability to be bio absorbed at a rate that coincides with the rate of formation of new bone, possess high levels of surface wetting properties that promote cellular adhesion and proliferation, and possess appropriate surface chemistry to promote cellular adhesion. In addition, a scaffold should possess sufficient mechanical strength to withstand the weight of any load placed on the scaffold in the wound area.[5]Finally, the scaffold should possess the capability to undergo sterilisation and be available for commercial manufacture.[2]

There is a well-established body of literature discussing how to perform surgical procedures to increase the thickness of keratinized tissue and how to restore lost amounts of soft tissue following plastic periodontal surgical procedures [2,4]. Most of these surgical procedures are performed concurrently with reconstructive surgery for the purpose of restoring biological functionality and stability to the area surrounding teeth or dental implants.[3] There has been much disagreement regarding the necessity of having keratinized tissue to support health of periodontal and peri-implant health[6].There are several factors that must be considered such as the establishment and maintenance of biological health, prevention of recession, aesthetics, and the ability to clean the reconstruction. Griffen and coauthors reported the identification of 53 different bacterial species in healthy periodontal tissue and 123 different bacterial species in periodontal tissue that had been compromised by periodontitis [7]. Dekina et al. found that a decreased concentration of lysozyme may support the growth of pathogenic or opportunistic microorganisms as well as the development of periodontitis [3].

Although a lot of research into the engineering of periodontal tissue has shown a lot of promise for new therapies [8] there are still many unknowns. Due to the complexity of structures that include organised layers of cells at micro levels, successful restoration and regeneration of the periodontal tissue is generally poorly understood and exceedingly difficult to predict. [9] Integration of the tooth to the surrounding tissue is

an essential part of effectively restoring the full function of the tooth. Recently, there have been many different strategies developed in regenerative medicine for regenerating dental tissue and restoring tooth-supporting tissues [4]. Within the scope of these strategies, the use of biomaterials could be an attractive approach to support the healing of soft-tissue periodontal tissues and promote healing and restoration of the function of the periodontal tissue.[10]

Biocompatibility of synthetic biopolymers such as Poly (amino acids) derives from their structural similarity to naturally occurring proteins and the fact that like all synthetic polymers, they have no intrinsic batch-to-batch variability and can be produced and controlled for strength and degradability. Biodegradability is pertinent to implantable devices, while scaffolding materials may be biodegradable depending on their application.[11] Cross-linked hydrophilic polymers (e.g., hydrogels) are emerging materials of choice for scaffolding in tissue engineering for several reasons.[12] First, hydrophilic polymers are readily available in a wide range of molecular weights and forms, making them highly versatile. [13]Secondly, hydrophilic polymers contain a large amount of water, creating structural properties similar to the ECM and soft tissue.[4] Thirdly, the mechanical properties of hydrogels are supportive of tissue engineering applications.[14]

While hydrogels offer a number of positive attributes due to their use as scaffold materials; one of their biggest challenges related to long-term storage is their high water content making them susceptible to microbial contamination.[15] The most commonly used method for the storage of tissue-engineered products that have been FDA approved (Apligraf® and Dermagraft®) is cryopreservation at -80 °C, yet, despite the popularity of this technique, it is both cost-prohibitive and logistically difficult due to cryopreserved products requiring special transport requirements.[16] Another possible method of storing these scaffolding materials would involve drying out the scaffolding materials sufficiently that chemical reactions leading to deterioration and bacterial growth would be mitigated or eliminated, followed by rehydration of the materials immediately prior to use. [17] Freeze-drying is a standard method employed for the preservation of heat-sensitive products; however, rehydrating the dried materials may have an effect on the structural performance properties of these scaffold materials.[16] At this time, there has not been enough collected data to define the extent of these effects.[18] A scaffold that can be easily housed and transported would represent a major advancement toward creating a "ready" product for tissue regeneration. Protein-based hydrogels have the potential to serve multiple purposes based on their response to stimulation, structural design, and biological properties [5]. Given the abundance of functional groups in both protein and polysaccharide biopolymers, it is uncommon for conjugation between the two classes of biomaterials to be examined for applications in medicine. This could complicate the purification and use of the resulting composite biomaterial or provide an unwanted interaction.[19] The majority of the research relating to proteins and polysaccharides has been on how the individual biopolymers can be modified for use individually. The covalent interaction of a polysaccharide and a protein results in the formation of a glycoconjugate, also called a proteosaccharide.[20] The carbohydrates that interact with proteins, such as lectins and antibodies, are the predominant forms of carbohydrate-protein interactions in the living system [6]. Lectin proteins utilize carbohydrate recognition domains to interact with various forms of carbohydrates. The antigen-binding site of an antibody is hypervariable, making these proteins the dominant protein components of the immune system [21]. The building blocks of the antigen-binding site of antibodies are amino acids. A glycoprotein interaction takes place when a polysaccharide antigen is presented. Proteosaccharide interactions with glycolipid membranes are dominant in most cases[3]. Many studies have been conducted that use combinations of proteosaccharides (e.g., alginate + gelatin) to enhance cell adhesion/recognition. Some examples of this are alginate + gelatin and silk + hyaluronic acid, among others.[22] Most times, researchers will employ these combinations because they believe they will counteract the negative qualities of an individual polymer. As opposed to synthetic polymers, proteosaccharides are associated with increased bioactivity and reduced toxicity. Therefore this systematic review will focus on the many different functions of proteosaccharides in the field of tissue engineering.[23]

STRUCTURED QUESTION

Does amino acid infused polysaccharide scaffold have a positive effect on soft tissue augmentation around dental implants?

PICO ANALYSIS

POPULATION-Clinical scenario requiring dental implants
INTERVENTION-Amino acid infused polysaccharide scaffold
COMPARISON- Non amino acid based;connective tissue graft(control)
OUTCOME-Soft tissue regeneration

PROTOCOL AND REGISTRATION

For this study, we followed the guidelines given by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISMA)

SEARCH STRATEGY

A Comphrensive literature search of the following databases were done which included studies of Pubmed, Pubmed central, Medline, Cochrane databases of systematic reviews, Mesh Science Direct, Embase databases.Articles were selected based on selection criteria.

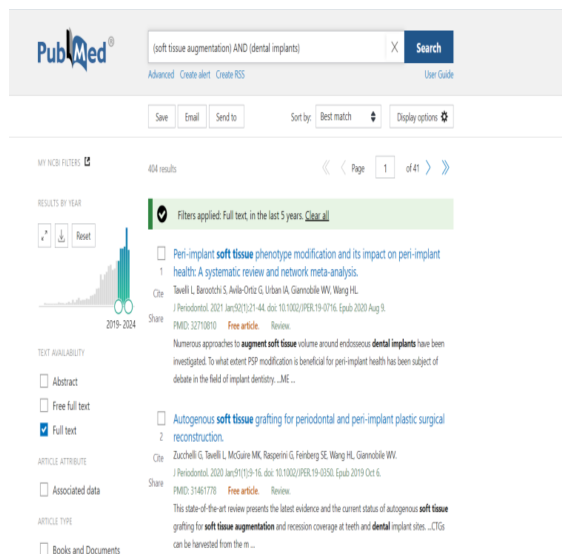


Figure 1: PUBMED search

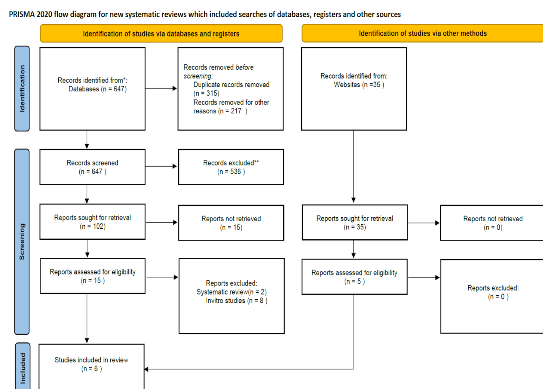


Figure 3 depicts the search strategy using PRISMA Flowchart

Sources of Electronic search

Search Terms

((((((((((((((((((Peri implant) OR (soft tissue defects)) OR (mucosal thickness)) OR (amino acid scaffolds)) OR (collagen matrix) OR (connective tissue matrix)) AND (polysaccharide)) OR (proline)) OR (beta glucan)) OR (alginic acid)) OR (scaffolds)) AND (Collagen membrane)) OR (Biomolecules)) OR (Stem cells)) OR (growth factors))

Literature Search Protocol

For the identification of studies included or considered for this systematic review, detailed search strategies were developed for the database searched. The search methodology applied was a combination of MeSH terms and suitable keywords. The keywords employed in this search were broadly classified into four categories describing population, intervention, outcome, and the type of study. Keywords within each group were combined using Boolean operator (OR) and the searches of individual groups were combined using Boolean operator (AND) to retrieve articles electronically.

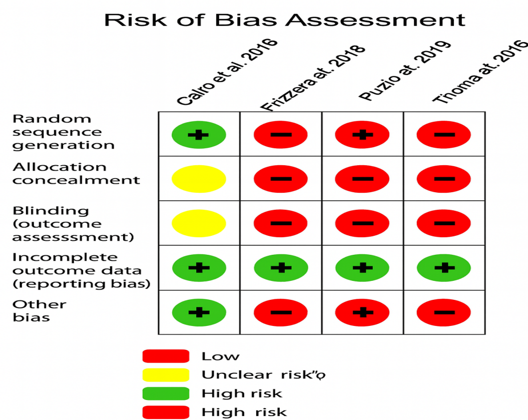
DATA EXTRACTION

Date of the included studies was extracted independently by two reviewers using a customized data extraction and entered into an electronic spreadsheet - Name of the authors, year of publication, study design, study groups, bone regeneration measurement, statistical analysis and results were recorded.

RESULTS

RISK OF BIAS ASSESSMENT:

ITEM	Cairo et al.2018	Hutton et al.2018	Frizzera et al.2018	Puzio et al. 2019	Thoma et al. 2016
Random sequence generation	Low	High	Low	Unclear	Unclear
Allocation concealment	Low	High	Low	Unclear	Unclear
Blinding	Unclear	High	High	High	High
Blinding (outcome assessment)	Unclear	High	High	High	High
Incomplete outcome data	Low	Low	Low	Low	High
Selective reporting (reporting bias)	Low	Low	Low	Low	High
Other bias	Low	High	Low	High	High



List of included studies

S.No	Study	Objective	Intervention	Evaluation Method	Increase in Soft Tissue Thickness	Result / Outcome	Justifica
1	**Cairo et al., 2018**	Comparison of xenogeneic collagen matrix scaffolds vs connective tissue grafts	60 subjects	Endodontic needle inserted 1 mm coronal to mucogingival junction	Significant difference favouring CTG	CTG showed greater dimensional stability and soft tissue gain than collagen matrix	CTG higher density greater vasculari potential xenogen collagen leading t mucosal thickenir
2	**Hutton et al., 2018**	Comparison of allodermal scaffolds vs connective tissue grafts	20 subjects (mean age 55 yrs)	CAD/CAM stent with 3 points of measurement (1, 3, 5 mm apical to mucosal margin) + endodontic needle	No significant difference	Both interventions produced comparable soft tissue thickness	Allodern had fibroblas integratio dimensio stability resulting equivaler outcome
3	**Frizzera et al., 2018**	Comparison of xenogeneic collagen matrix vs connective tissue grafts vs no graft	24 subjects (23–65 yrs)	CBCT small FOV measurements (2 mm below gingival margin)	Significant difference favouring CTG	CTG produced significantly greater soft tissue volume increase	Autogen connecti contains fibroblas growth unlike matrices graft, superior augment
4	**Puzio et al., 2019**	Acellular dermal matrix vs connective tissue graft	57 subjects (18–60 yrs)	Ultrasonic device (Pirop®) at two points: (1) CEJ-to-CEJ reference line, (2) mucogingival junction	Significant difference favouring CTG	CTG resulted in more consistent and stable soft tissue thickening	CTG's compatib inherent structure faster integratio compare processe matrices

DISCUSSION:

This systematic review includes articles that examined the use of various scaffolds for soft tissue augmentation. While the authors of these articles have examined many of the same types of products, they also have chosen varying methods of measuring the thickness of the soft tissue that is augmented.[3] Due to the heterogeneity of the included data, a meta-analysis could not be conducted.[24]

The study focused solely on the outcome of the thickness of the peri-implant soft tissue and how that relates to peri-implant tissue health, aesthetics, and overall well-being.[19] The protocols from the randomized controlled trials were considerably different in terms of materials used, follow-up periods, and times of augmentation among other variables. [25] The evidence to support claims that both types of grafts (substitute grafts and CTGs) created thicker peri-implant oral mucosae was clear based on the findings agreed upon by all authors included in this meta-analysis. The studies of Thoma et al. and Huber have provided supporting evidence for this conclusion by demonstrating that the ability of the volume stable collagen matrix to increase oral mucosa thickness when compared to CTGs.[26] However, the increase in thickness did not reach statistical significance.[27] The graft available to Hutton et al., which is likely to be a potential substitute for CTGs in terms of its ability to thicken oral mucosae, has not received approval for use in Europe (Alloderm, BioHorizons). In the studies included in this review, neither the XCM nor the ADM provided superior outcomes compared to the Gold Standard, CTG[28]. There is some evidence, as presented by Cairo et al. and Frizzera et al., to suggest that CTG had statistically greater results than XCM in four of the studies included in this review. [29]

Soft-tissue augmentation has been established as a standard practice along with implants in the aesthetic classification of dental implants and when placing an implant immediately after an extraction to minimize or prevent any dimensional changes that may occur with the bone and/or soft tissue surrounding it. [4] Nonetheless, it has been demonstrated that the use of biomaterials has increased the level of comfort and satisfaction for patients postoperatively with these types of procedures due to the failure to perform their second surgery on them. Patient Reported Outcome Measurements indicate that using substitute materials may provide pain-sensitive patients with an option for their procedure, as there is no requirement for a second surgical site.[5,6] Additionally, patients who may benefit from having lower risks of postoperative complications if using substitute materials could include patients who have experienced delayed healing (or wound healing problems) due to diabetes, particularly if the procedure will include the removal of the graft through secondary healing, or if the patient is on anticoagulant medication and has increased risk of bleeding.[28]

The risk associated with harvesting a CTG from the patient, as well as the complexity of the procedure, leads many surgeons who would prefer not to perform this procedure to have a preference for using other types of materials (substitutes). Further, therefore, the authors believe this may create a greater willingness to perform procedures to thicken soft tissue from the clinician's perspective.[8] One point the authors stress is that any procedure(s) undertaken to thicken soft

tissue around an implant (be it a CTG or other type of substitute material) should be performed only by skilled and experienced practitioners. However, it also cannot be denied there are similarities between the utilization of bone augmentation and the harvesting of autogenous bone and harvested autogenous bone blocks; for example, harvesting autogenous bone (especially large quantities or larger blocks) requires a lot of time and technical expertise.[4] The advent of bone replacement materials (of allogenic, xenogeneic, or alloplastic origin) has led to an expanded acceptance of these materials by dentists. [29]

Soft tissue thickness around dental implants influences the visibility of restoration material. When there is a greater thickness of mucosa covering the implant, there will likely be less ability to see the material underneath, thus creating a better aesthetic result; therefore, this is often seen by many patients as either among the top two, if not the most, important considerations. [3] In an in vitro study, Jung et al. found that after reaching a 3mm mucosa thickness, translucency effects from the restorative materials were no longer present, regardless of which type of restoration material was used. Based on parameters set by Cairo et al., 79% of sites treated with XCM and 93% of sites with CTG had reached a final thickness of at least 2.5mm, indicating these sites would fall into the classification of "thick" biotype. Furthermore, Puzio et al. had even greater success, showing that all study groups presented with a classification of thick biotype.[8]

One aspect of this study that may be important to practitioners is the variation in methodologies for assessing the thickness of mucosa and gingival biotypes. For some authors, this has been viewed as a key factor when planning for treatment.[6] A well-known article reported that the gingival biotypes could be consistently determined through a visual method; whereas another study stated that "the use of only visual inspection may not provide enough information to predict gingival biotypes for high-risk patients," which suggests that many of these patients will go unidentified. [21]This is confirmed by Puzio et al., whose research found that patients with gingival biotype classifications that were based on the use of ultrasound were frequently assigned to a different biotype classification than those who were assigned a biotype classification based on the use of a periodontal probe [3] For surgeons operating in esthetically challenging locations, the use of CBCT scans is now considered part of the standardized process for assessing and measuring such conditions prior to treatment. [12] However, the authors of this article believe that measuring soft tissues alone does not warrant the amount of radiation exposure that this assessment will produce, unless there is a need to evaluate and classify soft tissue thickness in conjunction with other imaging studies (e.g., implant placement) at the same time.[23] A recent study compared four different approaches to soft tissue thickness determination. There are various ways to conduct transgingival probing, such as: transgingival probing using a periodontal probe, transgingival probing with a stainless steel acupuncture needle, using an ultrasonic device, and utilising a colour-coded periodontal probe.[28] According to the study authors, the most reproducible measurements were taken using both the periodontal probe and the ultrasound device. However, measurements conducted using the periodontal probe had several drawbacks, including their invasive nature, the associated discomfort, and reduced accuracy.[2] Slack, et al., report that ultrasonic devices are able to record measurements of the gingival thickness to the nearest hundredth of a millimetre, while conventional periodontal probes only provide measurements to the nearest millimetre. There is an additional point that has not yet been adequately addressed but needs to be emphasized: the source of the biomaterials.[3] Currently, all xenogeneic membranes are derived from pigs (porcine tissues) and therefore, will not be acceptable to a number of people for religious beliefs, thus eliminating the potential for CTGs (cell-based tissue grafts).[29]

LIMITATIONS:

1) The different measurement methods used in the studies prevented the use of meta-analytic methods, thus resulting in a heterogeneous result.

2)The variability in the methods used to measure each of the parameters prohibits any definitive determination of advantage of one type of CTG versus any other that can be used universally.

3)With an increased risk of individual study bias, the authors found only one study with acceptable low-risks of bias.

CONCLUSION:

There was an increase in mucosal thickness as a result of the use of both CTGs and substitute materials. Out of the five studies, only two showed no difference between the two types of grafts (CTG & sub-CTG), while three studies did find significant differences, specifically that CTG had a significant advantage over the use of sub-CTG in all areas of comparison. CTG can be considered an acceptable treatment option with

respect to both its safety for dental implant tissue augmentation procedures and the added benefit of more robust mucosal tissue formation surrounding implants. The use of CTG still remains the traditional standard for soft tissue augmentation; however, for select situations, it may still serve as an acceptable option when only minor thickness increases may be required, for patients that are sensitive to pain, or for those patients that do not provide consent for CTG harvesting from their palates, or have insufficient palate harvesting sites. The use of bioengineered substitute materials may serve as acceptable options for dentists that are either untrained or unwilling to perform CTG harvesting. The majority of these bioengineered substitute materials today are utilized for improving wound healing properties, either through the use of collagen-based hydrogels or as anti-inflammatory agents, and have also been demonstrated to be effective in conjunction with collagen scaffolds (proline) and beta-glucan (polysaccharide) in promoting soft tissue regeneration, according to clinical trial findings documented by researchers.

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